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Experimental medical interventions in a public health emergency: an ethical review

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Abstract

The ethical challenges of researching in disadvantaged communities include those of informed consent, standards of care and issues pertaining to justice, including distributive justice. Research, specifically regarding epidemic infections, in underdeveloped countries is more difficult to carry out when the aforementioned challenges exist. In order to address an emergency epidemic public health challenge, all available treatment and other measures need to be implemented with urgency. If there is no known intervention for the disease causing the epidemic, the question is raised as to whether or not it is ethical to use an experimental investigational drug, which has not completed a clinical trial, in an attempt to address the crisis.

In this research paper I define the circumstances of a public health emergency epidemic in order to determine when it is appropriate to consider the use of experimental interventions. The 2014 Ebola crisis in West Africa and the on-going risk of Ebola recurrence is a case in point that demonstrates the formidable challenges the crisis of an epidemic present. I critically assess the existing regulatory guidelines for compassionate drug access and clinical trials in order to determine whether these regulations are appropriate within a public health emergency situation. I critically assess the major ethical and legal arguments that do and do not justify the use of experimental interventions. I lastly critically assess the major challenges regarding the use of experimental interventions within the context of autonomy and justice. I conclude that the arguments in favour of experimental interventions outweigh the arguments against them.

Acts of Parliament, Republic of South Africa

- Medicines and Related Substances Act (Act 101 of 1965)
- The National Health Act (Act 61 of 2003)
- The Consumer Protection Act (Act 68 of 2008)
- Constitution of the Republic of South Africa (Act 108 of 1996)

Case law

- *Soobramoney v Minister of Health, KwaZulu Natal* 1998 (1) SA 745 (CC)
- *S v Makwanyane 1995* (6) BCLR 665
- Minority judgement of Sach J in *Soobramoney v Minister of Health*, KwaZulu Natal 1998 (1) SA 745 (CC)
- *Lee v Minister of Correctional Services* 2013 (2) BCLR 129 (CC)

Acronyms

- EMA: European Medicines Agency
- EU: European Union
- FDA: The United States of America Food and Drug Association
- HPCSA: Health Professions Council of South Africa
- ICESR: The International Covenant on Economic, Social and Cultural Rights
- IMPA: Investigational Medicinal Product Application
- MAPPs: Medicines Adaptive Pathways for Patients
- MCC: Medical Controls Council of South Africa
- MIT: Massachusetts Institute of Technology

- NEWDIGS: United States of America New Drug Development Paradigms
- The Task Force: The Task Force of the American College of Critical Care Medicine
- USA: United States of America
- WHO: World Health Organization

Chapter 1

Introduction

Many health research studies sponsored by developed countries have been performed in developing countries. There is a great disparity between the healthcare systems of developed countries and those of developing countries. Resources and infrastructure are substantially reduced in developing countries and poor health conditions in general are linked to issues of ancillary care, such as sanitation, nutrition and access to water.[1 2] Major, complex ethical challenges have arisen from this. The ethical challenges of researching in disadvantaged communities include those of informed consent, standards of care and issues pertaining to justice, including distributive justice.

The validity of informed consent is challenged by differences in language, differences in socio-cultural traditions, low levels of formal education, differences in social values, as well as the lack of understanding of diseases and health.[1 3 4] If the available standard of care is poor within a developing country, determining the minimum standard of care to be administered whilst performing the research becomes relevant.[1 2] There are also many challenges related to achieving justice and fairness when conducting a clinical trial within a developing country. In order for research to be in line with the principle of justice, there needs to be an equal sharing of the benefits as well as the risk.[5] Much of the literature has scrutinized the high profit margins pharma companies make when there is little benefit to the study participants who bear the risk of the research.[1 6]

Research, specifically regarding epidemic infections, in underdeveloped countries is more difficult to carry out when the aforementioned challenges exist. Most epidemics arise from acute and communicable infections that most commonly occur in countries with poor healthcare resources and infrastructure; more often than not these are poor countries.[3] An epidemic infection is completely unpredictable, has a sudden onset and spreads rapidly and extensively.[3] Outbreaks occur in waves

and cycles spanning countries.[3] Adequate containment measures and isolation of infected persons are extremely difficult to implement in a country with an underdeveloped healthcare system. The development of an acute epidemic creates not only a public health emergency but also a global public health challenge.

In order to address an emergency epidemic public health challenge, all available treatment and other measures need to be implemented with urgency. If there is no known intervention for the disease causing the epidemic, the question is raised as to whether or not it is ethical to use an experimental investigational drug, which has not completed a clinical trial, in an attempt to address the crisis. Research within a developing country faces challenges; research specifically for an epidemic in a developing country presents further challenges; research specifically with an experimental drug within an epidemic in a developing country faces formidable challenges. In spite of these challenges and ethical debate around the use of an experimental intervention, I argue that it is ethical to use an experimental intervention.

The 2014 Ebola crisis in West Africa and the on-going risk of Ebola recurrence is a case in point that demonstrates the formidable challenges the crisis of an epidemic presents, as well as the controversy behind using an experimental intervention. The virus emerged initially in West Africa, notably in Guinea, Liberia and Sierra Leone.[7] These countries are all poor, and have poor healthcare resources and infrastructure.[8] Ebola is an infectious virus that presents with fever, vomiting, diarrhoea, internal bleeding that can result in organ failure and finally death.[7] [8] One report states that by the end of 2014 the Ebola virus had caused the death of more than 6000 people.[7]

Before the recent 2014 Ebola outbreak, Zmapp was an experimental intervention for the Ebola virus which was still under investigation.[9] The standard clinical trial process consists of different stages - a preclinical phase, phase I, phase II and phase III.[10] Only if the drug has satisfactorily passed each stage can it be made available to the public. The efficacy of Zmapp had only been established in

preclinical animal trials (phase I of the trial had not begun).[9] Safety in humans was not established. The physiology between human and some animal laboratory test subjects, like rats, is vastly different and therefore the side effects and risks of administering Zmapp to humans were unknown. The World Health Organization (WHO)[11] was faced with the decision of whether or not to use the experimental drug Zmapp in an attempt to get the Ebola epidemic under control and concluded that due to the "exceptional circumstances" of the outbreak, it was ethically justifiable:

> "…..it would be acceptable on both ethical and evidential grounds to use as potential treatments or for prevention of unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans, provided that certain conditions are met." [11]

The exceptional circumstances of the 2014 outbreak included: geographical factors and the extent of spread; the high fatality rate of the virus; the fact that little prior research had been done due to lack of commercial interest; and strong preclinical evidence.[11] The ethical justification given for use of the experimental drug Zmapp did not satisfy many ethicists. After the WHO gave the "go ahead" to use it, there was a flurry of literature that argued whether or not this decision was ethical.

Ethical debates arose not only about using an experimental drug; there was also controversy over the consent processes and standards of care available when accessing it.[7] Evidence in the literature had already demonstrated that intravenous fluid and electrolytes improved the outcome for those infected with Ebola, but due to the poor ancillary care available within these affected developing countries, the application of this baseline level of appropriate care created challenges.[7] As Zmapp is administered intravenously, the poor healthcare infrastructure stimulated ethical debate as to whether the standards of care available were appropriate for the treatment.[7] The validity of informed consent is also a challenging process, as the extremely ill patients (or proxy) need to understand fully that use of the drug is still experimental with unknown side effects. [9] I, however, believe that it was ethical to

use Zmapp due to the dire circumstances and because there were no other available interventions. The controversy of the use of Zmapp raises the question - is it permissible to use an experimental intervention in a public health emergency situation?

The first objective of this research report is to define the circumstances of a public health emergency epidemic in order to determine when it is appropriate to consider the use of experimental interventions. The second objective is to critically assess the existing regulatory guidelines for compassionate drug access and clinical trials in order to determine whether these regulations are appropriate within a public health emergency situation. The third objective is to critically assess the major ethical and legal arguments that do and do not justify the use of experimental interventions. The last objective is to critically assess the major challenges regarding the use of experimental interventions within the context of autonomy and justice.

The study design is a purely normative study with ethical-legal components which have been subjected to normative analysis. It is based on desktop and library-based research. No new data is collected or analysed. I employ the typical research methods and standards applicable to secondary data analysis and philosophical research. This will primarily involve the interpretation and critical analysis of salient texts and the positing and defence of new arguments. My critical analysis of relevant texts involve the definition and clarification of concepts; the identification and criticism of assumptions; the analysis and evaluation of theoretical frameworks; the development and defence of arguments; the use of counter-examples; and the articulation of the most plausible interpretation of significant concepts found in the sources. Sources of literature include, but are not limited to, articles at the University of the Witwatersrand Library, Online Library Sources, Pubmed, Juta online publications, and Google Scholar.

In Chapter 2, “Experimental interventions in a public health emergency”, I outline and define the scope of the study and present some working definitions pertaining to it. I define the nature of a

"public healthcare emergency", as well as "experimental interventions" (compassionate drug access in an emergency situation). Taking into consideration the circumstances that permitted the use of Zmapp, as well as the definition of a public health emergency, I then outline the circumstances as to when an experimental intervention is permissible. These circumstances include: an acute public health emergency epidemic situation; a high fatality rate of the infection; a highly infectious epidemic and no other available treatment options.

In Chapter 3, "Existing regulatory framework", I expand on the regulation permitting the use of experimental interventions. I critically assess the existing regulatory framework of compassionate drug use and clinical trials, the necessity for it, along with its limitations. In an emergency situation, the current regulatory framework allows for limited options in terms of new drug administration. The first is access to drugs approved for other indications and the second is preapproval of unregistered interventions (compassionate drug access). I defend the position that, if there is a suitable existing drug approved for another indication, this should be opted for first in an emergency epidemic.

I argue that the standard pathways for compassionate drug access are appropriate under "normal circumstances". In the case of a public healthcare emergency where large numbers of a population are infected with a rapidly spreading and potentially fatal illness, arguably the moral duties of the medical establishment change. There is a need for the legal system to create legal avenues to facilitate the use of treatments or drugs, which it would normally not be lawful to use on the public, in an emergency situation. The reason for this is that within an acute public health emergency epidemic situation the current regulation proves to be cumbersome due to the lengthy time frames for preapproval. Nonetheless, some regulation is still necessary. I highlight the complexity of striking a balance between adhering to regulations at the same time as addressing the epidemic crisis with immediate action.

Also in Chapter 3, I note that regulatory pathways for compassionate drug access do not stipulate whether a clinical trial should follow if access is granted. I therefore review the standard clinical trial process conducted under normal conditions. I then critically assess the different options of research study designs in order to determine if it is necessary to perform a clinical trial for an experimental intervention within an epidemic. I argue that research must still be done when compassionate access is granted but that it should not be mandatory to adhere to the traditional rules of a clinical trial.

In Chapter 4, "Arguments in support of and opposition to the use of experimental interventions", I establish that use of experimental interventions is morally acceptable. I demonstrate that there are no overwhelming legal or ethical arguments against the use of experimental interventions. I argue that under the circumstances of a public health emergency, experimental interventions are not only ethically justifiable, but it may also be the moral duty of the medical establishment and/or the state to use them in a bid to avoid the worst outcomes. It is therefore not only permissible, but ethically obligatory to intervene in such circumstances. I touch on different moral theories - principle-based morality, Kantian ethics, Utilitarian ethics, African based morality and Michael Walzer's concept of supreme emergency - to defend this position.

In Chapter 5, "Major challenges in the use of experimental interventions", I critically assess three of the major ethical challenges of using experimental interventions within the context of autonomy and justice. The informed consent procedure and a bare minimum in the standards of care are challenges which need to be addressed in order for experimental interventions to be ethical. It is a legal and ethical obligation to obtain informed consent. However, due to the nature of a public health emergency epidemic, I argue why deferred consent is realistic and I demonstrate that this is both ethically and legally acceptable, despite the intervention being experimental. I argue how the poor standards of care of the affected country draw on the budget strings in times of an epidemic crisis: if an experimental intervention is used, this should not negate the responsibility of raising the standard of care to implement infection control measures. I critically assess the challenges pertaining to justice

- specifically distributive justice, post-epidemic justice and social justice. If an experimental intervention is used, I define who gets the drugs first and what the necessary obligations of communities, sponsor researching companies and political leaders are during and after the trial to ensure there is fairness in the process.

In Chapter 6, “Conclusion”, I conclude that the arguments in favour of experimental interventions outweigh the arguments against them. The ethical debate around the use of experimental medical interventions in a public health emergency is complex and conflicted in that it comes with risks and unpredictable irregularities, yet such intervention is essentially a bid to save lives in a situation where no other options are available.

Chapter 2

Experimental interventions in a public health emergency

Introduction

In this chapter, I firstly define an experimental intervention. I then define a public health emergency. Using the 2014 Ebola virus as a case in point, I expand on the WHO deciding factors of "exceptional circumstances" that permitted the use of Zmapp. Based on the definitions of a public health emergency and the WHO list of exceptional circumstances, I compose my own list of exceptional circumstances in which is it permissible to consider the use of an experimental intervention. I base this research report on my own list of exceptional circumstances.

2.1 Definition of experimental interventions

Compassionate drug use programmes provide regulatory pathways to access unregistered medical interventions. In South Africa the provision for the compassionate drug use of unregistered medications is applied for via article 21 Applications to the Medical Controls Council of South Africa (MCC).[12]

Under article 4.17 it further states,

> "An exemption will be given for investigational and comparator medicines which:
>
> a) are new chemical entities…."[12]

Experimental interventions are analogous to "new chemical entities" for the purpose of this research report. To highlight the meaning further, "new chemical entities" is contrasted to point b in article 4.17:

> "b) are new or different dose forms, delivery systems and formulations of established medicines, which….."[12]

A "new chemical entity" is not a different dose, delivery system or formulation of an established existing drug. An experimental intervention is therefore defined for the purpose of this research report as a completely experimental, investigational new chemical. I expand further on the application of article 21 of the MCC[12] guidelines within South Africa in the regulatory guidelines for compassionate drug access in chapter 3 page 21.

2.2 Definition of a public health emergency

It is important to clearly define the nature and circumstances pertaining to an epidemic which results in a public health emergency situation because the numbers of diseases which can fall under the umbrella of the medical term "epidemic" are many. For the purpose of this research report, I focus on acute epidemics which are highly infectious and, once contracted, present with a high chance of fatality, thus creating a public health emergency. The WHO states:

> "A public health emergency (the condition that requires the governor to declare a state of public health emergency) is defined as an occurrence or imminent threat of an illness or health condition, caused by bio terrorism, epidemic or pandemic disease, or a novel and highly fatal infectious agent or biological toxin, that poses a substantial risk of a significant number of human fatalities or incidents or permanent or long-term disability." [13]

Another appropriate definition for public health emergency is:

> "Public health emergencies are defined as much by their health consequences as by their causes and precipitating events. A situation becomes emergent when its health consequences have the potential to overwhelm routine community capabilities to address them. Thus, the proposed definition focuses on situations whose scale, timing, or unpredictability threatens to overwhelm routine capabilities." [14]

The key phrase to be acknowledged from the above definition is "scale, timing, or unpredictability."[14] To clarify this further, I cite as an example the leading case of *Soobramoney v Minister of Health, KwaZulu Natal* [15] wherein the Constitutional Court denied an application by Soobramoney, who was in chronic renal failure, to receive kidney dialysis whilst waiting for a kidney transplant. Soobramoney specifically required the dialysis machinery in order to survive. The court claimed that, in view of section 27 (3) of the Constitution of the Republic of South Africa 1996, [16] Mr Soobramoney may have indeed needed dialysis urgently, but this did not constitute an emergency. The court defined emergency as a "dramatic sudden situation" or "event which is of a passing nature in terms of time".[15] There would need to be some suddenness, and at times unexpectedness in applying the concept "emergency medical treatment", which was not the case with Mr Soobramoney, since his illness was chronic. Soobramoney died from renal failure 2 days after the judgement was given. I refer specifically to epidemics that constitute a public health emergency as defined by the WHO and I concur with the court's definition of "emergency" as defined in the Soobramoney case.

I refer to the experimental treatment and research, as defined above, of "infected" persons only. I do not discuss the topic of vaccines, as experimental vaccines for healthy persons do not fall within the definition above of "public health emergency treatment". It is also controversial as to whether

vaccines fall within the ambit of what constitutes a medico-legal emergency in South African law. As such, the topic of vaccines falls outside the scope of this research report.

2.3 World Health Organization guidelines that justify Zmapp

The WHO issued a report produced by their advisory panel expanding on the "*exceptional circumstances"* of this specific Ebola outbreak that ethically justified the use of the experimental intervention Zmapp. The advisory panel consisted of 12 persons. The expertise of the panellists was varied, including "experience on bioethics, scientific research methods, Ebola research, experience in Ebola management, experience in humanitarian crises, patient safety advocacy and regulation of therapeutics". [11] I have summarised this report into pointers as follows:

1. Exceptional circumstances:
    - The 2014 outbreak was the largest ever and occurred in areas that had never been exposed to the virus before. It spanned different countries in West Africa.
    - Healthcare facilities were overwhelmed and lacked capacity, due to the already weak health systems.
    - The 2014 strain of virus was aggressive and virulent. The fatality rate was high for infected persons.
    - Before the 2014 outbreak, previous outbreaks had occurred intermittently for over 4 years. Over this time, there had been little prior commercial interest in developing treatments or vaccines. There had been incidences of sporadic disease, but it is during a prolonged outbreak that researchers are able to gather the most data. Little prior research creates an opportunity to push researchers into action.
    - The preclinical phase was in the advanced stages and some of the interventions studied were ready to be tested on humans. There was strong scientific data from the preclinical phase. [11]

2. Essential considerations prior to use of unregistered interventions

    - The use of Zmapp should not divert attention from infection control measures.
    - Experimental drugs should have at least completed the preclinical phase and safety on animal models should be established.
    - There should be adherence to the standard ethical principles associated with an ethical clinical trial.
    - Compassionate access outside of a clinical trial should be granted to all consenting persons.
    - Clinical data should be collected from all patients who compassionately receive the drug.
    - The standards of care should be considered when using an experimental drug. Experimental drug use does not negate providing the established measures of supportive care.[11]

3. Criteria for the prioritization and allocation of investigational interventions

    - Fair and just distribution of the experimental drug should be based on the following criteria: "Social usefulness" - certain members of the panel believed healthcare workers should be prioritized; clinical stage of the disease; and pregnant woman and children should be given priority.
    - Communities should be involved in the decision making.
    - There should be an emphasis on informed consent. The consent process should be easy to understand in the culturally appropriate language.[11]

Based on the definitions of a public health emergency, as well as the WHO guidelines for Zmapp, I propose the following list of requirements that pertain to the use of an experimental drug for the purpose of this research report:

2.4 The circumstances which justify the use of an experimental intervention:

1. Acute public health emergency:

   The imminent threat of a health condition caused by an epidemic infection that poses a substantial risk of long-term disability or death. There would need to be some suddenness, and at times unexpectedness in applying the concept "emergency medical treatment" for the epidemic. The situation's scale, timing, or unpredictability threatens to overwhelm routine capabilities.

2. Fatality :

   The epidemic infection is aggressive and virulent with high probability of death once contracted. "High chance of death" can be measured with a balance of probabilities of life versus death. The chances of death without the drug must exceed that of life in order for the use of an experimental intervention. Also to be considered is the value of surviving without gross disability as opposed to dying. To explain this further: if there were a 1 % chance of death, but an 80 % chance of gross disability and only a 19% chance of escaping unscathed, despite the fact that the chances of survival were 99%, the experimental intervention could still be justified. It is my opinion that gross disability as a result of being denied the drug can be ethically classed with death.

3. Acute highly infectious disease:

   The epidemic is highly infectious and members of the public are at risk of contracting the infection due to its rapid rate of spread. Examples of acute infectious epidemics include the smallpox virus, yellow fever, meningitis, cholera and the most recent outbreak of the Ebola virus.[3] Much research has focused on the HIV and TB epidemics, but these can be defined as "chronic emergency epidemics" or "pandemics", as in the Soobramoney case. I refer specifically to acute highly infectious epidemics that constitute a public health emergency.

4. No possible existing interventions:

   There is no established proven medical intervention for the epidemic infection. There is no other suitable drug established for other medical indications.

This list of exceptional circumstances is the salient theme of this research report and I refer back to them within each chapter. Specifically, in the next chapter I critically assess the regulatory guidelines as they pertain to the use of an experimental intervention under the exceptional circumstances defined above.

Chapter 3

Existing regulatory framework

Introduction

It is a basic standard of medical ethics that medication and other forms of medical treatment must be comprehensively tested for safety and efficacy before being used on the public. This is primarily because the public trusts the medical establishment to provide treatments which are safe and effective.[17] Generally speaking, there must be a moral duty on medical doctors and the wider medical establishment to provide treatments which are both safe and effective. This is a widely accepted norm.[17]

In order to test their safety and efficacy, medical treatment protocols and drugs go through extensive testing and trials before they may be used on the public.[17] The moral duty of ensuring that drugs have been tested might also be argued to rest on the state, as the state has a duty to pass laws designed to protect the public and make sure medical interventions are safe and effective. In South Africa, as in other countries around the world, the legal system enforces these safeguards for the benefit of the public by passing laws which prevent the use of untested treatments or drugs on members of the public without their informed consent, and by having highly developed processes and requirements for a medication or treatment to be approved as safe for public consumption.[18] These systems generally work well in the conditions for which they are designed, namely "normal conditions", other than that of a public healthcare emergency.

In the case of a public healthcare emergency, where there are exceptional circumstances as defined in Chapter 1, arguably medical treatment protocols of the medical establishment change. There is a need for the legal system to create legal avenues to facilitate the use of treatments or drugs which, in

the absence of the emergency, would not be lawful to use on the public. “Something” needs to be done in a public health emergency and in this chapter I explore the current available options for new drug administration. I critically assess whether this regulation is appropriate within exceptional circumstances. I also review the regulation of a clinical trial and critically assess whether this is necessary in a public health emergency situation.

3.1. New drug administration

In an emergency situation, the current regulatory framework allows for limited options in terms of new drug administration. The first is access to drugs approved for other indications and the second is preapproval of unregistered interventions.[19]

3.1.1 Available interventions approved for other indications

The first option is to administer drugs that are already available but have been approved for other medical conditions.[7 19] The advantage of this approach is that the stability of the drugs is already established. If existing drugs, approved to treat other conditions, are utilized, there must be rationale based on logical reasoning and scientific data to justify their use. The expected potential benefit must be weighed up against possible side effects. The advantage of making use of existing drugs approved for different conditions versus experimental drugs in epidemic situations is the obvious immediate availability of the existing drugs.[7 19] If there is clinical evidence to treat any epidemic infection with current drugs used to counter other diseases, the use of these drugs would be the preferable option. In theory, the existing drugs should not cause suffering but there is controversy around this point.[19]

Scientific knowledge and clinical theories based on rational reasoning of the physiology of the human body can be misleading. This is demonstrated through the findings regarding drugs that were believed to have worked based on the extrapolation of clinical knowledge from one context to

another, but did not work when tried within the new context. An example of this would be patients who present with cardiac arrhythmias after heart attacks. Patients with cardiac arrhythmias have greater risk of death than those who do not. It would be clinically logical to assume that antiarrhythmic drugs would be of benefit to such patients and that it would be unethical not to administer antiarrhythmic drugs. After a clinical trial was done to test this theory, the antiarrhythmic drugs produced an even a higher chance of death.[20] If the available scientific knowledge and clinical theories support the use of an existing drug in attempt to treat the epidemic infection (such as the antiarrhythmic drug in the example above), this example demonstrates that using an existing drug will not necessarily produce the desired outcome.

Despite the use of an existing drug carrying risk, due to its availability and lower possibility of risk in contrast to experimental drug use, this should be the preferable option in epidemic crises when there is no other known intervention. Although one cannot extrapolate the effects of a drug from one context to another with certainty, knowledge of an existing drug is still greater than that of an experimental drug.

It is instructive to refer back to my own list of exceptional circumstances in Chapter 1, where it states that, if there is a drug already approved for another indication, this drug should be prioritized. I have established now clearly the reason why. Therefore, within this research report from this point on, I refer specifically to situations where the option of an existing intervention is not available.

3.1.2 Compassionate drug access

"Compassionate" drug use and "expanded access" programmes provide regulatory pathways to access unregistered medical interventions. [7 9 19] In South Africa the provision for the compassionate drug use of unregistered medications is applied for via article 21 Applications to the Medical Controls Council of South Africa (MCC).[12]

Under article 4.17 it further states,

"An exemption will be given for investigational and comparator medicines which:

a) are new chemical entities

b) are new or different dose forms, delivery systems and formulations of established medicines, which

c) does not have consent to be sold in the Republic of South Africa"[12]

The Medicines and Related Substances Act 101 of 1965[21] makes provision for the application for unregistered medications for compassionate drug use. Under section 21 it states:

Council may authorize sale of unregistered medicine for certain purposes

(1) The council may in writing authorize any person to sell during a specified period to any specified person or institution a specified quantity of any particular medicine which is not registered.

(2) Any medicine sold in pursuance of any authority granted under subsection (1) may be used for such purposes and in such manner and during such period as the council may in writing determine.

(3) The council may at any time by notice in writing withdraw any authority granted in terms of subsection (1) if effect is not given to any determination made in terms of subsection (2).[21]

The South African MCC is the most advanced regulatory agency in Africa, and Section 21 of Act 101[21] is the sole guidance for the provision of preapproval of unregistered interventions. Currently under discussion within the MCC is the proposed Investigational Medicinal Product Application (IMPA) which is intended to "guide product development and facility design, and facilitate compliance with the regulations governing the registration of medicines for use in the country."[22]

There is a much need for reform in South African law and regulatory pathways for compassionate access. It is therefore relevant to review international regulations.

The United States of America Food and Drug Association (FDA) controls compassionate drug use in the USA.[23] There are different regulatory pathways within the FDA to accelerate access to investigational drugs. There are the following pathways within the FDA for compassionate drug access - "Fast track designation; Priority review designation, and Breakthrough therapy designation."[22] Also in the USA, 17 states have more recently passed a "Right to try" law. This law bypasses the FDA for compassionate drug use, but it does not surpass the necessary cooperation that is still required from the manufacturers. The "Right to try" law requires that all drugs have completed phase I of the trial process. Despite the rising popularity of this new law, to date, no person has gained access to drugs by implementing this law that was unavailable in the expanded access programmes.[24] Why the existence of the "Right to try" law has not resulted in further drug trials is unclear.

In the EU, European Medicines Agency (EMA) accelerated drug access regulatory pathways are similar to those of FDA and include "Conditional approval; Exceptional circumstances, and Accelerated assessment."[22] The USA and EU are currently reassessing the tight regulatory pathways for drug development. Athenaeum Group in the United Kingdom and the United States of America New Drug Development Paradigms (NEWDIGS) project led by the Massachusetts Institute of Technology (MIT) are converging and developing new models of "Adaptive Licensing" which offer alternatives in the process for preapproval of drug access.[25] The term "Medicines Adaptive Pathways for Patients" (MAPPs) has been subsequently derived from the models of "Adaptive licensing".[25] This is a brief synopsis of International regulation as I have focused this research report within a South African context.

In essence, all accelerated regulatory pathways have specific criteria that must be met in order for compassionate access and preapproval of a drug to be granted. Examples of the specific criteria

include: the procedure must have completed phase II or early phase III and the strength of early clinical data must be assessed along with risk/benefit profile. The proposed experimental treatment must be consistent with empirical knowledge.[22] It would be the ideal to combine the different regulatory approaches of the different countries into a common global approach with a uniform standard of the necessary criteria.[25]

These guidelines are helpful within a public health emergency situation to establish the baseline for when an experimental intervention can be used. The existence of regulations prevents potential abuse – an emergency epidemic does not permit the use of "any" experimental "chemical" as this could easily open the door for misuse. Regulation is therefore a necessity, but I shall demonstrate that it is not always a practicality.

3.1.3 Compassionate access in exceptional circumstances

A limitation in many countries within the compassionate drug use application process is the lengthy time before approval is acquired. [9] [26] [27] An example of the inconvenience and time delays for critically ill persons applying for compassionate drug use is highlighted in the compassionate application for use of the drug bedaquiline.[27] Bedaquiline was proving to be successful for the treatment of multidrug resistant tuberculosis. Janssen, the manufacturers, applied for preapproval while the drug was still in phase II of the clinical trial. Approval was granted for use in the USA. The process however was time-consuming and there was a 2 month delay from the first application to when the first patient received it. Critically ill patients may not have 2 months to spare while waiting for approval for the use of a particular drug. From a medical perspective, critically ill patients need to be treated immediately – but immediate access without any regulation would also problematic. I cannot make a suggestion as to how long the time frame should be, as further studies would need to be done to determine this answer. Simply put – 2 months is too long and immediate access is too quick.

Moldova is a country which lacks the legal framework for compassionate drug use. Patients in Moldova were unable to receive the life-saving Bedaquiline due to the issues in regulation. Several other countries in Europe followed America's lead and patients were granted preapproved access. In South Africa, there were delays in the process.[27] The MCC initially opted for a clinical trial instead of preapproval based on the precaution that the safety was not yet established and there was a "possibility of resistance to the drug before it was approved".[26] After lengthy discussions between the FDA and South African Department of Health, preapproval for Bedaquiline was obtained for South Africa.[27] The Bedaquiline example highlights the moral issue on an individualised level.

Within an acute emergency epidemic situation there is a need for immediate and urgent action. If Bedaquiline were required for an acute emergency epidemic, the flaws in the regulatory pathways for compassionate drug access would be exposed – lengthy delays endanger the public. The rationale for the regulatory pathways under normal circumstances is clear, as stated above – simply, regulations protect the public as well as the ill person. However, it seems odd to argue that for the benefit of public safety it is our moral duty not to act at once to curb the epidemic and rather wait out the stipulated lengthy pathways in order to comply with regulatory measures. This seems to be immoral.

The Bedaquiline example also serves to demonstrate the need for the integration of the South African regulatory approach with an international one and for a coordinated international approach due to the increasingly globalised nature of public healthcare emergencies. If one or other country were to lag behind, it would conceivably undermine the efforts of another country fighting a public healthcare emergency.

The concerns of the South African authorities regarding drug safety can be justified outside of a public healthcare emergency, but these concerns need to be relaxed in an emergency when time is critical. It is, however, instructive to note that regulation is still necessary to prevent exploitation and

abuse - as stated above - and therefore finding a balance between maintaining the integrity of regulation and enabling a swift response to an emergency is challenged.

3.2 Clinical trials

3.2.1 Clinical trials in normal circumstances

Section 72(7) of the National Health Act 61 of 2003[28] defines a clinical trial:

> *For the purposes of subsection (6)(c), "clinical trials" means a systematic study, involving human subjects that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment.*

Before a clinical trial begins, a research ethics committee must approve the study. The National Health Act[28] states under chapter 9, section 73 (1) and (2) (a) (b):

> *Health research ethics committees*
>
> *(1) Every institution, health agency and health establishment at which health research is conducted, must establish or have access to a health research ethics committee, which is registered with the National Health Research Ethics Council.*
>
> *(2) A health research ethics committee must-*
>
> *(a) review research proposals and protocols in order to ensure that research conducted by the relevant institution, agency or establishment will promote health, contribute to the prevention of communicable or non-communicable diseases or disability or result in cures for communicable or non-communicable diseases;*
>
> *(b) grant approval for research by the relevant institution, agency or establishment in instances where research proposals and protocol meet the ethical standards of that health research ethics committee.*[28]

The MCC application for a clinical trial expands further as to what is required before a clinical trial begins under article 2.12[29]:

> "Make sure that the rationale for doing the study is clear. It could be the next logical component in a series of studies (e.g. phase III following phase I or II trial). It could be to test different delivery mechanisms. It could be a 'marketing study'. Try to make sure the answer to the question 'Why should this study be done at all?' is clear and logical." [29]

And

> "State objectives and give rationale for each of them. Ensure that these are scientifically credible. Double check that each objective will in fact be 'analysed' in the statistics section – or else questions must be asked of sponsor / other about why the objective is included without analysis."[29]

The requirements of section 73 of the National Health Act[28] and the MCC[29] for a clinical trial application are stated above but it is important to understand the rationale and purpose of them. Research Ethics Committees ensure "ethical standards" have been adhered to before any research is implemented. There needs to be sufficient background studies and motivation to perform the research in the first place. In other words, there must be scientific evidence to provide rationale to investigate a drug.

Once the clinical trial begins, the estimated time frame to develop a new drug from start to completion can be up to 15 years.[19] The clinical trial process starts with an extensive preclinical phase. In theory, by the end of this phase the exact chemical structure of the compound is determined, along with how it is believed to act in the body, and any toxic effects are determined.[30] Despite this extensive preclinical research, Rid and Emmanuel states in the literature states that as little as 10% of clinical trials reach the commercial launch stage of a new drug.[31] Numerous studies

in recent years have demonstrated the lack of concordance between the effects of the drug on laboratory animal studies and the effect on persons and subsequently there has been much ethical and scientific scrutiny of this phase. It has been suggested that the shortcomings in the preclinical phase are attributed to problems within the "experimental design and conduct of it as well as issues within the reporting of the results".[32] Much research is currently being done in an attempt to improve the accuracy of the preclinical phase.[32] (Zmapp was administered at the completion of this phase. This point highlights the complexity of releasing such a new chemical even in dire circumstances - the result will not necessarily be what is hoped for.)

After the preclinical phase, under normal circumstances, the trial progresses to phase I. Phase I is a small study testing the drug on healthy volunteers to establish toxicity and safety within the human body. The trial then progresses to the recruitment of patients in phases II and III to determine safety, efficiency and dosage.[19] Specifically in phase II, "the drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety."[10] Within phase III, "the drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely."[10] Randomised controlled trials are viewed as the pinnacle of the research study design hierarchy. In some of phase II and all of phase III there is the control group that receives the current standard of care and usually a placebo, and an intervention group that receives the current standard of care plus the new drug.[26] Any new drug is therefore researched extensively from before the trial even begins to the completion of phase III. This process is regulated by the research ethics committee and regulatory bodies like the MCC to ensure ethical standards are adhered to. It is important to note the rationale for the rigidity of a clinical trial process: the public is protected from unsafe treatments.

The research process is vigorous in determining as best as possible a new drug's efficacy and possible side effects. No matter how vigorous this process is in attempting to prevent persons from

suffering adverse side effects and unnecessary harm (even possible death), the risk of it can never be completely eliminated.[19] An example of a drug that presented with unexpected adverse effects was within the clinical trial for the drug TGN1412 in 2006.[33] The drug was in phase I of development. Six healthy men were injected with TGN1412 and all were admitted to ICU with an extreme autoimmune reaction that resulted in multiple organ failure.[33] The failure of the clinical trial of TGN1412 serves to demonstrate that adverse and unwanted effects of drugs are possible – even when the formal regulatory process of the clinical trial is followed.

3.2.2 Clinical trials in exceptional circumstances

If compassionate access is granted in an epidemic situation and an experimental drug is used, the question of whether the use of the experimental drug is medical treatment or medical research is raised. I refer to the law to clarify this point. The National Health Act[28] defines health research under section 1(f) of definitions as follows:

> *(1) 'health research' includes any research which contributes to knowledge of-*
>
> > *(f) the development or new application of pharmaceuticals, medicines and related substances;*[28]

The use of an experimental intervention adds to the possible development of a pharmaceutical product and therefore the use of it is defined as "research". It is however relevant to note that the National Health Act[28] makes no provision for just how experimental "experimental research" is. This demonstrates that experimental drugs in experimental research, as defined within this research report, are within the realms of South African law. Be that as it may, the experimental drug will also be defined as "treatment" from a medical perspective if no other treatment option is available.

Therefore, it is logical to conclude that "treatment" and "research" are analogous to one another in a public health emergency situation.

The regulatory pathway for compassionate drug use does not necessarily require persons to be part of a clinical trial, despite the fact that using any experimental intervention is in essence "research". Zmapp was justified on compassionate grounds without a clinical trial for use by all infected persons in all the affected countries. A further consideration which emerged from the use of Zmapp is that compassionate drug use without further clinical testing is not only irresponsible but wasteful if it is not also used to collect data about safety and efficiency.[31 34] A clinical trial is necessary in order to determine if infected persons are recovering (or the opposite) by chance or due to the drug and the only way this can be determined is through a clinical trial.[31] It may indeed be optimal to perform a clinical trial; however it is challenging to implement the necessary standards of a clinical trial outlined above because of the exceptional circumstances within an epidemic.

In order to justify why it may not be necessary to perform a clinical trial, it is relevant to refer back to the rationale behind the clinical trial guidelines designed to protect the public from being exposed to unsafe treatments under "normal circumstances". These guidelines, however, become problematic when applied to exceptional circumstances because the public is not being protected when their lives are endangered without an intervention. The infected person's life is also in danger because of the nature of the infection. In other words, whilst a general rule may be important and essential, scenarios of public healthcare emergencies justify departure from the general rule, or the making of an exception in an attempt to deal with the emergency. So, as a general rule, all medications should be rigorously tested for efficacy and safety before being used on the public. However, in the case of a public healthcare emergency, this principle may arguably not apply. The traditional application of a clinical trial is therefore no longer applicable in the circumstances of a public health emergency epidemic.

Even if the standard process and "rules" for a clinical trial are no longer appropriate within an epidemic, research is still performed, as the drug is experimental; this makes it relevant to review the study designs to determine if any are appropriate. As stated above, randomised controlled trials are viewed as the pinnacle of the research study design hierarchy. Edwards argues that is impractical to perform research following the standard randomized control research method in an emergency epidemic. Edwards makes the suggestion of "wedged cluster designs" as an alternative.[19] In wedged cluster designs, the participants switch between the intervention and the control group at different points in time.[35] In an epidemic situation, all participants will then have access to the intervention, and new knowledge is generated simultaneously. The points in time when patients will switch over will be randomised.[35] Edwards argues that, when an effective existing treatment works, then a randomized study method should be employed. In wedged cluster designs, everyone benefits.[19] A flaw in this suggestion is that epidemics often occur in short outbursts and, due to their short duration, they are better suited to a short term study design.[35]

Another option within an epidemic is a "cluster randomised clinical trial".[17] This is possible to conduct if some groups (for example, only certain hospitals or certain districts, or certain countries etc.) are going to get access to a drug but others are not. In this case, the randomisation does not happen at the individual level but rather at the group (cluster) level. The group that receives the experimental drug is the intervention group; the participants who receive the placebo are the control group. The challenge in this study design is the challenge of distributive justice - who gets the drug? I discuss the issue of distributive justice next under Chapter 5. If the cluster trial is to be truly randomised, the groups would have to be randomly allocated to either the intervention group or the control group.

A further possibility is the observational study[17] design, which is similar to the cluster randomized trial, but the intervention is not allocated in a controlled way. A cohort study could be performed where participants who receive the drug are the exposed group and those who do not are the

unexposed group.[17] Each individual's exposure status is determined, their progress is followed for a specific period of time and their outcomes are determined exactly the same way as in a trial.[17] The flaw of this design is that it is not completely unbiased and not necessarily without error. In other words, if certain participants were more likely to get the drug than others, based on predictors related to their outcome (prognosis), then there could be errors in determining the effect of a drug. For example, if doctors gave the drug only to the sickest who needed it the most and the sickest were the most likely to die regardless of treatment, then the exposed group would be overrepresented in terms of deaths and the drug would look less effective than it actually is. This again points to issues pertaining to distributive justice: I expand on this in Chapter 5.

In summary, there are different choices as to which study design to follow within an epidemic situation. Each choice of design comes with different challenges. Researchers will need to reach consensus as to which study design is most appropriate for the nature of the scenario and the time of the epidemic. No hard and fast moral rule can be applied to study design when compassionate access is granted: I justify there are no hard and fast rules within a public health emergency epidemic next under Chapter 4, Michael Walzer's concept of a supreme emergency.

In this chapter I have established that, if in an existing drug is available, this should be used first. If there is not such a drug available, compassionate use of an experimental drug is the next step. There is a need to reform the laws to govern the pathways of compassionate drug use in order to strike a balance between speedy application and adhering to rules to avoid potential abuse. Generally, it is preferable for compassionate drug use also to form the basis of a clinical trial, but situations of dire need or emergency justify departing from this principle.

I have suggested that the regulatory pathways should be amended – but is this suggestion morally acceptable according to the major moral theories? I defend the position of why experimental interventions are ethically permissible next in Chapter 4. If there is moral worth in adjusting the

regulation to accommodate the emergency use of experimental interventions, there still will be challenges within the application of it. I critically assess these challenges in Chapter 5.

Chapter 4

Arguments in support of and opposition to the use of experimental interventions

Introduction

The simplest and most obvious option for a government facing a public health emergency is to do nothing, on the basis that, if there are no proven treatments, it is better to do nothing. This option seems flawed, because the experimental intervention offers hope in otherwise dire and even possibly hopeless circumstances. I touched on this in Chapter 3. It is problematic to suggest that it is our moral obligation to do nothing in an emergency healthcare situation, as the whole reason and purpose for the existence of the medical profession is to save lives, and to save the lives of a whole population if its survival or wellbeing is threatened. Indeed, this is also arguably one of the central purposes of having a society in the first place. This is exemplified by Rousseau's social contract theory which is based on the idea that persons consent to the members of a society, based on a social contract, to give them certain things, such as protection, food and shelter. [36]

The option of doing nothing in the face of a public healthcare emergency might be described as an absolutist position.[36] This is because it essentially relies on the moral or ethical view that moral rules are absolute, and that the moral rule relating to medical interventions is that no intervention may be used for any reason, no matter the stakes or the context, if it has not been proven to be both safe and efficacious according to the normal rules. An absolutist position will therefore be, to make sure the public is safe at all times, it is our duty (or the duty of the medical establishment and/or state) to allow the epidemic to continue regardless of the consequences of high fatality and the risk to the public because the rules cannot be broken. This seems problematic and not in line with ethical principles. When assessing the morality of using experimental interventions, it is relevant to refer back to the rationale and purpose for the general rule requiring all medical interventions to be tested

and proved safe and efficacious. The rationale for regulatory guidelines is that the public must not be exposed to dangerous or unsafe treatments, as public wellbeing and safety is to be protected. However, it seems absurd to argue that for the benefit of public safety and wellbeing it is our moral duty to do nothing in an emergency healthcare situation.

A thought experiment of an extreme, exaggerated example serves to demonstrate this point: Imagine a society living on a large island in the middle of the Pacific Ocean with all the resources and amenities needed to survive. An acute emergency epidemic infection strikes the island. The epidemic has a high chance of incurring fatalities and is highly infectious (the exceptional circumstances of this research report). There are no other known interventions. It is estimated that, if left unchecked, the infection will kill everyone on the island within two weeks. No one can leave the island as the rest of the world has quarantined it to prevent the spread of the disease. There is an experimental intervention available but the regulatory guidelines will take several weeks to approve its use. This is my own thought experiment, but it may well be similar to others in the literature I have read whilst formulating this research report. I do not claim that it is original, although I have formulated it myself.

In this scenario, it seems absurd to suggest that the society must do nothing until the regulation has been adhered to, as everyone will be dead within two weeks. If regulatory guidelines serve to protect public safety, surely there is a contradiction if the end result is the death of everyone? Doing nothing to try to save anyone seems to lead to absurd results, and this must be a reason for questioning whether it is correct or not. So, as a general rule, all medications should be rigorously tested for efficacy and safety before being used on the public. However, in the case of a public healthcare emergency, this principle may arguably be abandoned. The option of using the experimental intervention then becomes morally justifiable. If experimental interventions are exerted in an emergency epidemic, this will not only maximise the infected person's chance of survival, but also protect members of the public should the drug prove to be effective.

The history of medicine indicates that, in the case of a public healthcare emergency, the use of interventions with some downside (or with the risk of downside as they are not sufficiently tested) may well be justified. Take the case of smallpox, which may not be an acute emergency epidemic but serves to illustrate a point. Smallpox is not invariably life-threatening, although it could prove fatal in many cases. It also badly scars many of the persons who survive it. Dr Edward Jenner noticed that the milkmaids who worked with cows never contracted smallpox and theorised that it was as a result of having cowpox that these women seemed immune to smallpox.[37] This was merely a theoretical postulation, with no peer review or other proof of its truth or efficacy. In addition, the use of cowpox as a vaccine was itself risky, as a number of patients had adverse reactions. Nonetheless, for the greater goal of eradicating smallpox, the vaccine was tried and used and eventually smallpox was effectively eradicated.[37] By today's standards of research, the experiments Jenner conducted would be unethical and illegal. If his circumstances had involved a smallpox plague, with no chance of recovery and a high risk of fatalities, his actions would have been justifiable in terms of the case which I am presenting.

This smallpox case illustrates that, for the greater good, a risk may be taken. In other words, in order to try to achieve the eradication or containment of a serious illness, some degree of negative consequences or risk to the public may be tolerated. In the case of a rapidly spreading and potentially fatal illness, the case for intervention, even where such intervention poses risk, is that much stronger. If we take the principle to its logical extreme using a thought experiment, if everyone is going to die anyway, then anything that might possibly save even one person should be tried in the circumstances. The level of acceptable risk to public safety is relative – the greater the risk of the population dying out in full, or in a large part, or becoming seriously ill, the more treatment-related risk may be justified in trying to avoid and/or curtail disaster.

Having said this, the use of an experimental intervention can result in potential abuse: for the purpose of stopping an epidemic, an entire population could be euthanized under the guise of preventing the spread of a lethal disease. However, I maintain that the argument which I have already put forward regarding experimental drug use standards.

In the following sections, I shall discuss the moral theories pertaining to experimental drug use and answer the question of what is justifiable in an open and fair society based on human dignity and fairness. This is not only an ethical application but a legal test required by section 36 of the South African Constitution[16]and legal statutes of democracies. In this section, I touch various moral theories in an attempt to highlight their central tests for moral action, and then apply them to the context of a public healthcare emergency and the use of an experimental intervention. I expand on each of the following moral theories consecutively: Kantian ethics, utilitarian ethics, principle-based morality and African-based morality. Although it is not a moral theory, I also make reference to Michael Walzer's concept of supreme emergency. Inevitably, such an exposition will entail interpretation that a seasoned philosopher might consider simplistic. I acknowledge that the major moral theories are more complex than the simple explanations that I have given, but I have drawn on them to define the ethical criteria as it lines up with South African law to justify the use of experimental interventions.

4.1 Kantian ethics

Right and wrong in Kantian ethics is determined by the rationality of what we ought to do in any given situation.[38] Kantian ethics provide justification for the use of experimental interventions through the duty imposed on the state and the medical establishments to give assistance to the public in a public health emergency situation.

Kant believed people will know how they ought to act in any situation by virtue of being human. Kant believed that people are "rational agents", capable of making their own decisions based on their own free will. It is this trait of rationality that places human beings superior to animals. If a person is "rational", they have the ability to make their own moral choices.[38] If we deny a person the opportunity to exercise their own rationality and reason to determine what they ought to do, then we ultimately deny them their full humanity.[38]

An implication of Kant's theory in connection with the use of experimental drugs is informed consent. Infected persons will need to be told the intervention is experimental along with all other, if any, available treatment options. A patient will need to be informed about the nature of the disease and expected prognosis. Based on this information, the patient will be able to exert their own rationality and decide what to do.

Kant's formula of humanity can be used to determine if consenting to the experimental drug use is indeed a rational option. The formula for humanity: "Act so that you treat humanity, whether in your own person or that of another, always as an end and never as a means only."[38] "An end" recognizes that we should treat people with "respect, promote their welfare and avoid harm."[38] The implication of this statement is that the doctor must only use experimental drugs out of respect for the infected person, and the infected person must only accept experimental drugs out of respect for themselves.

Ethical obligations in the past have focused mostly on healthcare practitioners, but more recently a second source of ethical obligation is bestowed on organizations – patients have "rights" in their relationships with healthcare providers.[39] "Organizational ethics" motivates that healthcare organizations in general (not just practitioners) have an ethical obligation to help patients who are in desperate need.[39] [40] If experimental interventions serve to treat the public as "an end" then this application can be extended to the moral duty of institutions, to the state, as well as to the doctor.

In a public healthcare emergency, the intention behind using an experimental intervention is good. "The end"[38] is respectful. "For Kant, the only thing wholly good is a good will." [38] Kant was unconcerned with the consequences and therefore good intention would make it ethically justifiable to use the experimental intervention. The use of an experimental intervention is therefore ethically justifiable from both an individual as well as from an organizational perspective. Kantian ethics is nuanced and is suited to the challenging conditions and unpredictable outcomes of a public healthcare emergency. Kant's formula of humanity parallels with section 36 of the Constitution[16] in terms of respect for human dignity and freedom.

A "rational" decision to help another must not be emotive and there must be a "generalizable moral obligation" to help the person.[41] If there is a "generalizable moral obligation" to assist another, the moral judgements should rest on reasons that will apply to all other persons who are similarly situated.[41] Kant's Universal Law can be utilized to determine if the doctor has a generalizable moral obligation to use an experimental intervention and if proxy consent of such is ethical. The "categorical imperative" determines what we ought to do in a situation.[38] To determine the categorical imperative, the "maxim" in question will be: "As a doctor, I should give experimental medicine to this person; if it works, I could save the lives of many more." If this statement is "universalized", the maxim would read, "Whenever it is possible, I should give experimental drugs to persons in order to find a cure for an illness." This is clearly a contradiction in conception and thus not ethical. But if the maxim is applied to "persons infected with a fatal and highly infectious epidemic disease" and this is universalized to "all such epidemic situations" then there is no contradiction in conception. It is therefore ethical to justify the use an experimental intervention in an epidemic situation for a highly infectious and fatal disease.

Kantian ethics establishes that the morality in the intention behind the experimental intervention is good. The intention is good because it is a rational choice. Kant also has established the need for informed consent. I refer in greater detail to the requirements of informed consent under principle

based arguments and again in chapter5. Kantian ethics establishes that the intention to use an experimental intervention is good, but the consequences of using an experimental intervention need to be considered: I critically assess the consequences next.

4.2 Utilitarian ethics

Right or wrong is ultimately determined by the consequences. An outcome with the greatest good for the greatest number of people with equal consideration given to each of the affected persons is ethically justified in an utilitarian argument.[38] Though this is again a simplification – this time of utilitarian ethics - my intention is once again primarily an application rather than a close exegesis of utilitarianism. I consider the consequences if the experimental intervention is not given; the consequences if the drug proves to be successful; and the consequences if the drug proves to be unsuccessful. Within each of these considerations, I make reference to the patient, the public, and the state in order to give equal consideration to all persons.

Consequences if the experimental intervention is not given:

Consequences to the patient:

The consequences to infected persons if the experimental drug is not given can be evaluated by analysing the number of deaths and the number of survivors after an epidemic. The number of deaths in contrast to the number of survivors after the Ebola epidemic as reported by the World Health Organisation on 5 September 2014 were: 3944 confirmed cases of Ebola, 1759 deaths and 2185 survivors.[42] On the 6 December 2014, Sierra Leone reported 6317 laboratory confirmed cases.[43] On the 6 December 2014 the Sierra Leone Ministry confirmed that there were 1881 survivors from this caseload.[43] The chances of surviving the Ebola infection, based on these statistics, are 29.7%.

Past statistics of the death and survival rates of Ebola, when there was the bare minimum in medical knowledge of interventions to treat it, were: from August to November in 1976 there were 318 reported cases of Ebola in the Zaire region, of which 280 resulted in deaths.[42] These statistics demonstrate an 11.9 % chance of survival. It is thus evident that, once a person has contracted the virus, the statistical chances of death without an intervention are high. For a utilitarian these consequences are clearly negative.

Consequences to the public and the state:

Epidemic infections, such as Ebola, are highly infectious and, if there is no medical intervention, the public are at risk of contracting them. The development of an acute epidemic creates not only a public health emergency but a global public health challenge.

Consequences of a successful experimental intervention:

Consequences to infected persons:

The infected patients recover and survive.

Consequences to the public:

The public is protected from the possible harm of contracting the illness.

Consequences to the state:

The application of an experimental drug adds to the body of medical knowledge - scientific value is gained from using it. A successful drug can be used again in the future should another epidemic

situation arise. There is a cost to the state to perform the clinical research study and to supply the successful drug to all infected persons.

Consequences of a failed experimental intervention:

Consequences to the patient:

In the worst case scenario, the infected patient dies from the drug, but there is a strong likelihood that they will die anyway. In other words, there could be a few extra unnecessary deaths if it is assumed that someone would have lived had they not been administered the drug. It is possible that the drug produces negative side effects first and then the person dies. However, serious cases of Ebola produce profound symptoms, such as internal bleeding, septic shock and organ failure, before death.[44] Death as a result of a failed drug cannot medically be much worse than this. The only negative is, therefore, that a person's death could be hastened, but it is debatable as to whether this is in fact a negative consequence, as a hastened death would relieve suffering. The negative consequences of a failed drug to a patient are therefore not of great magnitude.

Consequences to the public:

There are no consequences to the public if the drug fails. It would be the same as if no intervention were used at all.

Consequences to the state:

Even if the drug fails, a positive consequence is that it still contributes to the body of medical knowledge, as scientists will then know this formula did not work. There is the wasted cost of a failed clinical trial.

In summary, a failed experimental intervention produces a few possible unnecessary deaths in infected persons, but if it proves to be successful, it will save many lives. If the drug were not given, the chances of death would be very high. Therefore, there are greater overall positive consequences to the greatest number of persons if the experimental intervention were done. It is therefore ethically justifiable to use it.

I thus far have established by expanding on Kantian and utilitarian ethics that there is good intention in and good consequences of using experimental interventions. These moral views line up neatly with principle-based morality, which I explore next.

4.3 Principle-based morality

Right or wrong is determined by the ethical principles of autonomy, beneficence, non-maleficence, and justice.[41] These four ethical principles justify the use of experimental interventions.

Autonomy

Blais[45] makes the distinction between autonomy in clinical ethics and autonomy in public health ethics. Clinically the doctor helps the individual patient to make the best autonomous decision. In public health ethics, the public's autonomy takes precedence over individual autonomy.[45] Persons may indeed have autonomous rights, but these rights are ethically limited when such a right imposes harm on another. The reason for this is that the rights of autonomy and informed consent are no longer applicable when the safety of the public is at risk. The position to overrule individual autonomy is not only ethical, but legally permissible. To expand on why this is so I refer back to "normal conditions" as to when informed consent is mandatory.

There are three elements that are ethically required for informed consent to be valid: the participant must be informed, have full understanding and participation must be voluntary. The Department of Health in South Africa states the following for consent to be valid:

> "Informed consent means that a participant has been informed of the risks and benefits of the research, understands such risks and benefits and is able to give consent to participation, without coercion, undue influence or inappropriate incentives."[46]

Informed consent is not only an ethical but a legal requirement in South Africa which is established clearly within The Constitution[16] as well as the National Health Act[28]. The constitution, in the Bill of Rights, in section 12 (2) (c) states,

> *(2) Everybody has the right to bodily and psychological integrity, which includes the right*
>
> *(c) not to be subjected to medical or scientific experiments without their informed consent.*[16]

The National Health Act 61 of 2003[28] (which was enacted after the Constitution) makes provision for the consent process for the research and experimentation on human subjects. This specific legislation seeks to give effect to the general constitutional right set out in section 12 of the Constitution[16]. In section 71 (1) (b) the National Health Act states[28],

> *(1) Notwithstanding anything to the contrary in any other law, research or experimentation on a living person may only be conducted –*
>
> *(b) with the written consent of the person after he or she has been informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health.*[28]

It is instructive to note that this provision of section 71[28] echoes the wording of section 12 of the Constitution[16], but is not identical to it. Whilst the two provisions are clearly similar and relate to similar issues, the provision in the National Health Act[28] does not simply refer to "informed consent" as section 12 of the Constitution[16] does, but rather fleshes this concept out by providing that a person must be "informed of the objects of the research or experimentation and any possible positive or negative consequences on his or her health".[28]

In line with the above, the Medicines Control Council[12] of South Africa states the following on the informed consent specifically with the use of unregistered medical interventions:

> "The patient must be fully informed that the drug is not registered with the authority.
> The patient must be fully informed about the possible benefits and risks of the product.
> The patient must sign the informed consent." [12]

It is clear therefore that, absent some or other special state of affairs justifying it, the general principle is that that no experimental medical treatment may be carried out on a person without their informed consent. If a patient who is a victim of an epidemic is able to give consent, this should be obtained. I discuss the challenges to obtaining this consent on page 60 of this chapter.

The wording of both section 12 of the Constitution[16], and section 71 of the National Health Act[28], refers to "medical or scientific experiments" and "research or experimentation on a living person" – in other words the consent to research and not to treatment. Does the law as it pertains to informed consent apply equally to research and treatment purposes in a public health emergency? I now expand further on the need for an interchange of meaning between "experimental treatment" and "experimental research" as it pertains to informed consent within a public health emergency

situation. I have already established the analogy in Chapter 2 of this research report but I reinforce this point again.

If section 71 of the National Health Act[28] and section 12 of the Constitution[16] are correctly interpreted according to the principles of statutory interpretation, "research" and "treatment" can be applied interchangeably. Whilst the Constitution[16] refers specifically to "medical experiments", this can plausibly include experimental medical interventions which are not for research purposes, but which are for treatment purposes. In any event, to use an untested treatment in the case of a public healthcare emergency does arguably amount to a medical or scientific experiment, albeit in a bid to save life or stop the spread of disease.

Within an emergency epidemic, it can be argued that the infected person is too ill to consent. A proxy consent would be the next step. It is instructive to note again that legislation provides no provision for proxy consent for adults in terms of research purposes, but does allow it for treatment purposes: as explained above, in my view, these terms should be interpreted in the same way. Sections 7 (1) (2) and (3) of the National Health Act[28] state the provisions for a proxy and delayed consent to emergency health services:

> *(1)Subject to Section 8, a health service may not be provided to a user without the user's informed consent, unless –*
>
> > *(a) the user is unable to give informed consent and such consent is given by a person-*
> >
> > > *(i) mandated by the user in writing to grant consent on his or her behalf; or*
> > >
> > > *(ii) authorised to give such consent in terms of any law or court order;*

(b) the user is unable to give informed consent and no person is mandated or authorised to give such consent, and the consent is given by the spouse or partner of the user or, in the absence of such spouse or partner, a parent, grandparent, an adult child or a brother or a sister of the user, in the specific order as listed;

(c) the provision of a health service without informed consent is authorised in terms of any law or a court order;

(d) failure to treat the user, or group of people which includes the user, will result in a serious risk to public health; or

(e) any delay in the provision of the health service to the user might result in his or her death or irreversible damage to his or her health and the user has not expressly, impliedly or by conduct refused that service.

(2) A health care provider must take all reasonable steps to obtain the user's informed consent.[28]

The Department of Health[46] makes provision for a proxy consent or delayed consent under article 3.4.1 for major incidents and research. It states:

"Proxy decision makers are not permitted for adult persons who lack capacity unless the proxy is a court-appointed curator. Neither the National Health Act 61 of 2003 nor the Mental Health Care Act 17 of 2002 makes provision for proxy decision makers for research purposes but they provide clear lists of proxy decision makers for treatment purposes." [46]

The Department of Health[46] guidelines for proxy or delayed consent in incapacitated adults for research purposes under article 3.2.4.3 are as follows:

> "The REC may approve a delay in obtaining informed consent for emergency care research if
>
> • the research is based on valid scientific hypotheses that support a reasonable possibility of more benefit than that offered by standard care; and
>
> • participation is not contrary to the medical interests of the patient;
>
> • the research interventions pose no more risk of harm than that inherent in the patient's condition or alternative methods of treatment;
>
> • the participant and her relatives or legal representatives will be informed of the participant's inclusion in the research as soon as reasonably possible, and advised of her right to withdraw from the research without any reduction in quality of care."[46]

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• participation is not contrary to the medical interests of the patient;

• the research interventions pose no more risk of harm than that inherent in the patient's condition or alternative methods of treatment;

• the participant and her relatives or legal representatives will be informed of the participant's inclusion in the research as soon as reasonably possible, and advised of her right to withdraw from the research without any reduction in quality of care."[46]

If proxy consent is unobtainable, deferred consent is appropriate due to the circumstances of a public health emergency. I defend this position now. It could be argued that section 12 of the Constitution[16] and section 71 of the National Health Act[28] are clear, and prohibit any use of experimental treatment without informed consent. These sections do not contain any wording saying that an exception will be made in the case of a public healthcare emergency. In the absence of any such wording creating an exception, it is in order to ask on what legal basis any exception is lawful.

It must be noted that a right in the Bill of Rights may only be limited "in terms of law of general application".[16] It is also important to note that section 39 of the Constitution[16] states:

(1) When interpreting the Bill of Rights, a court, tribunal or forum –

(a) must promote the values that underline an open and democratic society based on human dignity, equality and freedom;

(b) must consider international law; and

(c) may consider foreign law.

(2) When interpreting any legislation, and when developing the common law or customary law, every court, tribunal or forum must promote the spirit, purport and objects of the Bill of Rights.

(3) The Bill of Rights does not deny the existence of any other rights or freedoms that are recognised or conferred by common law, customary law or legislation, to the extent that they are consistent with the Bill.[16]

It can be observed that in section 12 of the constitution[16], is a right which "everybody has", meaning that no person may be subjected to medical or scientific experiments without their informed consent.[16] Whilst this refers expressly to "experiments", it is a fundamental principle of statutory interpretation in general, and especially so when interpreting a right in the Bill of Rights, that the words used in the Bill of Rights must be interpreted in light of the meaning and purpose of the Bill of Rights as a whole, and the provision in question in particular. It is therefore relevant to refer to the limitations of rights expressed in section 36 of the Constitution: [16]

(36) Limitation of rights

(1) The rights in the Bill of Rights may be limited only in terms of law of general application to the extent that the limitation is reasonable and justifiable in an open and democratic society based on human dignity, equality and freedom, taking into account all relevant factors, including-

(a) the nature of the right;

(b) the importance of the purpose of the limitation;

(c) the nature and extent of the limitation;

(d) the relation between the limitation and its purpose; and

(e) less restrictive means to achieve the purpose.[16]

Under section 39 (2) of The Constitution , the courts have a "general duty to give effect to the spirit, purpose, and object of the Bill of Rights in the Constitution." [16] However, although the rights in the Bill of Rights are provided for in the Constitution as a "cornerstone of democracy" (section 7 (1) of the Constitution)[16], section 7(3) of the Constitution also provides that "the rights in the Bill of Rights are subject to the limitations contained or referred to in section 36…"[16]

In other words, to interpret the relevant provisions of both the Constitution[16] and the National Health Act[28] and to assess whether any limitation of rights is justifiable under section 36 or not, we must look at the purpose of these provisions. In normal circumstances, the purpose is to protect the public from being harmed in the course of medical or scientific experiments. The purpose can also be applied to the justification of the use of experimental medical intervention to protect the public and prevent the spread of a highly infectious epidemic infection as well as attempt to save the life of an already infected person. Therefore in order to make them effective, these rights from section 12 of the Constitution[16] and section 71 of the National Health Act[28] need to be interpreted in light of section 36 of the Constitution[16]. If legislation is justified to protect the public from medical experimentation for academic purposes (research), then surely it must have been the intention of the legislature also to protect the public from experimental medical interventions, as the risks inherent in both scenarios are similar and overlapping?

I think it is essential to analyse and apply the above legal requirements to the facts of a conceivable public healthcare emergency. In essence, every South African has the right not to be subjected to experimental medical treatments without their consent - section 12 of the Constitution[16]. This right may only be limited in terms of a law of general application (section 36 of the Constitution[16]).

Furthermore, any limitation of the rights in the Bill of Rights must not only be limited in terms of a law of general application, but must also fulfil the other requirements of section 36.[16] The authors of the Bill of Rights handbook state the following on page 164[47]:

> "Limitation" is a synonym for "infringement" or, perhaps, "justifiable infringement"[47]

A law that limits a right infringes the right. However, the infringement will not be unconstitutional if it takes place for a reason that is accepted as a justification for infringing rights in an open and democratic society based on human dignity, equality and freedom.[47] In other words, not all infringements of fundamental rights are unconstitutional. Where an infringement can be justified in accordance with the criteria in Section 36 of The Consitution[16] it will be constitutionally valid.

The analysis for justifying the limitation of a right in terms of section 36[16] involves a two-stage approach. This involves assessing first whether there has been a limitation of any constitutional right. In order to do this, such right must be interpreted to ascertain the boundaries of that right.[47] Assuming that there has been a limitation of a constitutional right, it must then be justified in terms of section 36[16], otherwise it will be unconstitutional. The first requirement under section 36[16] is that any limitation must be in terms of the law of general application. The authors of the Bill of Rights handbook[47] note on page 168:

> "Only a "law of general application" can validly limit a right in the Bill of Rights. This is the minimum requirement for the limitation of a right. A limitation must be authorised by a law, and the law must be of general application. The law of general application requirement is the expression of a basic principle of liberal political philosophy and of constitutional law known as the rule of law."[47]

Turning to the specifics of this principle, the authors of the Bill of Rights handbook[47] note on page 169:

> "What forms of law qualify as "law of general application"? Though the Constitutional Court has not dealt with this question directly, it has given a wide interpretation to the meaning of "law" elsewhere in the Bill of Rights. On the strength of this interpretation it seems that all forms of legislation (delegated and original) qualify as "law", as does the common law (both the private law and the public law rules of the common law such as criminal law) and customary law. A mere policy or practice (even of an organ of State) cannot qualify as "law"."[47]

It is therefore clear that, in order to limit the section 12 right[16], there would have to be a law of general application - I note that this may well prove very challenging in an emergency scenario given time constraints. Legislation will need to be passed, and this is often a slow and involved process which is ill-suited to dealing with a public healthcare emergency.

It seems relatively clear that, if a law applied to all persons in the Republic of South Africa saying that they would be given experimental medical treatment in the case of a public healthcare emergency, this would be a law of general application. The real substantive debate under section 36[16] relates to whether a limitation of rights is justifiable in an open and fair society based on human dignity and freedom.

The authors of the Bill of Rights handbook [47]note on page 176:

> "This part of the limitation test requires a law that restricts a fundamental right to do so for reasons that are acceptable to an open and democratic society based on human dignity, equality and freedom. In addition, the law must be reasonable in the sense that it should not

invade rights any further than it needs to in order to achieve its purpose. To satisfy the limitation test then, it must be shown that the law in question serves a constitutionally acceptable purpose and that there is sufficient proportionality between the harm done by the law (the infringement of fundamental rights) and the benefits it is designed to achieve (the purposes of the law)."[47]

As noted by the authors of the Bill of Rights handbook[47] on page 176, the requirement of proportionality was as follows in the well-known case of *S v Makwanyane*:

"The limitation of constitutional rights for a purpose that is reasonable and necessary in a democratic society involves the weighing up of competing values, and ultimately an assessment based on proportionality. … The fact that different rights have different implications for democracy, and in the case of our Constitution, for "an open and democratic society based on freedom and equality", means that there is no absolute standard which can be laid down for determining reasonableness and necessity. Principles can be established, but the application of those principles to particular circumstances can only be done on a case-by-case basis. This is inherent in the requirement of proportionality, which calls for the balancing of different interests. In the balancing process, the relevant considerations will include the nature of the right that is limited, its importance to an open and democratic society based on freedom and equality; the purpose for which the right is limited and the importance of that purpose to such a society; the extent of the limitation, its efficacy, and particularly where the limitation has to be necessary, whether the desired ends could reasonably be achieved through other means less damaging to the right in question."[47]

The authors of the Bill of Rights handbook[47] note on page 177 that this requirement "was summarised as follows in *S v Bhulwana*:

> "The Court places the purpose, effects and importance of the infringing legislation on one side of the scales and the nature and effect of the infringement caused by the legislation on the other. The more substantial the inroad into fundamental rights, the more persuasive the grounds of justification must be."[47]

The first question to be considered is the nature of the right in question. The authors of the Bill of Rights handbook[47] note on page 178:

> "The proportionality enquiry required by section 36 involves weighing up the harm done by a law – the infringement of a fundamental right – against the benefits that the law seeks to achieve – the reasons for the law, or the purpose of the law. … A court must assess what the importance of a particular right is in the overall constitutional scheme."[47]

It is instructive to look at the case *of S v Makwanyane* to see how the analysis of the nature of the right comes into the reasoning. The authors of the Bill of Rights handbook[47] note on page 178:

> "S v Makwanyane was concerned with the constitutionality of the death penalty. The court held that the death penalty infringed the rights to life, to human dignity and to freedom from cruel, inhuman or degrading punishment. This meant that for the death penalty to be constitutional it would have to qualify as a reasonable and justifiable limitation of these three rights. The purposes of the death penalty, the benefits it was designed to achieve would have to be balanced against the harm it did – the violation of the three rights. The first consideration in this balancing exercise was the determination of the weight of the three rights, their importance in an open and democratic society based on freedom and equality."[47]

The authors of the Bill of Rights handbook[47] note further on page 178:

> "According to the Constitutional Court the "rights to life and dignity are the most important of all human rights, and the source of all other personal rights in … [the Bill of Rights]. By committing ourselves to a society founded on the recognition of human rights we are required to value these two rights above all others and this must be demonstrated by the State in everything that it does, including the way it punishes criminals. This meant that very compelling reasons would have to be found to justify the limitation of such important rights. … Given the importance of human dignity in the constitutional scheme its cruel punishment component carries no less weight."[47]

I argue that the use of an experimental intervention in a bid to save lives or stop an epidemic could conceivably pass the requirements of section 36[16] and be constitutional as a result. Our legislation does contain provisions to try to deal with scenarios where a person may be too ill to give consent at the time of treatment. Of course, this consent cannot really be fully informed, because the doctors themselves may not know the risks and rewards of the treatment fully or even sometimes at all.

I have defended the position that individual autonomy can be overruled in order to protect the public. Be that as it may, this argument does not negate individual autonomy and informed consent all together. Rather I suggest that researchers should strive to obtain informed consent, but if this is not possible because the patient is too ill to consent, it is still ethically and legally permissible to use the experimental intervention. If the infected person is able to consent then informed consent should be obtained. If a person is able to consent, there are still major ethical challenges in obtaining it and I expand on these challenges under in Chapter 6. My defence here rather demonstrates that individual autonomy is justifiably overruled in a public health.

Beneficence and Non-Maleficence

Beneficence is defined in the Belmont Report as maximising potential benefits to participants and to society and minimising the potential harms.[48] Two criteria can be applied to "maximising the good" of a situation. Firstly, it must be ascertained that the intention is to do good. I have established what this entails in my discussion in Kantian ethics. Secondly, the consequences of the action must be good. I have established in utilitarian ethics that the consequences are better if the experimental intervention is used.

International instruments such as the Declaration of Helsinki[49] ethically justify experimental drug use. Paragraph 35 states:

> "In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available."[49]

"Hope of saving life, re-establishing health or alleviating suffering"[49] are all in line with the principle of beneficence. The word "hope" sums up neatly the essence of using the experimental intervention. The Belmont Report expands on the "do no harm" principle in research by stating that avoiding harm requires the learning of what is harmful and, in the process of learning, persons will be exposed to the risk of harm.[48] There is risk with experimental interventions, but all research essentially contains risk. Too much caution can indirectly produce harm by failing to seize an opportunity to develop a possible cure.[19]

Justice

If justice is to be served within a public health emergency, it is relevant to review the rule of law further. South African legislation that authorizes the use of an experimental intervention is based on the following legal principles:

1. The doctor is obliged to act within the best interests of the patient.
2. Everyone has the right to life.
3. Everyone has the right to an environment that is not harmful to their well-being.
4. Healthcare establishments must implement the available measures to minimise disease transmission to protect personnel.

Each of these legal rights imposes a corresponding duty to act accordingly. If an experimental intervention is used, these legal principles will be adhered to and I demonstrate this with elaboration on each key principle consecutively below:

The doctor is obliged to act within the best interests of the patient

Healthcare providers have a duty to help their patients. The Health Professions Council of South Africa[50] states the following in the Guidelines for Good Practice, Booklet 1, section 5:

> "Health care practitioners should: Always regard concern for the best interests or well-being of their patients as their primary professional duty."[51]

It is the doctor's primary duty always to act in the best interests of the patient. If there is a medical intervention that holds possible promising results which the doctor believes is in the best interests of not only the patient but the public, then subject to patient consent (if possible), it is justifiable.

Everyone has the right to life

The Constitution in section 11 states that:

> *Everyone has the right to life.*[16]

Everyone has the right to life. If there is a possibility of sparing a person's life by using an experimental intervention, *the right to life* justifies its use. If the medical practitioner denies a patient who faces impending death a possible treatment which could avert death, this would be unethical.

In the case of *Hay v B,* a blood transfusion was given to a child against the parents' wishes.[52] The court overruled the parents' refusal of consent because the infant would die if the blood transfusion were not performed. "The court was not going to negate the essential content of the child's inviolable right to life as a human being, be part of a broader community and share in the experience of a humanity merely because administering the transfusion was against the wishes and the sincere belief of the parents." [52] The life-saving blood transfusion can be paralleled to life-saving intervention using experimental drugs. No person should have their right to life violated if there is a possible means to save their life.

In the case of *S v Makwanyane and Another* 1995 (3) SA 391[53] (the trial concluded during the Interim Constitution before the final Constitution of the Republic of South Africa, 1996, came into force), [54] the Constitutional Court considered whether the death penalty was to be allowed to continue under the Interim Constitution, as it was argued that the death penalty, including the

legislation allowing it (section 277 of the Criminal Procedure Act 51 of 1977 and other legislation sanctioning the death penalty) was inconsistent with the right to life and/or the right to dignity in the Interim Constitution. [53] Makwanyane was given the death penalty, and appealed this sentence on the basis that this penalty was unconstitutional. Makwanyane was successful, and the Constitutional Court found that the death penalty was inconsistent with either the right to life or the right to dignity in the Interim Constitution. These rights also appear in the Final Constitution of 1996. [16]

Although the case dealt with the death penalty and not with experimental interventions in a public health emergency, the *S v Makwanyane*[53] case is of relevance to my arguments because of the importance which the case placed on the right to life and the right to dignity. I think it can be argued, by analogy or by comparative reasoning, that this case can be paralleled or compared to the use of experimental interventions in that the patient who does not receive the drug is ultimately, in effect, receiving a death sentence. If the right to life is so fundamental as was held in the *S v Makwanyane*[53] case, it seems plausible to argue that the right to life should motivate and require the state to take certain measures in a public health emergency, including the use of experimental treatments.

The value of human life can be assessed further by examining "wrongful life" legal action cases. In wrongful life cases, disabled children have sued the medical practitioner (with the assistance of the parent) for failing to prevent their birth. The foundation of the argument lies in the medical practitioner's failure to provide information to the mother on the likelihood of a birth defect which would have given her the choice to terminate her pregnancy. This would have prevented the child from being born. The court has, however, ruled in favour of the value of life. In other words the value of a life, even if it is a disabled one, is better than no life at all.[55]

Withholding the drug to avoid a failed clinical trial is unacceptable. Persons who are infected with an epidemic infection will more than likely die if no intervention is given. If the experimental drug

proves to be a failure, as harsh as it sounds, the application of a lethal experimental intervention will result in an already impending death. Either way the people suffering from the disease were going to die. Judge Sachs stated that the right to life imposes a duty on others to respect one's right to life, but it also imposes a duty on oneself to live a dignified life. A dignified life, according to Sachs, includes a responsibility to also have a dignified death.[56] If the worst case scenario of an experimental intervention is the same as no intervention at all, according to Judge Sachs, such persons would need to accept their fate.

Everyone has the right to an environment that is not harmful to their well-being

The Constitution in section 24 states:

> *Everyone has the right*
>
> a. *To an environment that is not harmful to their health or well-being;*[16]

The National Health Act, chapter 1 section 2 (c) (ii) states:

> *(c) protecting, respecting, promoting and fulfilling the rights of-*
>
> *(ii) the people of South Africa to an environment that is not harmful to their health or well-being;*[28]

The right to a healthy environment is again reinforced within the Patients' Rights Charter.[57] The public who are not infected by the epidemic have the right to a healthy environment. Withholding a possible intervention that will create a healthy environment violates this right.

In the Constitutional Court case of *Dudley Lee v Minister for Correctional Services,*[58] Mr Lee contracted TB whilst in prison. Authorities knew that their conduct placed inmates, including the applicant, at risk of TB infection. Poor prison health management resulted in Mr Lee's becoming infected. [58] This case can be paralleled to the public contracting an epidemic infection in a hospital.

Dispensing a possible intervention is ethically justifiable as it protects the public. Although this was a civil case (a case for damages) where Lee sued the Government for failure to take steps to protect him from contracting TB, it seems to contemplate a legal duty on the part of the state in a scenario where there exists a health risk. The case decided that, because prison officials (being the state's representatives) had known of the TB risk, but had not taken any steps to deal with it or minimise it, the state was liable to pay damages to Lee for his contracting of TB.[58] This is not the same as a legal duty on the state to deal with a public health emergency, as the facts are different. However, I think it can be argued that, by analogy, if a legal duty exists on the state in the factual circumstances of Lee's case, arguably a similar legal duty exists on the state in a public health emergency to take all reasonable measures at their disposal. However, Lee's case was a civil case for damages, and was concerned with compensation, rather than compelling the state to take healthcare measure. I argue that this case highlights the proactive duties of the state in a context where a public health risk emerges (such as TB in a prison, which is in some respects similar to a public health emergency in a country).

<u>Healthcare establishments must implement the available measures to minimise disease transmission to protect personnel</u>

The National Health Act, chapter 2 section 20 (3) (a) (b) the rights of the healthcare personal are established:

> *(3) Subject to any applicable law, every health establishment must implement measures to minimise-*
>
> > *(a) injury or damage to the person and property of healthcare personnel working at that establishment; and*
> >
> > *(b) disease transmission.*[28]

Using the experimental intervention is a potential measure to reduce disease transmission and therefore is justifiable as it protects the rights of the healthcare personnel.

International guidelines

International law is parallel to South African law in respect to the rights of the patient, the public and healthcare workers as well as the provision of emergency medical care. The attainment of health is a basic human right. The International Covenant on Economic, Social and Cultural Rights (ICESR)[59], and the African Charter on Human and People's Rights[60] all state:

> "Everyone has the right to the enjoyment of the highest attainable standard of physical and mental health."

If the use of an experimental intervention is the only means a person has to achieve the "highest attainable standard of health" then its use is justifiable.

The WHO also states the following key aspect on the right to health:

> "The right to health contains entitlements. These entitlements include:
>
> Access to essential medicines"[61]

If there are no proven essential medicines available, and the experimental intervention is the only available "essential" medicine, this article might be interpreted to justify the use of it.

An international case which is in line with the refusal of emergency medical services is that heard in the Supreme Court in India - the Constitutional case of *Mazdoor Samity versus State of West*

Bengal .[62] The plaintiff fell off a train and sustained serious head injuries. He was denied access to the emergency department due to the lack of available beds. The court ruled that the state was bound by its constitutional obligation to "the right of life of every person and preservation of life being of paramount importance. The government hospitals and the medical officers in them are bound in this respect… that the obligation on the state stands irrespective of constraints in financial resources."[62]This case reaffirms that emergency medical care cannot be denied and, if there is an available option to offer the emergency care, then it is justified on the grounds of "the preservation of life being of paramount importance."

All the legal rights impose a corresponding *duty* to act accordingly in South African law. A breach of these legal rights *and* a corresponding breach in the duty to respond to them accordingly may give rise to civil liability in South African law. The duty to act within the law overlaps with a Kantian view of what our moral duties are. The ethical principles of beneficence and non-maleficence tie up neatly with a utilitarian argument. All ethical theories thus far display intertwining defences that justify experimental drug use. The African moral theory, which I elaborate on next, merges all three of the above mentioned moral theory defences into one.

4.4 African-based morality

Persons most susceptible to an epidemic live within the poorest parts of the world.[3 31 63] Parts of Africa are poor and therefore susceptible to an epidemic crises. Persons in Africa will have moral norms and reasoning which are not grounded in Western Culture. It is therefore pertinent to consider experimental drug use from an African ethical perspective.

A salient theme in African morality is the appreciation of what it means to be a person. Personhood is understood by translating the African saying "wir dzë wir".[64] This means a human being is a human being, simply by being human.[64] The definition of personhood implicates an emphasis of

respect for all human life. All human life whether disabled or abled, rational or emotive, intelligent or dull, baby or elderly is worthy. All persons, simply by virtue of being human, deserve to be treated with respect. The respect for human life can be teased down by translating the word "ubuntu". "Ubuntu" means humanness, but its meaning cannot be translated into one English word.[65] Ubuntu resists easy translation and subsequent philosophical ethical debate with "ubuntu" at its centre is complex and controversial. [66]

In the case *S v Makwanyane*[53], Madala and Mohammed both capture the essence of "Ubuntu" with this elaboration:

> "While [ubuntu] envelops the key values of group solidarity, compassion, respect, human dignity, conformity to basic norms and collective unity, in its fundamental sense it denotes humanity and morality. Its spirit emphasises respect for human dignity, marking a shift from confrontation to conciliation."[66] (Madala)
>
> "The ethos of an instinctive capacity for and enjoyment of love towards our fellow men and women; the joy and the fulfilment involved in recognizing their innate humanity; the reciprocity this generates in interaction within the collective community; the richness of the creative emotions which it engenders and the moral energies which it releases both in the givers and the society which they serve and are served by."[66](Mohammed)

"Ubuntu" is "oneness". "Ubuntu" implies all life is interconnected – persons are connected to God, and connected to the universe….to animals… to our ancestors….[67] Religion, morality, community and the individual are all interconnected into "one".[67] Ubuntu is therefore a moral principle but has spiritual, social and ethical implications.[66] In other words, morality and spirituality are the same in their essence. In Western culture, there is a clear distinction between religion and morality. A person need not have any religious understanding to apply moral reasoning. From an African perspective,

religion and morality are interdependent but intertwined with one another.[67] 79.8 percent of South Africans follow the Christian faith.[68] I therefore make reference to Christianity and the Bible to elaborate on the spiritual foundations of "ubuntu".

According to the Bible all persons are connected to God. God is good, God is power, God is abundance, God is blessing, God is truth, and God is love etc.[69] The same insights are found in sacred texts of other great religions like Islam and Hinduism. And African Traditional Religion holds similar beliefs. If persons connect to this universal pool of awareness or oneness or consciousness with God, there will be an inherent understanding of what is morally right and what is wrong. In other words, all people are born with a conscience – which is God in the form of the Holy Spirit within us. The Holy Spirit will always direct a person as to what is morally right in any situation. God is truth, therefore, if a person connects to God, the truth behind any ethical dilemma will be revealed.[69] The integration of morality and spirituality is clearly explained though this understanding of "oneness".

Metz explains that a true person in an African belief system is a person who exhibits good character. If a true -"full" - person exhibits good character traits, then a person who is not good will be less than "full".[65] The ultimate goal is for a person to become "full". In other words, to possess good and virtuous character traits.[65] The "fullness" of persons can be explained further: if persons are connected to God, who is living and fills persons, then through extension of this, persons may also be connected to the devil. Metaphorically and literally, the devil is death.[69] All persons are therefore connected to good (light, life, God) and connected to evil (darkness, death, the devil) at the same time. The ultimate goal is to become "full" of God, which in essence is life. As I explained previously, it is the Holy Spirit (God) which is life,[69] dwelling within humankind, which "fills" a person.

In ubuntu, an individual's needs should always be viewed with the whole community's needs in perspective. Social harmony is more important than individualistic competitiveness.[67] This holistic viewpoint of life naturally determines how people should treat one another- a person should treat others as they themselves would like to be treated. The reason for this is that in essence I am the same as you. "I am because we are, and since we are, therefore I am." [67]This is reinforced within the Bible:

> "The fear of the Lord is the beginning of wisdom and knowledge of the Holy One is understanding." Proverbs 9:10
>
> "Do not be deceived: God cannot be mocked. A man reaps what he sows." Galations 6:7
>
> "Give, and it will be given to you... For with the measure you use, it will be measured to you." Luke 6:38
>
> "Anyone who does wrong will be repaid for their wrongs, and there is no favouritism." Colossians 3:25
>
> "The King is mighty, he loves justice - you have established equity…"[69] Psalm 99:4

The Bible therefore says that a person must fear (in other words respect) the Lord. It is out of respect for the Lord that all persons obey his instructions. God is always just - every person will reap what they sew. In other words "you reap what you sew" is a Christian spiritual law: if you do wrong, wrong will come upon you and vice versa. It is therefore important that all persons treat others in the way they wish to be treated themselves. The Bible teaches a person the tools of how to "fill up" with God. There are similar teachings in the sacred texts of other great religious traditions, as well as within the proverbs, stories and sayings that are integral to African ethics.

Metz defines and extends the principles of ubuntu and "oneness" and developed them into a moral theory:

1. "To be a person in the true sense is to exhibit good character."

2. “An action is right just insofar as it is a way of living harmoniously or prizing communal relationships, ones in which people identify with each other and exhibit solidarity with one another, otherwise the action is wrong.”
3. “Do not fail to honour relationships in which people share a way of life and care for others’ quality of life, and especially do not esteem discordant relationships of division and ill will.”
4. “To respect friendly relationships, and especially to avoid prizing ones of enmity.”[65]

I now expand on each of these criteria as they apply to experimental drug use in an epidemic.

To be a person in the true sense is to exhibit good character

I have already explored that it is the doctor’s primary duty to always act in the best interests of the patient. To act in the best interest of the patient is to exhibit good character. I have also explored the concept of “Organizational ethics” which motivates that healthcare organizations in general (not just practitioners) have an ethical obligation to help patients who are in desperate need.

In order to determine what is right in a situation, the answer will lie in what brings people together. The same is for the opposite - what is wrong will drive people apart.

Implementing an experimental intervention will create harmony by bringing people together, as it is an attempt to save the life of the infected person. If the drug is successful, the person will live and return to the community in good health. Using the experimental intervention therefore creates an opportunity to live and “bring people together.”

If the experimental drug is not given, infected persons will be isolated from the community as part of infection control measures. If the epidemic has a high fatality rate, the person will be isolated from the community and then most probably die. Death “drives people apart”. (Whether death truly drives people apart is, however, debatable as, according to African beliefs, all ancestors who have passed

will ultimately be connected to the living.) It can, however, be accepted that death separates people on the earthly plane.

Do not fail to honour relationships in which people share a way of life and care for others' quality of life, and especially do not esteem discordant relationships of division and ill will.

Under my guidelines of the exceptional circumstances that permit experimental drug use on page 17, I expanded on the aggression of the epidemic within the balance of probabilities of life versus death. Also to be considered is the value of surviving with gross disability versus dying. Gross disability as a result of being denied the drug can be ethically classed along with death. If the balance of probabilities leans strongly towards death or gross disability without the drug, then using the drug would be in line with the ethical principle of beneficence if it could swing the balance towards life. Saving life, and sparing the quality of life with the experimental drug, is in line with "caring for others' quality of life." Not to use the drug is "ill will" as, without it, a patient's quality of life will not improve, as there is no other known medical intervention to bring about improvement.

To respect friendly relationships, and especially to avoid prizing ones of enmity.

I have explained above that experimental drug use is a "friendly" solution to an epidemic as it provides an opportunity to save life. The doctors' actions are "friendly" when using experimental drugs, as they are in with HPCSA guidelines (stated above). Each patient's decision to accept an experimental drug is "friendly" towards oneself - the experimental intervention is a choice based on respect for one's own life. This "friendly" decision of consenting to experimental drugs can be paralleled to a "rational" decision as defined by Kant. Not all "friendly" decisions will necessarily be rational, but in this case to be "friendly" to oneself requires one to be rational.

My synopsis of African moral theory might be oversimplified, as all the moral theories have been, but I believe this moral theory defends the strongest position in determining morality for the use of experimental interventions. African moral theory is not only a valuable tool for determining the ethics of experimental drugs, but I believe this theory is an entry point into making sense of many abstruse ethical dilemmas. I believe understanding morality rests within the simple truths which have been established for decades in African cultural belief systems.

African morality demonstrates the rationality, the consequences and the principles of experimental drug use – it is the right choice to make. Since each epidemic situation is, however, unique and unpredictable by nature[3], it will be instructive to view dealing with such situations as individual cases and not under a broad umbrella of a moral theory. I therefore expand on Michael Walzer's concept of a supreme emergency and apply it to experimental drug use.

4.5 Michael Walzer's Concept of "Supreme Emergency"

Walzer proposes a unique theory that there are certain times in life when supreme emergency action is necessary, even if that action does not comply with philosophical reasoning and moral theories.[70] In other words, the right action in an emergency situation may not necessarily be a moral action as defined by a moral theory but nonetheless it is the right choice to make at a particular point in time.

Walzer believes a supreme emergency response is necessary only when "our deepest values and our collective survival are in imminent danger."[70] In other words, not all emergency situations justify a supreme emergency response. Walzer expands on this further - there must be the "imminence of danger" and the "nature" of this danger must warrant an emergency response.[71] Both criteria need to be applied.

The recent Ebola epidemic is an example of when classifying a situation as a supreme emergency is justified. Such a situation would be when: the virus was producing a high fatality rate; there was no known cure for the disease; it was spreading rapidly; it was spanning countries. A recent update of the countries that were affected by the Ebola epidemic of 2014 include Guinea, Sierra Leone, Liberia, Nigeria, Senegal, Spain, United States of America, Mali, United Kingdom and Italy.[72] The 2014 Ebola outbreak produced a global public health threat. An extreme emergency response to control the outbreak was therefore justifiable. Ethicists might grapple with whether the decision to use Zmapp was moral, but at the end of the day, moral or immoral, Zmapp worked. The Ebola outbreak was contained and therefore the use of Zmapp was the right decision to make.

I agree with Walzer that, in certain situations, it is possible that "right" and "wrong" can happen at the same time.[70] It is right that countries should not be predisposed to an epidemic in the first place; it is right that poor healthcare resources should be addressed immediately; it is right to complete the clinical trials before using Zmapp or any investigational drug; BUT it is wrong not to make use of an investigational drug such as Zmapp.

An extreme emergency response, echoing utilitarian thought, must hold the intention of achieving a good end. There is an element of the doctrine of double effect within Walzer's defence of experimental drug use. The classical doctrine of double effect, drawing on Thomism, ethically justifies an action as long as the intentions behind that action are good:

> "An action with two possible effects, one good and one bad, is morally permitted if the action
>
> (1) is not in itself immoral,
>
> (2) is undertaken only with the intention of achieving the possible good effect, without intending the possible bad effect, although it may be foreseen,
>
> (3) does not bring about the possible good effect by means of the possible bad effect, and

(4) is undertaken for a proportionately grave reason."[73]

In the doctrine of double effect, the intention behind an action is most important because there are two possible different effects that can result from one intended action. The action of using an experimental intervention can have 2 possible results - the drug will either be ineffective/lethal or it will provide a cure for the epidemic infection. The ethical justification for using the experimental drug holds the intention that it will provide a cure, but the contrary is possible. Since the intention is good (moral) the doctrine of double effect justifies the use of it.

Walzer does not make reference to the morality of an action, but does justify an extreme action if the overall intention is for the greater good. Both the doctrine of double effect and Walzer justify an action, even if there are foreseeable negative consequences, because there are no other available options. The doctrine of double effect is *undertaken for a proportionately grave reason* which can be paralleled to Walzer's reasoning of *our deepest values and our collective survival [being] in imminent danger.*

Orend elaborates on Walzer's war ethics by defining criteria as to how "to make decisions in hell." In summary, these are: "that the action contemplated must at least be reasonably believed to work, that one should publically declare what one is going to do, appeal to the international community for outside support so the most extreme action might not be necessary, and lastly try to maintain right intention to use the measures contemplated only for the purpose and to the extent necessary."[71] These criteria for an emergency war situation can be applied to an epidemic crisis: The experimental intervention must have a favourable risk/benefit ratio; a public announcement must be made that the drug is experimental; an appeal to the international community must be made to generate international aid monies to assist the healthcare system in preventing a recurrence of infection; and lastly, immediately to stop use of the drug if it were to prove to be a failure, as soon as this were realized. The supreme emergency doctrine in war also has limitations: actions committed under it

cannot be applied except in dire circumstances and must be stopped once the supreme emergency has passed. In the case under discussion, this means that this doctrine cannot ever legitimately be used to cast aside standard medical research and treatment practice and cannot thus be used to circumvent the established standards of practice outside emergency situations.

4.6 Arguments in opposition to experimental interventions

I have established that five theories all reaffirm the moral claim that experimental drug use is permissible within a public health emergency. Are there any arguments against the use of them? The legal argument that could be proposed against the use of experimental interventions is the legislation that pertains to the Consumer Protection Act 68 of 2008 (CPA).[74] This Act implements a strict liability and hence no fault argument. In other words, fault issues are irrelevant - if there is harm, then there is liability. The CPA imposes strict liability on manufacturers of goods and/or service providers with the effect that, even if the manufacturer is found not to be at fault, if a consumer suffers harm as a result of a manufacturer's actions, or omissions, the manufacturer will be held liable. The CPA would hold all parties liable - from the service provider that dispensed the drug to the patient, to the manufacturer of the drug that caused the harm.

However, in order to sustain a delict within South African law, the harm itself and/or the conduct that caused the harm must be wrongful. Wrongfulness is defined in South African law in a policy basis which the court interprets through the lens of The Constitution. If there are ethical grounds for not providing experimental interventions which are further found to be inconsistent with the Constitution, then the conduct will be regarded as wrongful and all the service providers and manufacturers will be held liable. This act, however, will only have clout in an argument for a patient (or the family on behalf of the patient) who used a failed experimental drug intervention if the court could prove that the use of the experimental intervention were unconstitutional. There are strong

legal arguments in favour of experimental drug use - as outlined above - and therefore it would be difficult to prove its wrongfulness.

There is no ethical argument which rationalizes why the right to life should be overruled. All research is risky by nature, but within high risk situations, such as epidemics, it is ethically permissible to increase these risks if the trade-off is to save life. Therefore, there are no arguments against the use of experimental interventions.

In summary: Kantian ethics, utilitarian ethics, principle-based morality, African morality and Michael Walzer's concept of a supreme emergency all point in favour of experimental drug use in an emergency situation. The CPA[74] has no sustainable defence against the use of experimental drugs under the circumstances of and following the argument presented above. I have therefore proposed that there is moral worth in the need to reform the regulatory guidelines to allow speedy compassionate drug access, while still complying with some regulation to avoid abuse, to experimental interventions in a public health emergency. It is morally acceptable, but there are still challenges pertaining to informed consent, standards of care and justice when experimental interventions are used. I critically assess these challenges in Chapter 5.

Chapter 5

Major challenges of using experimental interventions

Introduction

I have argued why it is necessary to depart from the "normal rules" as they pertain to the regulatory guidelines. As a general rule, all medications should be rigorously tested for efficacy and safety before being used on the public. However, in the case of a public healthcare emergency, this principle may arguably be departed from for the duration of the crisis. This gives rise to the question as to whether the normal rule can be overlooked within the challenges of informed consent process, standards of care and justice. I critically assess each of these challenges consecutively below.

5.1 Informed Consent

I use the term "research" now as I have established clearly that research and treatment occur concurrently within an emergency epidemic situation. Since most epidemics occur in poor developing countries[63], many ethical challenges emerge within the informed consent process. Differences in language, differences in socio-cultural traditions, low levels of formal education, differences of social value, differences in priorities, as well as in the understanding of diseases and health, make the process of informed consent challenging in the standard non-emergency research process, let alone in an emergency situation. [1 75 4] Differences in social tradition (gender discrimination and male-headed households) become a challenge when a spouse or senior member of the family is required to assent to the treatment or research on behalf of the participant.[1] Low levels of formal education also raise challenges in respect of understanding, as well as the participant's inability to sign the consent form.[1 4] Therapeutic misconception is a common problem

in research trials, for example, where participants are of the understanding that the clinical trial is just an extension or part of their standard medical treatment.[76]

In order to address issues associated with language differences, low levels of formal education, differences of value, and the understanding of diseases and health, researchers should do their best to ensure complete understanding and knowledge, including information that is relevant, accurate and sufficient, is communicated in a language that the participant understands. Emanuel has suggested that local community leaders or representatives assist with the informed consent process. Emanuel suggests "spheres of consent", which is consent that is obtained across a range of persons, for example, the leaders and heads of households assent first before the participant's consent is obtained.[75]International guidelines, such as the Nuffield Guidelines[1] and the Declaration of Helsinki,[49] reinforce that family members or community leaders may assent to the research, but their assent does not supersede the individual participant's consent. Cultural norms must be respected but it does not mean they must not be critically analysed.[1] Researchers have an ethical responsibility to ensure there is no coercion from family and community members if assent is given. The Declaration of Helsinki under article 25 states,

> "Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees."[49]

Molyneux et al performed a study within Kenya to investigate community perceptions on the informed consent process. The study was done in a district where there is the highest amount of poverty, the lowest rates of literacy and highest gender inequality compared to other districts within the country.[4] In Molyneux's study, guidance from community leaders as to how the consent process should be implemented provided no unanimity. The study demonstrated a great diversity of views

amongst community leaders, as well as amongst the participants themselves.[4] This again reinforces why the informed consent of participants can never ethically be superseded by other parties, for example, male-headed households and community leaders.

The principle of layered consent may seem challenged but it is not impossible. Folayan has suggested that a "layperson" should form part of the ethics research community and assist with the administration of the protocols by giving constructive feedback. The drawback of this is that the "layperson" will need to have the capacity to do this. If relationships have been established from prior research protocols, this is possible. This "layperson" can form a link between community leaders and researchers in an emergency situation if the assent is necessary.[77] I think that these ideals might not be possible in an epidemic, but every effort should be made to strive towards them.

Even if the health practitioner or researcher were to follow the recommended ethical guidelines, is a participant, who is critically ill, charged with the emotions of having contracted an epidemic infection, with no background knowledge of research or a standard informed consent procedure, capable of full understanding of all of the implications of taking an experimental drug?[9] [78] Realistically the answer is no. Despite this, the researcher or healthcare practitioner has an ethical and legal obligation to use whatever creative means possible within a particular community to relay the appropriate information. This should be done in a manner such as that described by the guidelines advocated by the Department of Health to ensure there is full disclosure, full understanding and voluntary consent - if the participant is capable of giving consent:

`

> "Prospective participants should be helped to arrive at an informed decision by, for instance, use of appropriate language, selection of non-threatening environment and the availability of peer counselling."[46]
>
> And

> "Patients who are highly dependent on medical care deserve special attention when considering research participation. The gravity of their medical condition may require invasive measures that carry increased risk of harm. The quality of informed consent may be compromised by the effect the medical condition has on the participant's decision-making or communication abilities. A patient may be reluctant to refuse consent for fear that this may compromise his medical treatment. Adequate provision must be made for informing patients and their relatives about the research to ensure that stress and other emotional factors do not impair their understanding. The dependency of patients and their relatives on caregivers should not unduly affect research participation decisions."[46]

In Molyneux's Kenyan study to investigate community perceptions on the informed consent process, all community members requested more information about the study, the investigations and the results.[4] This is pertinent, as despite low levels of formal education, it demonstrates participants' desire for knowledge and to learn. An epidemic situation might well be emotionally charged, but this does not override the principle that human beings have an innate desire to understand when health is at stake, even if the researcher perceives the participant to be not "truly capable". All knowledgeable medical staff should share as much information on the experimental intervention as feasible to participants or representatives throughout each step of the process and as more information avails itself.

Two recent studies have been published that embrace technology in the informed consent process. I believe a "speaking book" is one of the most valuable suggested tools to address challenges in the level of understanding in the informed consent process. Dhai performed a study on the value of a "speaking book" to empower persons with low literacy levels on the research process.[79] The battery operated book had a sound track which "read" in appropriate languages a simple explanation of the research process. The study indicated it was highly effective. The contents of a speaking book can

include information for the informed consent process, the nature of the research process and background information on the drug that is to be researched.[79]

Tait et al performed another study using digital media (an iPad) for both children and adults to help with the informed consent process. The results of the study demonstrated that the children showed a significant increase in comprehension and understanding with the digital media compared to the traditional paper format. The adults showed no significant difference with either format. However, when the children and adults were asked if they would prefer the presentation from the digital media or from the traditional paper format, if they participated in future research studies, 67.9% of the children and 62.4% of the adults said they preferred the digital format.[76] The speaking book and digital media are educational tools, which not only empower persons, they also effectively address some of the aforementioned challenges within the informed consent process. Digital media should be an important consideration for informed consent in an epidemic situation wherein therapeutic misconception is one of the greatest challenges.

Speaking books and digital media have the major drawback of cost. I have expanded on the cost of the research under "Standards of care" next. In order for it to be ethical to use an experimental intervention, a bare minimum in the standards of care is required for the research to take place. Funds cannot, however, be withheld when it comes to informed consent.

5.2 Standards of care

What are the appropriate standards of care that researchers should adhere to when performing experimental research? Epidemics, such as the influenza epidemic in the United Kingdom,[80] can occur in first world countries. Most literature, however, indicates that acute epidemic infections start within the poorest countries in the world. [3 31 63 81 82] There is great disparity between the healthcare systems of developed countries and those of developing countries. Resources and infrastructure are

substantially less in developing countries and associated poor health is not only linked to poor resources but to the social determinants of health, such as education, sanitation, nutrition and water.[1] In order to curb an epidemic such as Ebola effectively, the importance of standards of care becomes highlighted.[31]

It has been estimated that the mortality rate would have been around 10 percent lower in the current Ebola outbreak had better standards of care been available.[7] The weakened infrastructure in Sierra Leone and the other affected countries in West Africa meant that it was not possible to implement basic measures for standards of care for infection control. Whilst infection control will not save the already infected person's life, it protects the lives of those who are healthy. Measures to avoid an infection spreading are simple and include the following: rapid diagnosis, isolation of infected persons, good hygiene and accurate mapping and monitoring of the infection: I expand on each of these below.[83] The current known established treatment for Ebola is supportive care. Supportive care involves the administration of intravenous fluids. Even this proved to be a challenge in the Ebola epidemic.

Laboratory analysis of blood tests is required for the diagnosis of Ebola virus. The collection of blood samples entails risk and maximum containment is necessary.[9] Rapid diagnostics ensure patients are isolated immediately.[83]

Limiting the spread of the epidemic can be achieved through the isolation of infected persons. Creating a contained environment can easily be achieved through improvements in basic health infrastructure. Isolation strategies should be implemented within hospitals, as well as within infected communities.

Good hygiene practices are simple and easy to implement: education is the key. Washing hands, covering one's mouth etc. are basic hygiene principles which radically reduce infection spread.

Florence Nightingale reduced the death rate from cholera, dysentery and typhus from 42 % to 2% by organizing laundry services, cleaning equipment and wards and implementing basic hygiene practices.[83] Research studies have been done to examine proper handwashing where isolation is implemented to curb the spread of infection. The results have shown that staff members were the main contributing factor to spread of infections within hospitals simply due to improper handwashing practices.[83] Disinfectants, gloves and gowns, along with proper education on personal hygiene, are cost effective measures to curb epidemics. Studies have shown that basic education of healthcare staff showing that infections are spread primarily through physical contact and not through airborne spread, reduces the spread of infections.[83]

Addressing the standards of care is thus an important requirement in order to curb an epidemic. A big question in ethical debate is: What is the appropriate standard of care to implement when researchers from first world countries perform research in an impoverished country where an epidemic has occurred? Is it not "double standards" for first world sponsor countries to perform research with a different standard of care in undeveloped countries from that which they would take in their own country? [1 84 85]

There are fundamentally two different categories that can be derived as a definition of appropriate levels of care;

> "Universal: the best treatment available anywhere in the world, wherever the research is conducted,
>
> Non- Universal: the treatment available in a defined region."[1]

There is no ethical normal rule for conducting research in developing countries. I believe in order for it to be ethically justifiable to use an experimental intervention, the standard of care must be elevated

to such a level that it addresses the established and effective means of infection control and supportive care, as expanded on above, to curb the epidemic.

In summary, the West African Ebola crisis seems to suggest that all too often the highest and most effective universal standard of care is inappropriate and the local available standard of care is equally inappropriate. The goal would be to sufficiently elevate the basic standards of care, such as infection control and supportive care, in order to implement established measures to curb an epidemic. Benatar makes the pertinent statement that it may indeed be impossible to immediately address the inequities in standards of care, but each progressive step towards the ultimate goal proves to be valuable.[86] I agree with Benatar's statement. The highest standard of possible care should always be aimed for within the allocated budget.

5.3 Justice

There are various challenges related to justice if experimental interventions take place within an epidemic. Parameters for distributive justice to determine who should get the drug first would need to be set. There are responsibilities for researchers and governments after the epidemic has subsided: firstly, to ensure that justice is served with future access to any proven intervention should the epidemic arise again, and secondly, to address the psychosocial problems that befall survivors. To ensure justice is served both locally within the community and globally between countries, there needs to be an equal sharing of responsibilities, benefits and risks. Justice is served through the development of collaborative partnerships between governments, community leaders, pharma companies and researchers to ensure this equal sharing. I have expanded on justice - specifically distributive justice, post-epidemic justice and local justice - consecutively below.

5.3.1 Distributive Justice

If experimental interventions are ethically permissible, who gets access to the experimental drug first? I refer specifically to distributive justice here. Gostin has suggested the following ethical criteria as to who gets the drug first.[87] I have summarized these criteria as follows:

1. Domestic health workers: Healthy health workers place their lives at risk to help others. Their skills are very much needed to assist infected persons and thus they should receive first priority access. Domestic health workers should get the drug first, but not foreign health workers, according to Gostin. Whilst foreign health workers also place their lives at risk, they are most likely to come from a first world country, and therefore are likely to possess personal protective equipment along with the education to prevent self-contamination.
2. Epidemic "hot spots": This is geographically where the epidemic is most active. Reducing infection spread in hot spot areas is a key to control it. The most experienced staff should be working in these areas.
3. Need: Vulnerable persons such as children, the elderly, those with mental and physical disabilities etc.
4. Good governance: Partnerships, including governments and local communities, should be established to ascertain need.[87]

In critique of Gostin's suggestions for distributive justice, I do not comment on the suggestion that healthcare workers should have first access to an experimental drug, as this argument falls within the scope of "experimental vaccines" which I have excluded from this research report. Having said this, despite falling outside of the scope of this research report, I disagree with Gostin's presumption that foreign healthcare workers will have the necessary training and appropriate protective equipment. All aid workers - local or foreign - should be given the same support without prejudice on the grounds of risk and need in the particular situation. I support, however, Gostin's valuable suggestion

of targeting geographical “hot spots” and developing strong local and governmental partnerships to help determine need.

The most critically ill persons who present with a stable yet reversible condition, but ultimately face the highest chance of death, should be chosen to receive the experimental intervention first. As harsh as it sounds, such persons will die anyway, and the experimental drug is their only hope. Reference to the guidelines for ICU emergency cases that are implemented in triage situations will determine who is the most critically ill and who should receive the drug first. The ICU triage policy should be extended into an epidemic triage policy. A triage policy will unavoidably affect the public, therefore the policy will have to be rational, reasonable and proportional in its objective in order for it to be consistent with the principles of legality, the rule of law and the Constitutional right to fair administrative action.[88] If the epidemic triage policy is consistent with already established ICU triage policy, which is indeed rational, reasonable and proportional to its objective, then the epidemic policy should be legally binding.

An example of such a triage policy is “The Task Force of the American College of Critical Care Medicine” (The Task Force).[89] The Task Force states that in triage situations, due to the limitation and expense of available resources, an ICU should be reserved for those patients with “reversible medical conditions who have a reasonable prospect of recovery”.[89] The Task Force gives a priority list from priority 1 to priority 4 based on who will benefit most, as indicated primarily by the diagnosis.

> “Priority 1: These are critically ill, unstable patients in need of intensive treatment and monitoring that cannot be provided outside the ICU. Usually, these treatments include ventilator support.
>
> Priority 2: These patients require intensive monitoring and may potentially need immediate intervention. No therapeutic limits are generally stipulated for these patients. Examples

include patients with chronic co-morbid conditions who develop acute severe medical or surgical illness.

Priority 3: These unstable patients are critically ill but have a reduced likelihood of recovery because of underlying disease or the nature of their acute illness.

Priority 4: These are patients who are generally not appropriate for ICU admission. Patients with terminal and irreversible illness facing imminent death ('too sick to benefit from ICU care') fall under this priority."[89]

All patients initially have the same diagnosis with Ebola. The vital signs and available clinical data from monitoring each patient determine the extent of the progression of the illness. Secondary medical conditions may develop, for example, the Ebola virus eventually can cause the patient to develop kidney failure etc. Invasive and more aggressive treatment, such as mechanical ventilation, kidney dialysis or blood transfusions will then be required.[90] The patient may also have a history of previous unrelated health issues. These individual diagnostics can be used to class patients in order of priority.

An example of an epidemic triage policy might therefore look like this:

Priority 1: Critically ill, unstable patients in need of intensive treatment and monitoring. Mechanical ventilation or other invasive treatment measures are required. The patient presents with a reversible clinical position but faces imminent death.

Priority 2: Patients who need intensive monitoring and may potentially require more aggressive and invasive procedures.

Priority 3: Critically ill and unstable patients with a low chance of recovery due to irreversible damage.

Priority 4: Patients who are critically ill, with irreversible damage. Any treatment would be futile.

My recommendation is to adopt a triage policy where priority 1 patients get the experimental intervention first, scaled down to priority 4 patients who are not suitable. The triage policy should be adopted in geographical "hot spots" where the infection is most prevalent, as well as in areas of need, as suggested by Gostin. Referring back to study design – if a triage policy is implemented then an observational study design could be appropriate. Having said this there would be no hard and fast rule of study design- rather researchers would need to take into consideration the specifics of the epidemic infection at hand and decide from there.

5.3.2 Post epidemic justice

There would need to be active engagements between governments and other relevant parties (such as pharma companies, researchers, and global health organizations) before the experimental intervention is given to negotiate affordable access to any proven interventions should the trial prove to be successful and should a future epidemic arise. It has been suggested that tiered pricing mechanisms be implemented in order to ensure affordability of the drug for the developing country.[77] If in future the Ebola epidemic is controlled in its early stages by the proven medical intervention, the quantities of the drug required would actually be small in comparison to other diseases, such as TB. Governments therefore should attempt to negotiate buying the drug at cost or even accessing it for free.[77]

Drugs are not the only thing that needs to be considered after an epidemic subsides. Support services for survivors are important. Studies on the Ebola survivors have demonstrated the psychosocial stigma that developed towards persons post infection. Survivors were shunned by the community. Many survivors lost most of their belongings – household goods and clothing – as they were either "burnt or taken away as part of infection control".[43] Due to their being stigmatised in the community, it was difficult for them to reintegrate and purchase new things. This indicates that there is an obligation to provide the necessary counselling services for survivors. It has been suggested that

counsellors accompany survivors on their return to their villages and communicate with traditional local authorities to provide the correct information and necessary education to reduce stigma and encourage future supportive care. [43] [45] I agree with this suggestion.

5.3.3. Local and social justice

Emmanuel suggests eight benchmark principles for research to be ethical in developing countries: collaborative partnership, social value, scientific validity, fair selection of study population, favourable risk-benefit ratio, independent review, informed consent and respect for recruited participants and study communities.[75] These ethical principles of research should be adhered to in order for the principle of justice to be served when an experimental intervention is used.

Developing relationships between community advisory boards and other local stakeholders is also important in terms of negotiating the appropriate benefits during and after the trial.[91] Forming partnerships at a community level allows for thorough interaction and assessment of local needs, assists in avoiding possible group harm, and gives a more thorough understanding of that community's cultures and values.[75] [92] There are other advantages of establishing partnerships at a community level, such as establishing trust between the community and the researcher, as well as raising awareness which assists in education about the research process.[91] When establishing local community partnerships, I believe the researcher has an ethical obligation to impart knowledge to the community on issues of justice, specifically on the negotiation for benefits after the epidemic has subsided if the drug works. Raising levels of knowledge and awareness of the research process empowers the community. Empowerment begets justice.

It can be argued that, due to the urgency in an epidemic, there is limited time for extensive consultation with community members prior to performing the research. As stated previously regarding the issue of informed consent, Folayan suggests that this concept of community

engagement can still be embraced through engagement with a “layperson” on the ethics committee. The layperson can then give active feedback to community members. This person can also review the research protocol and give constructive feedback, representing the community, on the research process.[77] The advantage of building authentic relationships within the research process is that it allows for a dual sharing of responsibility during the research process. The planning, overseeing and conducting of research and dissemination of results should be shared equally between the researcher, research funders and the community. The sharing of responsibilities will increase knowledge and empower local persons for sustainability.[91] This is important - even in an emergency. Therefore, the normal rules must be applied here.

In summary, having established that there are many challenges within informed consent, standards of care and justice related to the use of experimental intervention, I have demonstrated that these challenges can be overcome. I have established that the informed consent procedure needs to be adhered to as long as the patient is able to consent. If they are unable to consent, a proxy consent is the next step. If no proxy consent is available, deferred consent is justifiable due to the nature of the circumstances. There is much need for reform in South African legislation for informed consent to cater for emergency epidemic circumstances. I have made recommendations not only for the legislation of informed consent but I have also made ethical recommendations, such as a speaking book or electronic media to facilitate the informed consent process.

There is a baseline minimum in the standard of care required when performing the research and treating infected persons. Adequate infection control and supportive care measures are a bare minimum prerequisite if an experimental intervention is used. All available monies need to be prudently calculated to ensure there is sufficient funding to address the standards of care before the decision is granted to use an experimental intervention.

In order to ensure there is justice, specifically distributive justice, an epidemic triage policy should be implemented. Geographical “hot spots” should be targeted first. Collaborative partnerships should be formed with an equal sharing of responsibility between researchers, funders, governments, hospital personnel, and community lay persons to ensure there is fairness within the clinical trial process. Any post trial benefits, such as a fair distribution of gross profits should a drug patent of value be proven (unlikely though this is), should be negotiated before the trial begins. Post-epidemic access to the drug for future epidemic situations should be negotiated at cost price, if not for free.

Chapter 6

Conclusion

I argue that it is ethically permissible to offer experimental interventions to patients under certain circumstances in an emergency epidemic situation. In fact, it becomes ethically obligatory to make these interventions available under certain circumstances. These exceptional circumstances include: acute public health emergency epidemics which are highly infectious and demonstrate a high chance of fatality. There are major ethical challenges with this statement but, in my view, it would nonetheless be unethical to withhold possible interventions, which could not only save lives, but also protect members of the public.

There are limited options for new drug administration during an epidemic when there is no known established medical intervention. If there is available a suitable drug, which has been proved for another medical indication, this should be the preferable choice to address the epidemic. If there is no such drug, it is ethically justifiable to use the only other available option, which is an experimental intervention. Essentially, all research is risky by nature, but the high risks affiliated with an epidemic justify the increased risk of accessing a drug early.

South Africa is currently not on par with international compassionate access regulatory guidelines. However, globally many countries are reviewing their guidelines, providing an opportunity for South Africa to regulate simultaneously. It would be ideal to harmonise all guidelines into a common global approach. New guidelines need to take into account the urgency behind the situation but they also need to be implemented fastidiously to prevent any unnecessary harm in an already high risk situation.

Current regulation does not stipulate whether a clinical trial should be performed when compassionate access is granted. I have reviewed possible different options to perform a clinical trial under a public health emergency situation. Due to the nature of the circumstances and the urgent need for treatment, I argued that it is justifiable to depart from the normal rules of research and that a clinical trial should not be mandatory.

I have critically assessed the arguments in support of and in opposition to the use of experimental interventions. I critically assessed the use of experimental interventions from Kantian, utilitarian, principle-based morality, African-based morality and Micheal Walzer's concept of supreme emergency perspectives. I believe that the African moral theory provides the most holistic and useful tools to decipher the ethics of experimental drug use. The African moral theory draws together all the essential elements of the different moral theories I utilized within this paper. African morality considers the consequences, the duties of community members and the principles associated with experimental drug use. African morality also encompasses the issues that pertain to standards of care and justice within a clinical trial.

The salient theme within the moral theories is grounded in the right to life. The preservation of human life is of paramount importance and reigns supreme over all the arguments. There is no legal or ethical argument which rationalizes why the right to life should be overruled. All research is risky by nature, but within high risk situations, such as epidemics, it is ethically permissible to increase these risks if the trade-off is to save life when death is the only alternative.

I critically assessed two of the major challenges to performing research in developing countries – informed consent and standards of care - as they pertain to experimental interventions in epidemic crises. Informed consent procedure is a legal and ethical requirement if experimental interventions are used. South African legislation for informed consent is adequate if patients are capable of giving consent themselves. I have made suggestions for proxy and deferred consent, as South African

legislation is inadequate in this area. Differences in language and low levels of formal education are two of the many ethical challenges presented in the informed consent process. I believe a speaking book or some form of digital media is a mandatory requirement for informed consent, as it assists in addressing these challenges and helps to avoid therapeutic misconception.

The appropriate standards of care during compassionate drug access draw on the budget strings. In order for it to be ethically justifiable to use an experimental intervention, the standard of care must be elevated to such a level that the established and effective means of infection control and supportive care are implemented. Adequate supportive care, such as intravenous drips and any other known established measures, need to be given to both the experimental and the control groups in order for experimental drug use to be ethical.

As far as distributive justice goes, I have suggested an epidemic triage policy be implemented in geographical hot spots. For post-epidemic justice, I have recommended that, if a drug patent is developed, the patent should be supplied at cost, if not for free, should a future epidemic arise. It would be unethical to perform research and lace any drug patents with heavy profit margins to cater for future epidemics. Post-epidemic justice also takes into account the psychological trauma associated with an epidemic and the paramount importance of post- trial counselling. Local and social justice reinforce the importance of developing collaborative partnerships in an epidemic situation. The urgency of the situation does not negate responsibilities to uphold authentic partnerships from researchers to local stakeholders to community members.

The debate around the use of experimental interventions in a medical emergency is a complex one. In this research report, I have examined and discussed the many physical, ethical and legal issues surrounding the use of experimental drugs. All factors considered, the arguments in favour of experimental drugs outweigh the arguments against them

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