Title: AN ETHICAL ANALYSIS OF POST CLINICAL TRIAL ACCESS IN SOUTH AFRICA

Research Report

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Abstract

Clinical trials began in the 1940's and have evolved over the last 80 years with rigorous global regulations to support ethical trial conduct and participant safety. However there still exists a 'grey area' for what are appropriate and fair post-clinical trial access conditions. The ongoing ethical debate around post-trial access is common in developing countries especially as participants transition back to inferior medication following a clinical trial. Furthermore, there are fast-paced changes in clinical research such as the introduction of more innovative technologies and modernized protocols which have a knock-on effect for fair and equitable post-trial access conditions.

Even though global regulations like ICH-GCP and the Declaration of Helsinki 2024 give clear directives that access to clinical trial medication should be available to participants for as long as clinically benefiting, country regulations can differ with the interpretation and implementation of this clause.

In South Africa, the SAHPRA Guideline (South African Health Product Regulatory Authority) Continued access/Post-trial access (CA/PTA), version 4.0, 2022 is the cornerstone to define adequate post clinical trial access medication conditions. Hence it is vital that these guidelines[1] include the context of the South African participant's healthcare vulnerabilities to establish a fair framework.

For this research report, I have evaluated the relevant literature around post-trial access by assessing both the benefits and challenges in provisioning of research medication

[1] There are other guidelines in South African that impact the principles and decision making of post-trial access such as NDOH in Research 2024 and SA GCP 2020. However, the SAHPRA guidance, Version 4.0 is the specific focus in the context of this research.

once a trial is completed. Thereafter, I delve into the precise limitations with the current SAHPRA Guideline in the healthcare context (public and private) of the South African patient by focusing on three core premises. This is specifically for 1) ‘Standard of care’ as an alternative form of effective medication after a trial is completed, 2) The ‘minimum four-year access’ period to trial medication that is permitted by SAHPRA, 3) Advanced medicines technology, and innovative research designs and the post-trial consequences for trial participants. Each viewpoint and critical analysis are supported by examples and ethical theories to show the injustices that can occur for trial participants. At the end of each argument, I propose an alternative to how post-trial access guidance can be revised to have a more inclusive approach for the South African patient healthcare context.

Contents

List of Acronyms

Abbreviation	Full descriptive name
CA	Continued Access
CIOMS	Council for International Organizations of Medical Sciences
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Access and Quality Index
ICH	International Council of Harmonization
NHI	National Health Insurance
NIH	National Institute of Health
PTA	Post-Trial Access
RA	Rheumatoid Arthritis
SAHPRA	South African Health Products Regulatory Authority
SoC	Standard of Care
WMA	World Medical Association
WHO	World Health Organization

Chapter 1 Introduction

1.1. Background and Context

To continue the advancement of novel, life-saving medications, it is essential to have clinical trial participation by patients afflicted with the researched disease conditions (Novitzke, 2008, pp 31). In due course, their voluntary participation will pave the way ahead to enable more efficacious medication options to other affected patients in the 'real-world' who were not part of the stringent clinical trial testing phase.

Moreover, there are immediate benefits for those patients deciding to participate in a clinical trial. The continued research and development of clinical trials offers them an earlier prospect of disease alleviation with a superior/more effective medication. This is notably valid where there may have been either no or marginal opportunity for them to access other similar treatments or where existing treatment modalities are no longer effective for their medical condition (Doval et al, 2015 pp. 82-83). Therefore, it is as important to recognize that clinical trials may represent the advantage for a higher standard of healthcare and medicine that might not be routinely available for certain patients depending on their healthcare opportunities or economic status (Cho et al, 2018, pp 509-510).

As of 2024, there are an estimated 496 ,616 clinical trials conducted in over 222 countries (Clinicaltrials.gov, 2024). Although the African continent bears 25% of the global disease burden, there are only approximately 3% or 14 ,989 of clinical trials conducted in Africa and of these, just under 1% or 3,522 are ongoing in South Africa. (Hwenda et al, 2018, pp 1088). Despite the present low inclusion of Africa compared to other continents, it is

anticipated that clinical trials will continue to grow and advance in Africa owing to the rich diversity of the population, epidemiology of certain conditions, and the untreated disease burden opportunity for new research. Well recognized regulatory governance bodies like the U.S based FDA (Food and Drug Administration) are imposing stricter requirements to ensure diverse participant enrolment targets are fulfilled in clinical trials to ensure an adequately represented patient demographic (FDA Guidance Documents, 2020).

While the aspect of improving inclusion and diversity in clinical trials is under scrutiny by regulatory bodies, the long-known challenge of vulnerability in clinical trials, is still a topic for concern. This is especially for patients from developing countries. This vulnerability may be attributed to situations where their decision to participate is primarily due to a lack of access to medication, resources and dire economic circumstances (Bracken-Roche et al, 2017, pp 2,8-9). Hence even though diversity targets are being achieved to grow an inclusive participant representation, the vulnerability drivers for why they choose to participate should not be overlooked. The above point notwithstanding, once a country is selected to participate and the trial has received the necessary regulatory and ethical approvals in the country, the trial operations tend to move at a quick pace to ensure country enrolment targets are fulfilled. The patient will receive an informed consent form as a legal document to communicate trial information, risks and benefits and the agreement thereof. The treating physician will assess if they have met the required inclusion criteria and from this point onwards, it is essential that they adhere to the visit assessments outlined in the trial protocol for a fixed duration of time. The length of trial participation could range on average between 1 to 5 years or longer as deemed appropriate for the disease parameters being researched in a phase II or III or IV trial (El-

Hagrassy et al, 2018 pp 15). Ensuring strict protocol adherence by participants over this time will in turn augment the generation of accurate and statistically acceptable efficacy data to register new medical treatments (Kandi, Vadaketath, 2023, pp 6,8).

Reflecting on the earlier statement that although being included in a clinical trial represents an opportunity for early access to novel medication, these patients could be challenged with having continued/long term treatment with these innovative medical interventions in the aftermath of trial completion if commercial registration and availability in the country is absent (Usharani et al, 2016 pp 58-59). This ethical dilemma is especially true of countries, where there are disparate access conditions for trial participants who reintegrate back into existing health care systems. Specifically in a developing country such as South Africa with dual healthcare systems, the quality of the healthcare received at the end of a clinical trial can have significant differences for each participant based on their geographic location, the private or public infrastructure and medication options, and their economic status (Cook, 2015 pp 70, 78).Notwithstanding, the benefits of a clinical trial for those in need of effective medical treatments, the topic of post-trial access typically does not receive the necessary interrogation during trial start-up, to ensure comparable and continuous medical treatment plans for a patient once the trial has ended. In the case that clinical trials confer the advantages described above and offer great promise, at the time of trial inclusion, patients and clinical trialists may focus on alleviating immediate healthcare needs instead of deliberating the post-trial access options.

Owing to unequal access to medicines in many developing countries, it is crucial for clinical trial stakeholders including sponsors, government and regulatory bodies to

carefully plan and ensure continued appropriate access to the researched treatment after the trial ends.

Although the International Council for the Harmonization of Good Clinical Practice (ICH GCP) and the Declaration of Helsinki 2024 govern a global manifesto for the ethical conduct of clinical trials which includes post-trial access directives for sponsors and researchers (WMA, 2018), the country specific regulatory requirements are a strong influencer for the eventual post-trial access decision implemented. To further clarify: a participating clinical trial country may well enforce their own post-trial directives influenced by their healthcare dynamics and regulatory decisions. Hence despite the available guidance to support appropriate post-trial measures, the provisioning of the researched treatment in a post-trial setting can often be a complex situation, and more especially in developing countries with less robust or even divergent healthcare systems within a country (Cook et al, 2015 p 71).

In South Africa, SAHPRA (South African Health Products Regulatory Authority) is an entity of the National Department of Health and was established as a regulatory governance structure to uphold human and animal health welfare by making scientifically based regulatory decisions. The scope of SAHPRA extends to regulating the submissions and approvals of all health products investigated in South African clinical trials (SAHPRA About Us, 2022). Thus, SAHPRA as the government authority in the country is responsible for facilitating and effecting the necessary control on clinical trial requirements including post-trial guidance. The first South African Version 1.0 post-trial guidance was issued only in 2016 although clinical trials had commenced decades prior in the country (Wemos, 2017, pp4). The objective of the first post-trial guidance, was intended to have

a ‘social value’ and support individual participant access to beneficial post-trial medication. Following the initial publication, the guideline evolved over the next 7 years from 2016 to 2019 to the most recent 2022 version. The latest revisions include specific wording related to a participant’s access to medication is valid in the absence of ‘registered and marketed standard of care’ and furthermore that a minimum period of 4 years for posttrial provisioning is acceptable (https://www.sahpra.org.za/document/2-42-post-clinical-trial-access/, 2024). Whilst the initial attempt PTA Guideline aimed to address the gap of inequalities and provision fair access to beneficial medication, the revised guideline dated 3 August 2022, inserted specific clauses and wording as stated above, that require further ethical analysis to assess if the best interest of the trial participant can still be achieved through this guidance. It is for this reason, that the SAHPRA Post Trial Clinical Access Guideline Version 4.0, August 2022 will be the focus of critical analysis in my research objectives. Furthermore, this research is imperative for a developing country such as South Africa with polarized healthcare access conditions highlighted by stark differences between public and private health care treatment options.

According to the SAHPRA Guideline dated August Version 4.0 excerpt, “Post-trial access/Continued Access should be considered for Phase III studies when **no registered and marketed** standard of care is available in South Africa, provided that data from interim or final analyses shows that post-trial access / continued access is clinically justifiable in light of the study’s parameters and endpoints. **A minimum of 4 (four) years** after completion of the study is recommended as the acceptable period to provide PTA/ Continued access to the participants who derived benefit from the investigational product, unless there are compelling reasons for determining otherwise” (SAHPRA, 2022).

Consequently, following clinical trial completion, patients are reintegrated into the healthcare system they were originally a part of. Depending on their classification of healthcare (public or private sector), the type of medication accessible or available to certain patients widely differs in the real world. Moreover, in the case of biological or advanced modality interventions investigated in clinical trials, there is a high probability that this investigated medication will not be readily accessible to patients due to the high costs, even when registered/marketed in the country.

1.2. Research Question

Is the SAHPRA Post Clinical Trial Access/ Continued Access (PTA/CA) Guideline, Version 4.0 Dated 3 August 2022, ethically justifiable, given the specific contextual reality of South African patients?

1.3. Rationale

Despite significant progress in clinical trial methodologies over the years, there is a lack of research on how these advanced therapies and innovative trial designs impact post-trial access conditions in developing countries. Therefore, it is imperative to determine whether the current post-trial guidelines in South Africa take into consideration the recent progressive aspects of clinical research as well as the country healthcare and access to medication context. Moreover, clinical trials will continue to expand in South Africa owing to the rich genetic diversity of the patient population and certain disease epidemiology (Olatunji et al., 2023 pp 357). This will lead to an increasing awareness around the benefits of clinical trials in communities, and as such more patients may consider clinical trials as a viable option as an alternative option to their existing medical care. Reflecting

on these current and future changes, it is important to reassess aspects of the SAHPRA Guideline Version 4.0 August that could present an unjust situation for patients following the completion of a clinical trial.

There are other developing countries with a healthcare system such as South Africa, that have taken a stricter stance with post-trial access regulations and guidelines. This approach has not deterred the growth of clinical trials in those countries. Therefore, the SAHPRA Guidelines may also have the potential to be revised according to the needs of South African trial participants while still supporting a growing trial environment in the country.

This critical ethical assessment could support new guidance revisions and consideration for a future mechanism of post-trial access even when the South African National Healthcare Insurance (NHI) system is implemented.

1.4. Thesis Statement

I will argue that specific clauses/statements in the SAHPRA post-trial access/continued access guideline Version 4.0, 3 August 2022 require revision and reconsideration to ensure fairness for South African clinical trial participants.

1.5. Aim and Objectives

1.5.1 Research Aim

To defend my thesis statement that certain clauses/statements in the SAHPRA post-trial access/continued access guideline Version 4.0, 3 August 2022 require revision and reconsideration to ensure fairness for South African clinical trial participants.

1.5.2 Research Objectives

i. To provide an overview of the literature related to the ethics of post-trial access in clinical trials generally and more specifically in South Africa
ii. To argue that patients' face challenges accessing equivalent registered medications after trial completion, regardless of whether they use public or private healthcare
iii. To demonstrate how an absence/shorter duration of sufficient post-trial access exposes trial participants to additional clinical and non-clinical harms and exploitation
iv. To defend the claim that post-trial guidelines in developing countries like South Africa should incorporate country-specific contexts, especially given the rise of innovative research methodologies and protocol designs
v. To respond to and counter objections to my arguments

1.6. Research Design and Methods

This research project is purely normative and as such I will not collect interventional data assessments from human or animal subjects. My research dissertation will be conducted solely on an existing literature review analysis through relevant journals and publications, global and local regulatory clinical trial guidance and policies and a critical assessment thereof. As such it will not require an Ethics committee approval.

I will utilize the Wits Library to care academic search engines to perform a literature review. My initial literature and library-based research has been done through the following search engine tools and databases: WHSL, PubMed, Scopus, Google search.

I will also focus my ethical analysis on specific clauses of the SAHPRA Guideline Version 4.0, dated 3 August 2022 post-trial/continued access guideline pertaining to clinical trials. Literature findings will be ethically analysed and include clarification of key concepts and criticism of assumptions based on my research objectives.

1.7. Argumentative Strategy

I will base my argumentative strategy on the following premises:

1. South African clinical trial participants should have continued access to trial medication for an appropriate period following clinical trial completion. I will do this by showing the challenges with access to medicines in the South African healthcare system following clinical trial completion, utilizing theories of beneficence and respect of autonomy relative to trial participants,

2. Trial participants can be exposed to additional clinical and non-clinical harms in the absence of clearly defined post-trial access conditions. I will ground this argument on the unjust harms of prematurely stopping access to clinical trial medication by utilizing theories of non-maleficence and Kantian ethics principles related to the 'categoric imperative'
3. The future of Innovation design research can lead to further vulnerability for South African trial participants and hence the country context for access to medication should be included in post clinical trial guidelines. To argue this point, I will show how distributive justice should be at the forefront of influencing the guidelines so that trial participants receive the benefits that they deserve.

In this respect I will rely on moral theoretic pluralism as a construct for the argumentative strategy.

Argumentative Strategy summary

In summary my argumentative strategy will cover 3 premises:

a) The South African healthcare context for access to medication after clinical trial participation should be considered in the guideline,

b) A participant may be exposed to additional clinical and/or non-clinical harms in the absence/insufficient duration of post-trial access,

c) and lastly the impact of innovative research design of clinical trials may have ethical implications for participants relative to post-trial access conditions.

2. Chapter 2: Thematic overview of the literature

As an overview of the regulations of post-trial access were delved into in the previous chapter, I will now focus on the relevant arguments from corresponding authors in support of post-trial access and then similarly review those arguments that outline challenges with long-term post-trial access.

Additionally, the differentiation between post-trial access and post-trial care is relevant at this juncture of the literature overview, as the former refers to only the specific access of the investigational medicine being made available to a patient once the study ends. On the other hand, post-trial care includes access to investigational medication and encompasses the continued holistic medical management of a patient following completion of a clinical trial (Cho HL, Danis M, Grady C, 2018, p 510). Many authors express that these matters of post-trial care and access are intertwined and equally important (Ngwenya et al, 2021 p 5), and therefore for the purpose of this research report, I will discuss post-trial access to be inclusive of both components as per the above determination by the authors.

Firstly, I will examine the literature that supports post-trial access and then explore the literature that highlights the challenges associated with post-trial access.

2.1. Overview of literature supporting long term post-trial access

2.1.1. Medical Ethics

A basic premise underlying the principles of medical care is to ensure the physician acts in the best interest of their patients when providing treatment and clinical management. It is well accepted in medical ethics that when confronted with an ethical dilemma and the principles of beneficence and non-maleficence are to be balanced, the clinician should rely on this premise and do what is best for the patient (Tepper, 2017, pp 250-251).

However, relaying these principles to a post clinical trial access setting is complex as there are various stakeholders (clinicians, sponsor/pharmaceutical companies, ethics committees and local regulators) who are indispensable to the decision making to ensure appropriate access. Nevertheless, although post-trial access is a challenging undertaking, it is accepted by some authors as a “moral imperative in ethical research” (Cook K, Snyder J, Calvert J, 2016, p 71).

Furthermore, in a clinical trial setting, the informed consent form has been deemed as an assurance in proving a patient’s rights and wellbeing are protected in a clinical trial. However, to maintain the human dignity of clinical trial participants, this should not be misrepresented by a consent form. Assessing their clinical consequences beyond the clinical trial and into the ‘post-trial phase’ of the study is a meaningful approach to maintain human dignity (Cho HL, Danis M, Grady C, 2018, p 510).

Leading through on this point, in the literature supporting an effective mechanism of post-trial care, Cho et.al elaborate that post-trial responsibilities must consider that as post-trial access needs differ dependant on the patient profile, type of disease and access to healthcare, there should be an adaptive approach to support these “varying degrees” of

need. With this approach of distinguishing patients according to health care needs, and customizing an appropriate post-trial solution, it is presumed that post trial care is accorded to individual people to meet their actual needs. Subsequently, this lends to a more expansive approach for how post-trial care is managed and not viewed against pre-selected criteria related to generic timelines and funding (Cho HL, Danis M, Grady C, 2018, p 510).

Reflecting on from these highlighted arguments, it becomes apparent that the duration of access depending on the patient's disease/condition, and mechanisms of provisioning unregistered medicines outside a clinical trial need critical examination.

2.1.2. Consequences of inadequate post-trial access

It has already been pointed out that post-trial access is a complex responsibility as many stakeholders have shared accountability on this process. More importantly, when these considerations are overlooked, the consequences thereof have been observed in clinical trials where participants have dire outcomes without receiving continued access to life-saving medication, specifically documented with the oncology trials of Imatimib and Lapatinib in 2003. These medicines were not accessible to trial participants after the clinical trial concluded and approximately 30 000 people succumbed to death due to lack of continued access to these life-saving treatments (Usharani P, Naqvi SMH, 2013, p 58).

There have been other cases in clinical trials in areas of Oncology (Cetixumab, Pemetrexed) and HIV (Ziduvodine) reported where either denial of commercial access or lack of post-trial access have led to harmful situations for patients and caused their premature demise (Singh H, et al.,2019, p 5).

Closer to home in South Africa, cases are also noted where efficacy of a clinical trial medication in HIV (Tenofovir) is proven however the registration/commercialization of the trial medication by the sponsor/pharmaceutical company is not followed through in the country. As a result, clinical trial patients will never be afforded the opportunity to have access to these medications in real-life even though they contributed directly to the development (Singh H, Kakkar AK, Singh J, Manohar HD, 2019, p 5) .

Thus, indicating it is important to delineate a clear plan at the start of a clinical trial with post-trial access conditions to ensure patient well-being and safety is kept at the forefront of the decision-making process.

2.1.3. Post-trial access in Developing countries

The trend of conducting clinical research in low to middle-income countries continues to increase as the availability of participants linked to lower cost of trials as primary drivers (Da Silva et al. 2018, pp 1001-1002). Having a higher probability of commercialization of the investigational medication as well as national health insurance systems in place, post-trial access in first world countries does not receive as much attention or literature review compared to developing countries.

To this end, the recognition of these considerations towards low to middle income countries is seen with the Trust Project, 2017 where pharmaceutical company Roche has developed a robust process with early planning among stakeholders to ensure that patients who benefited the investigative treatment will continue to receive this treatment as needed (Kelman A, Kang A, Crawford B, 2019, pp 124-125). This is however not the universally accepted standard applied by other sponsor or pharmaceutical companies.

Following through, other authors highlight the South African perspective and aptly explain that abiding by human dignity should be the foundation for post-trial access provisioning (Andanda P, Wathuta J, 2018, pp 143-144). In clarifying the interpretation of human dignity, these authors explain that clinical trial participants are a vulnerable group and as such the option of post-trial access accounts for their inherent value as unique, autonomous human beings by showing respect beyond the confines of a clinical trial. Furthermore, the authors go on to state that for developing countries, an even broader position should be applied to include a benefits framework to extend beyond only the provision of post-trial medication. In this way the authors explain that the informed consent process should not be used as a mask to confer that human dignity has been preserved in the clinical trial process (Andanda P, Wathuta J, 2018, p 149).

In another argument beyond the borders of South Africa in Ghana and Tanzania, an empirical research study conducted by Ward C et al., on end of trial obligations in a paediatric malaria vaccine trial showed that the practicalities to fulfil this obligation are often a hurdle in developing countries. “Bridging the gap” at the end of the trial is more pertinent for these populations as their likelihood of having these available treatments make take years or longer, if ever, to become accessible. To this end, the baton for supporting end of trial obligations is inherited by the research field workers. These post-trial care methods produce a “divergent” way of support which brings into question if their healthcare needs were adequately and ethically addressed. Participants cited anxiety, abandonment, and disappointment at the end of this clinical trial (Ward C, et al. 2018, pp 261). Summarizing that it is vital that the actual implementation and follow-through

strategy on bridging the communication gap should involve all research stakeholders to produce a fair and equitable level of care at the end of the clinical trial.

Finally, it is important to note that the provisioning of post-trial medication is mandatory only across only 5 countries in the world, of which Argentina, Brazil, Chile, Finland and Peru feature and while other countries may follow ICH-GCP and the Declaration of Helsinki 2024 guidance, post-trial regulatory guidance are “recommendations but not mandatory” in these countries. It is also contemplated by the authors that there should be recognition for certain conditions e.g. HIV with more dire clinical consequences in patients if post-trial access is stopped at some point (Da Silva et al., 2018, p 1005).

In summary of this literature review, it is evident that consideration for the aspects related to the medical ethics of research, consequences with the lack of post-trial access and specificities of developing countries must be acknowledged and I will further critically analyse these concepts in this research report.

2.2. Overview of literature highlighting limitations/challenges of long-term post-trial access

2.2.1. Inducement and unfair advantage considerations

In citing the complexity of post-trial access, authors like Doval et al, 2015 express that this could constitute coercion or inducement of patients to participate in a study by promoting an indefinite provisioning of medication. Additionally, by virtue of already being included in a clinical trial, these patients have in any case been advantaged by receiving early access to medicines that they initially would not have had. Furthermore, upon completion of a clinical, they revert to the same clinical situation that they were in prior to trial inclusion hence are not in any way more disadvantaged. It is mentioned, that in fact it is more unfair to patient populations that have never had access to a trial to begin with, while those who were enrolled and have had early access to novel medicines (Doval D, Shirali R, Rupal S, 2015, p 83).

As agreed by Usharani et al., the validity of ethical and legal standpoints of post clinical trial access require investigation as the transparency of precise requirements are not clear even in global guidance. This is further compounded by the disparity in which clinical trial patients already have unequal access to the investigational medication instead of real-life patients. The authors agree that as the post-trial period cannot be indeterminate, there should still be a transitioning period to other available standard of care (Usharani P, Naqvi SMH, 2013, p 60). Other angles of consideration are that if new post-trial access rules are instated, an earlier generation of trial patients will be disadvantaged as they were managed according to previous limited post-trial access mechanisms. Therefore,

creating a present-day unjust situation across trial populations (Doval D, Shirali R, Rupal S, 2015, p 83).

2.2.2. Financial considerations

A corresponding outlook expressed is that in the case of indefinite post-trial access is that this proves to be a financially challenging situation for sponsors/researchers of clinical trials and hence may be curbing or negatively impacting research from being conducted in certain communities (Usharani P, Naqvi SMH, 2013, p 60).

Authors like Sofaer who completed a systematic review of approximately 75 publications on post-trial access, have also affirmed that the most highlighted criteria that does not support mandatory PTA, is that the cost of research in the country while the country itself may be penalized from research on the grounds of these demands. Other views stemming from this point are those of role-related responsibility in prescribing post-trial access as not a straight-forward process, therefore this aspect should be clarified up front to ensure that all stakeholders are involved in the decision making with post-trial access (Sofaer N, Strech D, 2011, p 174).

2.2.3. Post Trial access in Developing countries

Ngwenya et al. (2021) conducted a semi-structured interview with government and sponsor stakeholders and participants to assess their post-trial access understanding and implementation in a rural part of South Africa for an HIV study. These authors aimed to verify the pretrial agreements against actual implementation following trial completion. They also highlighted in as much as provisioning is highlighted in pertinent international guidelines, the interpretation of how these should be implemented as well as

responsibilities are not well understood by either participant or stakeholder which includes provincial government and sponsors. Even within participant groups, and investigator sites themselves there were mixed responses as to who should be the responsible/accountable stakeholder for the access provisioning, i.e. the sponsor or the department of health and even the role of the Investigator was highlighted as having some responsibility towards the continued development of programs to help communities. More importantly, how the participants felt once the trial had ended were related to desertion, lack of access and supported. The lack of transparency on processes could lead to more a “tokenistic” attempt at post-trial access than actual follow-through of the agreed conditions. It was clearly shown in this type of rural setting, that beyond trial medication provisioning other basic services including the clinic set-up, disease education and community upliftment are all valuable measures to support post-trial access and care (Ngwenya N, et al., 2021).

It is with these above literature reviews in consideration that I will review the SAHPRA CA/PTA clinical trial Version 3.0, 2022 guideline and argue for reforms on a more precise framework for South African clinical trial participants.

Chapter 3: The South African healthcare dynamics and challenge with post-trial access

In this chapter, I will argue that irrespective of whether a patient receives public or private medication access in the South African Healthcare system, this does not mean there are guaranteed equitable medication alternatives available after trial completion. I will point to examples that show how the healthcare system medication options can cause greater injustices for trial participants once they have completed a clinical trial. To accomplish this, I will bring into focus relevant aspects of the South African healthcare framework together with the SAHPRA Version 4.0 2022 post-trial regulations to show the lack of cohesion between both medication access in the country and certain statements in the guideline.

My argument will be grounded **firstly on** the **deficiencies of the public healthcare ecosystem** and then **secondly**, I will explore the corresponding challenges associated with the **private healthcare system**. Following which, I will review specific excerpts/statements of the SAHPRA Guideline Version 4.0, 2022 that don't reflect the South African healthcare context for access to medication.

In describing the shortcomings of participant access to medication following clinical trial completion, I will point to examples that show irrespective of the healthcare system the participant returns to, it can still equate to a morally unjust situation for South African trial participants. My supporting arguments will be centred around the bioethical theories of beneficence and respect for autonomy to show that specific statements in the SAHPRA Version 4.0 2022 guideline should have a more ethically sound approach to ensure participant well-being is preserved after trial completion.

Public Healthcare in South Africa

To begin with my first stance around the healthcare challenges in a developing country such as South Africa, there are numerous barriers to effectively access medical treatments. This has a direct consequence for a trial participant completing a clinical trial, who will revert to the available, registered medication in the healthcare system as an alternative to trial medication.

For a country population of 62 million, it is estimated that only 16% of South Africans have access to some type of private healthcare while the remaining 84 % South Africans are still heavily reliant on the government funded public healthcare system for this basic 'right to health' need (Abrahams et al, 2022 p 67). However, the public system is plagued with many challenges for patients to receive both quality and timely healthcare. Factors that directly contribute to this include 'sub-national' or provincial conditions where the socioeconomic status, geographical location can directly impact the quality of healthcare a patient is rendered (Achoki et al, 2022 p 472). These policies inevitably define the medication classes available at certain hospitals and clinic facilities. More specifically, these geographical location and conditions of policy become a major predictor of health equity, well-being, and life expectancy. As a result, the lower income band of the population who are highly dependent on the public infrastructure are most severely impacted by unpredictable, mediocre healthcare conditions. Further to these provincial specificities, and despite changes in government legislation and improvement measures to prioritize healthcare, various hurdles still exist to ensure patients have adequate medical care and treatments in public health facilities of South Africa. Another point to consider are the additional key contributors to poor healthcare delivery which include a

shortage of medicines, lack of equipment, unequal distribution of resources and increase in disease burden amongst other criteria (Maphumulo WT, Bhengu BR, 2019, pp 1-2). These challenges are indicative by the Healthcare Access Quality (HAQ) index score based on a range between 0 to 100, with a higher score suggesting a more advanced healthcare access infrastructure. Across the nine provinces in South Africa, the HAQ index varies between approximately 40 and 54 based on the 'economic advantages' of the province and perpetuated by 'inequities in service delivery, urban and rural utilization, and socio-economic factors' (Achoki et.al 2019, pp 477-478). These indicators show that irrespective of geography, equality in medical care in a public healthcare setting has a high likelihood to be compromised and more especially for those patients from lower income settings.

Beyond these provincial and economic nuances, another drawback for equitable medication access is the 'Essentials Medicines Listing' (EML) which is more largely utilized in the public healthcare system. Only specific medications are made available are based on the allowances and availability of the essential medicines listing (EML) at the treating public health facility. This can bring about limitations for which types of medications are available based on tender agreements between pharmaceutical companies/distributors and the Department of Health. Selected treatment options are influenced based on a 'budget to impact analysis' of the public state resources (Pharasi, Miot, pp 180, 182). Again, pointing to the economic influence of which medications can be made available to patient. Moreover, there is a high disparity between the "restrictive" essential medication list for participants in the public sector which are subject to genericization, and substitution compared to private sector approaches with multi-

disciplinary specialized care and more rigorous treatment options that are available in South Africa (Pinchevsky et al., 2018, p 388).

Private Healthcare in South Africa

While it could be said that private healthcare is an alternative where the public system is lacking, most ordinary citizens are unable to afford this option due to the country's economic conditions with an unemployment rate of 32.5% (Statistics South Africa on official unemployment rate in third quarter of 2024, South African Government, 2024), the highest in the African continent. Moreover, should some patients be in the minority group who have access to a privately funded healthcare model, access to certain medications is still restrictive based on the medical aid tiering plans that can be afforded by a patient (Mpanza et al, 2023 pp 3, 8). The private healthcare system also supports a selective approach to medications that it will reimburse, which allows for cost-effectiveness in the system (Perumal-Pillay V, Suleman F, 2020, pp). This means that those patients belonging to the private sector are subject to payment conditions and formulary recommendations of their provider and will not necessarily have access to most advanced, efficacious medication unless they are on a high-end plan or are able to afford additional copayments.

Furthermore, there could be a perceived advantage in society of availability of superior medication in the private sector. However, this perception can be debated by the introduction of single exit pricing/SEP system which has significantly impacted the registration/commercialization of new medications in the country. The SEP approach means a government gazetted pricing transparency of medication that is sold by

pharmaceutical companies and manufacturers. While the intended aim of this policy was to reduce profit of manufacturers, it instead caused a withdrawal and discontinuation of 3691 products over a 10-year period. It was also concluded that there was a negative impact overall with “reduced product availability on the market and impact on the cost and quality of healthcare to the patient. (Naidoo K, Suleman F, 2021).

Overall, all these aspects highlighting the disparate health equity system in South Africa, irrespective of private/public healthcare status, which can be attributed to many determinants such as the economic climate, private and public policies, geographic locations, healthcare facility resources and individual patient affordability. In considering these limitations, it can be envisaged that access to the most effective medication for both ordinary citizens as well as trial patients can be subject to many challenges.

SAHPRA Version 4.0, 2022 Guideline

After assessment of the public and private healthcare system dynamics, I will now focus my attention to the specific mention of alternative medical treatment options in the **SAHPRA 2022 guideline** stipulating, “*Post-trial access / Continued Access should be considered for Phase III studies when* ***no registered and marketed standard of care*** *is available in South Africa”*.

This clause insinuates that returning to ‘registered standard of care’ is an equitable treatment continuation for a trial participant once the clinical trial has ended.

However, the rationale of researching new investigative medications in phase 2 or 3 clinical trials are to target diseases that are not effectively treated by first tier medications

referred to as ‘standard of care’. For that reason, if ‘standard of care’ has not achieved effective disease control or recovery for an individual, clinical trials become a promising option. This context is important as it influences whether ‘standard of care’ reference is a fair and reasonable treatment option for trial participants.

In this way, the guideline does not consider the reality of the healthcare system in South Africa by deferring to the ‘standard of care’ as the most appropriate alternative for a trial patient and should have revision to be more specific to the South African patient situation.

Normative analysis

To deliberate why this excerpt/statement of ‘standard of care’ in the guideline could pose a morally unjust situation for trial participants, I will reflect on the ethical principles of beneficence and respect for autonomy that should be upheld in medical ethics.

From the perspective of beneficence, the treating physician in a clinical trial is initially offered the prospect to treat his/her patient with progressive, novel, and effective medication to ‘prevent conditions that cause harm and remove harm’ (Varkey B, 2023, p 19) for a patient by offering a hyper-care approach in disease management for a patient. As such, this creates the opportunity to act in the best clinical interest of the patient to support their improved health outcomes and disease mortality which were otherwise not adequately controlled prior to clinical participation on standard of care medication or others. Additionally, this benefit can be assessed based on Bester’s hybrid proposal of beneficence. If the treating physician’s view is that the clinical trial medication directly contributes to the ‘objective functioning’ of a patient’s overall health and well-being, and similarly the patient considers that continuation of the medication will support their ‘goal attainment’ of health (Bester JC, 2021, p 57), then in a clinical trial context the continuation

of treatment for as long as ‘beneficial’ to a patient is the ideal scenario to support an approach of beneficence.

To further illustrate this point is that although the registration and marketed medication listed on the ‘SAHPRA Registered Health Products database’ (https://medapps.sahpra.org.za:6006/) is referenced as a post-trial option, this does not predetermine that the trial patient will have access to the equivalent efficacy of medication as shown with the private and public healthcare treatment challenges earlier highlighted. Subsequently, while the clinical trial treatment is intended to offer therapeutic disease management, it is short-lived if the participant returns to a healthcare system where their chances of receiving a highly novel treatment as efficacious as the trial medication is not guaranteed based on the availability and access in the country.

Hence, without the safety net assurance that a trial participant will maintain the disease control they had achieved during the trial, this leads to an ethical dilemma for the treating physician. Trial patients may even succumb to regression of their condition based on sub-efficacious treatment that is unable to give them the same clinical benefit or alleviation for the severity of their condition that the trial medication had achieved. The treating physician intention and pledge of beneficence to a trial patient would then be reversed by this outcome.

The other ethical tenet that can be overlooked is the aspect of ‘respect for autonomy’ There are compounded injustices that participants can be subject to if this intrinsic value of a participant is not acknowledged. Reis-Dennis explores an interesting perspective with the “thick sense of autonomy” (Reis-Dennis S, 2020, p 5). In this notion, it is about forming

decision making on rules and regulations that are founded on respect and equality. By acknowledging the challenging medication access conditions of South African trial participants, it then allows for the intrinsic self-worth and value of an individual to be considered. Hence it is important for post clinical trial regulations to account for the varied healthcare system nuances that limit fair access to medication for South African participants.

Inevitably as earlier noted, trial patients are returning to treatment regimens/standard of care that are influenced by their different socioeconomic backgrounds and where access will be based on their geography, affiliated healthcare system and socioeconomic background.

Overall Chapter summary

To preserve and respect the autonomy of South African participants, with vastly different economic backgrounds, a thorough market analysis of access conditions and availability for a specific disease should be considered when post-trial access conditions are stipulated and approved by SAHPRA with a clinical trial submission. The standard of care aspect should not be a broad-based statement for trial participants as it will disadvantage those without the means or ability when returning to a real-world health system.

Overall, it highlights the distinct need for additions to the post-trial guideline to advise Sponsors to include the following rationale in their clinical study applications:

a) Distinguish the profile of participants (public or private sector and certain geographical areas of South Africa) in a clinical trial and the probability for them to have fair access to equitable registered medication upon trial completion i.e. a deeper analysis

depending on what medication these patients will access after the trial is completed. To support a regulatory post-trial access approval based on the participants' actual circumstances.

b) The maturity of registered 'standard of care' treatment options compared to other first world and developing countries should be assessed by SAHPRA as part of the trial application to determine if the South African patient is being respected following clinical trial completion.

In summary of this chapter, I have highlighted the challenges in ensuring equitable medication access in both the public and private healthcare system of South Africa and in doing so illustrated how these conditions can obstruct the principles of beneficence and respect of autonomy for trial participants. Thus, to ensure trial participants have access to effective medications following clinical trial treatment, the SAHPRA Guideline should be more deliberate with which treatment options are considered appropriate for a certain disease/indication in a post-trial setting.

Chapter 4: The unjust clinical and non-clinical harms of post-trial discontinuation

In the previous chapter, I focused my argument predominantly on how the South African healthcare system can disadvantage participants following clinical trial completion.

In this chapter, I will utilize this first argument as a grounding point to defend the claim that additional unjust clinical and non-clinical harms can occur in certain high epidemiology diseases in South Africa if post-trial access is not provisioned for a period that is relevant to the disease condition. I will do this by pointing to those specific harms that trial patients could be subjected to if the duration of post-trial access is not sufficient or absent altogether.

Earlier, I reflected on the specific clause of the SAHPRA 2022, Version 4.0 guideline that points to 'registered and marketed standard of care' as a fair alternative in Phase III clinical trials. However, in this ensuing argument, I will bring into focus, another clause of the guideline that alludes to **'minimum four-year period'** (https://www.sahpra.org.za/wp-content/uploads/2022/08/SAHPGL-CEM-CT-07_v4-Guideline-for-Post-Clinical-Trial-Access.pdf, p 4) in which post-trial access should be considered 'for those who derive benefit from the investigational product'. Amongst these unjust harms, I will firstly focus attention on those clinical harms impacting individual health outcomes for selected high disease burden trials. As a second point, I will delve into the non-clinical harms that can occur with premature termination of clinical trial ancillary support, particularly devices.

In both these examples, I will also account for the treating physician dilemma where post-trial access conditions do not support their ethical obligations as healthcare professionals. Considering the clinical and non-clinical harms, I will look to Medical Ethics and specifically the value of non-maleficence to show how the prescribed four-year duration

of post-trial access, can confer an injustice to the trial participants transitioning back to the real-world healthcare system.

Lastly, when assessing the unjust clinical and non-clinical harms, I aim to highlight those disease conditions that have a high epidemiology rate and healthcare burden in South Africa. These include examples of significant conditions such as diabetes (Pinchevsky, 2018, pp 383-384) and rheumatoid conditions (Adelowo et. al, 2021, p 383). Additionally in both examples, it covers the associated clinical harms irrespective of whether the trial medication is eventually registered and marketed in the country or not. To point to the evidence of the types of clinical and non-clinical harms that can occur, I will depict the potential negative health outcomes in the absence of appropriate disease control. These outcomes should be weighed up to recognize the impact on participants who no longer have access to clinical trial medication and devices.

Clinical Harms

To begin my argument that those disease conditions with high epidemiology rates and compounded disease burden in South Africa should have a higher focus in the country's post-trial access guideline, I will first review examples of inappropriate post-trial conditions and their clinical harms in these conditions. The conditions of Rheumatoid arthritis (RA) and Diabetes are related to immune and metabolic diseases respectively which are contributors to high costs of healthcare burden and mortality.

In a clinical trial setting, these patients who experience a high disease burden are supported by a sophisticated level of clinical care through frequent assessments and procedures for monitoring of disease activity as well as for evaluating the effectiveness of the researched medication (Bouzalmate-Hajjaj A et al, 2022, pp 1-2). This draws

attention to the primary intention a treating physician may elect for this hyper-care alternative in the form of a clinical trial for their patients to support better health outcomes.

In this first example of clinical harms, I allude to the immune condition of rheumatoid arthritis (RA) where although not immediately life-threatening does impose severe disease burden on a patient. RA is an incurable, progressive disease where patients experience joint damage, pain, and diminished mobility amongst other health outcomes. Without appropriate treatment intervention, patients can often progress to very severe disability limiting to an extent where there is severe impact on everyday functions (Shams S et al, 2021, pp 1,4, 19). In specific RA clinical trial programs conducted in South Africa and other countries, patients with moderate to severe disease, who were not responding to their current therapies were given the opportunity to be treated with a highly effective monoclonal antibody as clinical trial medication (Genovese CM, et al, 2020, p3). Dramatic improvements in their disease control are cited which include alleviation of rheumatoid arthritis symptoms, improved physical mobility, inhibition in progression of structural damage and notable quality of life improvement (Genovese et al, 2020, p 11-13).

However, following clinical trial completion, continuous post-trial access was not made available for South African participants in some clinical trials. Consequently, these patients returned to other available therapy in the South African market or their previous standard of care treatment which had initially been ineffective and why they were included in the clinical trial.

Leading through from these highly positive trial results, a new monoclonal antibody treatment is now registered as a highly effective treatment in rheumatoid arthritis in

several parts of the world but is not registered in South Africa, 8 years after trial completion (SAHPRA's Registered Health Products Database, 2023). To this end, the participants prognosis upon returning to the healthcare system can be inferred if they are treated with their previous ‘standard of care’. Progressive joint degeneration resulting in recurrence of existing symptoms, restrictive movement and eventual loss of mobility and reduced life span are all outcomes related to poorly managed rheumatoid arthritis (Shams S, et al, 2021, p.1). Following integration back into the real-world health system, whatever clinical remission gains that they would have made during the clinical trial would be undone in this type of degenerative condition, resulting in clinical harms for the patient.

Looking to the second example of Diabetes mellitus which is the “second leading cause of death in South Africa after tuberculosis” and is growing in prevalence in South Africa, is then compelling to understand post-trial implications (Sidahmed, S et al, 2023, p2).
To underscore this is that the country already has a strained diabetic management system with clear differences in diabetes management between the private and public sector management patients. In the public system, challenges include not meeting the required diabetes range/HbA1c target, medication shortages and lack of access to a multidisciplinary team of experts for their diabetes management (Pinchevsky et al, 2018, pp 382, 387-388). This can be seen to be a distinct disadvantage for previously uncontrolled diabetic trial patients returning to this healthcare system following access to novel clinical trial medication for diabetes. Poorly controlled diabetes conditions are far-reaching and are linked to various debilitating outcomes such as nerve damage (eyes, kidneys, peripheral damage of hands and feet) and cardiovascular complications (stroke, heart disease, etc.) increasing the risk of mortality.

Even with certain highly effective clinical trials conducted for Diabetes in South Africa with the example of Semaglutide (Ozempic), patients were treated with the trial medication for 75 weeks/ 1 year 6 months. (Davies et al, 2021, pp 972). No continuous post-trial access was available for trial participants as per the principle that other existing treatments were already available for Diabetes in the country. Although it is now registered on the South African market at an average cost of ~R5000.00 to R10 000 per month for 1 injection per week, dependant on dosage (MPR (Medicine Price Registry) - (medicineprices.org.za), public sector trial patients do not have access and even private sector patients will need to pay out of pocket for such an advanced modality of medication. For South African trial participants who were unable to reach their glycaemic control with accessible and available diabetes treatment at the time of trial inclusion, it is likely they would again trigger poor glycaemic control without continued access to the highly effective clinical trial treatment.

Normative analysis – Clinical harms

Reflecting on the clinical harms that patients may endure after trial completion, it is evident that especially for both these conditions of RA and Diabetes, even if a ‘4 year post-trial access period’ is granted after the core trial is completed, it will inevitably equate to a temporary ‘4-year delay’ until potential negative clinical harms will arise. These clinical harms stemming from ineffective medication access conditions related to socioeconomic health injustices previously alluded to.

If I draw on the principles of non-maleficence rooted in medical ethics and extrapolate this to the pharmaceutical sponsor duties together with the role of SAHPRA, then the intent to minimize clinical harms is based on a general time frame of 4 years but is not aligned what is the most effective duration to treat the disease. Both these role-players need to follow pertinent ethical guidelines such as the Council for International Organizations of Medical Sciences (CIOMS which guide the duties-based approach to post-trial access "*Similarly, the obligation will be greater when participants are not able to access the needed care or prevention within the local health system than in cases where this is readily available. The obligation may also be greater when there are no available alternatives with clinical effectiveness similar to the intervention that has demonstrated significant benefit than in cases where such alternatives exist*" (CIOMs, 2016, p 23).

This guideline succinctly speaks to the situation of the South African patient in terms of challenging access within the healthcare system as well as the aspect of alternatives if there is no corresponding registration in the country of certain trial medications.

Even treating physicians will be conflicted in their duty without a choice to continue with a highly effective treatment and resort to the most accessible option based on the participant's circumstances impacted by geographical location, socioeconomics and private/public healthcare access conditions.

These stakeholders then defer from their duties by relying on a duration based (4 year) post-trial access timeframe instead of a clinical based need for the patient. As such in placing 'time' as the appropriate driver to when post-trial access will end, they do not account for the harms that can occur when clinical trial medication is eventually retracted.

Participants are thus not treated as individuals with corresponding diverse circumstances under which they will access medication but rather as an ‘ends to a means’ to obtain clinical trial data within a defined period (Samuel K, 2024, Stanford Encyclopedia). By this account Samuel cites that “An agent treats another merely as a means if the other cannot share the proximate end or ends the agent is pursuing in treating him as a means”, which is then the equivalent of how the trial patient is treated if their outcome after a clinical trial is not appropriately analysed by the stakeholders.

When assessing the impact to preserve the duty and moral compass of Kantian ethics in these types of conditions, it should follow an approach of the ‘categorical imperative’ (Reis-Dennis S, 2020, p 5) to continue clinical trial medication as long as benefiting the trial participant with their disease alleviation unless it is their choice to discontinue, or they have confirmatory access to an effective class of treatment with a similar mechanism of action.

In failing to uphold such a type of imperative for uncontrolled disease conditions, it can adversely impact the participant as soon at the treatment is withheld or a similar effective treatment option is not available or registered in South Africa at the end of the trial. However, should there be a firm resolve and imperative on how to manage disease conditions of interest which are distinctively expressed in the guideline, it would ensure a rule to which trial stakeholders would need to adhere to. The ‘duty’ in this situation is first towards the participant to ensure they will not be exploited for clinical data gains while their own disease control is not sustainable in the long term.

Non-Clinical Harms

Whilst clinical trials may be perceived as medication research only, there are other supplementary tools and devices that are being included for holistic patient management in clinical trials. Thus, from an ethical viewpoint, it is important to dually consider those harms that may impact trial participants in a psychological way if access to any clinical trial treatment or ancillaries are abruptly cut off due to local regulations or post-trial access directives.

To contemplate the non-clinical harms that can occur, I look to evidences in a clinical trial in which implanted neural devices responsible for brain stimulation in depression were removed after the clinical trial period, although they were proving to be beneficial for the participants' mental health. The reason cited for removal was that the device was considered as an 'experimental' treatment. The Sponsor could not continue to maintain the device after the trial and nor would the healthcare system take responsibility of the device due to the high financial burden of maintenance (Lázaro-Muñoz G et al, 2022, pp 1033-1035). Even though the Informed consent form highlighted this aspect, at the end of the trial both the research teams and participants believed that the sponsors had a duty of 'non-abandonment' and owed reciprocity to the participants due to the "invaluable data" the participants had generated for the billion-dollar sponsor company. Participants were left in a helpless situation with having to return the device and some participants even deeming it "cruelty" to remove the device (Lázaro-Muñoz G et al, 2022, p 1033-1034). The retraction of this advanced support to manage their depression was no longer available with potential for depressive episode relapse in an already vulnerable

population. This example highlights that there can be untoward and unwarranted psychological impact by removing such a device, over and above the known clinical harms.

As another source of evidence, I will also look further at the non-clinical harms that patients were exposed in a diabetes clinical trial setting without the continued provision of post-trial ancillary support. Type 1 diabetes is an innate condition that requires the patient to have a highly regulated lifestyle and treatment choice to ensure their disease is well managed. If the condition is not managed, both microvascular (eyes, kidneys) and macrovascular (organ failure) damage can occur (World Health Organization (WHO), Diabetes, 2023). In this trial, a closed loop blood glucose device system was utilized that regulated participants blood glucose automatically. Upon completion of the Type 1 diabetes clinical trial, participants had to revert to the previous older technology of glucose control. As cited by the participants, the device in the clinical trial afforded them both psychological and emotional benefits, and better management of their condition. In returning the device, they knew they had to regress to a more primitive way of disease control and re-condition to old habits for diabetes management.

At the end of the trial, participants and their caregivers experienced emotional distress, frustration and anxiety knowing their device would be withdrawn. Hence those psychological harms related to anxiety and stress also creating further disadvantage for the participant and presenting an unjust situation that could further impede disease management. Even the treating research personnel were conflicted in knowing their patients would revert to the sub-standard system (Lawton J et al, 2019, pp 105-107, 109).

This points to another valid gap in how post-trial conditions can also conflict healthcare professionals regarding their Hippocratic oath of non-maleficence.

Normative analysis – Non-clinical harms

For these non-clinical harms, and particularly honing in on the duty of non-maleficence, it can be established that even by removing clinical trial supplementary devices and tools, can further amplify other psychological factors and cause unwarranted harms to the participant. While non-maleficence aims to 'prevent suffering' and to 'take the best course of action for the patient' (Varkey, 2020, p 18), in removing any devices and supportive tools, it nullifies the intent of non-maleficence.

In both these examples of evidence, the treating physician is aware of the detrimental impact caused to their patients but are unable to act otherwise to prevent non-maleficence as they don't have a decision-making role in this context of allowing the device use to continue. At this juncture, the treating physicians will need to resort to less advanced available mechanisms to assess and manage their patients' clinical conditions, based on what is most reasonably accessible.

In consideration of the above non-clinical harms' examples, I have pointed to how non-maleficence can be disregarded for the participant especially as they experience abandonment, psychological distress and vulnerability related to having removal of their ancillary care at the end of the trial. These are meaningful outcomes to deliberate for a trial participant, as these negative consequences arise as a direct result of the participation completion of a clinical trial, which may have otherwise not occurred.

Overall Chapter Summary

In this second argument I have evaluated both the consequences of clinical and non-clinical harms by alluding to evidence based on potential harms that can occur. It has been apparent that in the absence of a more detailed post-trial access plan by either the sponsor company or confirmatory access within the healthcare system, the participant may enter uncertain territory to access equivalent medication or removal of medical care following clinical trial completion. Similarly, researchers/health care professionals, due to their limited decision making and influence in post-trial access conditions also experience conflict and distress in supporting their patients through this ordeal and readjustment.

With specific reference to SAHPRA 2022, Version 4.0 guideline, broad-based statements related to “a minimum 4-year period” are vague and do not allow for more thorough decision making of post-trial access and can inflict both clinical and non-clinical harms on participants. Hence enrichment of this guideline can be done to safe-guard certain imperatives are followed to ensure the least harms to the trial participant:

a) Have a specific appendix to reference those conditions of high epidemiology and disease burden in South Africa, where there is inferior standard of care that may not be well supported by the 4-year access arrangement which trial sponsors may adhere to
b) To add context on the use of medical devices within clinical trials and stipulate the duration and access to these supplementary devices provisioned to trial participants to support their disease control and burden

Chapter 5: Innovative Medicines research, Adaptive protocol trial design as considerations for post-trial access

In this last part of my argument, I will argue that the criteria applied for post-trial guidelines in developing countries such as South Africa should be more inclusive of country specificities particularly considering the rise of Innovative medications research and adaptive clinical trial protocol designs. To argue this point, I will show how these emerging changes to protocol design should be given forethought in the PTA/CA guidelines[i] so that trial participants are not disadvantaged as innovation progresses in research and development. In the current SAHPRA Guideline Version 4.0, there is no reference clause to highly innovative study designs or medicines like nanobodies, cell and gene therapy as form of medicinal intervention which should be given alternate consideration for post-trial access.

To support this argument, I will focus firstly on the rise of innovation medicines research and the undesirable impact for participants in developing countries. This argument will be influenced by the ethical aspect of Distributive Justice relative to the South African participant. Secondly, I will describe the relevance of innovative clinical trial protocol designs and how it could mislead trial participant expectations unless the PTA/CA guideline has clarity on this unique approach in clinical trials. I will look to African Ethics as a significant consideration for PTA/CA guidelines in this regard.

Rise of Innovation Medicine modalities

Innovative medicine research addresses many challenging treatment frontiers by effectively targeting diseases utilizing a specialized mechanism of action at the originating site of the disease.

The rise of these innovative “precision medicines”, means that patients can receive an individualized medication which targets the genetic biomarkers and mutations that cause the disease. Besides the intended highly effective treatment way the medication treats the disease, other benefits include reducing unwanted side effects by targeting only the genome or protein causing the disease thereby removing harm to other organs or immune pathways (Enzmann H, 2016 pp 314-316). Hence for patients who are recipients of these newer treatment modalities on a clinical trial, there is a positive outlook for their disease management if treated with these novel therapies compared to other less advanced medications. Whilst these innovative medicines have a novel mechanism of targeted biological, specialized action “which treat chronic, complex and rare conditions...”, their highest pitfall is that they are exorbitantly priced compared to traditionally manufactured medications (Global Use of Medicines, IQVIA report 2024, pp 3). Some of these ‘advanced therapy medical products’ or ATMPs have been cited to have an annual per patient cost of between 5 million and 20 million South African rands as per current exchange rate (Hanna et al, 2016 p 7). In the context of a developing country such as South Africa with the previously cited access concerns, this excessive cost plays a major role in whether trial patients will realistically be able to access them outside a clinical trial context.

Furthermore, a significant statistic is that of the current regulatory and access environment in South Africa. As of 2019, generic medicines are prioritized over originator brands due to pricing of the latter, where generic medications contribute approximately 73.8% of all registered medications as of 2019. In this sense, South Africa is deemed “pro-generic” in a global market. Additionally patient access to originator medicines are met with a substantial delay from the time of registration until availability for participants in both the private and public sectors as most originator medicines were not dispensed even five years after they were registered by SAHPRA. This could be cited by challenges with funding and reimbursement, supply chain organization, price erosion of the originator brands. (Mpanza et al, 2023 pp 6-8). This is a critical point to consider as it already indicates a potential trend and stumbling block when innovative medicines at a much steeper cost are registered in the South African market. Albeit the high cost, these biotechnology specialty medicines and gene therapies will be a major driver to research and development growth and constitute approximately 43% of global research spend spending over the next 5 years, or until 2028 and beyond. (Global Use of Medicines, IQVIA report 2024, pp 3). For these reasons, it is inevitable that the clinical trial landscape in South Africa will also evolve in this direction of research.

The SAHPRA Guideline Version 4.0 refers to “PTA/CA *may* be necessary for particular diseases such as cancer or other dread or rare diseases for which no other medicines or Standard of care is available” (https://www.sahpra.org.za/document/2-42-post-clinical-trial-access/, 2024). This context creates a loophole if certain effective medications are already available that PTA ‘may’ or may not be required. Pharmaceutical companies

could defer to this statement in the case of high innovative medicines to make a case for why PTA would not apply when other medications are available.

To fully grasp the disadvantage of this clause, I lean on the notion of Distributive Justice and why this should have further consideration for South African patients.

Distributive Justice in healthcare relates to an ethical manifesto surrounding the “fair and equitable distribution of healthcare resource…determined by justified norms”. Relative to post clinical trial access, these justified norms surrounding the investigational medicine distribution can be extrapolated to the “needs, effort and contribution” (Varkey B, 2021 pp 20-21) of clinical trial participants. As cited in the earlier literature review, trial participants are the first in line recipients of both the intended benefits and risks of a researched medication. It is widely acknowledged that a clinical trial irrespective of the intended benefit, is still in an exploratory phase and as such can still cause unintended harm to trial participants. In this way, clinical trial participants are meeting all criteria as recipients of distributive justice by their *need* for an effective treatment or vulnerability of their disease and therefore they have chosen a clinical trial as an option where existing medications don’t work or are not accessible. They undertake the *effort* of routine clinical trial assessments, procedures and sacrifices linked to participation in time and potential loss of income earnings. Lastly from a *contribution* standpoint, it is their trial data and outcomes that directly influence whether an investigational product has met the primary endpoint and the corresponding shareholder investments in pharmaceutical companies. Thus, they have an invaluable role in the clinical trial success.

From a point of equity in this process, the participant is also at the receiving end of the associated trial risk and should also be on the receiving end of the benefit for as long as

possible. Especially as their likelihood to receive the medical in either public or private access conditions based on the distribution of resources and economic challenges.

If the SAHPRA Guidelines are inclusive of these innovative trial modalities and special conditions in the guidelines and the clause is updated to reflect “innovative biologics, etc. should have additional parameters defined for PTA/CA even if other medicines or standard of care are available”, it could shift the culture of clinical trials conducted in South Africa to thoughtful decision making to reduce disease burden distribution especially in less advantaged developing countries. Additionally, this regulatory based influence could permeate amongst the clinical trial sector and sponsor decisions around novel medicines access to trial participants from developing countries. In this way, Sponsors become more aware to distinguish between profit margins/commercialization and trial-related responsibilities and do what is the best interest of the country and patient disease burden or epidemiology for a particular condition where there are evident challenges with access to highly advanced medication.

Adaptive Clinical Protocol Design Trials

The other aspect coupled to innovative medicines research is the emerging methodology in how clinical trials are designed and conducted. Where traditional trials have a fixed duration of conduct, in innovative or adaptive design, trials can be abruptly ended earlier than planned if the statistical endpoint has been reached through an interim analysis (Korn EL, Freidlin B, 2017 p2). To supplement this approach, artificial intelligence (AI) is starting to play a significant role in research with the design of digital AI twin processes

that allow for simulation of the targeted medication in both human participants and through generative AI (Bordukova eta al, 2023, p 33-34, 39). Ultimately if efficacy data is reproduceable through AI processes, the promise is that these trial designs can be conducted with fewer patient numbers in a shorter timeframe which allows quicker registration and commercialization for sponsors and thus access for real-life patients.

However, from the perspective of the trial participant, the drawback encountered, is that their participation time on a clinical trial can be significantly reduced and they may not have the full benefit of the initial agreed upon trial duration with all its benefits, included in the informed consent form. Participants can be misled by assuming a trial will have a certain duration and resounding impact on their disease when it can be cut short as soon as the efficacy criteria is met. This may also impact on the agreed PTA conditions by the Sponsor if the trial timelines are short, with highly expensive innovative medicines tested and fewer participants required due to AI data alternatives. Subsequently by evolving into innovative medicines territory without the safety net for customized post-trial access for such trial designs, this could put South African patients in a precarious situation as trial participants benefits are diminished by having very short-term access to advanced modalities.

To assess the moral relevance of these changing trial designs on the SAHPRA post-trial guidance, I will look to African Ethics and how this should be factored into guideline pre-requisites or conditions with a separate clause to be added on such protocol designs. African ethics encompass various aspects around communitarian themes, personhood, character, and humanitarianism (Gyekye K, online 2011). For this argument I look to the

concept of how the “common good” and the “value of the human being” that should play a role in the SAHPRA PTA/CA guidelines.

The focus from sponsors/pharmaceutical companies are to have the trial performed in the shortest duration, in the fewest number of patients to register for commercial accessibility. However, while the adaptive design approach supports commercial access objectives, it doesn’t support the moral obligations around the trial participant who may have their trial benefits suddenly terminated. If the aspect of the “common good and value of the human being” is fully integrated into rapidly evolving innovative world of clinical trials through customized post-trial access, it allows for a fair return to the participants who have enrolled on a clinical trial. It considers the exceptional situation of the person to accommodate their extended treatment needs beyond a short clinical trial instead of focusing only on trial efficiency gains. As noted earlier, <3% of clinical trials are conducted in Africa. With the emergence of adaptive design, it means an added challenge as fewer patients are required in a shorter period to contribute to the commercialization of highly innovative, expensive medication. Hence it is ultimately the sponsor company that benefits with reduction of research and development cost. However, if there are African Ethics notions of the “common good” for the trial participant population considered, compensation to trial participants can be done in the form of a type of extended access for effective medication, even once the trial has ended. SAHPRA can also advocate for stronger PTA in situations where the disease under research is one in which the trial participant community is more afflicted by medication access challenges compared to other parts of the world. In applying this broader based thinking around a humanitarian standpoint, it gives an opportunity for patients from developing countries such as South

Africa, to have reasonable benefit from trial medication in the potential absence of commercial availability.

Overall Chapter Summary

To summarize this argument, I have shown that with specialized/innovative medicines, there is a steep associated cost which in turn has a downstream impact on the pricing model, and availability of such medications in developing countries. As such the probability of the participant having access to the medication in its registered form once the trial has ended is doubtful which can be highlighted as the first disadvantage for trial participants. The more prominent access of these medications is seen in higher income countries where the commercialization of these medications is forecast, with a bleaker outlook for developing countries (Aitken M, Kleinrock M, Pritchett J, 2023).

In light of the dual impact of both limited or no access to the novel therapy and potentially a shorter time on the trial and reduced participant numbers in a country based on adaptive design protocols, this means less participants being able to enroll in a country or the opportunity for the full benefits of a clinical trial.

It is thus important to consider both the elements of Distributive justice and African Ethics notions to make a fair assessment of how the South African post-trial guidance should be inclusive of these emerging changes. To this point, I would propose that the SAHPRA PTA/CA guideline adds a specific clause related to Innovative Design medicines and protocols where there is a more attentive method of post-trial access that is applied for these situations. This could either be in terms of a longer access period or alternatively a

commitment by sponsor companies to fulfil a larger social responsibility based on the country's epidemiology and severity, treatment options with certain diseases.

Overall, the advent of more specialized innovative therapies should be included in the context of the guideline as it becomes a more normalized way of clinical research into the near future.

Chapter 6: Response to Objections

I will now explore the potential objections that could arise with reference to the arguments that I've raised on why the SAHPRA post-trial access guidelines should be revised to target the healthcare dynamics of the South African patient.

In this section, I will respond to plausible objections for each of the following chapters:

A) Chapter 3: The South African healthcare dynamics and challenge with post-trial access

The first argument focused on how deficiencies in the South African healthcare system could unfairly disadvantage trial participants returning to this system. I argued that access to effective medication could be threatened, as neither the standard of care medication in public healthcare nor private healthcare could be relied upon for an equitable transition from efficacious clinical trial medication.

Objection: It could be objected that there may not be a rationale for imposing revisions in the SAHPRA Guidelines based on **an impending change to a National Health Insurance (NHI) healthcare system in South Africa** as declared in June 2023 (Solanki et al, 2023, p 13). It could be said that a nationalized health system will mean that South Africans will have equal right to healthcare and **access to medication into the near future** and as such the guidelines will not need amendment or revision.

To respond to this point, I contend that a utilitarian view that NHI can solve the unmet post-trial access needs of trial patients, is a flawed perspective. Although a nationalized healthcare system is well intended to support patient access to medication through a stratification method for equalized distribution of medication and resources, it has proven

challenging in similar third world countries. Specifically for South Africa, the biggest challenge anticipated for NHI implementation is the financial constraint linked to funding from tax revenues, that could lead to 'inequality and fragmentation of the health system' (Cashin, Dossour, 2021, pp 1-3). Some issues cited to obtain equitable access to medication in countries with a healthcare benefits package such as Ghana, Kenya, Nigeria, Rwanda and Tanzania include: limitation of benefits based on contracted services, 'pro-urban and pro-private' healthcare funding and sustainability, patient lack of education around enrolment into the national scheme, poor quality of services, lack of resources, and unfair distribution of services (Flourence et al, 2023, pp. 12-14) These in turn leading to disparate access to medication as well as healthcare services. Accordingly, with these challenges of similar countries considered, the NHI implementation in South Africa to may be plagued with various challenges before it can be a fully equitable model for patients. Furthermore, other issues anticipated include the legal recourse by impacted stakeholders citing that the NHI bill imposes 'constitutional infringements', by challenging the economic resilience of such a model in an already 'weak and stagnant economy' with an existing inequitable healthcare infrastructure, and societal inequalities as a foundation to this system (Solanki et al, 2024). It can be seen that the South African NHI model must overcome various new and existing healthcare hurdles to deliver the promise of equitable access to medication for all South Africans, to ensure both quality healthcare and medications are made available to all citizens.

Hence, with the challenges in scope of the NHI model, to have a fully robust and effective system can may take many years until equity can truly be achieved. As a result, this alternative design as a nationalized healthcare system design will still not be adequate to

meet the needs of post-trial access and hence to maintain an approach of beneficence for trial patients, the SAHPRA Guideline should have reform with reference to 'standard of care'.

B) Chapter 4: The unjust clinical and non-clinical harms of post-trial discontinuation

In the second argument, I defended the claim that if the duration of post-trial access is inadequate for the disease condition, it could lead to unjust clinical and non-clinical harms for a patient after clinical trial completion. In this case SAHPRA recommendation in the post-trial guideline is 'a minimum of 4 years…' and I argued that this timeframe is insufficient especially for certain high prevalence, debilitating diseases as well as medical device clinical trials.

Objection: The objection that could be raised on this second argument may that of a consequentialist rule-based viewpoint in that **clinical trial patients deserve no further exceptions to healthcare opportunities compared to other South African patients**. For instance, it could be reasoned that trial participants already have an advantage by having first hand exposure to novel therapies and on this basis, post-trial access conditions do not need to further accommodate trial participants. This would be grounded in the notion that the healthcare needs for the greater majority of the population are prioritized instead of those of trial participants only. It could be said that more emphasis and plans medication access for all patients will alleviate the healthcare burden in South Africa and support sustainable broader healthcare reforms and less harms to patients.

As a response to this objection, I lean on specific justifications for why clinical trial participants are deserving to have such 'exceptional' consideration with revisions for post-trial access, even if it does not meet the needs of all South African patients. Firstly, the voluntary nature of clinical trials means trial participants consent to be at the forefront of risk and potential adverse effects of experimental medications. Trial participants may already be afflicted with vulnerable circumstances, not limited to age, gender, economic/financial circumstances, minority groups, etc. (Bracken-Roche, et al, 2017 p 8). Despite this, due to their dire need for treatment, they accept both the intended benefit and risks that could result in adverse side effects, irrecoverable health consequences and mortality through signing a consent form (Da Silva et al, 2018 pp 1002, 1008). While there could be a definite benefit to trial participants themselves from efficacious treatment exposure, there is a strong altruistic component for how this benefits the global patient society for a specific disease. Those reasons being that they directly contributing to many other noteworthy aspects, including: sharing their biological/genetic material for analysis to contribute to learnings in science and discovery, if the medication is proven effective, this has a direct positive impact on the share prices, profit and earnings of pharmaceutical companies, by being the first line recipients of risks, side effects, this allows dosage modifications and optimal use in the real-world setting. While all South African patients deserve the 'right to healthcare', and should be fully entitled to this right, it cannot be achieved by refuting the rights and privileges of trial patients.

To this end and contrary to the potential claim of this objection, if trial patients continue on post-trial medication for an acceptable timeframe, it will instead allow for more healthcare benefits for the country. Some of these benefits can be seen in the generation

of long-term safety and efficacy data for country epidemiology statistics, reduced burden on the healthcare system especially if revoking the intended medication or device could eventually lead to clinical or non-clinical harms as per the earlier cited examples. Hence to conclude this response is that while trial participants may receive the advantage of access to 'cutting-edge' medication, it is nevertheless warranted that they receive an appropriate duration post-trial access according to their vulnerabilities and other contributions to science.

C) Chapter 5: Innovative Medicines research, adaptive trial design as considerations for post-trial access

In the last argument, the premise I put forward was that clinical research is evolving at a rapid pace with new methodology for how trials are being conducted as well as the types of innovative new medicines that are being tested. This progress in turn should influence post-trial access conditions. I argued that it is important for the SAHPRA PTA/CA guideline to account for these significant changes to clinical research.

Objection: Following through on the logic of this argument, it could be objected that due to the rapid changes and progression of clinical trials and research, South Africa could be disregarded as a research country with more detailed or demanding post-trial access conditions. As a result of this, and with an already low incidence of clinical trials conducted on the African continent, this could lead to broader exclusion in clinical trials overall and be a hurdle to early medication access opportunities for those patients in need. Furthermore, it could be objected that it would not be sustainable for the pharmaceutical companies to continue provisioning post-trial access based on individual country needs.

I respond to this objection based on two angles, which is firstly that there is an inevitability that trials in Africa and South Africa will grow because of the need for genetic heterogeneity and inclusive geographical representation of clinical trial patients. Secondly, that having more expansive post-trial guidelines in other developing countries have not deterred clinical trials but in fact have had a more positive impact on both trial participation and as such supported country selection by Sponsor companies.

To elaborate on the first stance, is that pharmaceutical companies are dependent on developing countries to meet clinical trial enrolment numbers for certain types of disease conditions. The reason for this is that as patients in lower economic countries have limited/no commercial access to innovative medication such as cell and gene therapies (Hendricks et al, 2023 pp 180, 182), hence their willingness and need to participate in clinical trials is higher compared to first world countries. Moreover, another point to consider in specialized and innovative medicines trials, is that patients from first world countries may be rejected through trial exclusion criteria. The reason for this would be if they have had treatment exposure to therapies with similar mechanism of action which are registered and available in those countries. In comparison, this is less likely to occur in the developing countries where medications are not yet registered/accessible, making patient enrolment more straightforward. In this way, the inequitable global healthcare distribution becomes a marker for clinical trial growth in developing countries.

Following through on another angle to this objection, I will respond with an example in a developing country such as Brazil which shows an example of fairness in post clinical trial access conditions. Brazil has a country specific post-trial guideline with endorsed long-term post-trial access conditions. Brazil follows the United Nations resolution

2002/32 which defends that “right to drug access is part of the human right to health” (Campos, 2012). In this guideline, it is highlighted that not only does the State have an obligatory responsibility to support this decision of long term post-trial access, but so too does the pharmaceutical sector. In this sense, the Brazilian post-trial directive, has asserted basic human rights and shared responsibility of post-trial access as the cornerstone of their “ethical-legal guideline”. This has not stagnated the growth of clinical trials in the country, but instead Brazil is considered a high performing country whose participation is vital in future clinical trials (Junior, Albuquerque, 2016). With respect to this example of Brazil, it can be reasoned that participants benefit by having access to transformative medicines while also being guaranteed access for as long as benefiting. This constitutes a system of distributive justice and fairness for the participant and does not negatively impact access to clinical trials for a developing country.

Chapter 7: Conclusion

In closing, I have made arguments related to both deficiencies in details with certain explicit clauses and lack of clauses in the SAHPRA version 4.0 guideline relative to the South African healthcare system:

1. "*Post-trial access / Continued Access should be considered for Phase III studies when **no registered and marketed standard of care** is available in South Africa"*.
2. **'minimum four-year period'** in which post-trial access should be considered 'for those who derive benefit from the investigational product'.
3. Lastly, I have looked at the lack of information/context of **innovative medicines technology and the adaptive research designs** in the SAHPRA Version 4.0 guideline.

For each of these references to the SAHPRA Guidelines Version 4.0, I have proposed the following considerations relative to each statement above:

1. Based on the principle of beneficence, standard of care therapies as an equivalent medication alternative should not be a theorized as a 'one size fit all' approach but instead the guideline should allow for the unique real-life circumstances of those trial participants who lack access to medication following clinical trial completion
2. Instead of a 4-year minimum period, there should instead be consideration for the specific disease that is being researched and the consequences for participants if they do not have longer term access for some disease. Therefore,

the guideline should support with an appendix of certain life-threatening or debilitating diseases with more direction and details for stakeholders (such as sponsors and clinical trial sites) on how to manage post-trial access duration in these types of trials.

3. With respect to Innovative design in clinical research, I put forward the proposal that the post-trial guidance should be inclusive of more transparent context when these advanced medications are administered in clinical trials. As these advanced medications could have a far superior efficacy to standard of care, it is important that the consequences for the participants' are considered when transitioning off clinical trial medication.

In conclusion of my research report, I have shown how the current SAHPRA version 4.0 guideline overlooks medication access obstacles for the South African clinical trial patient, fails to address local economic and healthcare context and does not align with the modernization of clinical trials. The normative arguments put forward are centred on the respect for the participant circumstances/autonomy, avoiding non-maleficence, and promoting distributive justice for trial participants, I have shown how there are clear advantages of revising the guideline to be more inclusive of the South African patient access to medication context, reduce harms and promote fairness for trial participants.

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[i] Footnote 1: There are other guidelines in South African that impact the principles and decision making of post-trial access including NDOH in Research 2024 and SA GCP 2020. However I will focus specifically on the SAHPRA guidance, Version 4.0 for the purpose of this research report.