INCIDENCES ASSOCIATED WITH ENALAPRIL-INDUCED ANGIOEDEMA, IN A PUBLIC REGIONAL HOSPITAL, LIMPOPO PROVINCE (SOUTH AFRICA)

BLESSING MUREMELA (2400944)

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SUPERVISOR

Dr Neelaveni Padayachee, University of the Witwatersrand, Department of Pharmacy and Pharmacology, South Africa

CO-SUPERVISOR

Dr Varsha Bangalee, University of KwaZulu-Natal, Discipline of Pharmaceutical Sciences, South Africa

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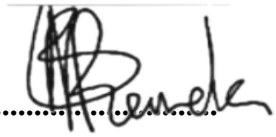
DECLARATION

I, **Blessing Muremela, Student Number [2400944],** declare that this Dissertation/Research Report is my own work. It is being submitted for the degree of Master of Pharmacy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination, at any other University.

Signature of Student..... 

Date… .....04 October 2023.

DEDICATION

This work is dedicated to my parents - Muremela L.S & Muremela M.G.

ABSTRACT

Background

The study explored enalapril-induced angioedema reactions at Tshilidzini Regional Hospital (South Africa), from January 2017 to December 2019. The aim was to identify and describe incidences of enalapril- induced angioedema in a public regional hospital, over a three-year period.

Materials and Methods

A retrospective record review was undertaken at Tshilidzini Hospital. Data were collected from medical files of patients who had experienced enalapril-induced angioedema, between January 2017 to December 2019. Cases were retrieved using the pharmacovigilance ADR database records. Demographic information, medical history, clinical presentations, therapeutic management and outcomes were collected and consolidated on a data collection tool. A Microsoft Excel spreadsheet was used to record the information which was then interpreted utilizing the Statistical Package for Social Sciences (SPSS) version 29. Ethical clearance was acquired from the University of the Witwatersrand Human Research Ethics Committee (Medical).

Results

Forty cases (37.3%) of enalapril-induced angioedema were included out of a total of hundred and seven cases reviewed from the Pharmacovigilance ADR database records. The results indicated that demographic details - gender, age and race - affected the incidence of enalapril-induced angioedema. Out of the forty cases, most were female (95%) and between the ages of 50-59 (25%) and 70-79 (25%). Majority of the participants presented with swollen lips (34%) and tongue (24%) as clinical presentations of enalapril- induced angioedema. All participants were counselled and they discontinued enalapril after the incident. Hospitalization occurred in 15% of the participants and death occurred in 5% of the participants.

Conclusion

Amongst the cases reviewed, swelling of the lips and tongue was reported to be the most common clinical presentation of enalapril-induced angioedema. The study findings suggest a need for awareness among all healthcare professionals, so that they could identify and treat

enalapril-induced angioedema as well as report all incidences. ACE-induced angioedema may be occurring more regularly but may not be known due to misdiagnosis and underreporting by healthcare professionals. This shows that healthcare professionals must constantly be conscious about the significance of reporting enalapril-induced angioedema to improve patients' safety and treatment outcomes. More reporting of incidences and further research is required for healthcare professionals to become knowledgeable about this life-threatening condition.

Keywords: Enalapril, angioedema and public health

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ABBREVIATIONS

ACEi	:	Angiotensin-Converting Enzyme Inhibitors
ACE-AE	:	Angiotension-Induced Angioedema
ADR	:	Adverse Drug Reactions
ARBs	:	Angiotensin Receptor Blockers
BP	:	Blood Pressure
CCBs	:	Calcium Channel Blockers
CVDs	:	Cardiovascular Diseases
DOH	:	Department of Health
EML	:	Essential Medicine List
LP	:	Limpopo Province
SA	:	South Africa
SAHPRA	:	South African Health Products Authority
SSA	:	Sub-Saharan Africa
STG	:	Standard Treatment Guideline
UMC	:	Uppsala Monitoring Centre
WHO	:	World Health Organization

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Hypertension is a serious health concern. It accounts for 10.4 million deaths globally, and it is estimated that 1.39 billion adults are affected by it (Mills et al., 2020; Sharma et al., 2021). This section summarizes the present study background, describes the problem that initiated the study, states the research objectives, formulates the research questions as well as highlights the aim and significance of the research. In addition, the discussions will focus on - the health crisis of non-communicable diseases in SA, adverse drug reactions and deaths associated with using enalapril.

Hypertension poses a significant threat to developing cardiovascular conditions and when untreated, it causes high morbidity and mortality rates (Schellack & Malan, 2014). Poor and middle-income countries have a rising hypertension rate compared to high-income countries (Jongen et al., 2019). South Africa (SA) has a significant health crisis in relation to non-communicable diseases and, as a result, faces a quadruple burden of diseases (Mayosi et al., 2009; Samodien et al., 2021). The quadruple burden of diseases in SA includes high rates of diseases which includes - communicable ones like HIV/AIDS and tuberculosis, non-communicable ones including cardiovascular disease (CVD), maternal and infant mortality, and injury-related ailments (Modjadji, 2021). CVDs account for almost one-sixth of all deaths (17.3%) in SA (Heart and Stroke Foundation South Africa, 2016) as well as causing 13% of all deaths in Sub-Saharan Africa (SSA) (Yuyun et al., 2020).

Hypertension has a high prevalence in SA, especially amongst the black ethnic group (Rayner, 2010). Hypertensive-related diseases ranked number six of the top diseases that caused 19,900 deaths, in SA, in 2015-2017 (Mortality and causes of death in South Africa, 2017). The black ethnic group were estimated to be 80.7% of the total SA population, while white, Indian and coloured ethnic groups were estimated to be 7.9%, 2.6%, and 8.8%, respectively (Department of Statistics South Africa, 2019). The rising rate of hypertension in SA was reported to be 35.1%, with more than 90% of patients with uncontrolled blood pressure (Rayner et al., 2019); a study conducted in the Limpopo Province (LP) revealed a prevalence of 41%, which confirmed that hypertension is a rising health crisis in SA, particularly, in rural areas (Ntuli et al., 2015).

Enalapril is an Angiotensin-Converting Enzyme (ACE) inhibitor prescribed extensively and effectively to treat of cardiovascular conditions, including high blood pressure and heart failure (Hayn et al., 2017). ACE inhibitors stop the conversion of angiotensin I into angiotensin II and inactivate the breaking down of bradykinin, decreasing peripheral vascular resistance, thus lowering blood pressure (Porter & Kaplan, 2011). Members of other ACE inhibitor classes include - lisinopril, perindopril, benazepril, captopril, quinapril, ramipril and trandolapril (Rossiter, 2016). ACE are used worldwide, by approximately 40 million people (Sanchez-Borges & Gonzalez-Aveledo, 2010), and are currently the primary cause of angioedema in the United States (Banerji et al., 2017). ACE inhibitors are typically regarded the preferred medication for treating hypertension and diabetic nephropathy, although, they are associated with adverse drug reactions, which include a constant dry cough and life- threatening angioedema (Moholisa et al., 2013).

Angioedema is a widely-known, unfavourable drug reaction to angiotensin- converting enzyme inhibitor therapy (Terreehorst et al., 2019). It commonly presents as localised swelling seen on the face, lips, tongue and may block the airways, therefore, may result in mortality (Chiriac et al., 2018); it is also manifested by inflammation of the skin and mucosal layer, which can be deadly if the upper airway is obstructed (Ali et al., 2019). Additionally, angioedema may affect the visceral systems, such as the gastrointestinal tract and oropharynx (Nzeako, 2010). ACE-induced angioedema may occur at any administration time, either as soon as the initial treatment or after years of taking the medication (Matshitisho, 2012). ACE- AE is a severe adverse drug reaction to ACE inhibitors that some patients may experience recurrently (Rasmussen et al., 2017).

A prospective study by Kostis et al., (2005) found that 86 out of 12 557 patients had enalapril-induced angioedema in a 24-week treatment period, which indicates a 0.68% incidence rate. In a similar study, two enalapril-induced angioedema cases presenting swelling of the lips were reported in a rural setting in Kenya (Okumu, et al., 2018). A 74-year-old female was reported in Botswana as showing signs of oedema of the face and tongue with difficulty in breathing just two days after the administering of enalapril (Anish & Gabremedlin, 2016).

ACE inhibitors-induced angioedema was found to have a 1.4% mortality rate with a higher risk than angioedema caused by other drugs (Cheah et al., 2017). In SA, twelve incidences associated with enalapril-induced angioedema have been reported, causing the death of four

patients (Cupido & Rayner, 2007). In addition, two asphyxia death cases were reported in SA caused by swelling of the tongue and blockage of the upper respiratory as a result of ACE-inhibitor treatment (Tiemensma et al., 2010). Decloedt (2009) reported a cerebral angioedema case, describing how enalapril-induced angioedema can be life-threatening. A 79-year-old male reported a history of five recurrent episodes in four months of cervicofacial enalapril-induced angioedema; the patient recovered with the discontinuation of enalapril which emphasises the need for withdrawal of the ACE-inhibitor causing angioedema once patients show certain symptoms (Ungureanu & Madalan, 2019).

Thiazide diuretics and Calcium Channel Blockers (CCBs) are commended and approved as an initial-line therapy for uncomplicated hypertension in black people because of their effectiveness in reducing blood pressure compared to ACE inhibitors (Seedat et al., 2014) (Akunne & Adedapo, 2019). Black hypertensive patients are considered more susceptible to ACE inhibitors-induced angioedema because they have lower urinary kallikrein levels and may have decreased endogenous bradykinin levels (Tiemensma et al., 2010). A study by Ogedegbe and colleagues (2015) confirmed that black people on ACE inhibitor-based regimens have fewer positive outcomes than white people on the same regimen, showing that antihypertensive treatments' effectiveness may be affected by patients' ethnic group and age (Mpe, 2007). Thiazide diuretics are the most cost-effective treatment for uncomplicated hypertension compared to other antihypertensive medications (Ernst, 2005).

ACE inhibitors cause angioedema frequently than is typically reported as a result of poor diagnosis, insufficient documentation by healthcare professionals and unrecognised symptoms; these may cause the deterioration of the condition to a fatal event (Piller et al.,2006). Underreporting of cases delays the management that can be put into place to limit any catastrophic adverse drug events (Guner & Ekmekci, 2019). The South African Health Products Regulatory Authority (SAHPRA) monitors the safety of medications some of which may be withdrawn from the market provided there are comprehensive adverse drug-reaction reports (Mehta, 2011). Healthcare professionals, therefore, should know about adverse-event reporting as they play an essential role in the pharmacovigilance system (Najafi, 2018).

1.2 PROBLEM STATEMENT

Enalapril is widely used for treating cardiovascular diseases globally and locally, although it raises the risk of angioedema. According to the literature, enalapril-induced angioedema can be life-threatening (Cupido & Rayner, 2007). Hypertension is widespread in SA, particularly, among the majority black ethnic group (Rayner, 2010; Seedat et al., 2014); which raises the risk of induced angioedema, among this group, when enalapril is used, therefore policy changes need to be implemented to reduce the incidences and deaths caused by enalapril.

According to the literature, healthcare workers lack understanding and training in handling enalapril-induced angioedema and in reporting adverse-drug reactions (Nishad et al., 2019; Leru et al., 2020). Because of this healthcare professionals need more awareness and training in enalapril-induced angioedema with ADR reporting to improve patient outcomes, hence, the rationale for this study.

1.3 RESEARCH QUESTION

- What are the risk factors associated with or contributing to enalapril-induced angioedema?
- What are the common clinical presentations of enalapril induced angioedema?

1.4 AIM AND OBJECTIVES

1.4.1 Aim

To identify and describe incidences and contributing risk factors associated with enalapril-induced angioedema, in a public regional hospital, for the period, January 2017 to December 2019, to bring about improved patient outcomes.

1.4.2 Objectives

- To describe the incidences and severity of angioedema induced by enalapril
- To analyse clinical presentations and contributing risk factors associated with enalapril-induced angioedema.

1.5 LITERATURE REVIEW

This section will discuss various studies on enalapril, angioedema, hypertension and pharmacovigilance systems undertaken, internationally and nationally, providing a background information for the study. The discussions will, additionally review outcomes of adverse drug reactions, reporting systems, why drug safety is essential as well as compare the public healthcare sector with the private healthcare sector in SA. The process will also involve an exploration of the literature on the incidences, clinical presentations and therapeutic interventions associated with enalapril-induced angioedema. An overview, summary, and evaluation of the current knowledge regarding topic, hence, will make up the literature review (Snyder, 2019).

1.5.1 Overview of Hypertension

Hypertension is a haemodynamic known condition typified by an increase in peripheral vascular resistance, which can cause myocardial infarction, renal failure, strokes, and death (Sever & Messerli, 2011; Schellack & Natalie, 2014). The condition has been recognized as the most prevalent, crucial risk factor for Cardiovascular Disease (CVD), and has been increasing in both poor and middle-income nations (Sharma et al., 2021). Literature has shown that Africa has the greatest rate of hypertension globally, with low-middle-income countries bearing over 80% of the burden associated with the disease (Pillay, 2021). Researchers have confirmed that both developed and developing countries, such as South Africa, are both significantly affected by hypertension but with low control and poor awareness in the developing countries (Smith, 2014; Ibrahim, 2018).

Many reports in the literature have shown that SA is amongst the countries with the greatest rates of high blood pressure in Southern Africa and worldwide, as well as having low rates of diagnosis, poor patient awareness, low treatment and management (Ware et al., 2019; Masilela et al., 2020). Similarly, Van de Vijver et al., (2013) pointed out that HPT occurrence in SA has escalated rapidly over the past two decades and predicted that the rate will further increase; as reported by WHO, 27.4% of males and 26.1% of females in SA have hypertension (Jongen et al., 2019). Another study reported that hypertension is rising in rural areas, for example, in the Limpopo Province, with an estimated increasing rate of 38.2 % in 2016 (Maimela et al., 2016), hence, the current research set in a rural area in the Limpopo Province is very relevant.

In a South African study, the prevalence of untreated hypertension, between those aged 15 and above was found to be 13.5%, and 48.7% of hypertensive people were undiagnosed and unscreened (Berry et al., 2017). Many studies revealed that rapid urbanisation, unemployment rates in SA, consumption of western diets and excessive alcohol intake, may be some of the many contributing factors to the occurrence of uncontrolled HPT in SA (Kandala et al., 2021; Adeniyi et al., 2016). This shows that there is a gap in understanding and considerable unmet demands for better health-promotion programs to increase hypertension awareness (Jongen et al., 2019). An important factor in preventing and managing high blood pressure in patients diagnosed with hypertension is lifestyle adjustment with or without antihypertensive treatment (Amoah et al., 2020), therefore, continuous research and implementation of findings are crucial to improve patients' health.

1.5.2 Private Health-Care Sector vs Public Health-Care Sector in SA

Literature indicates that there is a considerable disparity between the rich and poor in SA resulting in a healthcare system that is separated into two categories - private and public -with the public sector serving a greater number of residents (Kandala et al., 2021; Komape, 2013). There are clear gaps between the public and private healthcare divisions, with the public division defined by disadvantages such as - lengthy waiting times, hurried appointments, outdated facilities and limited resources. In contrast, the private sector provides better services with more resources, but is more expensive, thus, not accessible to everyone (Young, 2016). In addition, public healthcare facilities in SA are also confronted with unavailability of prescribed medications, such as, antihypertensive chronic drugs that harm blood pressure control (Rampamba et al., 2021).

In SA, there is persistent socioeconomic inequality, a heavy burden of diseases, and inequitable healthcare delivery. It is vital, therefore, that new health systems addressing and overcoming these concerns must be explored, to bridge the healthcare inequalities gap (De Villiers, 2021). According to Maphumulo & Bhengu (2019), in South Africa, various national health programs have been introduced and amended, but many have failed to provide the intended fundamental standard of service. Public health programmes and services remain inadequate in SA, while the burden of diseases increases, necessitating a critical evaluation to inform the health system's strengthening (Malakoane et al., 2020). The estimated 8.22 million hypertensive people in

South Africa who lack private health insurance place a considerable economic strain on public health systems, necessitating the identification and implementation of a cost-effective hypertension treatment. The control of hypertension must be prioritised in South Africa by implementing efficient population-based policies and solutions (Peer et al., 2013). Hypertension is very prevalent in many African countries, due to low awareness and BP control (Okello et al., 2020), therefore, the cost of medications, knowledge of patient-based risk factors and contraindications should all be considered before selecting a hypertensive regime for a patient (Seedat & Rayner, 2011). BP control management in South Africa depends on addressing problems affecting the hypertension regime (Pender, 2019).

1.5.3 Pharmacovigilance Systems Globally and in South Africa

Pharmacovigilance is pharmacological science and practices concerned with identifying, evaluating, comprehending, and preventing ADR or other drug-related reactions (WHO, 2002). Researchers have shown that pharmacovigilance is critical for public health protection, because it prevents, detects, collects and analyses ADR reports which evaluates the safety of medicines, for people (Maqbool et al., 2019; Sienkiewicz et al., 2021). The global pharmacovigilance systems were triggered by the thalidomide disaster in the 1960s, which caused infants to be born with congenital disabilities (Kim & Scialli, 2011). According to Jose et al., (2021) the pharmacovigilance systems enhance medication safety by reducing ADRs incidences and providing a warning network for healthcare providers, regulators, manufacturers, and consumers.

The pharmacovigilance systems in South Africa were established in 1987 and became a member of the WHO collaborating centre -Uppsala Monitoring Centre in 1992 which collaborates on international drug monitoring (Mehta et al., 2017). The Regulatory Pharmacovigilance unit of SAHPRA in collaboration with NDoH is responsible for SA pharmacovigilance systems while Uppsala Monitoring Centre (UMC) is a collaborative worldwide centre for drug monitoring. According to WHO guidelines, governments should set up a national PV centre that will consider the effectiveness and safety of a medical product in their specific setting (WHO, 2006). The drug safety information received from countries' pharmacovigilance centres aids in developing essential drug lists and standard treatment guidelines.

The usage of medication has increased over the last three decades in Africa, however, the usage has not been backed up by adequate pharmacovigilance systems to observe and ensure the safety of these medicines (Isah et al., 2012). Studies have shown that a fully functioning national PV system is essential and should be in a position to consolidate reports on how to decrease the considerable burden of drug-induced diseases. This should be in addition to providing evidence-data to guide treatment policies, which should subsequently improve outcomes of common diseases, such as HIV, TB, and hypertension (Mehta et al., 2017; Dheda, 2016). Pharmacovigilance is critical in addressing issues emanating from medicine's ever-changing potency, unanticipated potential for damage and in a bid to achieve drugs expected therapeutic outcomes (Jeetu & Anusha, 2010).

1.5.4 Outcomes of Adverse Drug Reactions (ADR)

Adverse Drug Reaction (ADR) is a negative, unfavourable and unwanted response to a medicine and occurs when taken by people for the prevention, identification, or treatment of a condition or during the modification of the physiological functions of the drug (WHO, 2002). ADRs pose a global public health threat, endangering patients' safety and this eventually may lead to death (Jo et al., 2022). ADR endangers the lives and wellbeing of patients and results in unnecessary waste of government funds (Yan, 2021). According to Mejia (2020) in a Spanish study, ADRs caused 8.4% of urgent hospital admissions in that year. There have been advances in pharmacovigilance in recent years, despite that, the impact of ADRs on public health continues to be significant due to the increasing usage of medicines (WHO, 2006), with limited research available on them (Giardina et al., 2018). ADRs extends the duration of stay in hospital, which raises the financial burden of additional medical care (Fasipe et al., 2019). Clinical trials are frequently the only source of information on a health product's safety and effectiveness when it is first registered and available in a country. Consistent drug safety monitoring, however, is also critical because initial clinical trials do not identify all possible adverse events as they are not extensive enough and may not include all types of patients (SAHPRA, 2020).

The concept of drug safety is critical to a patient's health, therefore, some categories of patients, such as, pregnant women, paediatrics, and the elderly, should be given extra care and monitoring because they are vulnerable groups (Alshammari, 2016). The safety of medications in paediatrics is a major health issue around the globe. Children are more susceptible to adverse

drug reactions, which can lead to lifelong impairment and death (Khan et al., 2021). South Africa's high HIV prevalence affects the rate of ADR; for example, the occurrence of ADR in two paediatric hospitals was found to be 3.8 ADR per 100 drug-exposed admissions caused by antiviral drugs (Mouton et al., 2020). In South Africa, one in every twelve admissions is due to ADR, with HIV and TB medicines being the most common causal drugs, reflecting the country's high HIV and tuberculosis load (Mouton et al., 2016). Clinical trials have limitations in detecting rare and very rare ADRs, hence, pharmacovigilance is critical in detecting these. Information on drug safety is, therefore, important in influencing healthcare policies and ensuring public safety (Anusha et al., 2017).

1.5.5 The Reporting of Adverse Drug Reactions (ADR)

Literature shows that ADR underreporting is a global problem that results in strain on the health and economic sectors (Khan et al., 2020; Guner, 2019) and despite the existence of national reporting systems, most countries are underreporting. A study in Israel found that the rate of adverse-medication reaction reporting was low (Shchory et al., 2020). SA was also reported to have a recognized low-reporting of adverse-medication reactions (ADR) data, and that the effects have become more evident in the past years (Pillay et al., 2021). Current literature indicates that ACEi-induced angioedema is underreported, despite the acknowledge of the significance of reporting ACE-related angioedema incidences to improve outcomes and lower the associated morbidity and deaths (Manzur-Barbur et al., 2022). The Western Cape Province in SA has a drug surveillance program that collects data on ADR from public health sectors, from the data, enalapril was found to be one of the most common ADR-causative drugs reported from 5486 confirmed ADR cases (Jones et al., 2020). There is still a need in low-income and developing countries to establish active pharmacovigilance programmes that will be used to retrieve data to influence healthcare policy and practice (Kiguba et al., 2023). ADRs significantly affect the wellbeing and health of patients, given the increasing dependency and diversity of medicines, currently (Khalil & Huang, 2020).

The majority of pharmacovigilance systems throughout the world rely on spontaneous reporting systems, although, similar, to other systems around the globe, South Africa suffers from under-reporting of ADRs by healthcare practitioners (Mehta, 2017). Guner (2019) pointed out that pharmacovigilance requires involvement of all health care professionals in a significant way, as its systems depend, highly, on the participation of all healthcare providers.

Education for healthcare professionals is essential to enhance their knowledge, outlook and the practice of ADRs' reporting (Terblanche, 2018). Many countries have even included ADR reporting from patients in their pharmacovigilance systems, since patients have a different perspective, to healthcare professionals, on medication safety, (Hariraj, 2018). This is despite the fact that it is assumed that the majority of patients do not understand the existing ADR procedures, therefore, pharmacovigilance awareness should be promoted among the public to enhance patient safety (Pillay, 2021).

1.5.6 Incidences Associated with Enalapril-Induced Angioedema

Angioedema is a clinical condition usually characterised by inflammation of the subcutaneous layer of the skin (Pines et al., 2021). Enalapril is an ACE inhibitor usually utilized to manage high blood pressure and congestive heart failure and is also associated with adverse reaction-induced angioedema (Faruqi & Jain, 2021). Studies have shown that angioedema induced by enalapril or any Angiotensin-Converting Inhibitor (ACEi) is a known adverse drug reaction, occurring among 0.1 - 0.7% of patients who received treatment, globally (Alharbi et al., 2018; Montinaro et al., 2020). Other researchers have pointed out that, although ACEi-induced angioedema incidence rate may seem low, the rate of usage of ACEi is increasing worldwide due to the rising number of patients with congestive heart failure, diabetes, and diabetic neuropathy, which makes ACEi-induced angioedema common in clinal settings (Sharma & Nagarajan, 2022).

Researchers like Gang et al., (2013) and Pall et al., (2021) have shown that angioedema commonly presents to the emergency department with ACE inhibitors as its primary aetiology due to the overwhelming number of patients taking the medication. ACEi can cause adverse reactions, like coughs and angioedema at approximately the rate of 5-35% and 0.7% respectively (Bezalel et al., 2015). The occurrence rate of ACE-induced angioedema incidences (ACE-AE) has been estimated between 0.1% and 2.2% of treated patients (Hirshchy et al., 2018). A study conducted in the United States, in 2008, reported that 0.20% of patients on medication have developed ACEi-induced angioedema (Brown, 2017). Enalapril-induced angioedema has been described as a condition that is also typical in Botswana's emergency rooms (Anish et al., 2016).

Kainat et al., (2021) maintain that the timing of the occurrence of the reaction, varies from months to years, after the initial administration and may recur even after discontinuation of the drug. Another study, however, revealed that angioedema is generally common within the first year of intake, with the exception of some cases occurring later (Manzur-Barbur et al., 2022). The time frame of recurrence was highlighted in another study which discovered that most angioedema attacks happen within 12 months after discontinuation (Kallepalli et al., 2018). According to literature ACE-AE was reported as non-dose related (Squillante et al., 2021). Literature reports an escalation in ACE- related angioedema cases in the last decade, showing an increase in the incidence risk (Inomata, 2012). Every patient on ACE inhibitors must be observed and warned about this potentially fatal adverse event, because ACE-AE can occur years after the initial treatment intake (Goyal et al., 2022).

1.5.7 Risk Factors Associated, Clinical Presentations and Outcomes of Patients Found with Enalapril-Induced Angioedema

1.5.7.1 Risk Factors Associated

Many studies have reported that higher risk of ACEi-angioedema is associated with the African race, suggesting a genetic effect and the incidence rate may be up to five times higher in comparison to other races (Rasmussen et al., 2020; Guyer et al., 2022). A study that compared ACE-AE and non-ACE-induced angioedema found that 80% of patients in both groups were of the African race and that 8% of ACE-AE patients had a history of previous reactions to ACE-AE (Weisman et al., 2020). Another study that investigated the number of deaths associated with angioedema between 1979 and 2010 in the United States, found that 55% of deaths related to ACE-AE, were among the black race (Kim et al., 2014). An increased prevalence of ACE-AE reactions was found to be more associated with women aged between 50 and 70 (Asad & Gohar, 2020). Other predisposing factors, include - older age, smoking, seasonal allergies and a history of previous ACEi-induced reactions (Salem & Alchakaki, 2016). There is a relation between angioedema and dry cough, a common adverse effect of ACEi; it is also reported in the literature that a patient on enalapril with a side effect of dry cough, is likely to develop ACE-induced angioedema in the future (Kainat et al., 2021).

1.5.7.2 Clinical presentations and outcomes of patients found with enalapril-induced angioedema

ACEi was reported as a notable cause of angioedema-related reactions that annually lead to hospitalisation (Awsare et al., 2021). Weisman (2020) reported that ACEis were the causative agents of 50% of angioedema admissions over the last 4 to 5 years. Clinical presentations commonly include swelling of the face, with or without tongue swelling while some patients may present with cough and bronchospasm (Banerji et al., 2017). Swelling sites associated with ACE-induced angioedema also include the lips, larynx, pharynx, and tongue and may cause airway blockage and death if not treated correctly (Awsare et al., 2021). Difficulty in speaking, shortness of breath, and hoarseness of voice due to ACEi were also reported as some of the presentations (Grewal et al., 2020). Other studies also demonstrated that ACE-AE can occasionally affect the gastrointestinal tract causing abdominal pains, diarrhoea and vomiting (Salem et al., 2016; Dabek et al., 2021).

Researchers have reported that up to 50% of ACE-induced incidences presented to the emergency departments are potentially fatal and may cause death, if the upper airway is compromised (Bezalel et al., 2015; Wisecarver et al., 2017). Another study has shown that angioedema reactions may last from 48 to 72 hours, and the majority of these cases require hospitalisation (Montinaro et al., 2020). Clinical presentations of ACE-induced angioedema may be unpredictable in some cases, according to Kainat et al., (2021), thus, continuous patients' and healthcare professionals' education is essential to reduce unwanted adverse outcomes.

1.5.8 Therapeutic Management and Interventions Done in Patients Found with Enalapril-Induced Angioedema

Researchers, like Potter & Peter (2019), maintain that there is a challenge in angioedema identification and treatment in certain social-economic and healthcare settings in South African; this may result in initial diagnosis often being missed or delayed. Patients' clinical history and intake of ACEis are used to diagnose ACE-Angioedema as well as other differential diagnoses of angioedema (Cabellero & Pedrosa, 2016). Jackeviciute et al., (2018) emphasised the significance of teaching practitioners about ACE inhibitor-induced angioedema, as their knowledge is a critical component of diagnosis. SA and other developing countries do not have a variety of effective angioedema treatments available on their markets (Wentzel et al.,

2019), a fact which poses a challenge to physicians with the treatment of ACE-AE. Corticosteroids and other antihistamines, for example, have been considered ineffective in managing ACE-AE (Depetri et al., 2019). Discontinuation of the ACE drug is also a recommended management of ACE-AE; however, the adverse reactions may continue even after months and years of discontinuation (Nishad et al., 2019). This is an indication that, although, ACE-AE is potentially life-threatening, standardised treatment is still lacking (Hirshchy et al., 2018; Judge et al., 2021).

Currently, there is a gap in knowledge on ACE inhibitor-induced angioedema, emphasizing a necessity for ACE-AE awareness in hypertensive patients and healthcare professionals to ensure appropriate diagnosis and treatment (Pines, 2020). Healthcare professionals, therefore, must continually educate patients about medications and their side effects (Bulus et al., 2016). A thorough medical history is required to provide effective treatment for all angioedema patients (Ungureana & Madalan, 2019).

It has been established that adverse drug events were generally underreported worldwide (Whitehead et al., 2021); for instance, ACE-Angioedema was reported to be significantly unreported in Denmark, which severely restricts the available data, indicating that the actual incidence rate of ACE-Angioedema may be much greater than what is currently reported in the country (Cornwall et al., 2019). Due to the infrequent reporting of these adverse reactions and the underreporting of these incidences in the presently available studies, angioedema related to the use of ACE is a disregarded side effect (Manzur-Barbur et al., 2022), with only a 1.1% reporting rate, hence, 98.9% cases unreported (Marliyeni et al., 2021).
public regional hospital.

1.6 SIGNIFICANCE OF THE STUDY

Incidences associated with enalapril-induced angioedema have not been thoroughly investigated in the Limpopo Province, SA. The findings will enable a comparison of data obtained from other areas on this subject, will enhance understanding of the condition, thus, will help health care professionals to identify, treat and manage the condition more effectively. Research indicates that incidences associated with enalapril-induced angioedema are occurring, regularly in SA, therefore the results will be relevant and significant in the present setting of SA.

1.7 CONCLUSION

This section presented a background summary on the topic of hypertension, pharmacovigilance systems, ADR events, as well as ACEi-induced angioedema in local and international contexts. Hypertension in South Africa is prevalent and using enalapril increases the risk of adverse incidences associated with enalapril-induced angioedema. Literature also reviewed that there is inadequate ADR and ACEi-induced angioedema reporting in SA and this compromises drug and patient safety, therefore, healthcare professionals need more training to be able to comprehensively narrate the picture. Chapter 2 describes the research methodology in depth.

CHAPTER 2: METHODS AND MATERIALS

2.1 INTRODUCTION

The research methodology is a detailed guide on how the study of a specific topic was carried out (Igwenagu, 2016), hence, it focuses on the processes utilized by the researcher to explore the research question, as well as justification for the choices made (Patel & Patel, 2019). In other words, this chapter covers a comprehensive outline of the materials and procedures that were applied in this research. In addition, the data collection tool used and the procedures followed (Appendix 1), as well as the reliability and validity of the instrument were discussed.

2.2 MATERIALS

All materials, kits and instruments are listed in Appendix 1

2.3 METHODS AND STUDY DESIGN

A retrospective descriptive quantitative research was undertaken, to investigate the adverse drug reactions in enalapril-induced angioedema. A descriptive study gives a detailed description of a phenomenon and its characteristics (Nassaji et al., 2021) and in this present study this approach was deemed appropriate since the aim was to identify and describe the incidences of enalapril-related angioedema in terms of the contributing factors.

The quantitative research approach systematically investigates a phenomenon using numerical data obtained through statistical and mathematical tools (Adedoyin, 2020). Results from this category of research provide answers to questions such as - who, how many and what - by quantifying and analysing factors the data (Apuke, 2017). In the present study descriptive quantitative study was appropriate because it was used to describe and quantify the incidences into percentages and statistics.

2.5 SITE OF STUDY

The study was conducted at Tshilidzini Regional Hospital in Shayandima, Vhembe District, Limpopo Province, in South Africa. Vhembe District consists of six district hospitals, one specialised and one regional hospital, 115 primary health care facilities, eight community health centres, and eighteen mobile clinics (Department of Health, Limpopo, 2018). In 2016

Vhembe District had approximately 1 393,949 people residing in the area (Stats SA Community Survey, 2016).

This research site was selected because:

- It is a regional hospital acting as a referral facility in that area with professional health specialists, therefore, providing services to diverse range of patients.
- It is in a rural area in Limpopo, hence, appropriate setting, since literature indicates that the rate of hypertension is rising in Limpopo and the whole of South Africa (Ntuli.,2015; Sharma et., 2021).

2.6 POPULATION AND SAMPLING

The sample consisted of all records fitting the inclusion criteria – which included cases with enalapril-induced angioedema from the hospital pharmacovigilance adverse-drug reaction records, from 1 January 2017 to 31 December 2019. Sampling was done using consecutive convenience sampling; this type of sampling is a non-random method in which the investigator samples the population that meets specific criteria and is accessible for the study (Etikan et., 2016). Consecutive sampling, therefore, included all cases which met the criteria and were available within the study period (Mathieson, 2014); this sampling method was selected as it was suitable for the time period of the study.

Table 2.6.1: Inclusion and Exclusion Criteria

Inclusion	***Exclusion***
Adults 18 years of age and older	Pregnant women
Individuals with co- morbidities	

2.7 DATA COLLECTION

Data from patients' medical files were reviewed based on the inclusion criteria and the approval from the Pharmacy Manager and the Hospital Management. Cases were retrieved using the pharmacovigilance ADR database records. The name and surname of each patient were allocated a number which were entered into a data collection tool, ensuring patient confidentiality. Medical history, clinical presentations, management and patient outcomes were retrieved and consolidated on a data-collection tool to achieve the objectives (Annexure 1).

2.8 DATA ANALYSIS

A Microsoft Excel spreadsheet was utilized to record the information from the data-collection tool which was then analysed utilizing the Statistical Package for Social Sciences (SPSS) version 29. Data information were summarised using frequencies and percentages then these were presented using tables and graphs. A checklist format was utilized in the data-collection tool to eliminate observer bias. Unadjusted Odds Ratios (OR), Adjusted Odds Ratios (AOR) and their 95% Confidence Intervals (CI) with a *p*-value less than 0.05 were reported for all statistically significant results and coefficient plots were used to present the findings of the final multivariate mode. The ethical principles of reliability and validity were adhered to with the data ensure quality reproducibility.

2.9 RELIABILITY AND VALIDITY

2.9.1 Reliability

Reliability is the extent to which an evaluation instrument yields reliable and accurate results whenever utilised (Phelan & Wren, 2007). The steps taken to assure the reliability of the information included:

- The use of relevant study design.
- Information was not altered to achieve a certain outcome.
- The raw data was only available to the gatekeepers and the researcher.
- A single researcher recorded the collected data on a Microsoft Excel spreadsheet for each patient, ensuring that the process was done accurately and consistently.
- Every third entry into the Microsoft Excel spreadsheet was checked for correctness.

- Data were analysed with assistance from a biostatistician, ensuring accuracy.

2.9.2 Validity

In a quantitative study, validity is the extent that an idea is measured precisely (Heale & Twycross, 2015). Construct validity, content validity, face validity and external validity were observed for this study. Construct validity indicates how well the concept is translated (Drost, 2011) and in this study, this was ensured by conducting an exhaustive literature review to extract relevant key items of the study. Face validity refers to how well a selected research tool appears to measure a concept under study (Drost, 2011). Content validity is the amount to which the items on the data-collection tool include all dimensions of the concept (Bhattacharyya et., 2017). In this study, a senior pharmacist checked the data-collection tool for face validity and content validity. External validity indicates whether the results can be used to make conclusions about other groups of people (Pannucci & Wilkins, 2010). In the present study, external validity was improved by using minimal exclusion criteria, which allowed a broad representation of the general public, thus, making the data collected closely relatable to other contexts.

2.10 ETHICS

Ethical clearance was acquired from the University of the Witwatersrand Human Research Ethics Committee Medical (M210150). A permission letter to undertake the research was acquired from the Department of Health, Limpopo Province (Annexure 2) and another one from the Tshilidzini Hospital CEO and Pharmacy Manager to access patients' files and adverse-drug reaction database (Annexure 3). Patients' confidentiality was maintained by replacing their identifiable information with record numbers. The POPI Act was observed, therefore, no identifying information, hospital file numbers were required on the data-collection tool. Completed data collection tools were retained for the duration of the research.

2.11 CONCLUSION

This section presented the methods and materials utilised in the study. The succeeding, Chapter 3, presents the results and discussions.

CHAPTER 3: RESULTS AND DISCUSSIONS

3. RESULTS

The chapter presents the findings and data analysis along with their interpretations. Themes that addressed the same study questions were all presented and analysed together. Inferential statistic and Comparative Data analysis-scientific format are used to present the findings regarding the incidences associated with enalapril-induced in Angioedema in a public regional hospital.

3.1 DEMOGRAPHICS

This section highlights the characteristics of the participants who were sampled for the study in terms of their age, gender and race. The data was recorded to establish the relationship between demographics and enalapril-induced angioedema.

Table 3.1: Demographic Information

Demographic Information	N=Value	Percentage %
Age	50 -59 10	25.0
	60-69 7	17.5
	70-79 10	25.0
	80-89 7	17.5
	90-99 6	15.0
Gender	Female 38	95.0
	Male 2	5.0
Race	Black 40	100

Table 3.1.1: Descriptive statistics of participants' age

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
2.1 Age	40	50.0	99.0	72.70	14.583
Valid N (listwise)	40				

3.1.2 T-test core on gender demographics and enalapril-induced angioedema

M: Male

F: Female

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
F-TOT	Equal variances assumed	.072	.788	1.552	558	.121	.12401	.07993	-.03299	.28101
M_TOT	Equal variances assumed	1.228	.268	-1.332	558	.183	-.07566	.05680	-.18723	.03591

Table 3.1.2 indicate that T-test core on gender demographics and enalapril-induced angioedema. The study tested the gender regarding the incidences associated with enalapril-induced angioedema in a public regional hospital tested at significance value of .01 which at 95% confidence interval. The calculated t (-.03299) is lower than the critical 95% confidence interval. Therefore, there is no significant difference on female. The calculated t (-.18723) is lower than the critical 95% confidence interval on male. The study implies that enalapril-induced in angioedema affected mostly female during the period were study conducted.

3.1.3 T-test core on age demographics enalapril-induced angioedema

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	T	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
50-59 _TOT	Equal variances assumed	.280	.597	.036	558	.971	.00368	.10085	-.19441	.20176
60-69 _TOT	Equal variances assumed	1.042	.308	-.071	558	.944	-.00840	.11890	-.24194	.22514
70-79 - TOT	Equal variances assumed	12.692	.000	-.689	558	.491	-.08965	.13010	-.34519	.16589
80-89 - TOT	Equal variances assumed	1.436	.231	.763	558	.446	.06737	.08826	-.10599	.24073
90-99_TOT	Equal variances assumed	2.832	.093	-2.637	558	.009	-.28672	.10874	-.50031	-.07314

Table 3.1.3 indicate T-test core on age demographics and enalapril-induced angioedema. The study tested at significance value of incidences associated with enalapril-induced angioedema in a public regional hospital at significance value of .01 which at 95% confidence interval. The calculated t (-.03299) is less than the critical 95% confidence interval. Therefore, there is no significant difference incidences associated with enalapril-induced in angioedema in a public regional hospital affected 60-69 years patient. The calculated t (-.34519) is less than the critical 95% confidence interval at age of 70- 79 years. The calculated t (-.06737) is less than the critical 95% confidence interval at age 80-89 years. The study implies that enalapril-induced angioedema affected mostly patient of age of 50-59 and 70-79 during the period were study conducted.

3.2 MEDICAL HISTORY

	N	Minimum	Maximum	Mean	Std. Deviation
Previous attacks of angioedema	40	1.00	5.00	3.4261	.83672
Previous allergies? If yes specify	40	1.00	5.00	3.0293	.75307
History of smoking	40	1.00	5.00	3.6825	1.21693

Table 3.2 present the test; the continuous Improvement variables are tested to compare the mean scores among the variable. .83672 test previous attacks of angioedema. .75307 test previous allergies. The study implies that after conducting t-test concluded that history of previous allergies and history of previous attacks contributed to the risk of induced angioedema.

3.3 CLINICAL PRESENTATIONS

This section shows the clinical presentations from the participants in this study. The Table below describes the clinical presentations as part of the objectives of this study to demonstrate incidences associated with enalapril-induced angioedema. This information, therefore, is provided to establish the relationship between clinical presentation and enalapril-induced angioedema and to relate the incidences with clinical presentations.

Table 3.3 showing Clinical Presentations of Incidences Associated with Enalapril-Induced Angioedema Found among the Participants (some participants experienced more than one clinical presentation)

Clinical Presentation	Frequencies (n)
Face	14.0
Lips	32.0
Tongue	23.0

3.4 THERAPEUTIC MANAGEMENT AND INTERVENTIONS

This section describes the therapeutic management and interventions given to study participants found with enalapril-induced angioedema. The data, therefore, was recorded to investigate and describe the management and intervention provided for patients who had developed enalapril-induced angioedema by the healthcare professionals. Table 3.4 includes the outcomes of the management and intervention strategies made available to participants who had developed enalapril-induced angioedema and had required hospitalization.

Table 3.4 Therapeutic Management and Outcomes of Participants that Required Hospitalization

Participants	Gender	Age	Presentations	Treatment Given	Clinical Outcomes
1	**F**	**91**	-Swollen and Protruding tongue. -Difficulty in breathing. -Developed angioedema on the 2nd day of Enalapril administration.	-Withdrawal of the ADR causative agent replaced with Amlodipine. Hydrocortisone and Promethazine IV were given.	'Admitted and transferred to ICU to be monitored for 24 hours - Recovered
2	**F**	**55**	-Swelling of lips and tongue. -Difficulty in breathing	- Withdrawal of the ADR causative agent replaced with Amlodipine. Hydrocortisone IV	Admitted Recovered
3	**F**	**86**	-Swelling of face, lips & tongue -Difficulty in breathing -Airway obstruction	Promethazine & Hydrocortisone IV Adrenaline IV	Died
4	**F**	**62**	-Swollen upper lip -Coughing	Not known	Admitted for a few days. Recovered

5	**F**	**75**	Swollen lips and tongue for 3 days -Difficulty in breathing.	Promethazine IV Hydrocortisone IV Prednisone	Died
6	**F**	**50**	-Developed angioedema on the 1st day of Enalapril administration. -Palpitations and decreased heavy voice - Decreased vision	Hydrocortisone IV -Allergex tablets -Amlodipine issued replacing Enalapril	Hospitalized Recovered

3.5 DISCUSSION

In this section, the findings of the present study will be discussed taking in relation to the available literature on incidences associated with enalapril-induced angioedema. The findings will be presented in line with - the demographics, clinical presentations, therapeutic interventions and clinical outcomes for the participants - with the aim of describing comprehensively, the incidences and contributing risk factors of enalapril-induced angioedema.

The purpose of the study was to identify and describe the incidences related to enalapril-induced angioedema. The percentage prevalence of enalapril-induced angioedema in the present study was reported to be forty cases (37.3%) out of one hundred and seven ADR reports recorded in the study hospital over three years. Sanchez and Gonzalez-Aveledo, (2010) conducted a five-year retrospective study in an allergy clinic in Venezuela, where the incidence of ACEi induced angioedema was reported to be 0.37% with enalapril as the most causative drug. Banerji et al., (2018) conducted a retrospective study using electronic records in an academic centre United states, where the incidence of ACEi was reported to be 0.7% during the five years study period and 0.23% in the first year of administration. Incidence rate of ACE-induced angioedema was reported to be 0.1-0.2% worldwide. However, SA incidence is unknown (Tiemensma,2010). This present study indicates that there is a gap in the reported enalapril-induced angioedema incidence rate in SA. Additional research is still relevant to investigate the incidence rate of enalapril-induced angioedema in SA using a large population.

The present study presented and described the common contributing factors of enalapril-induced angioedema in the study. The present study found the common contributing factors to be the age of 50-59 (25%) & 70-79 (25%), female gender and previous history of angioedema and allergies. Many contributing factors in literature for ACEi-induced angioedema have been reported, which include black gender, female gender, rash, smoking, age older than 65 years, allergies, and recent initiation of ACEi (Sanchez & Gonzalez-Aveledo,2010). Kostis et al., (2005) conducted a prospective study in twelve countries, where the contributing risk factors of enalapril- induced angioedema were reported as age greater than 65 years, seasonal allergies, history of drug rash. Age was reported to be younger in the present study compared with the literature, with the present study reporting the age of risk to be starting from 50 years whereas the other international literature shows 65 years and above.

Day et al., (2023) conducted a study in Cape Town (SA) where the risk factors of angioedema were reported to be age (28-48 years) and being of female gender. The results in the present study are similar to what has been published in the literature regarding risk factors age, gender, medical history, and race to affect enalapril- induced angioedema.

The study described and presented clinical presentations of enalapril- induced angioedema. The results of the current study reported swelling of the lips, tongue and face as the common clinical presentations, with swelling of lips reported to occur more frequently than the other presentations. Some participants experienced more than one clinical presentation at the same time. Other secondary clinical presentations found were - coughing, pruritis, difficulty breathing, and difficulty in speaking. Okumu et al., (2018) reported two patients that experienced enalapril-induced angioedema in a rural health facility in Kenya, where one patient presented with swelling of the lips, tongue and face while the other patient presented with swelling of the upper lip. Both cases had similarities in presenting with swelling of the lips. Tiemensma et al., (2009) reported a case study in SA presenting with swelling of the tongue and obstruction of the airway which led to death. Whereas Cupido & Rayner, (2007) reported a study in Cape Town (SA) where the patient presented with swelling of lips and tongue. Literature reported swelling of the lips, tongue, face and mouth floor as the most common clinical manifestation of ACEi-induced angioedema (Ciaccio, 2011). The clinical presentations of enalapril-induced angioedema in the present study and literature were aligned reporting swelling of the face, lips and tongue to be the common clinical presentations of enalapril induced angioedema.

The study described the severity, therapeutic management and outcomes of enalapril-induced angioedema. The results of the current study depicted that most of the sampled participants recovered after discontinuation of enalapril with only 15% hospitalization and 5% death. The fundamental subsequent processes for evidence of ACEi angioedema are the detection and discontinuation of the offending ACE drug (Okumu et al., 2018), after that, supportive therapy should be given (Tharayil et al., 2014).

Cosme et al., (2019) conducted a study in Portugal where hospitalization due to ACE-AE reactions was found among 71.6 per 100 000 hospitalizations. Day et al., (2023) conducted a study in Cape Town (SA) about angioedema where 13% were hospitalized with 14% airway obstruction caused commonly by ACE-induced angioedema. In this study, 15% of the participants were admitted due to ACE-AE similar to the literature which highlights the

severity of this condition, therefore, patients' and healthcare professionals' education on enalapril-induced angioedema should be improved to minimize the occurrence and severity of the condition.

3.6 CONCLUSION

Patients who are taking ACEis should be monitored for angioedema, and in addition, be closely monitored after experiencing ACE-induced angioedema. Discontinuation of the ACEi and patient counselling is essential in the management of this condition thus health care professionals need to be educated so that they can counsel patients and improve their outcomes.

CHAPTER 4: CONCLUSION

4.1 CONCLUSION

In this section, conclusions are extracted from the results which are discussed following the objectives; recommendations are suggested while also acknowledging the study's limitations. The study aimed to identify and describe incidences and contributing risk factors associated with enalapril-induced angioedema, in a public regional hospital, for the period, January 2017 to December 2019, to bring about improved patient outcomes.

Forty cases of enalapril-induced angioedema fitting the inclusion criteria were found, between 1 January 2017- December 2019, at Tshilidzini Regional Public hospital. The findings revealed that enalapril-induced angioedema incidences are occurring, and some cases can be severe and fatal. This suggest that patients on enalapril should be monitored by healthcare professionals and counselled about the adverse reactions the medication may cause. This study contributes to the recognition of enalapril-induced angioedema and its management, thus, will improve patient safety. It highlights how serious the adverse reactions are and brings awareness to healthcare professionals to monitor patients on enalapril and also report, comprehensively, any adverse reactions.

4.2 LIMITATIONS OF THE STUDY

Underreporting of incidences by healthcare professionals, of these potentially life-threatening adverse reactions, limits the available data on the prevalence of the condition. ACE-induced angioedema may be occurring more than the available data depicts but the true picture may not be known due to underreporting by the healthcare professionals. This study indicates a significant gap in healthcare professionals' reporting of adverse reactions, a lack which compromises patients' safety.

4.3 RECOMMENDATIONS FOR FURTHER RESEARCH

The researcher gives the following recommendations based on the study's findings:

- Frequent healthcare professional training on ACE-induced angioedema and reporting of adverse reactions.

- Frequent review and evaluation of standard treatment guidelines and essential medicine list.
- Continuous development of healthcare professionals concerning diagnoses and management of ACE- induced angioedema.
- Further research concerning incidence rate of enalapril induced angioedema in SA

CHAPTER 5: REFERENCES

REFERENCES

Adedoyin, O. 2020. Research Methodology. *Journal of Near East University*. [Online] Available at:https://www.research.net/publication/34059420_Research_Methodology [Accessed 21 March 2023].

Adeniyi, O.V., Yogeswaran, P., Longo-Mbenza, B. & Goon, D.T. 2016. Uncontrolled Hypertension and its Determinants in Patients with Concomitant Type 2 Diabetes Mellitus (T2DM) in Rural South Africa. *PLOS ONE,* 11(3): 1-12. [Online]. Available at: e0150033. https://doi.org/10.1371/journal.pone.0150033[Accessed 21 March 2022].

Akunne, O. & Adedapo, A.D. 2019. Antihypertensive Prescription Among Black Patients Without Compelling Indications: Prescription, Effectiveness, Quality and Cost of Medication. *Health Services Research,* 19(373): 1-8. [Online]. Available *doi:10.1186/s12913-019-4202-2.* [Accessed 21 March 2022].

Alharbi, F.A., Alharthi, A.A. & Alsaadi, F.N. 2018. Perindopril-induced angioedema of the lips and tongue: a case report. *Journal of Medical Case Reports*, 12(1): 1-4. [Online]. Available at: https://doi.org/10.1186/s13256-018-1910-x. [Accessed 21 March 2023].

Alshammari, T.M., Alshakka, M. & Aljadhey, H. 2017. Pharmacovigilance System in Saudi Arabia. *Saudi Pharmaceutical Journal*, 25(3): 299-305. [Online]. Available at: https://doi.org/10.1016/j.jsps.2016.09.008. [Accessed 20 March 2022].

Anusha, L.I., Aashritha, M. Teja, K. & Sridhar, R. 2016. A Review on Pharmacovigilance and its Importance. *World Journal of Pharmacy and Pharmaceutical Sciences,* 6(1): 300-310. [Online]. Available at *doi:10.20959/wjpps20171-8280.* [Accessed 20 March 2023].

Amoah, M.E., Okai, E.D., Manu, A., Laar, A., Akamah, J. & Torpey K. 2020. The Role of Lifestyle Factors in Controlling Blood Pressure among Hypertensive Patients in Two Health Facilities in Urban Ghana: A Cross-Sectional Study. *International Journal of Hypertension*, 2020: 1-8. [Online]. Available at: doi: 10.1155/2020/9379128. PMID: 33005451; PMCID: PMC7508215. [Accessed 20 September 2022].

Apuke, O. 2017. Quantitative Research Methods: A Synopsis Approach. *Arabian Journal of Business and Management Review (Kuwait Chapter),* 6(11): 40-47. [Online]. Available at: Doi:10.12816/0040336. [Accessed 21 March 2023].

Ali, H.A., Lomholt, A.F., Mahmoudpour, S.H., Hermanrud, T., Bygum, A., Buchwald, C.C., Jakobsen, M.A. & Rasmussen, E.R. 2019. Genetic Susceptibility to Angiotensin-

Converting Enzyme- Inhibitor Induced Angioedema. *PLOS ONE,* 14(11): e0227056. [Online] Available at: doi:10.1371/journal.pone.0227056. [Accessed 20 March 2023].

Andrew, N., Gabb, G. & Fante, M.D. 2011. ACEI Associated Angioedema: A Case Study and Review. *Australian Family Physician*, 40(12): 985-988. [Online]. Available at: ACEI associated angioedema - A case study and review (racgp.org.au). [Accessed 20 March 2023].

Anish, N. & Gabremedhin, A.M. 2016. An Encounter with Enalapril-Induced Resistant, Life-Threatening Angioedema at Rural Health Center in Botswana. *Indian Journal of Critical Care Medicine: Peer-reviewed, Official Publication of Indian Society of Critical Care Medicine*, 20(10): 613. [Online]. Available at: doi:10.4103/0972-5229.192060. [Accessed 20 March 2022].

Asad, H. & Gohar, A. 2020. Incidence of Angiotensin-Converting Enzyme-Associated Angioedema among African Americans Compared to other Races. *Chest Journal*, 156(4): A1123. [Online]. Available at doi: https://doi.org/10.1016/j.chest.2019.08.1026. [Accessed 20 February 2022].

Awsare, S., Chirikian, D. & Rogers, J. 2021. Administration of Tranexamic Acid as Treatment for Angiotensin Converting Enzyme Inhibitor-Induced Angioedema: A Case Report. *Case Reports in Acute Medicine*, 4: 71-75. [Online]. Available at https://doi.org/10.1159/000517621. [Accessed 20 September 2022].

Banerji, A., Blumenthal, K., Lai, K. & Zhou, L. 2017. Epidemiology of ACE-Inhibitor Angioedema Utilising a Large Electronic Health Record. *The Journal of Allergy and Clinical Immunology in Practice*, 5(3): 744-749. [Online]. Available doi:10.1016/j.jaip.2017.02.018.[Accessed 20 September 2022].

Berry, K.M., Parker. W.A., Mchiza, Z.J., Sewpaul, R., Labadarios, D., Rosen, S. & Stokes, A. 2017. Quantifying Unmet Need for Hypertension Care in South Africa Through a Care in South Africa through a Care Cascade: Evidence from the SANHANES, 2011-2012. *BMJ Glob Health*, 2(3): e000348. [Online]. Available doi:10.1136/bmiqh-2017-000348. [Accessed 10 September 2022].

Bernstein, J.A., Cremonesi, P., Hoffmann, T.K. & Hollingsworth, J. 2017. Angioedema in the Emergency Department: A Practical Guide to Differential Diagnosis and Management. *International Journal of Emergency Medicine*. 10(15). [Online]. Available at: doi:10.1186/s12245-017-014-z [Accessed 21 March 2023].

Bezalel, S., Mahlab-Guri, K., Asher, I., Werner, B. & Sthoeger, Z.M., 2015. Angiotensin-converting enzyme inhibitor-induced angioedema. *The American journal of medicine*,

128(2), pp.120-125. [Online]. Available doi: 10.1016/j.amjmed.2014.07.011. [Accessed 21 March 2023].

Bhattacharyya, S., Kaur, R., Kaur, S. & Ali, S.A. 2017. Validity and Reliability of a Questionnaire: A Literature Review. *Chronicles of Dental Research Dec,* 6(2):16-22. [Online]. Available at http: www.cdronline.org. [Accessed 10 June 2020].

Brown, T., Gonzalez, J. & Monteleone, C. 2017. Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema: A Review of the Literature. *The Journal of Clinical Hypertension*. 19(12): 1377-1382. [Online]. Available at: Doi:10.1111/jch.13097 [Accessed 21 March 2023].

Bulus, J., Shuaibu,J., Lenka, N.M. & Gyede, S.G. 2016. Angiotensin-Converting Enzyme Induced Angioedema: The Need for Patient Education. *Nigerian Journal of Family Practice,*7(4). [Online]. Available at: https://www.ajol.info/index. [Accessed 21 March 2022].

Byrd, J.B., Touzin, K., Sile, S., Gainer, J.V., Yu, C., Nadeau, J., Adam, A. & Brown, N.J. 2008. Dipeptidyl Peptidase IV in Angiotensin-Converting Enzyme Inhibitor-Associated Angioedema. *Hypertension.* 51(1): 141-147. [Online]. Available at: Doi:10.1161/HYPERTENSIONAHA.107.096552. [Accessed 21 March 2023].

Caballero, T. & Pedrosa, M. 2016. Angioedema Due to ACE Inhibitors. *Current Treatment Options in Allergy*, 3: 401-415. [Online]. Available at :doi:10.1007/s40521-016-0099-8.

Cheah, C., Dass, K. & Guthrie, A. & Dalal, B. 2017. Angiotensin-Converting Enzyme Inhibitors- Induced Angioedema Is Causing More Deaths. *American College of Chest Physicians Journal,* 152(4): 1056A. [Online]. Available at doi: https://doi.org/10.1016/j.chest.2017.08.1090. [Accessed 21 March 2020].

Chiriac, A., Brzezinski, P., Betiu, M. & Foia, L. 2018. Angiotensin-Converting Enzyme Inhibitors Induced Angioedema. *Journal of Cardiovascular Emergencies,* 4(1): 47-50. [Online]. Available at doi:10.2478/jce-2018-0004. [Accessed 21 March 2020].

Ciaccio, C.E. 2011. Angioedema: An overview and update. *Missouri Medicine,108(5):*354-357. [Online]. Available at Angioedema: an overview and update - PubMed (nih.gov). [Accessed 21 March 2023].

Cicardi, M., Zingale, L., Bergamaschini, L. & Angostoni, A. 2004. Angioedema Associated with Angiotensin-Converting Enzyme Inhibitor Use. *Archives of Internal Medicine,*

164(8): 910-913. [Online]. Available doi:10.1001/archinte.164.8.910. [Accessed 21 September 2020].

Cornwall, J.E.L., Bygum, A. & Rasmussen, E.R. 2019. ACE-Inhibitor Related Angioedema is not Sufficiently Reported to the Danish Adverse Drug Reactions Database. *Drug, Healthcare and Patient Safety*, 11: 105-113. [Online]. Available doi:10.214/DHPS.S205119. [Accessed 21 September 2021].

Cosme, J., Spinola, A., Ferreira, M. & Barbosa, M.P. 2019. Hospitalization Due to Angioedema without Urticaria in a Portuguese Center: Five Year Retrospective Study. *Acta Med Port*, 32(11): 714-720. [Online]. Available at: https://doi.org/10.20344/amp.11893 [Accessed 21 March 2023].

Cupido, C. & Rayner, B., 2007. Life-Threatening Angio-Oedema and Death Associated with the ACE Inhibitor Enalapril. *South African Medical Journal*, 97(4): 244. [Accessed 12 April 2020].

Dabek, R.J., Pina, N.A., Sheber, B., Axentiev, A., Scott, M.C. & Sheber, B.A. 2021. A Case Report of Delayed Post-operative Angioedema Associated with Angiotensin-Converting Enzyme Inhibitor Use. *Cureus Journal of Medical Science, 13*(10): 1-3. [Online]. Available at http://www.samj.org.za/index.php/samj/article/view/794. [Accessed 21 March 2023].

Day, C., Van der walt, J., Crombie, K., Hendrikse, C.& Peter, J. 2023. Acute Angioedema in Cape Town Emergency Centres and a Suggested Algorithm to Simplify and Improve Management. *South African Medical Journal*, *113*(8): 1340-1346. [Online]. Available at https://hdl.handle.net/10520/ejc-m_samj_v113_n8_a12. [Accessed 21 September 2023].

Decloedt, E., Freercks, R. & Maartens, G. 2009. Cerebral Angioedema Associated with Enalapril. *British Journal of Clinical Pharmacology*, 68(2): 271-273. [Online]. Available at doi:10.1111/j.1365-2125.2009.03452.x. [Accessed 10 March 2022].

Department of Statistics South Africa. 2019. Statistical Release P0302 Mid-Year Population Estimates. Accessed 10 June, 2020, [Online]. Available: https://www.statssa.gov.za/publications/P0302/P03022019.pdf.

Department of Health Limpopo. 2018. Vhembe District Health Plan 2018/19- 2020/21. Department of Health South Africa. [Accessed 10 June, 2020] [Online]. Available http://www.health.gov.za/DHP/docs/DHP2018-21/Limpopo/Vhembe_District.pdf

Depetri, F., Tedeschi, A. & Cugno, M. 2019. Angioedema and Emergency Medicine: From Pathophysiology to Diagnosis and Treatment. *European Journal of Internal Medicine, 59*: 8-13. [Online]. Available at :doi:10.1016/j.ejim.2018.09.004. [Accessed 21 March 2023].

De Villiers, K. 2021. Bridging the Health Inequality Gap: An Examination of South Africa's Social Innovation in Health Landscape. *Infectious Disease of Poverty*, 10(19): 1-7. [Online]. Available https://doi.org/10.1186/s40249-021-00804-9. [Accessed 21 March 2023].

Dheda, M., 2016. *Meeting South Africa's Pharmacovigilance Challenges in the Face of Rapidly Increasing Public Health Treatment Programmes*. [Online]. Available at: https://ukzn-dspace.ukzn.ac.za/bitstream/handle/10413/17721. [Accessed 21 March 2023].

Drost, E.A. 2011. Validity and Reliability in Social Sciences Research. *Education Research and Perspectives*, 38(1): 105-123. [Accessed 10 July 2020] http://www.researchgate.net/publication/261473819.

Emanuel, S. & Hawarden, D. 2018. ACE Inhibitor-Induced Angioedema. *Current Allergy & Clinical Immunology*, 34(2): 108-110. [Online]. Available at: https://hdl.handle.net/10520/ejc-caci-v34- n2-a11. [Accessed 21 March 2023].

Ernst, S. 2005. Hypertension Guideline Adherence of Private Practitioners and Primary Health Care Physicians in Pretoria. *South African Family Practice*, 47(3): 51-54. [Online]. Available. doi:10.1080/20786204.2005.10873202. [Accessed 21 March 2022].

Etikan, I., Musa, S. & Alkassim, R. 2016. Comparison of Convenience Sampling and Purposive Sampling. *American Journal of Theoretical and Applied Statistics*, 5(1): 1-4. [Online]. Available at doi:10.11648/j.ajtas.20160501.11. [Accessed 21 March 2022].

Faruqi, A. & Jain, A. 2021. *Enalapril. In StatPearls [Internet]*. Stat Pearls Internet Publishing.

Fasipe, O.J., Akhideno, P.E. & Owhin, O.S. 2019. The Observed Effect of Adverse Drug Reactions on the Length of Hospital Stay among Medical Inpatients in a Nigerian University Teaching Hospital. *Toxicology Research and Application*, 3: 1-7. [Online]. Available at doi:10.1177/2397847319850451. [Accessed 21 March 2022].

Gang, C., Lindsell, C.J., Moellman, J., Sublett, W., Hart, K., Collins, S. & Bernstein, J.A. 2013. Factors Associated with Hospitalization of Patients with Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema. *Allergy and Asthma Proceedings*, 34(3): 267-273. [Online]. Available at: doi:10.2500/aap.2013.3664 [Accessed 21 March 2023].

Giardina, C., Cutroneo, P.M., Mocciaro, E., Russo, G.T., Mandraffino, G., Basile, G., Rapisarda, F., Ferrara, R., Spina, E. & Arcoraci, V. 2018. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. *Frontiers in Pharmacology,* 9: 350. [Online]. Available at: doi:10.3389/fphar.2018.00350 [Accessed 21 March 2023].

Grewal, E., Sutarjono, B. & Mohammed, I. 2020. Angioedema, ACE Inhibitor and COVID-19. *BMJ Case Reports CP*, 13(9): e23788. [Online]. Available at: doi:10.1136/bcr-2020-237888 [Accessed 21 March 2023].

Goyal, A., Cusick, A.S. & Thielemier, B. 2022. *ACE Inhibitors.* StatPearls Internet Publishing.

Guner, M. & Ekmekci, P. 2019. Healthcare Professionals' Pharmacovigilance Knowledge and Adverse Drug Reaction Reporting Behaviour and Factors Determining the Reporting. J*ournal of Drug Assessment,* 8(1): 13-20. [Online]. Available at: doi: 10.1080/21556660.2019.1566137. [Accessed 21 March 2022].

Hayn, J., Trainotti, S., Hoffman, T.K. & Greve, J. 2017. Drug-Induced Inhibition of Angiotensin-Converting Enzyme and Dipeptidyl Peptidase 4 Results in Nearly Therapy Resistant Bradykinin Induced Angioedema: A Case Report. *The American Journal of Case Reports,* 18: 576-579. [Online]. Available at doi: 10.12659/AJCR.901960. [Accessed 15 March 2022].

Heale, R. & Twycross, A. 2015. Validity and Reliability in Quantitative Studies. *Evidence-Based Nursing,*18(3): 66-67. [Online]. Available at doi:10.1136/eb-2015-102129. [Accessed 15 March 2022].

Hirschy, R., Shah, T., Davis, T. & Rech, M.A. 2018. Treatment of Life-Threatening ACE-Inhibitor–Induced Angioedema. *Advanced Emergency Nursing Journal*, 40(4): 267-277. [Online]. Available at doi: 10.1097/TME.0000000211. [Accessed 15 September 2022].

Hariraj, V. & Aziz, Z. 2018. Patient Reporting of Adverse Drug Reactions (ADRs) Survey of Public Awareness and Predictors of Confidence to Report. *Therapeutic Innovation & Regulatory Science,* 52(6): 757-763. [Online]. Available at doi:10.117/2168479017745025. [Accessed 15 September 2022].

Ibrahim, M.M. 2018.Hypertension in Developing Countries: A Major Challenge for the future. *Current Hypertension Reports, 20,*38:1-5. [Online]. Available at: doi:10.10007/s11906-0839-1 [Accessed 21 September 2023].

Igwenagu, C. 2016. *Fundamentals of Research Methodology and Data Collection*. [Online]. LAP Lambert Academic Publishing. [Online]. Available at: https:www.researchgate.net/publication/3.303381524 [Accessed 21 March 2023].

Inomata, N. 2012. Recent Advances in Drug-Induced Angioedema. *Allergology International*, 61(4): 545-557. [Online]. Available at: doi:10.2332/allergolint.12-RAI-0493. [Accessed 21 March 2022].

Isah, A.O., Pal, S.N., Olsson, S., Dodoo, A. & Bencheikh, R.S. 2012. Specific Features of Medicines Safety and Pharmacovigilance in Africa. *Therapeutic Advances in Drug Safety*, *3*(1): 25-34. [Online]. Available at: doi:0.1177/2042098611425695. [Accessed 21 March 2023].

Jackeviciute, J., Pilvinis, V. & Pilviniene, R. 2018. Fatal Outcome of Late-Onset Angiotensin-Converting Enzyme Inhibitor Induced Angioedema: A Case Report. *Medicine*, 97(31): e11695. [Online]. Available at doi:10.1097/MD.000000000011695. [Accessed 21 March 2023].

Jeetu, G. & Anusha, G. 2010. Pharmacovigilance: A Worldwide Master Key for Drug Safety Monitoring. *Journal of Young Pharmacists*, 2(3): 315-320. [Online]. Available at doi:10.4103/0975-1483.66802. [Accessed 10 March 2022].

Jo, H.G., Jeong, K., Ryu, J.Y., Park, S., Choi, Y.S., Kwack, W.G., Choi, Y.J. & Chung, E.K. 2022. Fatal Events Associated with Adverse Drug Reactions in the Korean National Pharmacovigilance Database. *Journal of Personalized Medicine*, 12(1): 5. [Online]. Available at doi: 10.3390/jpm12010005. [Accessed 10 March 2023].

Jongbo, O. 2014. The Role of Research Design in a Purpose Design in a Purpose Driven Enquiry. *Review of Public Administration and Management,* 3(6): 87-94. [Online]. Available at: https://arabianjbmr.com/RPAM-index.php. [Accessed 16 April 2020].

Jones, J., Swart, A., Tommy, E., Cohen, K., Stewart, A., Voget, J. & Blockman, M. 2020. Adverse Drug Reactions Reported to a Provincial Public Health Sector Pharmacovigilance Programme in South Africa. *SAMJ: South African Medical Journal*, 110(12): 1226-1230. [Online]. Available at: doi:10.7196/SAMJ.2020.v110i12.14721. [Accessed 16 April 2021].

Jose, J., Al Rubaie, M.H., Al Ramimmy, H. & Varughese, S.S. 2021. Pharmacovigilance: Basic Concepts and an Overview of the System in Oman. *Sultan Qaboos University Medical Journal*, 21(2): 161. [Online]. Available at: doi:10.18295/squmj.2021.2102.001. [Accessed 1 April 2022].

Jongen, V.W., Lalla-Edward, S.T., Vos, A.G., Godik, N.G.., Temelman, H., Grobbee, D.E., Deville, W. & Klipstein-Grobusch, K. 2019. Hypertension in a Rural Community in South Africa: What they Know, what they Think they Know and what they Recommend. *BMC Public Health*,19(341): 1-10. [Online]. Available at: https://doi.org/10.1186/s12889-019-6642-3 [Accessed 21 March 2023].

Judge, R., Kolaski, S. & Qadeer, F. 2021. Use of Tranexamic Acid Prevents Intubation in ACE Inhibitor-Induced Angioedema. *International Journal of Critical Care and Emergency Medicine*, 7(3): 127. [Online]. Available at: doi:org/10.23937/2474-3674/1510127 [Accessed 21 March 2023].

Kainat, A., Phang, C.R, Ain, N.U. & Agarwal, B. 2021. The First Occurrence of Angioedema After Discontinuation of Angiotensin-Converting Enzyme Inhibitor. *Cureus*. 13(11): e19552. [Online]. Available at: doi:10.7759/cureus.19553. [Accessed 21 March 2023].

Kallepalli, A. & Yusin, J.S. 2018. Time Frame of Recurrent Angioedema Following Discontinuation of Angiotension Converting Enzyme. *The Journal of Allergy and Clinical Immunology*, 141(2): AB35. [Online]. Available at: doi:https://doi.org/1016/j.jaci.2017.12.115.

Kandala, N., Nnanatu, C.C., Dukhi, N., Sewpaul, R., Davids, A. & Reddy, S.R. 2021. Mapping the Burden of Hypertension in South Africa: A Comparative Analysis of the National 2012 SANHANES and the 2016 Demographic and Health Survey. *International Journal of Environmental Research and Public Health*, 18(5445): 1-18. [Online]. Available at: https: doi.org/10.3390/ijerph1805445 [Accessed 21 March 2023].

Kaplan, A.P. 2008. Angioedema. *World Allergy Organization Journal*. 1: 103-113. [Online]. Available at: https://doi.org/10.1097/WOX.0b013e3187aecbe [Accessed 21 March 2023].

Kiguba, R., Olsson, S. & Waitt, C. 2023. Pharmacovigilance in Low-and Middle-Income Countries: A Review with Particular Focus on Africa. *British Journal of Clinical Pharmacology*, 89(2): 491-509. [Online]. Available at: https://doi.org/10.1111/bcp.15193 [Accessed 21 March 2023].

Kim, J.H. & Scialli, A.R. 2011. Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease. *Toxicological Sciences*, 122(1): 1-6.doi: 10.103/toxsci/kfr088[Accessed 21 March 2023].

Kim, S.J., Brooks, J.C., Sheikh, J., Kaplan, M.S. & Goldberg, B.J. 2014. Angioedema Deaths in the United States, 1979–2010. *Annals of Allergy, Asthma & Immunology*, *113*(6): 630- 634. doi: 10.1016/j.anai.2014.09.003[Accessed 21 March 2023].

Khan, Z., Karataş, Y. & Rahman, H. 2020. Adverse Drug Reactions Reporting in Turkey and Barriers: An Urgent Need for Pharmacovigilance Education. *Therapeutic Advances in Drug Safety*, 11: 204-209. [Online]. Available at doi:10.1177/2042098620922483. [Accessed 21 March 2023].

Khan, Z., Karataş, Y. & Kıroğlu, O. 2021. Evaluation of Adverse Drug Reactions in Paediatric Patients: A Retrospective Study in Turkish Hospital. *Frontiers in Pharmacology,* 12: 786182. [Online]. Available at doi 10.3389/fphar.2021.786182. [Accessed 21 March 2023].

Khalil, H. & Haung, C. 2020. Adverse Drug Reactions in Primary Care: A Scoping Review. *BMC Health Services Research,* 20(1): 5. [Online]. Available at *https://doi.org/10.1186/s12913-019- 4654-7.* [Accessed 21 March 2023].

Komape, L.J. 2013. *Exploring Public Perceptions of South African Private and Public Hospitals and Preferences for Health Care Providers. Research Report for the Master of Public Health Degree.* Johannesburg: University of Witwatersrand, Faculty of Health Sciences. [Accessed 21 March 2023].

Kostis, J.B., Kim, H.J., Rusnak, J., Casale, T., Kaplan, A., Corren. & Levy, D. 2005.Incidence and characteristics of angioedema associated with enalapril. *Arch intern Med,* 164(14): 1637-42. [Online]. Available at doi:10.1001/archinte.165.14.1637. [Accessed 21 March 2023].

Leru, P.M., Anton, V.F., Bocsan, C., Muntean, A. & Boda, D. 2020. Acquired Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors-Experience of Hospital-Based Allergy Center. *Experimental and Therapeutic Medicine,* 20(1): 68-72. doi:10.3892/etm.2020.8474.

Loftus, P.A., Tan, M., Patel, G., Lin. J., Helman. S., Badhey, A., Du, E., Smith, R.V., Fried, M.P. & Ow, T.J. 2014. Risk Factors Associated with Severe and Recurrent Angioedema: An Epidemic Linked to ACE-Inhibitors. *The Laryngoscope,* 124(11): 2502-2507. [Online]. Available at: https://doi.org/10.1002/lary.24777. [Accessed 10 March 2022].

Maimela, E., Alberts, M., Modjadji, S.E, Choma, S.S., Dikotope, S.A., Ntuli, T.S. & Van

Geertruyden,J .P. 2016. The Prevalence and Determinants of Chronic Non-Communicable Disease Risk Factors among Adults in the Dikgale Health Demographic and Surveillance System (HDSS) Site, Limpopo Province of South Africa. PLOS One.11(2): e0147926. doi: 10.1371/journal.pone.0147926.

Malakoane, B., Heunis, J.C., Chikobvu, P., Kigozi, N.G. & Kruger, W.H. 2020. Public health System Challenges in the Free State, South Africa: A Situation Appraisal to Inform Health System Strengthening. *BMC Health Service Research* 20(58): 1-14. [Online]. Available at: https://doi.org/10.1186/s12913-019-4862-y. [Accessed 21 March 2023].

Manzur-Barbur, M.C., Mejia-Sanjuanelo, A.M., Martinez-Avila, M.C., Manzur-Jattin, F., Garcia-Dominguez, J.C. & Orozco-Seba, B. 2022. Enalapril-Induced Angioedema: A Forgotten Adverse Event. *Clinical Case Reports*, 10(6): 1-4. [Online]. Available at: https://doi.org/10.1002/ccr3.5944 [Accessed 21 March 2023].

Maphumulo, W.T. & Bhengu, B.R. 2019. Challenges of Quality Improvement in the Healthcare of South Africa Post-Apartheid: A Critical Review'. *Curationis*, 42(1): a1901. [Online]. Available at: https://doi.org/ 10.4102/curationis. v42i1.1901.

Maqbooi, M., Dar, M.A., Rasool, S. & Gani, I. 2019. A Program in Practice. *Journal of Research in Health Sciences*. 1-2(3): 82-86. [Online]. Available at: http://dx.doi.org/10.26739/2523- 1243/-2019-1-10 [Accessed 21 March 2023].

Marliyeni, R., Kardela, W. & Bellatasie, R. 2021. Angioedema Adverse Drug Reactions Associated with ACE Inhibitor: A Review. *Journal of Pharmacy and Biological Sciences*, 16(1): 12-20. [Online]. Available at: doi:10.9790/3008-1601041220.

Masilela, C., Pearce, B., Ongole, J.J., Adeniyi, O.V. & Benjeddou, M. 2020. Cross-Sectional Study of Prevalence and Determinants of Uncontrolled Hypertension among South Africa Adult Residents of Mkhondo Municipality. *BMC Public Health*, 20(1069): 2-10. [Online]. Available at: https://doi.org/10.1186/s12889-20-09174-7 [Accessed 21 March 2023].

Mathieson, K. 2014. Making Sense of Biostatistics: Types of Nonprobability Sampling. *Journal of Clinical Research Best Practices,*10(10): 1-2. Accessed 10 July, 2020 from https://www.magiworld.org/Journal/2014/1410_Biostatistics64.pdf.

Matshitisho, M. 2012. The use of Angiotensin-Converting Enzyme Inhibitors in General Medicine. *South African Family Practice*, 54(4): 313-315. [Online]. Available at doi:10.1080/20786204.2012.10874241. [Accessed 21 June 2020].

Mayosi, B.M., Flisher, A.J., Laloo, U.G., Sitas, F., Tollman, S.M. & Bradshaw, D. 2009. The Burden of Non-Communicable Diseases in South Africa. *The Lancet*, 373(9693): 934-935.

Mehta, U.C. 2011. Pharmacovigilance: The Devasting Consequences of not Thinking about Adverse Drug Reaction. *Continuing Medical Education*, 29(6): 247-251. [Online]. Available at http://cmej.org.za/index.php/cmej/article/view/2170/1827 [Accessed 20 April, 2020].

Mehta, U., Kalk, E., Boulle, A., Nkambule, P., Gouws, J., Rees, H. & Cohen, K. 2017. Pharmacovigilance: A Public Health Priority for South Africa. *South African Health Review*, 2017: 125-133.

Mejía, G., Saiz-Rodríguez, M., Gómez de Olea, B., Ochoa, D. & Abad-Santos, F. 2020. Urgent Hospital Admissions Caused by Adverse Drug Reactions and Medication Errors—A Population-Based Study in Spain. *Frontiers in Pharmacology*, 11: 734.

Mills, K.T., Stefanescu, A. & He, J. 2020. The Global Epidemiology of Hypertension. *Nat Rev Nephrol*,16(4): 223-225. doi: 10.1038/s41581-019-0244-2.

Modjadji, P. 2021. Communicable and Non-Communicable Diseases Coexisting in South Africa. *The Lancet Global Health*. 9(7): 889-890. [Online]. Available at: doi:https://doi.org/10.1016/s2214-109x(21)00271-0 [Accessed 21 March 2023].

Moholisa, R.R., Rayner, B.R, Owen, E.P, Schwager, S., Stark, S., Badri, M., Cupido, C.C.& Sturrock, E.D. 2013. Association of B2 Receptor Polymorphisms and ACE Activity with ACE Inhibitor-Induced Angioedema in Black and Mixed-Race South Africans. *The Journal of Clinical Hypertension*, 15(6): 413-419. [Online]. Available at: doi: https://doi.org/10.1111/jch.12104[Accessed 21 March 2023].

Montinaro, V. & Cicardi, M. 2020. ACE Inhibitor-Mediated Angioedema. *International Immunopharmacology*, 78: [Online]. Available at: doi: 10.1016/j.intimp.2019.106081. [Accessed 21 March 2023].

Mortality and Causes of Death in South Africa: Findings from Death Notification.2017. Pretoria: Department of Statistics South Africa. [Online]. Available at: http://www.statssa.gov.za/publications/P03093/P030932017.pdf [Accessed 20 September 2020].

Mouton, J.P., Fortuin-de Smidt, M.C., Jobanputra, N., Mehta, U., Stewart, A., de Waal, R., Technau, K.G., Argent, A., Kroon, M., Scott, C. & Cohen, K. 2020. Serious Adverse Drug Reactions at Two Children's Hospitals in South Africa. *BMC Paediatrics*, 20(1): 1-14.

Mouton, J.P., Njuguna, C., Kramer, N., Stewart, A., Mehta, U., Blockman, M., Fortuin-De Smidt, M., De Waal, R., Parrish, A.G., Wilson, D.P. & Igumbor, E.U. 2016. Adverse Drug Reactions Causing Admission to Medical Wards: A Cross-Sectional Survey at 4 Hospitals in South Africa. *Medicine*, 95(19): e3437.

Mpe, M.T. 2007. Choosing Antihypertensive Treatment for a South African Population. *South African Family Practice,*49(8): 27-30. doi:10.1080/20786204.2007.10873617.

Najafi, S. 2018. Importance of Pharmacovigilance and Role of Healthcare Professionals. *Journal of Pharmacovigilance,* 6(1): . doi:10.4172/2329-6887.1000252.

Nassaji, H. 2015. Qualitative ond Descriptive Research. *SAGE Journals*, 19(2), pp. 129-132. doi:https://doi.org/10.1177/1362168815572747.

Nishad, A., Arulmoly, K. & Abeysundara, P. 2019. A Forgotten Cause of Allergy at ER that is Still Difficult to Diagnose and Treat at Poor Resource Setting. Angioedema after Using Angiotensin Converting Enzyme Inhibitors for 4 Years. *Case Reports in Immunology*, (2019). doi:10.1155/2019/1676391.

Ntuli, S.T., Maimela, E., Alberts, M., Choma, S. & Dikotope, S. 2015. Prevalence and Associated Risk Factors of Hypertension amongst Adults in a Rural Community of Limpopo Province South Africa. *African Journal of Primary Health Care & Family Medicine*, 7(1): 847. DOI: 10.4102/phcfm.v7i1.847.

Nzeako, U. 2010. Diagnosis and Management of Angioedema with Abdominal Involvement. *World Journal of Gastroenterology*, 16(39): 4913-4921. doi:10.3748/wjg.v16.i39.4913.

Ogedegbe, G., Shah, N.R., Phillips, G., Goldfield, K., Roy, J., Gyamfi, J., Torgersen, C., Capponi, L. & Bangalore, S. 2015. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitor-Based Treatment on Cardiovascular Outcomes in Hypertensive Blacks versus White. *Journal of the American College of Cardiology*, 66(11): 1224-1233. *http://dx.doi.org/10.1016/j.jacc.2015.07.021*.

Okello, S., Muhihi, A., Mohamed, S.F., Ameh, S., Ochimana, C., Oluwasanu, A.O., Bolarinwa, O.A., Sewankambo, N. & Danaei, G. 2020. Hypertension Prevalence, Awareness, Treatment, and Control and Predicted 10-year CVD Risk: A Cross-Sectional Study of Seven Communities in East and West Africa (SevenCEWA). *BMC Public Health*, 20: 1-13.

Okumu, M., Ochola, F., Bodo, C., Apuoyo, K., Odhiambo, N. & Ng'ong'a, A. 2018. Enalapril-Induced Angioedema. *Cureus*, 10(5): e2572. doi:10.7759/cureus.2572.

Pall, A.H., Rasmussen, E.R. & Wadelius, M. 2021. Pharmacogenetics of Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema. *Pharmacogenomics*, 22(6): 319-321.

Pannucci, C.J. & Wilkins, E.G. 2010. Identifying and Avoiding Bias in Research. *Plastic and Reconstructive Surgery*, 126(2): 619-625. doi:10.1097/PRS.0b013e3181de24bc.

Patel, M. & Patel, N. 2019. Exploring Research Methodology: Review Article. *International Journal of Research and Review*. 6(3): 48-55.

Peer, N., Steyn, K., Lombard, C., Gwebushe, N. & Levitt, N. 2013. A High Burden of Hypertension in the Urban Black Population of Cape Town: The Cardiovascular Risk in Black South Africans (CRIBSA) Study. *PLOS One*, 8(11): e78567.

Pender, K. & Omole, O. 2019. Blood Pressure Control and Burden of Treatment in South African Primary Healthcare: A Cross-Sectional Study. *African Journal of Primary Health Care & Family Medicine*, 11(1): 1-7.

Phelan, C. & Wren, J. 2007. *Exploring Reliability in Academic Assessment.* s.l.:s.n. Retrieved 16 April, 2020, from https:www.uni.edu/chfasoa/reliabilityandvalidity.htm.

Piller, L.B., Ford, C.E., Davis, B.R., Nwachuku, C., Black, H.R., Oparil, S., 4Tamrat M. Retta, T.M., Jeffrey L. & Probstfield, J.L. 2006. Incidence And Preandtors of Angioedema in Elderly Hypertensive Patients at High Risk for Cardiovascular Disease. *The Journal of Clinical Hypertension*, 8(9):613-675. doi:https://doi.org/10.1111/j.1524-6175.2006.05689.X.

Pillay, S., Pillay, D. & Pillay, R.S. 2021. The Burden of Hypertension in Kwazulu-Natal Province, South Africa: A 6-year Perspective. *South African Medical Journal*, 1(111): 159. doi:10.7196/SAMJ. 2021.v111i2.15.56.

Pines, J.M., Poarch, K. & Hughes, S. 2021. Recognition and Differential Diagnosis of Hereditary Angioedema in the Emergency Department. *The Journal of Emergency Medicine*, 60(1): 35-43.

Porter, R.S. & Kaplan, J.L. eds. 2011. *The Merck Manual (19th Ed.).* United States of America: Merck Sharp & Dohme Corp.

Potter, P. & Peter, J. 2018. Life-Threatening Hereditary Angio-Oedema: Challenges of Care in South Africa. *SAMJ: South African Medical Journal*, 108(4): 254-255.http://dx.doi.org.7196/samj.2018.v108i4.12824.

Rampamba, M.E., Meyer, J.C., Helberg, E., Brian, G. 2021. Medicines Availability among Hypertensive Patients in Primary Health Care Facilities in a Rural Province in South

Africa. *Journal of Research in Pharmacy Practice,* 9(4): 180-185. [Online]. Available at: DOI: 10.4103/jrpp.JRPP_20_49 [Accessed 21 March 2023].

Rasmussen, E.R., Von Buchwald, C., Wadelius, M., Prasad, S.C., Kamalewaran, S., Ajgeiy, K.K., Authried, G., Pallesen, K.A.U. & Bygum, A. 2017. Assessment of 105 Patients with Angiotensin-Converting Enzyme-Inhibitor Induced Angioedema. *International Journal of Otolaryngology*. [Online]. Available at: *doi:10.1155/2017/1476402.* [Accessed 10 September 2022].

Rasmussen, E.R. et al., 2020. Genome-Wide Association Study of Angioedema Induced by Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Treatment. *The Pharmacogenomics Journal,* 20: 770-780. [Online]. Available at: https:doi.org/10.1038/s41397-020-0165-2. [Accessed 21 March 2023].

Rayner, B. 2010. Hypertension: Detection and Management in South Africa. *Nephron Clinical Practice*, 116(4): c269-273. [Online]. Available at: doi:10.1159/000318788. [Accessed 21 March 2023].

Rayner, B., Jones, E., Veriava, Y. & Seedat, Y.K. 2019. South African Hypertension Society Commentary on the American College of Cardiology/American Heart Association Hypertension Guidelines. *Cardiovascular Journal of Africa*, 3(3): 184-187. doi:10.5830/CVJA-2019- 025.

Rossiter, D., ed. 2016. *South African Medicines Formulary (12 Ed.).* Cape Town: South African Medical Association.

Salem, D. & Alchakaki, A. 2016. Treatment of Severe ACE inhibitor Angioedema: Current and Future Therapies. *Consultant*, 56(2): 134.

Samodien, E., Abrahams, Y., Muller, C., Louw, J. & Chellan, N. 2021. Non-Communicable Disease- A Catastrophe for South Africa. *South African Journal of Science,*117(5/6): 1-6. *doi:10.17159/sajs.2021/8638.*

Sanchez-Borges, M. & Gonzalez-Aveledo, L. 2010. Angiotensin-Converting Enzyme Inhibitors and Angioedema. *Allergy Asthma & Immunology Research,* 2(3): 195-198. doi:10.1080/20786204.2010.10873974.

Schellack, N. & Malan.2014. An Overview of Fixed-Dose Combinations of Antihypertensive Drugs in South Africa. *The South African Family Practice*,56(4): 206-211. [Online]. Available at: *doi:10.1080/20786190.2014.953868.* [Accessed 21 March 2020].

Potlog Shchory, M., Goldstein, L.H., Arcavi, L., Shihmanter, R., Berkovitch, M. & Levy, A. 2020. Increasing Adverse Drug Reaction Reporting—How can we do Better? *PLOS One,* 15(8): e0235591.

Sienkiewicz, K., Burzyńska, M., Rydlewska-Liszkowska, I., Sienkiewicz, J. & Gaszyńska, E. 2021. The Importance of Direct Patient Reporting of Adverse Drug Reactions in the Safety Monitoring Process. *International Journal of Environmental Research and Public Health*, 19(1): 413.

Seedat, Y.K., Rayner, B.L. & Veriava, Y. 2014. South African Hypertension Practice Guideline. *Cardiovascular Journal of Africa*, 25(6): 288-294. doi:10.5830/CVJA-2014-062.

Sever, P.S. & Messerli, F.H. 2011. Hypertension Management 2011: Optimal Combination Therapy. *European Heart Journal*, 32(20): 2499-2506. [Online]. Available at: https://doi.org/10.1093/eurheartj/ehr177 [Accessed 21 March 2023].

Sharma, P. & Nagarajan, V. 2013. Can an ARB be Given to Patients who have had Angioedema on an ACE Inhibitor? *Cleveland Clinic Journal of Medicine*, 80(12): 755-757. [Online]. Available at:doi:10.3949/ccjm.80a.13041. [Accessed 21 March 2023].

Sharma, J.R., Mabhida, S.E., Myers, B., Apalata, T., Nicol., E., Benjeddou., M.,Muller, C. & Johnson, R. 2021. Prevalence of Hypertension and its Associated Risk Factors in a Rural Black Population of Mthatha Town, South Africa. I*nternational Journal of Environmental Research and Public Health*, 18(3): 1215. doi:10.3390/ijerph18031215.

Smith, S.M., Gong, Y., Handberg, E., Messerli, F.H., Bakris, G.L., Ahmed, A., Bavry, A.A., Pepine, C.J. & Cooper-DeHoff, R.M. 2014. Predictors and Outcomes of Resistant Hypertension among Patients with Coronary Artery Disease and Hypertension. *Journal of Hypertension*, 32(3): 635.

Snyder, H. 2019. Literature Review as Research Methodology: An Overview and Guidelines. *Journal of Business Research,* 104: 339. doi: HTTP:// doi.org/10.1016/j.jbusres.2019.07.039.

South African Health Products Regulatory Authority. 2020. Communication to Healthcare Professionals: Guideline for Adverse Drug Reactions (ADRs) Reporting for Healthcare Professionals. [Online]. Available at https://www.sahpra.org.za/wp-content/uploads/2020/04/ADR-Reporting-Guideline_HCPs_v1 for-commenting_March-2020. [Accessed 21 March 2023].

Squillante, M.D., Trujillo, A., Norton, J., Bansal, S. & Dragoo, D. 2021. ACE Inhibitor Induced Isolated Angioedema of the Small Bowel: A Rare Complication of a Common Medication. *Case Reports in Emergency Medicine*, *2021*. Published Online 2021 Feb 13. doi: 10.1155/2021/8853755. PMCID**:** PMC7896855.

Standard Treatment Guidelines and Essential Medicines List for South Africa.2020. [Online]. Available at: https:www.knowledgehub.org.za/e-library[Accessed 21 March 2023].

Terblanche, A. 2018. Pharmacovigilance and the Reporting of Adverse Drug Reactions. *SA Pharmaceutical Journal*, 85(6): 65-68.

Terreehorst, I., Reitsma, S. & Cohn, D. 2019. Current Treatment of Angioedema Induced by ACE Inhibitors. *Current Treatment Options in Allergy*, 6: 18-26. doi:10.1007/s40521-019- 0203-y.

Tiemensma, M., Burger, E. & Dempers, J. &. W. 2010. Fatal Angioedema Induced by Angiotensin Conversion Enzyme (ACE) Inhibitors. *South African Family Practice,* 52(3) 217-218. doi:10.1080/20786204.2010.10873974.

Tharayil, A.M., Chanda, A.H., Shiekh, H.A., Elkhatib, M.S., Nayeemuddin, M. & Alshamandy, A.A.A. 2014. Life Threatening Angioedema in a Patient on ACE Inhibitor (ACEI) Confined to the Upper Airway. *Qatar Medical Journal*, 2014(2): 92-97. [Online]. Available at: doi:10.5339/qmj.2014.15 [Accessed 21 March 2023].

The Heart and Stroke Foundation South Africa. 2016. Cardiovascular Disease Statistics Reference Document. Vlaeberg, South Africa. [Online]. Available at http://www.heartfoundation.co.za/wp-content/uploads/2017/10/CVD-Stats-Reference-Document-2016-FOR-MEDIA-1.pdf [Accessed 23 September 2020].

Unger, T., Borghi, C., Charchar, F., Khan, N.A., Poulter, N.R., Prabhakaran, D., Ramirez, A., Schlaich, M., Stergiou, G.S., Tomaszewski, M., Wainford, R.D., Williams, B. & Schutte, A.E. 2020. International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*, 75(6): 1334-1357.

Ungureanu, R. & Madalan, E. 2019. Angioedema, a Life-Threatening Adverse Reaction to ACE-Inhibitors. *Romanian Journal of Rhinology*, 9(36): 177-181. [Online]. Available doi: https://doi.org/10.2478/rjr-2019-0023. [Accessed 21 March 2022].

Van de Vijver, S., Akinyi, H., Oti, S., Olajide, A., Agyemang, C., Aboderin, I. & Kyobutungi, C. 2013. Status Report on Hypertension in Africa-Consultative Review for the 6th Session of the African Union Conference of Ministers of Health on NCDs. *The Pan African Medical Journal,* 16(1*)*:38-55. [Online]. Available *doi:10.11604/pamj.2013.16.38.3100.* [Accessed 21 March 2023].

Ware, L.J., Chidumwa, G., Charlton, K., Schutte, A.E. & Kowal, P. 2019. Predictors of Hypertension Awareness, Treatment and Control in South Africa: Results from the WHO-SAGE Population Survey (Wave 2). *Journal of Human Hypertension*. 33(2):

157-166. [Online]. Available at: doi:10.1038/s41371-018-0125-3 [Accessed 21 March 2023].

Weisman, D.S., Arnouk, N., Asghar, M.B., Qureshi, M.R., Kumar, A., Desale, S., Camire, L. & Pineda, S. 2020. ACE Inhibitor Angioedema: Characterization and Treatment Versus Non- ACE Angioedema in Acute Hospitalized Patients. *Journal of Community Hospital Internal Medicine Perspectives*, 10(1): 16-18. [Online]. Available at https://doi.org/10.1080/20009666.2020.1711641 [Accessed 21 March 2023].

Wentzel, N., Panieri, A., Ayazi, M., Ntshalintshali, S.D., Pourpak, Z., Hawarden, D., Potter, P., Levin, M.E., Fazlollahi, M.R. & Peter, J. 2019. Fresh Frozen Plasma for On-Demand Hereditary Angioedema Treatment in South Africa and Iran. *World Allergy Organization Journal*, 12(9): 100049.

. [Online]. Doi:10.1016/j.waojou.2019.100049[Accessed 21 March 2023]

Wisecarver, I., Kamboj, S., Galambos, D., Korah-Sedgwick, M., McCarron, R. & Lopez, F. 2017. An Extreme Presentation of Angiotensin Converting Enzyme Inhibitor-Induced Angioedema. *The Journal of the Louisiana State Medical Society*, 169(6): 171-176.

Whitehead, W.J. & Reid, J.M. 2022. Underreported Risk of Lisinopril-Induced Angioedema in a Veteran Population. *Annals of Pharmacotherapy*, 56(4): 430-435.

World Health Organization, 2002. *The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products.* [Online]. Available at: https://apps.who.int/iris/handle/10665/42493. [Accessed 21 March 2023].

World Health Organization, 2006. *The Safety of Medicines in Public Health Programmes: Pharmacovigilance an Essential Tool.* [Online]. Available at: https://apps.who.int/iris/rest/bistreams/5148/retrieve. [Accessed 27 March 2023].

World Health Organization. 2021. *Guideline for the Pharmacovigilance Treatment of Hypertension in Adults. Geneva.* [Online]. Available at:https://apps.who.int/iris/bitstream/handle/10665/344424/9789240033986-eng.pdf. [Accessed 27 March 2023].

Yan, Z., Feng, Z., Jiao, Z., Chen, C., Wang, G. & Feng, D. 2021. The Severity of Adverse Drug Reactions and their Influencing Factors Based on the ADR Monitoring Center of Henan Province. *Scientific Reports*, 11(1): 20402.

Young, N., Clark, D. & Cook, B. 2012. The Management of Antihypertensive-Associated Angioedema. *Journal of the Intensive Care Society*, 13(1): 25-27. doi:10.1177/175114371201300108. [Accessed 27 March 2023].

Young, M. 2016. *Private vs Public Healthcare in South Africa.* [Online]. Available at: https://scholarworks.wmich.edu/honors_thesis/2741. [Accessed 26 March 2023].

Yuyun, M.F., Sliwa, K., Kengne, A.P., Mocumbi, A.O. & Bukhman, G. 2020. Cardiovascular Diseases in Sub-Saharan Africa Compared to High-Income Countries: An Epidemiological Perspective. *Global Heart*, 15(1): 15. *DOI: https://doi.org/10.5334/gh.403.* [Accessed 27 March 2022].

ANNEXURES

1. DATA COLLECTION TOOL

2. ETHICS APPROVAL CERTIFICATE

3. LETTERS OF ACCEPTANCE TO CONDUCT STUDY, FROM THE TSHILIDZINI HOSPITAL

4. LETTER OF APROVAL TO CONDUCT STUDY FROM THE HOSPITAL PHARMACY

5. LETTER OF APROVAL TO CONDUCT STUDY FROM THE DEPARTMENT OF HEALTH, LIMPOPO PROVINCE

5. PLAGIARISM DECLARATION

6. TURNITIN REPORT

ANNEXURE 1: DATA COLLECTION TOOL

1. GENERAL INFORMATION

Name and surname of data collector	
Hospital Name	
Date	
Study Number	

2. DEMOGRAPHICAL INFORMATION

Age	
Gender	
Race	

3. MEDICAL HISTORY

3.1 History of enalapril administration? Tick appropriate answer

First Intake	1 Month	1 year	≥ 5 years

	Yes	No
3.2 Previous attacks of angioedema?		
3.3 Previous allergies? If yes specify.		

3.4 History of smoking?		

4. CLINICAL PRESENTATION

4.1 What did the patient present with? Tick appropriate answer

	Face	Lips	tongue	Other
Swelling				

	Yes	No
4.2 Did the patient present with pruritus?		
4.3 Did the patient present with urticaria or rash?		

5. THERAPEUTIC MANAGEMENT AND INTERVENTIONS (Tick appropriate answer)

	Yes	No
5.1 Any intervention?		
5.2 Intervention not known		
5.3 Patient Counselling		
5.4 Medication Discontinued		
5.5 Pharmaceutical Therapy given Specify:		
5.6 Others. (Specify):		

6. CLINICAL OUTCOMES (Tick appropriate answer**)**

	Yes	No
6.1 Patient recovered?		
6.2 Patient recovering?		
6.3 Further ADR recurrence?		
6.4 Patient not recovering?		
6.5 Outcome Unknown.		
6.6 Death?		

ANNEXURE 2: ETHICS APPROVAL CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO:	Ms B Muremela School of Therapeutic Sciences Department of Pharmacy and Pharmacology Division of Pharmacy Medical School University E-mail: 2400944@students.wits.ac.za
CC:	Supervisor: Drs N Padayachee and V Bangalee <Neelaveni.Padayachee@wits.ac.za> and <HREC-Medical Research Office@wits.ac.za>
FROM:	Mr Iain Burns Human Research Ethics Committee (Medical) Tel: 011 717 1252 E-mail: Iain.Burns@wits.ac.za
DATE:	2021/11/10
REF:	R14/49
PROTOCOL NO:	**M210150** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)
PROJECT TITLE:	*Incidences associated with Enalapril-induced angiodema in a public regional hospital, Limpopo Province*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Ms B Muremela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210150

NAME: (Principal Investigator)	Ms B Muremela
DEPARTMENT:	School of Therapeutic Sciences Department of Pharmacy and Pharmacology Division of Pharmacy Medical School University
PROJECT TITLE:	*Incidences associated with Enalapril-induced angiodema in a public regional hospital, Limpopo Province*
DATE CONSIDERED:	2021/01/29
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Drs N Padayachee and V Bangalee
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/11/10

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in January and therefore reports and re-certification will be due in the month of **January** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

15/11/2021
Date

ANNEXURE 3: LETTER OF ACCEPTANCE TO CONDUCT STUDY FROM THE HOSPITAL

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF
HEALTH
TSHILIDZINI REGIONAL HOSPITAL

Ref: S2/5/1
Enq: Maladzhi KC
Date: 27/ 08 /2021
Tel: 015 964 4200. Ext 4557

DEPARTMENT OF HEALTH
TSHILIDZINI HOSPITAL
27 AUG 2021
P/BAG X 924 SHAYANDIMA 0945
LIMPOPO PROVINCE

TO.: University of the Witwatersrand
Johannesburg
Human Research Ethics Committee (Medical)

To Whom It May Concern

SUBJECT: REQUEST FOR PERMISSION TO CONDUCT RESEARCH AT TSHILIDZINI REGIONAL HOSPITAL.

Tshilidzini hospital is willing to allow Ms. Blessing Muremela, Id no: 9604140370081 to conduct the research in the institution provided the following:

1. Ethical committee of the University has approved the research.
2. Head of department (Health) has also approved.
3. Hoping that the above information will suffice you.
4. Thanking you in advance.

Chief Executive Officer

2021/08/27
Date

Tshilidzini Hospital.Private Bag X924, SHAYANDIMA, 0945Tel:015 964 4200, FAX 015 964 1492/015 964 1072
Physical Address: R524 PUNDA MARIA ROAD
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ANNEXURE 4: LETTER OF APROVAL TO DO CONDUCT STUDY FROM THE HOSPITAL PHARMACY

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA
DEPARTMENT OF HEALTH

TSHILIDZINI REGIONAL HOSPITAL

ENQ: Phaswana TE

Date: 06/09/2021

Tel:0159644200

To: University of the Witwatersrand

Johannesburg

Human Research Ethics Committee (Medical)

To Whom It May Concern

SUBJECT: REQUEST FOR PERMISSION TO CONDUCT RESEARCH AT TSHILIDZINI REGIONAL HOSPITAL, PHARMACY DEPARTMENT.

The pharmacy department is willing to allow Ms .Blessing Muremela, ID: 9604140370081 to conduct the research within the department provided the following.

1. Ethical clearance from the University Ethical Committee
2. Head of department provisional (Health) approval.
3. CEO approval letter
4. Hoping that the above information will suffice you.

Phaswana

Pharmacy Manager

06/09/2021.

Date

Annexure 5: LETTER OF APROVAL TO CONDUCT STUDY FROM DOH Limpopo

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Department of Health

Ref : LP_2022-01-012

Enquires : Ms PF Mahlokwane

Tel : 015-293 6028

Email : Phoebe.Mahlokwane@dhsd.limpopo.gov.za

BLESSING MUREMELA

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below**;**

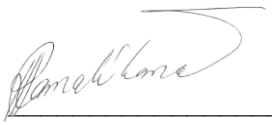
INCIDENCES ASSOCIATED WITH ENALAPRIL-INDUCED ANGIOEDEMA IN A PUBLIC REGIONAL HOSPITAL, LIMPOPO PROVINCE

1. Permission to conduct research study as per your research proposal is hereby granted.
2. Kindly note the following:
   a) Present this letter of permission to the institution supervisor/s a week before the study is conducted.
   b) The approval is **ONLY** for Tshilidzini Hospital.
   c) In the course of your study, there should be no action that disrupts the routine services or incurs any costs to the Department.
   d) After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   e) The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   f) The approval is only valid for a 1-year period.

g) If the proposal has been amended, a new approval should be sought from the Department of Health

Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated



_____ __15/02/2022_____

Head of Department **Date**

Private Bag X9302 Polokwane

Fidel Castro Ruz House, 18 College Street. Polokwane 0700. Tel: 015 293 6000/12. Fax: 015 293 6211.

Website: http/www.limpopo.gov.za

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UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I BLESSING MUREMELA (Student number: 2410944) am a student registered for the degree of MASTER OF PHARMACY in the academic year 2023.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 04 October 2023

ANNEXURE 6: TURNITIN REPORT

Turnitin Originality Report

- Processed on: 03-Oct-2023 2:17 AM SAST
- ID: 2183827284
- Word Count: 14633
- Submitted: 1

Blessing Muremela Incidences associated with Enalapril Induced Angioedema 2023 New (1) (AutoRecovered) blessy (1)-ebef2ad4-47c8-414d-b9cb-5bd6f1b0a95d.docx By Blessing Muremela

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