TITLE: Understanding the requirements and barriers to providing Post-Trial Access (PTA): A review of continued access to effective medicine

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Declaration

I declare that this research report is my unaided work. It is submitted for the degree Masters in Applied Ethics for Professionals, at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any other degree or examination in any other university.

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31 May 2024

Abstract

Clinical trials are essential in establishing the safety and efficacy of investigational products and are a mandatory requirement for the registration of a new medicine. Additionally, clinical studies offer access to new therapies, innovative treatments or more effective treatments which may not be readily accessible to the general population. Clinical trial participants receive investigational medicine during the study conduct phase as a study benefit and as compensation for their voluntary participation. In resource-limited countries, this may be the only option available to access new and effective medicine. Therefore, continued treatment access becomes of greater value. However, providing PTA presents ethical considerations which need to be addressed. The provision of PTA to effective medicine can be viewed as an inducement to join a study and creates inequalities between diseased patients, as it excludes other diseased patients who did not participate in the study or patients who were excluded from participation in the study. However, prior to addressing these controversies, it is necessary to establish first whether clinical trial participants have a moral claim to PTA provision. This report seeks to establish the moral requirement for PTA provision to address the ethical issues around providing continued access to effective medicines outside clinical trial settings. The first two chapters will focus on discussing the evolution of clinical trials, highlighting the ethical issues surrounding continued access to effective investigational products. The principles of bioethics will be discussed in detail in Chapter 2 to draw out the moral claims which mandate the requirement to provide PTA to efficacious medical therapy offered during the study. In Chapter 3, I will argue for the moral requirement for providing PTA using the principles of bioethics as a framework. In Chapter 4, I will discuss the challenges and PTA solutions. In my conclusion, I will reiterate my support for the mandatory requirement and implementation of PTA until the Investigational Product is commercially available and accessible to all trial participants, emphasising the importance of this stance.

Concepts and Terms

1. **clinical research**/**clinical studies**/**clinical trials**: will be used interchangeably, all concepts refer to research studies conducted on humans.
2. **participants**/**volunteers**/**patients**: will be used interchangeably, terms refer to research human participants who consent to take part in a clinical trial.
3. **clinical trial sponsor** refers to an individual or institution that financially funds the design, conduct and operation of a clinical study, such as a pharmaceutical company, non-governmental organisation (NGO), academic institution or investigators/researchers.
4. **host country** refers to the country in which a clinical study is conducted.

Acronyms

CA - Continued Access

DoH - Department of Health

DoH - Declaration of Helsinki

GCP - Good Clinical Practice

ICF - Informed Consent Form

IEC - Independent Ethics Committee

IP - Investigational Product

IRB - Institutional Review Board

NGO - Non-governmental Organisation

PrEP - Pre-Exposure Prophylaxis

PTA - Post-Trial Access

RA - Regulatory Authority

SA - South Africa

SAHPRA - South African Health Products Regulatory Authority

STIs - Sexually Transmitted Infections

WMA - World Medical Association

Table of Contents

Declaration 1

Abstract 2

Concepts and Terms 3

Acronyms 4

Chapter 1: Introductory Overview 7

Chapter 2: Principles Governing Ethical Clinical Trials 9

2.1 Introduction 9

2.2 Clinical Trials and the Post-Trial Access Overview 9

2.2.1 Post-Trial Access Considerations 11

2.2.2 A Prima Facie Case for the Ethical Justification of the Post-Trial Access 13

2.3 Relevance of the Principlism Approach 15

2.3.1 The Principle of Respect for Autonomy 17

2.3.2 the Principles of Beneficence and Non-Maleficence 23

2.3.3 The Principle of Justice 25

2.4 Conclusion 27

Chapter 3: Arguments for the Post-Trial Access Provision 28

3.1 Introduction 28

3.2 Moral Requirements for Post-Trial Access Provision 28

3.3 Application of the Justice Principle 29

3.4 Applying the Non-Maleficence and Beneficence Principles 31

3.5 Applying the Principle of Respect for Autonomy 32

3.6 Switching to Available Standard of Care 33

3.7 Conclusion 35

Chapter 4: Challenges and Solutions to Post-Trial Access Provision 36

4.1 Introduction 36

4.2 Objections to Post-Trial Access Provision 36

4.2.1 The deterrent of cost 36

4.2.2 Undue Inducement 37

4.2.3 Inequalities Between Participants and Non-participants 38
4.3 Solutions for Ensuring the Post-Trial Access Provision 38
4.3.1 Responding to Worries About Cost 38
4.3.2 Responding to the Possibility of Undue Inducement 40
4.3.3 Responding to Increasing Inequalities 41
4.4 Conclusion 42
Chapter 5: Conclusion and Recommendations 43
5.1 Conclusion 43
5.2 Recommendations 44
References 46

Chapter 1: Introductory Overview

Clinical studies done on human volunteers within a research environment are essential for establishing the safety and efficacy of medicines. These clinical studies also offer access to new therapies, innovative treatments or more effective treatments which may not be readily accessible to the public. Clinical study volunteers receive investigational medicine at no cost during the study conduct as an added benefit in exchange for their voluntary participation. In resource-limited countries, this may be the only medical treatment route that is available to access new and effective medicines. Therefore, continued access to effective medicine post-study becomes of greater value to clinical study participants who are living in resource-limited countries. In the context of South Africa (SA), where resources are limited, clinical studies thus contribute plausibly to a just distribution of effective medicines. The Good Clinical Practice (GCP) Guidelines in SA reinforce the principle of distributive justice and its relevance in SA by emphasising justice in research, specifically on the risk-benefit ratio, where those who take on the risks should receive the benefit (SA GCP, 2020). An independent ethics review required for approval to conduct a clinical study in SA requires an explicit justification of the reason why the research will be conducted in SA. According to the SA GCP Guidelines 2020, clear guidance for participants about Post-Trial Care must be provided, as well as a plan for Post-Trial Access (PTA) provision. While PTA appears to be acknowledged as important in SA, it is stipulated merely as a recommendation where possible. It has no lawful enforcement that backs it up to ensure that non-compliance to approved PTA plans is punished.

The focus of this report will be centred on establishing whether there is a moral requirement to provide PTA. In view of this analysis, the report will reflect on whether research participants have any ethical right or claim to access effective medicine post-study and whether any such claims are justifiably defeasible in a resource-limited country like SA. This report will also highlight the emergent barriers to providing PTA and suggest possible solutions to overcoming the challenges of continued access. Along with an exploration of the ethical justifications for PTA, the report will provide an in-depth review of the arising circumstantial mandates for PTA provision in SA. This research report is motivated by a need to critique the gap in knowledge in post-trial ethical obligations and considerations, particularly focusing on the complex ethical issues or challenges

around providing PTA to effective medicines once a clinical study has ended. The scope of this research will be limited to the geographical context of South Africa and clinical trials conducted in SA. Ultimately, I will argue that there is a moral requirement for PTA provision that needs to be backed by lawfully binding guidelines. The ethical requirement to provide PTA is not defeated by considerations such as limited resources and financial costs. In conclusion, I will make recommendations for stricter legal enforcement of PTA guidelines than is currently in place. A consequence of my argument is that the guidelines need to be updated and PTA made mandatory. PTA provision is closely linked to participants' basic human rights, thereby affecting their health and well-being. Consequently, the right to access healthcare must be protected as failure to do so results in the exploitation of study participants and violation of their humanity.

In order to develop this argument, the entry of discussion in Chapter 2 will be used to provide an overview of the principles that have formed the foundational cornerstone of ethical clinical trials. By identifying the relevant ethical principles governing ethical clinical trials, those same principles can be drawn on to assess whether PTA is ethically mandated. In Chapter 3, I will argue in favour of the requirements for PTA provision, expanding on and applying the principles from Chapter 2. I will argue in Chapter 3 that there is an ethical requirement for providing PTA in a country like SA, even though the current guidelines fail to recognise the importance of these requirements. There are, however, important objections to the provision of PTA, which might explain why SA's guidelines do not enforce PTA. In Chapter 4, therefore, the report will review the challenges and barriers that surround PTA provision with suggestions for plausible solutions to ensure PTA provision feasibility. Chapter 5 will draw out my conclusion and recommendations. In summary, using the principles of principlism in bioethics as the framework, one can deduce that there is a moral requirement to provide PTA to effective Investigational Product (IP), and I will provide a probable course of action to be taken to resolve the objections and limitations to providing PTA in a resource-limited country such as SA. In my recommendations, I will stand in support of the mandatory requirement and implementation of PTA until the IP is commercially available and accessible to all trial participants.

Chapter 2: Principles Governing Ethical Clinical Trials

2.1 Introduction

This chapter will provide an overview of clinical trials, PTA and the associated ethical considerations regarding post-trial obligations that ideally need to be met regarding study participants. As a framework for analysing the ethical considerations that govern clinical trials, which are conducted with integrity, this report will unpack the four principles of principlism, which were developed in part to ensure that clinical studies are conducted ethically. These principles will be utilised as a framework to establish the ethical claims participants might have on the researchers or that ought to be protected as they directly affect and have an impact on clinical trial participants.

I will argue that the principles of Respect for Autonomy, Beneficence, Non-maleficence, and justice as the cornerstone principles of bioethics are the key ethical drivers which directly influence the essential ethical considerations that ought to be in place to ensure the integrity of a clinical trial is upheld. Upholding and protecting the principles of principlism verifies the moral integrity of a clinical study as they form the fundamental foundation upon which clinical trial guidelines documents are established. Respect for Autonomy, Beneficence, Non-maleficence, and justice have a direct bearing on the mandates required to provide PTA, which I will discuss in detail in Chapter 3.

2.2 Clinical Trials and Post-Trial Access Overview

Clinical trials are research studies done on human volunteers in order to test the safety and efficacy of a medicine or IP. Clinical trials play a pivotal role in the development and registration of innovative products or finding new effective medicines. Data gathered from clinical trials support regulatory approval and marketing authorisation. The country's health authorities regulate clinical trials, independent Ethics Committees or institutional regulatory committees (SA GCP Guidelines, 2020). The South African Health Products Regulatory Authority regulates the registration of medicines in SA and also provides guidelines for GCP. Compliance with SA GCP Guidelines is mandated by section 90(s) and 72(6)(c) of the National Health Act, Act No. 61 of

2003, as well as Regulation 30 of the Medicines and Related Substances Act, Act No. 101 of 1965, as well as by the national research ethics guidelines (SA GCP Guidelines, 2020). Research data gathered from clinical trials is required as part of the registration process to get a new medicine registered and available to a larger population group. Additionally, clinical trials play a vital role in providing access to new therapies that would otherwise not be easily accessible to clinical trial participants. This may be due to cost factors or pricing fees and a lack of streamlined medical access policies and distribution centres, to name a few of the barriers to accessing medical therapy in resource-limited countries.

PTA or Continued Access (CA) refers to the provision of effective medicine post-study or outside of a clinical study setting. This programme may be either through an extension study with a lean protocol, section 21 application, or expanded access programmes (SA GCP Guidelines, 2020). These various extended access programmes provide a way for patients to receive IP outside of the clinical trial setting. PTA provision is typically limited to the provision of clinically proven effective IPs or treatments, although it may, in some instances, include the provision of already available treatments that might have been administered during the study (Declaration of Helsinki, 2000). These IPs or treatments would have initially been made available to clinical trial participants during a clinical study (SA GCP Guidelines, 2020). PTA is particularly important for participants who benefited significantly from a study's IP as well as to study participants who may not be able to access the study medicine independently once the trial ends due to cost or availability. This is because, although the IP may have been proven to be effective, it may not be authorised for use in the country due to implications of high selling costs or delays in getting the IP approved and registered for commercial use.

This results in a barrier to access for trial participants who benefited from the medical therapy during the conduct of the trial. However, the provision of effective investigational products after a study has ended varies per clinical study sponsor or institution's PTA provision policies. Some clinical study sponsors may make access provisional for investigational products until it is approved or available commercially. In contrast, other clinical study sponsors may extend access beyond market approval and commercial availability (Sanofi, 2019). The South African GCP

Guidelines on PTA mention a minimum of four years after completion as the acceptable period to provide PTA to the participants who derive benefits from the IP. However, while PTA provision guidelines exist, PTA provision is merely stipulated as a recommendation where possible. Therefore, this statement of recommendation bears no lawful repercussions when a clinical study funder or institution does not make provision for PTA, nor does it adhere to their PTA plans, which were provided initially in order to get the study approved.

2.2.1 Post-Trial Access Considerations

At the end of the study, participants faced the eventuality of transitioning from a clinical setting where they received close follow-up and monitoring into the routinely available standard of care setting. In a low-income country like SA with limited resources, an alternative therapy may not be available due to various reasons such as the approval of the IP not receiving immediate market approval (Naidoo et al., 2021). The implication of this transition raises ethical concerns on the moral acceptability of introducing study participants to a medical lifestyle that is fully subsidised with high care and close monitoring, often for several years at a time, only to later shift them back to a lifestyle of medical care that is less than what they have become accustomed to or simply none at all. The impact of a medical transition makes the subject vulnerable and pre-exposes them to psychological and physical traumatic experiences (Naidoo et al., 2021). Consequently, because study participants receive less monitoring and care than they were previously exposed to, they can become victims of a steady decline in their medical health and well-being (Naidoo et al., 2021).

In SA, the impact of a medical transition after a study ends implies that participants who do not have medical aid insurance or cover to transition back to better-resourced private facilities only have the availability to option to transition back to resource-limited state hospitals or clinics (Dal-Ré, *et.al* 2016) The reality of this socio-economic limitation leads to low access to effective medical treatment and increased vulnerability. This also affects study participants' dignity and right to participate in decision-making on matters affecting their health (Patients Right Charter, 1999). The impact of such transitions is more impactful in long-term studies which are conducted over two to five years. For participants who do not have medical cover, the option is to transition

to an overburdened and resource-limited state facility, which may result in them needing to change their treatment therapy to the available standard of care or not being provided with any treatment at all. To some, the therapy changes or breaks in therapy may pose a risk to the participants' health where no comparable or satisfactory alternative standard of care treatment is available (Naidoo et al., 2021).

Data gathered from clinical trials has the potential to demonstrate that the IP has provided substantial evidence of efficacy or demonstrates superiority over the comparator. This gives rise to a new set of ethical dilemmas, in particular, whether the sponsor should then offer the Investigational Product to all study participants (including those who were on the standard of care treatment arm) until the demonstrated superior IP is commercially available or accessible to them, or to offer the IP only to those on the investigational treatment, or active, arm.

Tackling these fundamental dilemmas requires addressing closely conjoined moral dilemmas such as: Should the study participants on the active treatment arm be switched to the available comparator even though its efficacy is less effective or inferior to it? UNAIDS (2000) has a requirement for studies investigating HIV vaccines, which states explicitly that "Any HIV preventive vaccine demonstrated to be safe and effective should be made available as soon as possible to all participants on which it was tested".

Practically, this would mean that a study conducted with one arm being pre-exposure prophylaxis (PrEP) and the other arm being an investigational HIV vaccine, which has been proven to be safe and effective, which also necessitates that the HIV vaccine be provided to all study participants at the end of the study.

Moreover, post-study booster shots should ideally be provided to all participants post-study, irrespective of the associated costs. Some sponsors have already adopted this higher obligation and have taken the ethical responsibility to switch to PTA for all study participants involved in the clinical trial (on active or comparator arms) as an ethical commitment to the patient's well-being and basic human rights (Pfizer Policy,2023). This moral commitment then becomes a pivotal driver which motivates a review of CA to IP post-study.

2.2.2 A Prima Facie Case for the Ethical Justification of Post-Trial Access

The change or discontinuation of IP that has demonstrated clinical effectiveness in study participants in a clinical trial puts a burden of compromise on them and adds risks to their health. Furthermore, there is a risk of the emergence of new adverse reactions of participants developing resistance to medical treatment or of being less responsive to further treatments (Aldinger et al., 2017).

These are important considerations as they draw particular attention to the medical risks and impact of switching clinical participants' medical therapy. However, it has not yet been proven that the provision of PTA provision is a moral requirement, let alone a legal one. This is because the healthcare of participants is closely monitored and regulated by law only during the conduct of a study, as data gathered therein is required as supporting documentation for registration of the new IP. However, data gathered from PTA programmes is not required for the submission for registration of a new IP, nor does it demonstrate that these considerations are anything more than considerations which are already recognised in existing PTA guidelines that merely state that PTA is a recommendation for use where possible.

The South African PTA Guidelines make provision for non-adherence to the guidelines provided that justification is provided, which needs to be reviewed on a case-by-case basis. For study participants where PTA provision plans are not adhered to for justified reasons or are simply not available, the alternative option will be to refer patients to state hospitals or clinics for CA treatment, even if an effort is made to recognise the importance of PTA provision in a study's protocol.

From the review of the existing South African PTA Guidelines (2020), it is evident that these guidelines have not implemented a comprehensive consideration of the critical medical effects of switching medical therapy and the long-term effects of eminent decline in the well-being of study participants. Additionally, the effects of a sudden influx of study participants needing medical treatment from public state facilities have not yet been taken into consideration. Most concerning is what kind of impact this could potentially have on the already overburdened

healthcare system in SA. The challenge in this regard is in linking all the pertinent PTA considerations to a responsible post-study transitioning plan that is practically sound and morally justified and protects the rights and dignity of study participants.

Upon review of the pertinent PTA considerations discussed above, additionally, we should be driven to reflect on whether to mandate clinical study sponsors to adopt a moral position and commitment to providing PTA to all clinical trial participants. Surely, the well-being of those who bear the burden of research ought to take first preference and be given the highest regard, and substantial benefits sharing should accrue to all study participants. If the well-being of study participants is not put at the forefront of a clinical study's endpoints, what effect does this have on the participants' basic human rights?

Suppose we decide to advocate for all clinical trial funders or institutions to take on the ethical responsibility to provide PTA. Should the provision of PTA be mandatory or a recommendation where possible, as is currently the case? Secondly, should we be concerned about undue inducement to join the study if participants are informed upfront of the option of CA to treatment post-study? Limited or insufficient access to healthcare is a major motivator for participants to join a clinical study (Dainesi & Goldbaum, 2011), so should special consideration be considered for participants who fall into this circumstantial vulnerability? Is it financially sustainable to provide PTA for all trial participants, and for what period can it be feasible?

These are complex ethical questions that need to be addressed with precision, and deliberate consideration needs to be implemented in addressing them. In tackling these complex questions, there are, however, many variables that are presented in the resolution pathway, including the need to address what should happen after a study ends, what the accompanying responsibilities ought to be, and, additionally, how these will be monitored and regulated.

Although reviewing the post-trial obligations of various parties at this stage may appear to be shifting from the focus of this report, that being whether there is any ethical requirement for PTA provision, the two topics are closely connected and intermingled. With this closely knit relationship in place, it becomes very difficult to discuss the moral claims of PTA independently

without reviewing, at minimum, a broad overview of the post-trial obligations of trial funders or institutions. According to the Department of Health's patient charter, "No one shall be abandoned by a health care professional worker or a health facility which initially took responsibility for one's health" (Patient Rights Charter, 1999). Under clinical trial conditions, medical care obligation starts from the time the participants sign the informed consent documentation (SA GCP Guidelines, 2020). The clinical trial researcher, clinical trial sponsor or study funder assumes full responsibility for study participants who have taken the IP. Therefore, this implies that the study care obligation to the participants is acquired from signing informed consent forms. Therefore, the continuity of care obligation becomes relevant and difficult to ignore when establishing whether or not participants have a moral claim to the PTA provision.

To develop this prima facie case for the PTA to understand better the necessity of protecting the rights of clinical trial participants and to ascertain whether there are any closely related obligations on the side of researchers, sponsors, or funders, it is useful to review the principles that clinical trial guidelines are established upon. It will be worthwhile to take a backstep and review the history that has driven the reasons why these principles have become so important, along with some of the key guiding documents founded on the principles of bioethics that have informed medical decisions. The field of bioethics originated as an extension of medical ethics; it is a field of study that was extended to review complex ethical issues not covered in the scope of medical ethics (Kuhse & Singer, 2009). Bioethics considers ethical issues such as patient's rights and interpersonal relationships that go beyond medical ethics, which mainly focuses on doctor-patient relationships only. With further advancement in the fields of medicine, biosciences, and technology, more complex ethical issues will undoubtedly arise that need to be reviewed, which in turn will necessitate a new field that would address these complex ethical issues (Kuhse & Singer, 2009).

2.3 Relevance of the Principlism Approach

Bioethics in clinical trials is not only instrumental as a framework to solve complex ethical problems and challenges. Still, it has also become the foundation for good clinical practices used in clinical research studies. Bioethics typically adopts a principlism approach, where the four main

principles of bioethics are Respect for Autonomy, Beneficence, Non-maleficence, and justice. These four principles of bioethics have become the standard methodology when resolving complex bioethical issues in order to determine the best action. The application of these principles to solve ethical dilemmas has coined the term principlism, which has been widely accepted due to its ease of use and applicability (Kuhse & Singer, 2009).

The principles of bioethics have been largely refined by Beauchamp and Childress' series of books titled *Principles of Biomedical Ethics,* now in the eighth edition (Beauchamp & Childress, 2019). International ethical guidelines for clinical studies are centred around the use of principlism in an effort to resolve ethical issues in medicine. Although Beauchamp and Childress (2019) have refined the use of principlism to govern ethical decisions in medicine, which has, in turn, informed medical practice guidelines, the use of principles of bioethics has, however, long been used as an ethical framework in the medical field.

Respect for Autonomy is underpinned by the conception of personal/decisional autonomy, which is understood in the field of bioethics as the individual's right to self-govern and make their own decisions (Kuhse & Singer, 2009). The Principle of Beneficence refers to a moral obligation to remove conditions that will cause harm, protect the rights of patients and act in their best interest (Beauchamp & Childress, 2019, p. 160). Non-maleficence refers to a moral obligation not to harm (Beauchamp & Childress, 2019, p. 116). The principle of justice refers to the fair and equitable treatment of individuals, which is of key interest in the provision of PTA (Beauchamp & Childress, 2019, p. 116). The principle of justice becomes relevant when we look at the distribution of opportunities, burdens, and resources. Particularly relevant to SA is the just distribution of medical benefits derived from efficacious medical treatment in a clinical study. In the next discussion, I will explain these principles in more detail and focus on their implication towards the conduct of ethical clinical trials before turning to how they might apply to PTA in Chapter 3.

2.3.1 The Principle of Respect for Autonomy

The Principle of Respect for Autonomy refers to the obligation to respect the autonomous choices of patients and their autonomous decisions concerning their health care. As a core principle of bioethics, the Principle of Respect for Autonomy drives the requirement for informed consent in clinical trials and medical treatment (Beauchamp and Childress 2019). Autonomy means to self-govern or self-rule. In the field of bioethics, it is understood as the authority to make one's own medical decisions or to make medical choices without any undue influence. Undue Influence, as explained by Emanuel et al. (2005), meets the criteria for undue inducement when it leads towards a decision with great risk and harm towards the one that is unduly influenced. In the next discussion, the report will consider past historical events that will highlight the importance of the Principle of Respect for Autonomy.

The Nuremberg Code is a historical clinical trial guidance document which was developed to focus attention on the fundamental rights of research participants and the responsibilities of investigators. It was an early document that captured the Principle of Respect for Autonomy by requiring participant consent. The Code was ratified following World War II in response to the abusive and exploitative clinical trials undertaken by Nazi scientists and doctors. It provides an international standard for clinical research ethics, where the ten principles established by this Code for medical practice have now been extended into general codes of medical ethics (Nuremberg Code, 1947).

Under the Nuremberg Code, informed consent was viewed as essential and assured voluntary participation of research subjects (Manson & O'Neill, 2007). The Nuremberg Code asserts that:

> *The person providing consent should have the legal capacity to give consent and must be able to exercise free will and freedom of choice without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion, and must have adequate knowledge and comprehension of the subject matter in question so as to be able to make an informed decision guided with understanding and enlightenment. This implies that the person from whom*

> *informed consent is obtained should have the legal capacity to give consent and should be in a position, both socially and economically, to exercise free consent and self-rule over their choices and medical decisions. An informed understanding and enlightenment require that before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs, or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity* (Nuremberg Code, 1947).

The 1931 Guidelines being used in Germany at the time of World War II also mentioned obtaining consent from human participants as absolutely mandatory:

> *Innovative therapy may be carried out only after the subject, or his legal representative has unambiguously consented to the procedure in light of relevant information provided in advance. Where consent is refused, innovative therapy may be initiated only if it constitutes an urgent procedure to preserve life or prevent serious damage to health. Prior consent could not be obtained under the circumstances"* (German 1931 Guidelines).

While both the Nuremberg Code and the 1931 Guidelines point out the importance of voluntary consent, the Nuremberg Code was the first detailed, authoritative statement of the consent requirements in biomedical ethics (Manson & O'Neill, 2007). The actions of the doctor's trial led to stricter requirements for informed consent, viewing informed consent as providing assurance and evidence that there has been no forced participation.

The Nuremberg Code, however, is not regularly reviewed and updated. The importance and relevance of a continuous review of existing guidelines and laws governing clinical research were

brought to the fore during the trial of the Nazi doctors who performed unethical experiments on civilians and vulnerable groups such as prisoners of war. The Nuremberg medical professionals and scientists who were trial defendants requested that their actions be judged on the basis of the 1931 Guidelines in force in Germany at the time.

The prosecutors denied the defendants' request, choosing instead to try the defendants for crimes against humanity, incorporating the Nuremberg Code in the judgement (Ghooi, 2011). The principles introduced in the Nuremberg Code incorporated ethical codes which existed in the 1931 Guidelines (Ghooi, 2011), including requiring voluntary consent, which were grossly ignored under the Nazi government even though they existed at the time of rulership.

The Nuremberg trial demonstrated that there exists a possibility to bridge the obligation to obey the law and the obligation to obey morality. We have a moral duty to obey the law, but equally, we have a moral duty to obey the demands of morality and choose between what is right and decent (Fuller, 1958). This case highlights the compelling reason why law cannot be separated from morality as well as the need to review existing guidelines and ensure they are legally binding and upheld by a force of law as a backup; however, most importantly, to enforce its compliance. There is a need also for continuous oversight and systems to be put in place that will establish the requirements of compliance. Let us take a step back and consider the following important question: How should we understand the Principle of Respect for Autonomy? Why is it linked to informed or voluntary consent? One natural way of interpreting Respect for Autonomy in the setting of clinical research would be the right to decide whether or not to participate in a clinical study without any undue external influence.

Beauchamp and Childress' *Principles of Biomedical Ethics* highlights ways in which Respect for Autonomy can be viewed and understood as a concept of respecting the autonomous choice of an individual. Their understanding of the concept of the Respect for Autonomy principle is viewed from the individual's decision-making in medical practice and research. Beauchamp and Childress focus on the decision-making that leads to autonomous choice rather than general capacities for self-governance and self-management. In the field of clinical trials, Respect of Autonomy thus

refers to a type of autonomy termed decisional autonomy. Decisional autonomy refers to an individual's ability to make informed medical choices and voluntary medical decisions.

The conditions that must be met when analysing autonomous actions and respecting decisional autonomy include informed consent. That is the ability of patients to understand the medical information shared while having made available to them all the associated risks and benefits as well as alternative options should they choose to participate (Childress, 2012). The second condition that must be met is that of voluntary consent or participation. That is freedom from any type of control or influence towards making a particular medical decision (Childress, 2012). The Respect for Autonomy in this regard thus gives rise to two obligations; namely negative and positive. Negative obligation refers to the obligation to not unduly influence a medical decision, whether from external or internal forces or influence. Positive obligation refers to the requirement to ensure that the patient's decision is adequately informed.

Informed consent requires that individuals be provided with adequate information to make an informed decision and freely choose whether to participate in the study or not. Respecting autonomy means that a potential participant needs to be provided with sufficient time to consider, consult and ask questions about the trial before being asked to choose whether to participate (SA GCP Guidelines, 2020). The Principle of Respect for Autonomy obligates one to refrain from subjecting the actions or choices of others to controlling influence, coercion, or manipulation of information. As a common practice, when one thinks of Respect for Autonomy within a clinical trial setting, one is led to expect the availability of an Informed Consent Form, which should serve as the main assurance that an autonomous decision was made. The informed consent document and the standards of seeking consent have been explicitly set out over the years as medical ethics have developed. The Informed Consent Form (ICF) seeks to protect patients by requiring their consent for all medical interventions and participation in research.

In promoting decisional autonomy, Beauchamp and Childress (2019) argued that focusing on the autonomy of a person in terms of self-governance and self-management is not sufficient to affirm Respect for Autonomy. As "autonomous persons who have self-governing capacities, and generally manage their health and well-being sometimes fail to govern themselves in particular

choices because of temporary constraints caused by illness, depression, ignorance, coercion, or other conditions that limit their judgement or their options" (Beauchamp & Childress, 2019).

Beauchamp and Childress's *Principles of Biomedical Ethics* highlights ways in which Respect for Autonomy can be viewed and understood as a concept of respecting the autonomous choice of an individual. An example is given to further clarify this, based on an autonomous person who signs a consent form for a procedure without reading or understanding the form. Such persons can act autonomously but fail to act so in this circumstance, presumably because they place their trust in the treating physician and, therefore, autonomously choose to rely on the medical expertise of the physician regarding their authorisation. Beauchamp and Childress (2019) further clarified that the act should not be seen as an autonomous authorisation of the procedure because such a person lacks material information about the procedure. Similarly, they provide a further example of some persons who are generally incapable of autonomous decision-making but who can, at times, make autonomous choices.

They cite that "patients in mental institutions who cannot care for themselves and have been declared legally incompetent may still be competent to make some autonomous choices, such as stating preferences for meals, refusing some medications, and making phone calls to acquaintances" (Beauchamp & Childress, 2019, p. 78). Beauchamp and Childress (2019) have instead presented a conditional theory account which gives a simplified account of conditions to be met in order to analyse whether a choice taken is autonomous. They state that actions should be analysed as autonomous based on persons who act (1) intentionally, (2) with understanding, and (3) without controlling influences that determine their actions (Beauchamp & Childress, 2019, p. 78). Beauchamp and Childress (2019) believed that the conditional theory account is coherent with the account of autonomy for biomedical ethics: (1) Intentionality, (2) Understanding, and (3) Non-control (Beauchamp & Childress, 2019, p. 79).

This progression to include ICFs as a means to respect autonomy, however, has not gone without a fair share of criticism and challenges. Manson and O'Neill (2007) discussed some of the informed consent limits as the extension of informed consent requirements progressed from research ethics to clinical practice. The authors highlighted the limitation of informed consent in

medical practice as problematic and unacceptable. An example of these limitations includes denying treatment to patients who cannot give informed consent because of incompetence and impaired competence as a result of illness or injury, which is more common in medical practice. Manson and O'Neill (2007) asserted that medical ethics cannot parallel research ethics and that informed consent should not be a universal or even a normal requirement.

Likewise, the presence of an Inform Consent Form cannot provide adequate assurance that a decision or choice that emanates from an individual is autonomous. This is because the ICF documents are often drafted in a language that is complex and not easy to understand for the average layman. Fischer et al. (2021) Additionally, even though translated ICFs may be made available for the study participants, often the investigators who take consent may only be able to conduct the consent process in English as that may be their proficient language. Therefore, the current practice as it stands is not an adequate practice for respecting autonomy.

Walker (2020) also found that this understanding of Respect for Autonomy as respecting the intimate connection between autonomy and decision-making in health care and research, as presented by Beauchamp and Childress (2019), is lacking. Beauchamp and Childress justify the obligation to solicit decisions from patients and potential research subjects by appealing to the Principle of Respect for Autonomy (Beauchamp & Childress, 2019). However, this understanding fails to address key questions, such as whether, at the core, we ought to respect persons or their autonomous choices.

Walker (2020) argued that many of the choices we make as autonomous persons are not themselves autonomous; therefore, when a choice is not autonomous, then it is not deserving of respect. How should physicians respond when autonomous patients make decisions that appear to be non-autonomous? Beauchamp and Childress (2019) argued that a physician could override such choices; however, Walker (2020) argued against overriding the non-autonomous decisions of autonomous persons, stating that their right to decide what is done with their bodies deserves respect. Walker (2020) highlighted these moral issues as scratching the surface of the many other unresolved or emerging issues in the Respect for Autonomy concept that have not been adequately addressed. Manson and O'Neill's (2007) critique of informed consent practices also

highlighted some of the challenges. Walker (2020) stated that this demonstrates some critical moral work left aside by the concept of the Respect of Autonomy principle.

I tend to agree with the observations brought forward by Walker (2020) and Manson and O'Neill (2007), particularly regarding what should be considered for individuals whose social status or economic circumstances do not promote or nurture independent decisions and respect for their dignity or personhood. In a resource-limited country like SA, the provision of medical therapy to trial participants certainly raises ethical issues of vulnerability and inducement. Trial participants have limited access to medical treatment; clinical trial participation is, therefore, often the only avenue to access new innovative medical therapies that participants would not otherwise have access to.

In such conditions, it therefore becomes vital that the principles of bioethics are in place to protect this vulnerable population group in ways that go beyond just an ICF. It is, therefore, not sufficient to exclusively respect the choices of trial participants who have provided their written, signed informed consent. However, further deliberation needs to go into evaluating the nature of the autonomous choice undertaken. The Principle of Respect for Autonomy in conditions involving a vulnerable population should lead towards respect for independent choices. However, equally important is that the respect for the dignity and personhood of the vulnerable must be considered and protected. We should, therefore, understand the respect of a person and their choices while also taking into consideration the different types of autonomy that exist under varying circumstances.

2.3.2 The Principles of Beneficence and Non-maleficence

The development of another influential bioethical document, the Belmont Report**,** is founded upon three ethical principles of bioethics, namely, Respect for Persons (which later became Respect for Autonomy), Beneficence, and justice. It is an ethical principles and guidelines report developed in 1978 specifically for the protection of human subjects in research (Nagai, 2022). How, then, can we understand the Principle of Beneficence, and what implication does the principle have on the protection of trial participants' rights? Probably, the best definition of the

principle lies in understanding the demands of the principle. The Principle of Beneficence puts in place a moral demand directed towards those who have taken over the right to care for trial participants to ensure that continuity of care is maintained, ensuring continued benefits for participants (Patient Rights Charter, 1999). The Principle of Beneficence demands an obligatory responsibility to protect study participants' rights, to do no harm, to remove conditions that will cause harm and to act in the best interest of clinical study participants (Kuhse & Singer, 2009). A trip down the historical archives for evidence of gross violation of the Principles of Beneficence and Non-maleficence led to the development of the Belmont Report, which was prepared as a guidance document in response to historical and unethical clinical trials that were conducted on human research participants. One such unethical study was the Tuskegee Syphilis Study, in which African American males in Alabama were not provided with available treatment for syphilis.

The majority of the trial participants were sadly only given a placebo treatment. The study started in 1932 when there was no approved treatment for syphilis, but by the year 1947, penicillin was the standard cure for the disease (Robert, 2000). The researchers did not, however, provide the available standard treatment to their study participants, choosing instead to continue in the analysis of untreated syphilis. One cannot help but link the similarity of the placebo treatment observed in this unethical study to the current ethical contention reviewed in this report. That is a question of whether there is any unethical behaviour/practice in the standard approach of switching study participants to an available treatment comparator even though it may be less effective or maybe contra-indicated to the research group.

How can we morally justify the discontinuation of an effective treatment as being different from providing a placebo treatment, as the researchers in the Tuskegee Syphilis Study did? We need to deliberate on the continuous analysis of emerging ethical challenges that arise as the landscape of clinical trials evolves, lest we find ourselves repeating the same unethical practice of past clinical trials, which, now, looking back on it, have obvious gross ethical violations. How, then, were these violations overlooked and found to be acceptable under the existing ethical codes/guidelines at the time? This brings home the importance of a need for continuous review and ratification of guidelines to ensure that they evolve to address the diverse ethical challenges

arising in the ever-changing landscape of clinical research, as already highlighted above. An in-depth ethical review goes beyond ticking boxes in an existing checklist criterion. It includes stretching beyond the obvious options to determine acceptability, relevance, situational practicality, and, more importantly, challenging wrong behaviours.

The Principle of Beneficence is closely linked to the principle of Non-maleficence. Although Beauchamp and Childress (Beauchamp & Childress, 2019) argued that the principles are each distinct and have critical moral distinctions, for the benefit of our investigation, Non-maleficence and Beneficence will be grouped. We can understand Non-maleficence as a principle that requires that medical decisions or actions be weighed against possible risks and benefits, in order to avoid risks that cause harm. Non-maleficence refers to a moral obligation not to harm (Beauchamp & Childress, 2019).

The Tuskegee Study grossly violated the principle of Non-maleficence in that the participants were not given the drug over the years during the study conducted with untreated syphilis, even though penicillin was available for treatment. This resulted in high death rates in African American men with untreated syphilis as study participants were exploited and denied life-saving medical treatment. Further developments in the protection of human subjects in research led to more ethical standards being established. The American National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research is one such example, established by the American Congress in 1974 following the Tuskegee Syphilis Study and its violations of Beneficence and Non-malevolence. The Commission was charged with identifying ethical principles that should govern biomedical and behavioural research involving human subjects (Iserson, 1999), giving rise to the Belmont Report mentioned above. I turn now to the last principle mentioned in the Belmont Report and *Principles of Biomedical Ethics*: justice.

2.3.3 The Principle of Justice

Justice in a clinical study setting can be understood as the just distribution of benefits and burdens. Beauchamp and Childress (2019) linked the principle of justice to distribution,

explaining the term *distributive justice* as the fair, equitable, and appropriate distribution of benefits and burdens**.**

The most recognised ethical guidance document that is founded on the principles of bioethics is the Declaration of Helsinki statement, which has been revised five times since its first adoption in 1964 by The World Medical Association which highlights the importance of justice. This ethical document for medical research involving human subjects emerged from the Nuremberg trials, with the original draft having firm roots in the Nuremberg Code (Carlson 2004). The most controversial revision was paragraph 30 of the Declaration of Helsinki concerning the provision of treatment to research participants.

This revision stipulates that 'At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study' (Declaration of Helsinki, 2000). There have been many debates centred around this statement with some critiques stating that the Declaration of Helsinki has shifted its roles from an ethical guidance document to a document that is interested in social justice (Howard, 2006).

I tend to disagree with this thinking pattern as the issues of justice are closely linked to ethical clinical trial conduct. Therefore, the injustice of resource sharing cannot be avoided. I also tend to agree with writers such as Brian Berry (2007), who stated that institutions have a rectification function, which he explains is a function to correct acts of past injustice. Institutions can assist with offsetting unjust distribution of resources so they should seek means whereby they can alleviate the pressing needs and burdens of those who contribute towards their success and end goals. The coined term for the distribution of goods, benefits and advantages to the study participants is benefit sharing (Dauda & Dierick, 2017).

In resource-limited settings, the fair and just distributions of benefits are of paramount importance. The reality of limited healthcare access in SA implies the referral or transition of participants to an already overburdened state hospital, which is often not adequate to ensure the CA of medical therapy. The existing ethical document, such as the SA GCP Guidelines and

Declaration of Helsinki, addresses issues of just distribution of benefits by stipulating that study participants are to be assured of beneficial therapy at the end of the study. This will be further discussed in the next chapter.

2.4 Conclusion

The existing injustices in SA are a result of historical injustices that have perpetuated financial inequality and inadequacy of the Government to meet the basic needs of access to healthcare for all its citizens. Therefore, institutions or study funders that conduct studies in SA need to be cognizant of the unique challenges that plague the citizens of the country. These resource challenges are different from those of first-world countries that do not face the similar resource limitations that SA faces. In the next chapter, I draw on the principles of justice and the other principles of principlism in reviewing whether there is an ethical claim that clinical trial participants have to access effective medicine after a clinical study. The history of injustices that have overshadowed resource-limited countries like SA cannot be ignored.

Nor can we ignore the consequences of unjust limitation of access to healthcare that individuals are faced with and how this might influence decision-making. Because of this limitation to access to health resources, clinical study participants in SA are classified as a vulnerable group. The WMA recommendation is that vulnerable groups and individuals should receive specifically considered protection. Research has shown that referral to state hospitals after study end is ineffective (Grady, 2005), with limited resources being the main contributory factor. Therefore, those who conduct clinical trials in SA ought to be cognizant of the unique challenges of limited access to healthcare. This consideration implies that the pressing need for medical access is alleviated for trial participants who have contributed to research and bear its burden (Ewuoso et al., 2022). In return, they ought to receive reciprocal justice for altruistic acts, as will be argued in the next chapter.

Chapter 3: Arguments for Post-Trial Access Provision

3.1 Introduction

Clinical trial participants are key stakeholders in further research and development of new medicine that has not been made available to the larger populations. Clinical trial participants benefit from receiving innovative or new IP, which may be proven to be more efficacious than the available standard of care. In some circumstances, IP received within a clinical trial setting may be the only treatment option available to study participants. However, one needs to be aware that not all clinical trials succeed or are beneficial. Some clinical trials are discontinued early due to a lack of adequate clinical response. So, it remains important for participants to be informed of the likelihood that the research investigation they embark on may not succeed or may provide no clinical response or evidence to demonstrate the efficacy of the investigated product. Equally, participants need to be informed of the PTA plans during the informed consent process, which allows them to make an informed decision on whether or not to participate in the study. The main focus of this chapter will be to present the claims that support the requirements for PTA in order to ascertain whether there is an ethical claim for post-trial provision of effective IP after a study ends. In the following discussions, I will present the ethical considerations in favour of the PTA provision, drawing on the ethical framework of the principles of bioethics to develop the prima facie case presented in Chapter 2, section 2.2.2. The chapter will also provide accounts of arguments in favour of the moral requirement to give access to effective medical therapy to all study participants who have demonstrated evidence of the benefits of medical therapy, not just those who were on the treatment arm of a study.

3.2 Moral Requirements for Post-Trial Access Provision

The end of a clinical study brings with it many challenges and ethical dilemmas that need to be addressed, such as the risk to health of discontinuing effective medical treatment. A treatment discontinuation or change in effective therapy poses potential harm to the health of the participant. An even weightier risk is the potential to develop drug resistance. The provision of effective medicine is essential for maintaining a derived clinical benefit, as discontinuing or

changing treatment may pose health risks to the patient. Providing PTA to medical therapy that has demonstrated clinical benefit and disease management for study participants ensures that effective disease management is managed post-study. By continuing access to effective medicine, the subject's healthcare is prioritised. That ensures that the subjects' rights and medical well-being are protected and also that the interests of the study participants are placed at the forefront. In the following discussion, we will elaborate in-depth on the link between PTA provision and ethical claims to benefit by applying the principles of bioethics.

3.3 Application of the Justice Principle

Sponsors of clinical trials often interpret the scope of responsibility for PTA provision until the IP is registered or becomes commercially available (Naidoo et al., 2021). The reality, however, is that even after a medicine is registered and has received market approval, access to the study participants is not assured. The participant may not be able to access the IP after approval due to high costs. In some cases, the cost of the registered product may never be approved by medical insurers or government-funded healthcare facilities (Naidoo et al., 2021). This means that the study participants who are able to afford treatment have to pay the costs out of their own pockets. This creates an inequality between participants who have medical insurance and those participants who cover their costs (Neema, 2001). Therefore, the contribution of study participants who have sacrificed their time and braved the potential risks during the clinical research treatment phase becomes insignificant as they are not able to enjoy accrued benefits for contributing towards the research investigation.

Because of the cost barrier, study participants who derived medical therapy benefits from IPs found themselves with limited or no access to healthcare after the study ended (Naidoo et al., 2021). This amounts to an unfair distribution of benefits and unfulfilled ethical requirements. We can understand benefits as a concept of benefit being given in return for clinical participation (Dauda et al., 2016). Within the clinical research setting, the concept of benefit translates to the equitable allocation of benefits derived from research, such as IP, which is proven safe and effective. Alternatively, the accumulated knowledge is acquired via investigative research. This benefit acquired through clinical research studies is desirable as it counterbalances power

differences that may exist between researchers and those who fund research (Ewuoso et al., 2022). However, in order of priority, the provision of IP after the study ends remains the most desirable benefit in resource-limited countries where access to healthcare is limited.

In other cases, the sponsors may choose not to register the IP in the host country in which the clinical trial is conducted, thus putting an additional burden on trial participants to access the IP outside of the clinical trial settings. This is because access to the IP will require an import licence from the Department of Health, and that application places a financial and administrative burden on the study participants. CA to IP that is not intended to be registered in the host country from which the clinical trial is conducted represents a pressing need for study participants who derive therapeutic benefits during the study conduct. This pressing need must be addressed by the researchers or those who fund the clinical trial so that participants do not bear the burden of securing means to access effective therapy independently (Ewuoso et al., 2022). IP provided to study participants is a benefit derived as a result of study participation. Therefore, the allocation of this benefit must be equitable and accessible to those who have contributed to the investigative study. Benefit sharing as a concept can be understood as sharing benefits with the participants who have participated in clinical research trials (Dauda et al., 2016). Ewuoso et al. (2022) view this act as a reciprocal act which shows humanity towards the study participants and is compliant with the equitable allocation of burdens (Ewuoso et al., 2022). This also agrees with the Declaration of Helsinki guidance document, which states that the benefits that result from research study need to be equally distributed to trial participants (Declaration of Helsinki, 2000).

The provision of PTA ensures that we avert the misuse of study participants only as a means to advance science, viewing their usefulness only as subjects from which to gather clinical data during a clinical trial. Using study participants merely as a means to gather data to test for the safety and efficacy of an IP is thus morally impermissible. With the provision of PTA and advocating for its provision as a requirement rather than a recommendation where possible, we are able to avert the exploitation of study participants, protect their rights and well-being and also further the ends of justice by ensuring that those who have volunteered realise a long-term benefit for their participation in a study (Sica, 2002). Similarly, the ethical obligation to provide

PTA cannot be considered using a universal cause of action across all circumstances. We cannot be ignorant of the complex requirements of justice in a resource-limited country like SA and of the barriers to the distribution of benefits in clinical trials.

3.4 Applying the Non-maleficence and Beneficence Principles

The end of a clinical study brings with it many challenges and ethical dilemmas that need to be addressed, such as the health risk of discontinuing effective medical treatment. Discontinuing effective treatment or change in effective therapy poses potential harm to the health of the participant, and even riskier is the potential to develop drug resistance. The principle of Non-maleficence has a direct influence on PTA. Discontinuing medication that has been demonstrated to be effective to a study participant can be harmful to study participants and may put their health at risk and, therefore it does not adhere to the moral requirement not to harm others.

The provision of effective medicine is essential for maintaining a derived clinical benefit, as discontinuing or changing treatment may pose health risks to the patient. Providing PTA to medical therapy that has demonstrated clinical benefit and disease management for study participants ensures that effective disease management is managed post-study. By providing continuing access to effective medicine, the subject's healthcare is prioritised. It ensures that the subjects' rights and medical well-being are protected and also that the interest of the study participants is placed at the forefront. In the following chapter, we will discuss in-depth the link between the PTA provision and the ethical claim to benefit study participants and remove conditions that inflict harm.

Discontinuing study medication that has been demonstrated to be effective to a study participant can be harmful to study participants; it may put their health at risk and, therefore, does not adhere to the moral requirement not to harm others. Even though this moral claim is valid, it is also important to consider some of the ethical issues encountered during the conduct of a clinical trial, such as the decision to terminate a clinical trial early due to inadequate efficacy results, intolerable adverse drug reactions or serious adverse reaction, or having to end a study early because the study objectives are met earlier than anticipated. This does not, however, negate

the responsibility of those conducting the clinical trial to create a transition plan for participants to best return to their pre-trial treatment regimen (Sica, 2019). Another ethical concern involves clinical investigators who are paid for their obligations for safety monitoring only until the completion of the study. In such cases there is less interest and commitment from investigators after the study ends as they are not paid for any related monitoring incidentals (Cho 2018). This raises the question of when the safety monitoring and responsibilities can be concluded. The Principle of Beneficence underpins the ethical claim that must be protected for clinical study participants to ensure CA to beneficial medical therapy post-study.

3.5 Applying the Principle of Respect for Autonomy

The Principle of Respect for Autonomy in clinical trials has been largely centred around the requirement for an ICF as a means to ensure that the rights of the trial participant are protected. However, the Principle of Respect for Autonomy also requires that we respect the personhood of people participating in clinical trials. Furthermore, therein lies a responsibility to protect participants' dignity and ensure that the vulnerable condition of limited access to health, which may influence their decision to participate in a clinical trial, is protected. The requirement for ICF in a clinical trial ensures that voluntary consent is obtained.

The requirement for a detailed informed consent process emphasises ensuring a full understanding of all the study requirements, risks and benefits, as well as shared responsibilities. In accordance with the South African Health Products Regulatory Authority (SAHPRA) Guidelines (2020) for Post-Trial Access or Continued Access, 'the possibility of PTA or CA should be disclosed to and discussed with potential participants during the initial informed consent process or via a separate consent process' (Post-Trial Access or Continued Access Guidelines, 2020). That would require that the PTA plans be included in the ICF and shared with participants during the informed consent process. The implication is that the PTA provision would be part of the information on which a participant bases their decision to participate. Where CA is withdrawn, even for justified reasons, this means that the basis on which someone has made a decision then changes. In resource-limited conditions where there is limited access to healthcare, participation in the study is largely influenced by access to medical treatment with the assurance of CA after the study has

ended. This amounts to a vulnerability and classification of these types of trial participants into a vulnerable population group, as the decision to participate in a clinical trial is influenced by the option of accessibility to healthcare and continuous monitoring. Autonomy in such circumstances is quite complicated because PTA could also be viewed as a form of undue inducement. This concern, however, is misguided and should not constitute any concern for clinical trials that are conducted ethically; I will tackle this in detail in Chapter 4.

The Principle of Respect for Autonomy for vulnerable populations should extend to consideration for their personhood and protecting their basic human needs to access effective medical therapy. There raises a salient moral requirement to help ease the burdens and share the rewards of benefits derived from clinical trials with those who contribute towards the investigative process, which, at a minimum, is a demonstrative act of humanness and friendliness.

This salient moral requirement is possibly sparked by the shared regard and esteem for human life and humanity that is common among human beings who have pure moral values. Showing indifference to the serious needs of vulnerable people who contribute to research would constitute a failure to exhibit friendliness with disregard for the personhood of the trial participants (Ewuoso et al., 2022). Choosing not to respect the dignity and personhood of the vulnerable points towards exploitation and a lack of sensitivity towards those who bear the risk and burden of the investigative process of clinical research studies.

3.6 Switching to Available Standard of Care

A trial should not be approved and receive favourable approval simply because the study arms both contain active treatment, meaning that there is no placebo. However, there also needs to be a review of the comparator/standard of care arm. Regulators such as the SAHPRA and independent local Ethics Committees also need to review the suitability, availability, and current relevance and effectiveness of the available standard of care during treatment. For example, according to the National Department of Health Guidelines for Sexually Transmitted Infections (2018), penicillin remains the first line of treatment for syphilis. The guidelines, however, recognise the resource limitations in SA, such as the effect of the global shortage of penicillin,

the increasing antibiotic resistance rates in SA and circumstantial contra-indications, and therefore recommend doxycycline as a second-line treatment. This highlights some of the limitations and challenges that participants will need to deal with when PTA is not prioritised. What will be the recourse when there is no available effective comparator or when the available standard of care is no longer effective at disease management?

Justifying that participants will be switched to the available standard of care after the study should not be ticked off as an acceptable post-study treatment plan or option. The available standard of care needs to be assessed, so there needs to be a review of switching participants from a demonstrated efficacious investigational treatment of syphilis not only to a first but to a second-line comparator as well, which may further compromise the health of participants and increase the risks of participants receiving less effective treatment therapy.

Regulators of clinical studies should not approve or accept study designs involving placebo or less effective comparators when there is demonstrated effective treatment, even though it might be registered in other countries. Study participants should be prioritised and given the best available treatment as an act of reciprocity, humanness, and kindness in response to the sacrifice and study burden that a study demands from participants.

The South African GCP Guidelines on PTA require a minimum of four years after completion as the acceptable period to provide PTA to participants who derived benefits from IP (Post-Trial Access or CA Guidelines, 2020). However, while PTA provision guidelines exist, PTA provision is merely stipulated as a recommendation where possible, thus making provision for a waiver from PTA where it is deemed not to be feasible. Some study sponsors have taken a higher moral stand and are determined to make access provisions for IP to be approved or on the market, which can take several years.

At the same time, other sponsors may suggest extending access beyond market approval until the registered IP is commercially available to all study participants (Sanofi, 2019). This variation in PTA duration and availability is a clear indicator of quite flexible guidelines, with loopholes for when the guidelines cannot be fully adhered to. The availability of PTA guidelines as a

recommendation rather than as a clear mandatory requirement opens options for non-compliance and self-determination of what constitutes fulfilment of a pivotal moral requirement.

3.7 Conclusion

Although there are available PTA guidelines in SA, study regulators such as the South African Health Products Regulatory Authority (SHAPRA) and Ethics Committees need to deliberate on the relevance and practicality of these guidelines against the backdrop of increasing resource limitation in our country. This includes an oversight approach for adherence and compliance to the proposed PTA recommendations. Post-trial access provision is an essential component to ensure that participants are not exploited and that their safety and well-being are considered beyond their usefulness during data collection for the registration of a product. The accompanied responsibilities of PTA include arranging the transition to other forms of clinical care, thus ensuring the existence of appropriate follow-up, and arranging social support services to ensure a smooth transition to arranged clinical care (Ngwenya et al., 2022).

The provision of PTA meets the ethical obligation prescribed by Kant to ensure that human beings are never treated as a means to an end but as ends in themselves. When researchers and sponsors do not provide PTA, they fail in their ethical responsibility to ensure that participants receive uninterrupted effective healthcare treatment and, therefore, do not act in the best interest of the patients (Neema, 2001). Study participants who have demonstrated gaining clinical benefit from IP benefit from receiving treatment for their disease and having managed medical health and well-being. This equilibrium should not be compromised as it denies subjects' healthcare rights and respect for their personhood.

Chapter 4: Challenges and Solutions to Post-Trial Access Provision

4.1 Introduction

Thus far, this report has argued that there is an ethical claim to PTA provision in resource-limited countries like SA. Based on the principles of bioethics, this moral claim has been substantiated and has proven to be an essential requirement rather than a recommendation where possible. Nevertheless, even if there are important considerations in favour of PTA, they might be defeated by other considerations or objections. This chapter is aimed at providing an in-depth review of the barriers that surround PTA. The report will also review some of the objections that have been argued against the PTA provision with a focus on recommending customised responses that may provide solutions to these challenges. The central argument will be centred around the view that PTA is not defeasible. Therefore, we have a moral requirement to make PTA provision mandatory and legally binding.

4.2 Objections to Post-Trial Access Provision

In analysing and understanding the nature of the ethical dilemmas surrounding PTA provision, the aim is to provide a probable solution towards the right cause of action while addressing fundamental philosophical questions that impact all stakeholders that are involved in clinical trials. The decision to provide PTA presents various ethical considerations. Therefore, realising that the requirement for continued treatment access to clinical trial participants after a study has ended is often accompanied by diverse ethical considerations and barriers. Here, I will consider three such objections: that mandating PTA can deter research in a country, that PTA can be a form of undue inducement, and that PTA can cause inequalities between participants and non-participants.

4.2.1 The Deterrent of Cost

The requirement for mandatory PTA for beneficial treatment is desirable. However, it may inevitably become a hindrance for sponsors to perform clinical trials in a country where PTA is required. This additional trial access obligation may be viewed as an additional cost to performing

clinical trials and a barrier to performing clinical trials in countries where it is mandated (Brody, 2002). PTA provision raises controversy around who should assume the responsibility of care after a study has ended and how long the duration of the obligation of care should be. Because of this uncertainty, it becomes difficult to calculate the cost to company expense that PTA provision incurs. For companies not willing to incur the additional expense of PTA provisional costs, CA requirements become a major deterrent to performing clinical research in a host country where PTA provision is mandated. Another objection that has been raised regarding PTA is its limited focus on Post-Trial Care, which focuses on IP access only and omits other equally important aspects of the care of participants that go beyond the drug trials (Rosario et al., 2016). Additional care should be provided through study conduct, which includes the healthcare investigator-patient relationship and access to medical treatment and monitoring. Investigators involved in clinical studies are paid for their time during the conduct of the study for managing and providing safety oversight of patients from the time they sign informed consent until the study ends (Rosario et al., 2016).

After the study ends, because there is no longer reimbursement for the investigators for additional care, the investigators reduce the amount of oversight monitoring and care to none or the bare minimum. Another objection is that the burden costs do not appear sensible to companies that operate for profit whose main responsibility to shareholders is to maximise profits.

4.2.2 Undue Inducement

Another objection that has been raised is that PTA may be seen as coercion to join a clinical study, particularly in circumstances of limited access or when no therapies are available. Furthermore, in the case of clinical trials in resource-poor settings where many patients would not otherwise have access to treatment, the provision of PTA may raise ethical issues of vulnerability, inducement, and coercion. Because of the limited access to healthcare, clinical trial participation offers an alternative option to access new or innovative therapies that might not otherwise be available. This influence on participation prioritises ethical concerns over inducement for study

participation, as well as the compromised voluntariness that is necessary for informed consent (Emanuel et al., 2005). This socio-economic limiting condition is unique to SA. Because of limited access to healthcare, the participants fall under vulnerable patient groups or populations as they are individuals who can be persuaded to join a study simply because it is the only option they have to access medical treatment.

4.2.3 Inequalities Between Participants and Non-participants

Some authors have argued that providing PTA to former study participants increases inequalities between them and those who did not or could not participate. Thus, it has the potential to increase tensions within the larger population or community (Neema, 2001). Against the backdrop of the noticeable differences in SA between the haves and the have-nots, this further exacerbates the socio-economic inequalities that exist. Access to information on ongoing clinical trials is easily accessed by those who have information during the recruiting phase of the study.

4.3 Solutions for Ensuring Post-Trial Access Provision

In view of the objections to the PTA provision, this report will respond to these objections by arguing that the financial cost to PTA should be a collaboration and cost evenly distributed between the major stakeholders, meaning the government of the country from which research is conducted and the clinical research funder or researcher responsible for conducting the study. The possibility of undue inducement in clinical trials that are ethically designed, reviewed, and approved by an independent Ethics Committee is close to impossible. Undue inducement requires substantial risk of serious harm, which threatens fundamental human rights which are protected by laws governing clinical regulations. The diversity of available delivery of programmes PTA that offer access to IP beyond clinical trial participants, including other diseased patients, prevents PTA programmes from being exclusionary.

4.3.1 Responding to Worries About Cost

Some researchers have attempted to address the need for CA to be effective medicine through the approach known as a ‘reasonable’ availability requirement (Grady, 2005). The requirement

stipulates that medicines should be made reasonably available. This requirement is limited to medicines that were demonstrated to be effective from data gathered from clinical trials; the efficacious medicine needs to be available at a reasonable cost to the participants and the host country. Although this approach seemingly addresses the challenges of exploitation of the study participants and the host countries, it does not adequately address the barrier to CA. A reasonable cost to a participant who has been receiving the medicine during the conduct of the study at zero cost is not a particularly clear-cut option. During the recruitment phase of the study, the financial affordability of the participants is not assessed to ensure that post-trial, they will be able to afford the medicine offered at a reasonable cost. The term 'reasonable' also seems to be very illusive and general. What seems reasonable to one individual differs vastly from each circumstance. To one individual it may be the difference between disposable cash for buying food for a family or buying medicine. To the next individual, it may be disposable cash to afford a family holiday. Even if reasonable financial affordability were to be assessed or form part of the inclusion criteria into a study, there is no assurance that the financial state of the trial participant will remain fluid enough to afford to buy the medicine after the study has ended.

Another challenge to the reasonable availability requirement affects medical health insurers. Even though the medicine may be approved and made reasonably affordable, the medical aid may still not cover the full cost of the medicine. The reasonable cost might not be the best solution to overcome the cost barrier to PTA because of the socio-economic restrictions that burden countries with a clear divide between the rich and poor. It does, however, channel us to find another customised solution that will be sensitive to the existing socio-economic restrictions in resource-limited countries. Taking into consideration the financial limitation and constraint in resource-limited SA, it is necessary, therefore, that the bare minimum of Post-Trial Care be provided to trial participants. The result of this limitation will be a requirement to limit access to IP only. Even though the participants are also provided with safety monitoring and access to medical procedures and treatment during study conduct, the order of priority necessitates that access be limited to the provision of IP only. The provision of PTA after the study ends empowers the investigators to continue to act in the best interests of their patients and continue managing and treating diseases recorded in their medical history (Naidoo et al., 2021), albeit with fewer

monitoring requirements. This ensures that the cost of Post-Trial Care is kept to the bare minimum, however, not compromising on the healthcare of the participant. It helps to maintain investigator-patient trust and confidence in the medical care relationship established through the conduct of the study (Naidoo et al., 2021) because of the established relationship of care established during the trial conduct and the investigator's ethic of the Hippocratic oath that binds doctors. The concern about the lack of interest in the medical care of participants will not cease when the reimbursement for continuous monitoring is ceased.

Although the limitation of PTA costs, which are stated as not being sensible to companies that operate for profit, is understandable, equally as important is the supererogatory act to provide PTA. It is unethical for a company to be focused only on profits simply and to terminate clinical trial responsibility post-study prematurely. The provision of PTA requires a combined effort from all the stakeholders, including the government of the host country. A collaborative effort between all stakeholders rather than transferring all responsibility of care to one party will ensure the feasibility and success of PTA plans. An example of this could be the host country government providing tax incentives to those companies conducting clinical trials within the country or partially funding PTA provision. This potentially offers a middle road that might cancel out a deterrent of cost for conducting research in a PTA-mandated country. Moreover, it is sensitive to the existing socio-economic conditions existing in the country. Hence, so as not to add additional burden to trial participants or solely transfer the responsibility of post-care to those conducting the research.

4.3.2 Responding to the Possibility of Undue Inducement

Often, when the concern of the threat of undue inducement in objections against providing PTA is brought up as a risk of coercion. However, undue inducement may be confused with inducement. Inducement aims to change people’s behaviour; this is a phenomenon that all individuals come across daily, irrespective of participation in a clinical study. Advertisements that are broadcast on television, billboards or radio are all mediums of inducement that we come across daily, and they raise no ethical concerns about violating autonomy or voluntariness (Emanuel et al., 2005). Undue inducement, on the other hand, is coercion towards a change in

an individual's behaviour that leads to a decision that one would not normally take in ordinary circumstances. This leads to substantial risks or harm that compromise patients' well-being (Emanuel et al., 2005). The necessary elements for undue inducement include the following requirements, which need to be available to warrant undue inducement:

(1) an offered good: Individuals are offered something valuable or desirable to encourage them to do something.
(2) excessive offer—when the offered good is so large or in excess that it is irresistible.
(3) poor judgement—the offer leads individuals to exercise poor judgement regarding an important decision.
(4) risk of serious harm—the individual's poor judgement leads to a high probability that they will experience harm that seriously contravenes their interests. As related specifically to clinical research (Emanuel et al., 2005).

Compliance with SA GCP Guidelines is mandated by the National Health Act, Act No. 61 of 2003; Medicines and Related Substances Act, Act No. 101 of 1965, as well as the national research ethics guidelines (SA GCP Guidelines, 2020).

Regulatory bodies such as the SAHPRA and independent local Ethics Committees are instituted and managed for regulatory approval of study trials to protect the rights of study participants and safeguard against gross risks and harm so that unethical trials are not conducted or approved. Therefore, undue inducement is not an acceptable option in environments wherein clinical trials are regulated to ensure that they fulfil the basic ethical requirements of clinical trial conduct.

4.3.3 Responding to Increasing Inequalities

To address the objection to the inequality of access to medical treatment availability for those who participate in clinical trials, I will demonstrate how pharma companies, who are the major funders of clinical trials, have responded to such objections. They have responded by diversifying the delivery of programmes of PTA in an attempt to avoid PTA programmes being a platform that promotes inequality and exclusion (Neema, 2001).

These include delivery programmes such as compassionate use platforms, where the pharma companies make provision for participants who do not or cannot participate in clinical trials. Efforts of developing support to provide expanded access outside a clinical trial are expanded to those patients diagnosed with serious or life-threatening diseases or conditions (Pfizer Policy,2023). The burden of responsibility lies with applicants to prove that patients have exhausted the approved treatment options available locally and where there is no availability of clinical trials or where they are currently not eligible for clinical trials (Pfizer Policy,2023).

Unlike regular PTA programmes, the compassionate use platform requirements are less flexible and more stringent. All the following requirements must be met (FDA Expanded Access, 2022): 1) Patient has a serious or immediately life-threatening disease or condition. 2) There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition. 3) Patient enrolment in a clinical trial is not possible. 4) Potential patient benefit justifies the potential risks of treatment. 5) Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication (Pfizer Policy,2023).

The provision of PTA to efficacious medicine provides a distribution platform when resources are limited. It also aids in increasing the choices available for patients, particularly in circumstances of limited access.

4.4 Conclusion

Indeed, there are substantial objections raised against the PTA provision. However, these have been addressed through customised solutions that take into consideration the socio-economic constraints in resource-limited countries. Although reasonable availability or provision of fair benefits could prevent general exploitation in research, PTA provision in SA is necessary to prevent the exploitation of participants who fall into vulnerable population groups who are victims of the socio-economic conditions that plague the country. Therefore, the requirement for PTA provision remains.

Chapter 5: Conclusion and Recommendations

5.1 Conclusion

Chapter 1 of this research report provided an introductory overview of the emerging post-study challenges faced by clinical trial participants who derived benefits from investigational medicinal products. Chapter 2 reviewed some of the principles that govern ethical clinical trials. However, in order to provide a comprehensive moral justification and moral claim, the direction of the report took a step back in history to examine some of the historical cases in bioethics that paved the way towards current trial conduct and key clinical guideline documents.

These cases have a direct link to key developments in bioethics, which gives rise to four principles of bioethics: Respect for Autonomy, Beneficence, Non-maleficence and justice. Using the principles of bioethics. Chapter 3 analysed in theory what the implications are for PTA and provided detailed mandates for CA for effective medical therapy. Chapter 4 reviewed the challenges and probable solutions to PTA provision, which are customised for limited-resource countries like SA.

The continuing debates about PTA requirements and the ethical claim around its provision are a clear indicator of the gap in knowledge and lack of guidelines that are customised to fit the socio-economic conditions of resource-limited countries and are centred on protecting the moral requirement of PTA. There is still a gap in knowledge and available literature coverage regarding the socio-economic limitations of access to health after clinical trials in resource-limited countries. Furthermore, knowledge of what the PTA provision mandates are under such limiting conditions and what the ethical requirement of the PTA provision should be to provide effective medicine after a study ends can be accomplished. In this in-depth review of the mandates for PTA provision, we were able to draw attention to the importance of having PTA guidelines that are regulated and monitored closely for compliance, as opposed to merely making a recommendation where possible.

We recognise, however, that more studies are needed to provide a framework on how PTA plans should be implemented and monitored for adherence and compliance. However, we have been

able, through this in-depth review of the mandates of PTA provision, to demonstrate that when PTA is not mandated, there is an emergent risk that participants will be exploited and continue to face the risks and burdens of research participation while the benefits accrue to others.

There is a moral requirement to reciprocate the sacrifice and burden taken by trial participants during the clinical study conduct (testing of the Investigational Product) through CA of IP in which they derived clinical benefit. PTA is morally justified as a medium to protect the rights of altruistic study participants who take on the burden of clinical studies in order to advance medicine and science. Furthermore, PTA safeguards the medical well-being of participants who would otherwise not have access to effective medical therapy outside of the clinical trial setting. This paper has also highlighted the practical actions taken or to be taken by sponsors of clinical trials in order to address the ethical considerations after the studies end. Furthermore, it also recommended solutions that are available to ensure continuing access to effective therapies post-trial.

5.2 Recommendations

The internationally accepted guideline, the Declaration of Helsinki (2000), stipulates that CA to beneficial medical therapy must be provided post-study for participants that are to be transferred to the available comparable local standard care of therapy. This recommendation has been questioned concerning its practicality, especially in resource-limited countries like SA. Nevertheless, the ethical questions that were debated concerning this statement do not eliminate the moral requirement for PTA provision when a study ends. The in-depth review of the mandates for PTA has provided substantial persuasion on the moral requirement for PTA provision after a study ends. The clinical trial researchers of the sponsor should continue to provide access to the IP to all of the trial participants who have derived medical benefits. This CA should not be restricted to a time frame of when the IP is commercially available. As we discussed in earlier chapters, in resource-limited settings, this does not translate to immediate availability and access. Instead, the PTA access to beneficial medical therapy must continue until the IP is commercially available and accessible even to the study participants who are switched back to state facilities. There must be a mandatory requirement to provide PTA, and it should not be

included as a recommendation where possible, as is currently the case. A consequence of this position is that PTA plans need to be detailed in terms of how they will be implemented, and regulatory bodies such as SAHPRA and Ethics Committees need to monitor the implementation thereof so that it moves from a theoretical perspective to one that is backed by the force of law. Studies are still needed to inquire how this recommendation can work in practice and inform regulatory and legal frameworks. This important recommendation on the necessity of regulation of PTA plans by law is influenced by its relatedness to fundamental human rights, which are protected by law. The recommendation for ensuring PTA success should be a combined effort from multiple stakeholders, including local government, including collaborative partnerships with clinical trial researchers or funders.

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