THE FINANCIAL BURDEN OF POLYPHARMACY IN TYPE 2 DIABETIC PATIENTS AT MANKWENG HOSPITAL, LIMPOPO PROVINCE

by

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[redacted]

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DECLARATION

I, **GINAT MOTHAPO**, hereby declare that the work on which this study is based is original, except where acknowledgements indicate otherwise.

This dissertation is submitted for the degree **Masters in Pharmacy** at the University of Limpopo. Neither the whole work nor any part of it has been submitted before for any degree or examination at this or any other university.

Signed……on the……day of……

DEDICATION

I would like to dedicate this work firstly, to God almighty for making it possible for me.

I dedicate this to my beautiful daughter (Blessing Mothapo) and my entire family for all their sacrifices throughout my study period, if it wasn't for their love and kindness I wouldn't have made it.

Lastly, I dedicate this work again to God.

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ABBREVIATIONS AND ACRONYMS

ADA	American Diabetes Association
ATP	Adenosine Triphosphate
CVD	Cardio Vascular Disease
Df	Degree of freedom
DM	Diabetes Mellitus
GDP	Gross Domestic Profit
GIP	Gastric Inhibitory Polypeptide
HbA1c	Haemoglobin A1c
IDF	International Diabetes Federation
M	Mean
OTC	Over the Counter
PPARy	peroxisome proliferator-activated receptor gamma
SA	South Africa
SAMF	South African Medicines Formulatory
SD	Standard deviation
SUR1	Sulphonylurea Receptor 1
TZD	Thiazolidinediones
UK	United Kingdom
UNICEF	United Nations Children's Fund
WHO	World health organisation
T2DM	Type 2 Diabetes Mellitus

ABSTRACT

Introduction: Polypharmacy is highly prevalent within the population of patients with diabetes mellitus (DM), with patients being prescribed with four or more medications with mainly preventative medications for cardiovascular complications. The increase in the prevalence of polypharmacy has a major impact on the drug expenditures. Meanwhile, the management of DM is expensive, and the cost affects individuals, families, society, health care providers, and national productivity. The largest component of financial cost is accounted for by medicines. Furthermore, with DM being the second cause of mortality rates in South Africa there is a need for cost of illness studies in order to develop intervention programs to ameliorate or prevent this lifestyle disease

Objectives: To identify the medications the patient was taking that were considered as polypharmacy in the management of type 2 diabetes mellitus (T2DM), to calculate and analyse the costs of the medications and to quantify the financial burden of polypharmacy in T2DM patients.

Method: This research was a quantitative study, providing the numeric description of the economic cost of polypharmacy. The financial burden of polypharmacy was retrospectively measured using descriptive statistics. The study was conducted using T2DM patient files (n=115) from the outpatient section of the pharmacy as well as from the records department whereby all DM patients' files were retrieved by aid of a DM register from outpatient department (OPD). The data sheet enabled recording of information that was divided into three sections namely the demographic information, the diagnosis profile, as well as the medications. The cost of drugs was retrieved from the pharmacy purchase invoices for the years 2016 and 2017 as well as Department of Health medicines registry for the retail prices. Data was analysed using statistical Package for Social Sciences (SPSS) version 25 for descriptive analysis and Microsoft Excel ™ was used for calculation and quantification of the financial burden. The independent t test was used in Microsoft Excel™ for statistical significance of differences.

Results: The distribution of the population by gender revealed that 68% of females were on polypharmacy as compared to 32% of males. The results also showed that majority of participants accounting 71% of the population were falling within the age

group of 51-70 years, meanwhile the least number of participants accounting 1% of the population were between the age group of 30-40 years.

The total cost of the treatment regimen for the two years of the study period was found to be R179303.50 in hospital (Mean=R35860.80, SD=R58945.15, n=115) and the possible cost of polypharmacy was found to be R1517379.00 in retail (Mean=R303475.76, SD=480115.84, n=115). The difference was statistically significant t (16) = 2.11, p=0.04 (1 tail) at 95% confidence interval. This means that the average cost per patient per year is R1558.18 and R129.93 per month in hospitals but R6597.30 per year and R549.78 per month in retail for the management of T2 DM patients who are on polypharmacy. These numbers are 4 times higher than patients who are on monotherapy.

Conclusion: Polypharmacy imposes a high financial burden on the management of T2DM for the government and for patients in cases where medications like insulin which is the most costly component of five out of nine detected regimens are unavailable in hospitals and they therefore have to buy at retail pharmacies. The appreciation and understanding of these costs in real terms by health professionals and decision makers, can add value to processes of budget allocations to pharmaceutical services.

Recommendations: Doctors and pharmacists should work together to optimize the quality of care for patients with T2DM but also consider the cost aspect when prescribing and dispensing treatment regimen for a patient. The patient's prescriptions must be thoroughly reviewed and rationalised according to recent progress of the patient. Non-pharmacological management of T2DM is the mainstay of therapy and prevention so pharmacist and doctors needs to emphasize more on those rather than dispensing a lot of medications to patients that can manage to control their condition with no medications prescribed. Lastly, preventative programs for T2DM needs to be prioritized.

CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

This chapter introduces the background of the study, provides its rationale, research aim and objectives, as well as broad research questions to be answered. The justification and context for the study is also discussed. Both the purpose of the study which deliberates the research questions and the significance of the study are elaborated. The individual objectives are cited and discussed from both the research questions and the main aim of the study.

1.2 BACKGROUND AND RATIONALE FOR THE STUDY

Diabetes mellitus (DM) is a serious condition with life threatening complications and affects people of all ages (Harrabi, Harbi & Ghamdi, 2014). Its prevalence is projected to rise to 552 million cases by 2030 worldwide (Whiting, Guariguata, Weil & Shaw, 2011). Data from International Diabetes Federation (IDF) estimates that 7 % (3.85 million) of South Africans between the ages of 21 and 79 years had diabetes in 2015. On the other hand, DM was ranked as the number two leading cause of deaths in South Africa in 2015 according to Stats SA (Bateman, 2017).

Management of DM is expensive, and the cost affects individuals, families, society, health care providers, and national productivity (Khowaja, Khuwaja & Cosgrove, 2007). The largest component of financial cost is accounted for by medicines (Quaye, Amporful, Akweongo & Aikins 2015). The characteristics and complications of DM often need a multiple medication regimen, normally using drugs from several therapeutic classes (Peron, Ogbonna & Donohoe, 2014). Moreover, DM and its complications increase costs putting pressure on publicly funded healthcare system (Canadian DM Association Clinical Practice Guidelines Expert Committee, 2013). This problem arises when there is high usage of different treatment regimen for different patients. In most cases a combination of a least two drugs, is used to manage the disease, leading to increased costs for DM management. The use of two or more drugs to treat the same condition, or the use of two or more drugs of the same chemical

class; or the use of two or more agents with the same or similar pharmacologic actions to treat different conditions, is referred to as polypharmacy (Brager & Sloand, 2005).

Polypharmacy has been described as a major risk factor for adverse drug reactions while ageing has a strong impact on the pharmacokinetics and pharmacodynamics, comorbidity, and patterns of medication that may contribute to an increased risk of adverse events (Davies & O'mahony, 2015). A literature review study found a high incidence of polypharmacy among geriatric patients (Ahmed, Nanji, Mujeeb & Patel, 2014). A study conducted in the United Kingdom (UK) indicated that polypharmacy is highly prevalent within a population of diabetic patients where 84% of that population were prescribed four or more medications. Fifty-nine percent of the same population were prescribed mainly preventative medications for cardiovascular complications (Gadsby, Galloway & Sinclair, 2012). A study conducted in South Africa by Hemraj, (2015) found a prevalence of 75% of polypharmacy in the elderly with the number of medicines per patient ranging from two to twenty-one. In the same study, polypharmacy was more prevalent in females and in patients aged between 60 to 69 years.

The increasing prevalence of DM and the high cost of the treatment, presents challenges to diabetes cost control (Tao, 2011). Economically, diabetes imposes an increasing burden on national health care systems. Research has reported that the total costs for direct medical costs of diagnosed diabetes in the United States in 2013 were $176 billion which is about R2292 billion (American Diabetes Association, 2013). In South Africa the cost per person per annum with diabetes was approximately R5000.00 in 2010 and then increased to R26743.69 in 2015 (International Diabetes Federation, 2015).

The South African National Department of Health was given 13.5% expenditure budget for health programs as a share of total government expenditure in 2017 (UNICEF 2017). According to Savedoff, 2007 this total expenditure on healthcare accounted for 8.8% of the Gross Domestic Profit (GDP). Meanwhile, according to the world bank, no more than 5% of the country’s GDP should be spent on health care.

A report by IDF estimates that the economic cost of diabetes in Sub-Saharan Africa in 2015 totalled $19.5 billion, equivalent to 1.2% GDP. More than half of this economic

cost (56%) was on accessing diabetes treatment, including medication and hospital stays (International Diabetes Federation, 2015).

Polypharmacy is a growing problem with negative clinical consequences and a resulting increase in the economic costs of healthcare (Sergi, Rui, Sarti &Manzato, 2011). It may result in unnecessary health expenditure, directly due to redundant drug sales, and indirectly due to the increased hospitalization caused by drug-related problems (Hovstadius, 2010). Furthermore, admission rates will increase since an increasing population age is associated with high risks of side effects, in the elderly (Medeiros-Souza, Santos-Neto, Kusano & Pereira, 2007).

1.3 PROBLEM STATEMENT

Polypharmacy is highly prevalent in hospital settings (Duerden, Avery & Payne, 2013), it is aggravated in part by high incidents of side effects in the elderly population as well as poor adherence to treatment and poor clinical outcomes. The risks of this side effects from cases of polypharmacy could further result in additional incurred costs in the form of hospitalizations (Marabella, 2015).

Management of diabetes is expensive, and the cost affects individuals, families, society and national productivity (International Diabetes Federation, 2015). In cases where the medications are not available at public institutions, the patients often concede the cost of polypharmacy by buying at retail pharmacies (Kojima, Bell, Tamura, Inaba, Lubimir, Blanchette, Iwasaki & Masaki, 2012).

Even though it is acknowledged that polypharmacy puts a serious financial burden on the patients and public health system, there is little on ground data on the financial cost of polypharmacy associated with the management of T2DM in South Africa (Hemraj 2015). Studies that examine costs of management of diseases do not provide a detailed scrutiny of individual prescriptions of patients over a particular treatment period.

1.4 RESEARCH QUESTIONS

- What are medication regimen that are considered polypharmacy that T2DM patients are taking?
- How much do these medication regimen costs per patient per year?
- What is the financial burden of polypharmacy in relation to management of T2DM at Mankweng hospital, Limpopo Province for the years 2016 and 2017?

1.5 AIM OF THE STUDY

The aim of the study was to determine the financial burden or economic cost of polypharmacy associated with the management of T2DM patients.

1.6 OBJECTIVES OF THE STUDY

The objectives of the study were as follows:

- To identify the medication regimen that are considered polypharmacy that the patient was taking.
- To calculate and analyse the costs of the medications per prescription and collectively.
- To quantify the financial burden of polypharmacy in T2DM patients.

1.7 IMPORTANCE OR SIGNIFICANCE OF THE STUDY

This study aimed to provide research data on costs associated with polypharmacy in the management of T2DM in hospital settings in South Africa. This study intensively scrutinised the cost of polypharmacy associated with treatment and management of T2DM in a public funded rural hospital over a determined period of time. Studies that examined costs of management of DM did not provide a detailed scrutiny of individual prescriptions of patients over a particular treatment period. Because individual patient prescriptions were surveyed, this study conducted a detailed cost burden analysis per patient giving a clear picture of the total cost burden to the main hospital budget allocation to pharmaceutical services.

The appreciation and understanding of the amount of cost in real terms by health professionals and decision makers, can add value to processes of budget allocations to pharmaceutical services. Furthermore, processes of disease management can be rationalised along patient comfort and safety as well as through a thorough cost-benefit analysis. This should be done where possible to minimise incidences of drug tolerance that may result from poor adherence to treatment and irrational prescribing to save costs.

1.8 SUMMARY

The background, rationale, significance as well as the aims and objectives of the study were discussed in this chapter. This chapter also gave a brief justification of polypharmacy and its implications in the background. The problem statement and significance of the study were also discussed. The next chapter provides a review of relevant literature and what was found by other researchers who investigated similar problems.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, an overview of studies relevant to this study will be provided. It will start by providing different definitions of polypharmacy by several studies. Types of polypharmacy, the causes and then the consequences polypharmacy will be briefly discussed. It will further illustrate how the economic cost of polypharmacy was determined in available literature. A look into diabetes mellitus and its management will also be also covered.

2.2 POLYPHARMACY

Polypharmacy has been defined as the concurrent use of multiple drugs, and some researchers have discriminated between minor (two drugs) and major (more than four drugs) polypharmacy (Viktil, Blix, Moger & Reikvam, 2007). Although the term polypharmacy has evolved over time and is often used to mean many different things in different situations, its basic definition is quite simple, prescribing or taking more drugs (Rambhade, Chakarborty, Shrivastava, Patil & Rambhade, 2012). The mainstay definition is the concomitant use of multiple drugs (Masnoon, Shakib, Kalisch-Ellett & Caughey, 2017).

Despite an abundance of literature on the subject, there is no universally accepted definition of polypharmacy. It is defined as the use of a number of medications taken at the same time, the number of medications varies from two to fiive or more (Akyol, 2007). Some definitions include over the counter and complementary medications, while others consider prescription medications only (Hammond & Wilson, 2013). The definition of polypharmacy in this study is using two or more drugs to treat T2DM based on the standard treatment guidelines for the management of T2DM.

Polypharmacy is an expression that has been commonly used for many years in medicine. The term has been used both positively and negatively. Formerly polypharmacy has been considered something to be avoided but it is now accepted that in many circumstances' polypharmacy can be therapeutically beneficial. This

means that polypharmacy has the potential to be beneficial for some patients, but also harmful if poorly managed (Duerden *et al*., 2013). Since polypharmacy is a consequence of having several underlying medical conditions, it is much more common in elderly patients (Ahmed *et al.,* 2014). Polypharmacy is a problem of substantial importance, in terms of both direct medication costs and indirect medication costs resulting from drug-related morbidity (Rambhade *et al.,* 2012)

2.3 POLYPHARMACY PREVALENCE

The literature reports found that polypharmacy continues to increase and is a known risk factor for important morbidity and mortality. Therapeutic guidelines have evolved and made the treatment of conditions more complex and hence leading to polypharmacy.

Among the prevalence studies of polypharmacy that was conducted worldwide, on the prevalence study conducted by Haider, Johnell, Thorslud & Fastbom (2007) under the topic: Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992-2002, the results have revealed that the prevalence of polypharmacy increased 3-fold from 18% in 1992 to 42% in 2002.

Moreover, a study in UK indicated that polypharmacy is highly prevalent within the population of patients with diabetes with 84% of the population being prescribed with four or more medications of which 59% of that population have been prescribed with mainly preventative medications for cardiovascular complications (Gadsby *et al*., 2012). A South African study has found 75% prevalence of polypharmacy in the elderly with the number of medicines per patient ranging from two to twenty-one. Polypharmacy was more prevalent in females when compared to the males and the age group of 60-69 years had the highest prevalence (Hemraj 2015).

A retrospective cohort study of the 2007 Emilia-Romagna outpatient pharmacy database has shown that 39,4% of the population were taking five or more medications and approximately one-third (36.1%) of elderly exposed to polypharmacy were prescribed 11 or more distinct medications (Slabaugh, Maio, Templin & Abouzaid 2010).

However, the study that aimed to assess the prevalence of polypharmacy in one Austrian center with total of 543 patients with the median age of 82 years (the elderly), 58.4% of the patients met the given criteria of polypharmacy (>6 drugs). The mean number of drugs taken was 7.5. Unnecessary drugs were found prescribed in 36.3% of all patients, drugs to avoid in 30.1%, duplication in 7.6%, wrong dosage in 23.4% and possible drug-drug interactions in 65.8% (Schuler, Dückelmann, Beindl, Prinz, Michalski & Pichler 2008). Nevertheless, polypharmacy has been documented as a major risk factor for adverse drug reactions while ageing has a strong impact on patterns of medication that may contribute to an increased risk of adverse events (Ahmed *et al*., 2014).

Jokanovic, Tan, Dooley, Kirkpatrick & Bell (2015) researched the prevalence of polypharmacy in Long Term Care Facilities worldwide by consolidating the results obtained in available studies on references such as International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature, and the Cochrane Library. The custom time range of search was from 2000 to 2014. Out of forty-four studies that met the inclusion criteria of the study, polypharmacy was most often defined as 5 or more (*n* = 11 studies), 9 (*n* = 13), or 10 (*n* = 11) medications. Prevalence varied widely between studies, with up to 91%, 74%, and 65% of residents taking more than 5, 9, and 10 medications, respectively.

2.4 TYPES/ CLASSES OF POLYPHARMACY

Same-Class polypharmacy

Same class polypharmacy refers to the use of more than one medication from the same class (Kukreja, Kalra, Shah & Shrivasta 2013). This approach usually stems from word-of-mouth reports about differences among medications of the same class. The clinician might believe that one is better for some other effect and that another of the same class is better for some other property, so the patient receives prescriptions for two very similar drugs (Brager & Sloand, 2005).

Multi-Class polypharmacy

Multi-class polypharmacy is the use of full therapeutic doses of more than one medication from different classes for the same symptom cluster (Adeponle, Obembe, Adeyemi & Suleiman, 2007). It may be caused by a condition that may be over diagnosed clinically. Evident in these scenarios is the need to gather detailed information about the patient's symptoms and the symptoms' relationship to the primary illness as a whole rather than simply to treat each individual symptom (Brager & Sloand, 2005)

Adjunctive polypharmacy

Adjunctive polypharmacy is the use of one medication to treat the side effects of another medication from a different class (Kukreja *et al*., 2013). Polypharmacy of this kind usually occurs when a patient is poorly controlled. Therefore, the clinician adds another medication that may help leading to the ‘prescribing cascade (Rambhade *et al*., 2012). Prescribing cascade is said when signs and symptoms (multiple and nonspecific) of an adverse drug reaction is misinterpreted as a disease and a new treatment/drug therapy is further added to the earlier prescribed treatment to treat the condition. This inherits the potential to develop furthermore side-effects and thus making a prescribing cascade (Dagli & Sharma, 2014).

Augmentation polypharmacy

Augmentation polypharmacy refers to the use of one medication at a lower than normal dose along with another medication from a different class in full therapeutic dose for the same symptom or the addition of a medication that would not be used alone for the same symptom cluster (Adeponle *et al*., 2007). It may be caused by an inadequate knowledge of receptor pharmacology or a lack of attention to it. While attempting to change the patient's medication, the clinician lowers the dosage of drug A while adding and raising that of drug B. In this cross-titration there may be a period during which the patient is doing worse because neither drug A nor drug B is at a high enough level. Some clinicians will then go back to the starting dosage of drug A but continue treatment with drug B. Alternatively, during the cross-titration, the patient may be doing better, and the clinician may assume that the improvement is due to the

combination of drugs; the clinician stops there and leaves the patient on both. (Brager & Sloand, 2005).

Total polypharmacy

Total polypharmacy is the total count of medications used in a patient, or total drug load (Kukreja *et al*., 2013). It can be classified as minor (two drugs) or major (more than four drugs) polypharmacy (Viktil *et al*., 2007).

2.5 CAUSES OF POLYPHARMACY

Polypharmacy can be caused by several factors which includes but not limited to multiple prescribers, aging population, complex drug therapies, psychosocial contributions and adverse drug reactions that may be interpreted as new medical conditions (Austin, 2006). Below is a discussion of some of the factors contributing to polypharmacy.

Coexisting medical conditions

A major reason for polypharmacy is that a patient may be having many co-existing medical conditions, thereby necessitating multiple drug therapy, particularly in patients with chronic debilitating disorders (diabetes); increasing demand for health care; therapeutic advances as well as excessive prescribing (Queneau, 2006).

The comorbidities of diabetes commonly include hypertension, dyslipidaemia, depression, and coagulopathies, each of which may require one or more drugs for adequate control. Add to this, other conditions that often accompany diabetes, such as hypothyroidism, heart failure, and osteoporosis, and the total number of possible medications needed becomes significant (Austin, 2006). In the case of diseases such as DM combinations of two to three different medications are common and recommended. If medications for symptomatic relief are added, it is easy to see why patients end up with a large number of medications (Sharmar, 2016).

Multiple prescribers

Being under the care of several specialists is a major reason for polypharmacy and patients see different physicians for their medical problems (Cantlay, Glyn & Barton, 2016). Patients with a chronic disease such as diabetes often see specialists in addition to their primary care providers. Each of these providers may prescribe medications, adding to a growing list of drugs on a patient's profile. There is a stronger tendency for drugs to be added to a patient's regimen than for drugs to be discontinued. The continuous addition of drugs over time, without periodic re-evaluation of the drug regimen, is one of the major contributors to the development of polypharmacy (Austin, 2006).

Another cause of polypharmacy is that the documentation of why a medication was prescribed initially is often missing in the medical record, making decisions to consider termination of a treatment difficult to make later. As a result, there is a tendency for doctors to let patients continue the medications they are taking, especially if the indications are unclear or unknown (Sharmar, 2016).

Aging population

The burden of polypharmacy falls especially hard on the elderly, who incur the highest incidence of chronic conditions coupled with reduced or fixed incomes and therefore inability to afford the cost of multiple medications. As the population ages, the incidence of chronic conditions increases. Treatment of elderly patients with diabetes requires special considerations, especially in how aggressively diabetes should be treated. Treatment decisions should consider age and life expectancy, comorbid conditions, cognitive status, living arrangements, and severity of vascular conditions (Busse & Blümel, 2010).

Complex drug therapies

The variety of expert panel recommendations, clinical practice guidelines, and other national standards for medical treatment has grown exponentially in the last decade. Many of these guidelines overlap, and sometimes they contradict each another. Clinical practice guidelines rarely address the treatment of patients with three or more chronic diseases, and such patients make up half of the population. Guidelines and

quality assurance initiatives largely ignore the issue of marginal benefits of multiple medications as recommended by various sets of treatment guidelines (Gorard, 2006)

Psychosocial contributions

Patients and their families often demand medications and frequently ignore explanations about why drug therapy may not be in their best interests (Austin, 2006).

Adverse drug reactions

The prevalence of problems associated with multiple medications is probably underestimated. Increasing the number of medications prescribed increases the risk of adverse reactions. The interaction of aging, concurrent comorbidities, pharmacokinetics, and polypharmacy places the elderly at increased risk of adverse drug reactions. Reactions to existing treatments may be misinterpreted as new medical conditions requiring treatment with additional medical or surgical intervention. For example, edema caused by a thiazolidinedione might be mistaken as a sign of new-onset heart failure or as a worsening of pre-existing heart failure. This may lead to the addition of a diuretic or the use of compression stockings if the root cause of the edema is not determined (Shah & Hajjar, 2012; Austin, 2006).

2.6 CONSEQUENCES OF POLYPHARMACY

Polypharmacy may result in occurrence of adverse drug events drug-drug interactions, potential duplication of therapy, Increased costs, decreased adherence to the drug regimen, emergency department visits, hospitalizations, additional medical or surgical interventions as well as a decreased quality of life.

Treatment related consequences

Polypharmacy may result in increased rates of adverse drug reactions, as a frequent consequence of drug-drug interactions and errors in medication-taking (Queneau, 2006). The physician may hesitate to prescribe a new essential medication to the patient already taking five or more medications thus; polypharmacy can lead to under-treatment (Sharmar, 2016).

Patient related consequences

Polypharmacy also places a burden on patients to remember when and how to take all prescribed medications. Multiple medications increase the risks of inappropriate medication use and non-adherence (Sharmar, 2016). Medication adherence among patients with chronic conditions is disappointingly low. Adherence rates are lessened by complex drug regimens, incomplete clarification of benefits and side effects, lack of recognition of a patient's lifestyle as well as cost of medications (Austin, 2006)

Cost related consequences

Adverse drug interactions as a result of multiple medications, errors in taking medications by the patient as well as non-compliance by the patient due to untoward medical effects may all result in both direct and indirect additional costs for the health services provided by the hospital (Queneau, 2006).

2.7 THE ECONOMIC COST OF POLYPHARMACY

Polypharmacy is recognized as an expensive practice. The US Center for Medicare and Medicaid Services estimates that polypharmacy costs more than US $50 billion annually (Bushardt, Massey, Simpson, Ariail & Simpson, 2008). The cost of medications is affected by its dose and the duration of treatment with the respective drug (Zhu, Ascher-Svanum, Faries, Correll & Kane 2008). The studies indicate that the cost of polypharmacy is high and represents a significant economic impact. Yet there are few studies reporting the cost of polypharmacy and their focus being the elderly or psychotic population, literature on the cost of polypharmacy in diabetic patients in South Africa is currently unavailable

Determining the cost of polypharmacy

Several studies determine the cost of polypharmacy differently. Zhu *et al* (2008) on their cost of antipsychotic polypharmacy in the treatment of schizophrenia study, they determined the cost of polypharmacy by calculating the average daily costs and assessed the total annual costs of all medications prescribed in the year. To enhance relevance of the findings, the average daily and total annual costs of polypharmacy were also estimated using more recent drug prices to obtain the differential cost.

Hovstadius & Peterson (2013) determined the cost of polypharmacy by use of the Swedish prescribed drug register which is individual based and contains data for outpatient prescriptions at all Swedish pharmacies. They calculated the cost of polypharmacy by use of the public financed drug cost, the number of prescription drugs per individual and the cost per defined daily doses.

Other studies include the number of visits per year for the same unit cost, the cost of medicine drug per year, and the cost of the service arising from pharmacy visits (Santibanez-Beltran, Villarreal-Rios, Galicia-Rodriguez, Martinez-Gonzalez, Vargas-Daza & Ramos-López, 2013).

In general, the cost of polypharmacy can be categorized into direct and indirect costs (Rambhade *et al*., 2012). The direct costs include drugs acquisition costs purchased by the government in publicly funded institutions at contracted tender prices and sometimes by the patients at private retail pharmacies with taxed retail prices in cases where the medications are unavailable at hospitals (Hovstadius, 2010). The indirect costs include the incurred costs as a result of hospitalizations due to adverse drug effects or noncompliance as the two factors are closely related to and therefore occur as a result of polypharmacy as stipulated in several literature. Hospitalization costs include the hospital stay, professional fees, tests and ward consumables (Lim, Ong, Chan, Loke, Ferguson & Daniels, 2012).

2.8 DIABETES MELLITUS

Diabetes Mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Such a deficiency results in increased concentrations of glucose in the blood, which in turn damage many of the body's systems, in particular the blood vessels and nerve (WHO, 2017)

Several pathogenic processes are involved in the development of DM (American Diabetes Association, 2014). B-cell dysfunction is a critical component in the pathogenesis of type 2 DM (Oslowski, Hara, O'Sullivan-Murphy, Kanekura, Lu, Hara, Ishigaki, Zhu, Hayashi, Hui & Greiner, 2012). This results in deficient insulin secretion by the cells which causes a deficient action of insulin on target tissues which ultimately results in insufficient or abnormal carbohydrate, fat and protein metabolism (Kasuga,

2006). The primary cause of hyperglycaemia is the impairment of insulin secretion as well as the defects in insulin action at target tissues (Peterson & Shulman, 2006).

Symptoms of marked hyperglycaemia include polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycaemia. Acute, life-threatening consequences of uncontrolled diabetes are hyperglycaemia with ketoacidosis or the nonketotic hyperosmolar syndrome (American Diabetes Association, 2014).

2.8.1 Types of Diabetes Mellitus

Type 1 DM

It is formerly known as insulin-dependent in which the pancreas fails to produce the insulin which is essential for survival (WHO 2017). Type 1 DM is the more severe type of DM and it occurs more frequently in children and adolescents, but can develop at any age. It is characterized by the complete lack of insulin secretion (Barbara & Ruthanna 2011).

Type 2 DM

This is the type of DM that is based on decreased effectiveness of insulin or a relative deficit of insulin (Barbara & Ruthanna, 2011). It is formerly named non-insulin-dependent which results from the body's inability to respond properly to the action of insulin produced by the pancreas. T2DM is much more common and accounts for around 90% of all DM cases worldwide. It occurs most frequently in adults (WHO, 2017).

2.8.2 Causes of Diabetes Mellitus

Type 1 DM is caused by beta-cell destruction, usually leading to absolute insulin deficiency. The beta cell destruction may be due to autoimmune disorder which is caused by the body attacking its own pancreas with antibodies, and therefore the damaged pancreas will not produce insulin. It may also be idiopathic diabetes, whereby there is no known aetiology (American Diabetes Association, 2014).

In T2DM, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycaemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before DM is detected (American Diabetes Association, 2014). This form of DM accounts for 90–95% of those with DM thus it is the most common form of DM. It is due to genetic factors or when the body does not use insulin produced by the beta cells properly; this is known as insulin resistance. People with this type of DM do not need insulin treatment to survive (Barbara & Ruthanna, 2011).

2.8.3 Diagnosis of diabetes mellitus

When diagnosing DM the following symptoms must be present in a patient for a definitive diagnosis to be made (polyuria, polydipsia, blurred vision, weight loss) or metabolic decompensation (diabetic ketoacidosis or hyperosmolar nonketotic state) of diabetes mellitus must be present in addition to a random plasma glucose level of 11.0 mmol/L, or greater. Alternatively, the following levels may also be used: Fasting plasma glucose level of 7.0 mmol/L or greater, oral glucose tolerance test level of 11.1 mmol/L or greater, in a patient who presents with the classic symptoms of hyperglycaemia or hyperglycaemic crisis or a haemoglobin A1c level that is equal to, or above 6.5% (Labuschagne, Matsaung & Mametja, 2017).

2.8.4 Management of type 2 diabetes mellitus

Treatment of DM encompasses pharmacological and non-drug therapies which both target reduction of glycemia. Decreasing glycemia is an effective means of reducing long-term microvascular and neuropathic complications (ADA, 2014). The glycemia must be maintained within the normal non-diabetic range so that the microvascular complications of the disease, which are costly to treat and associated with major morbidity and mortality can be prevented (Defronzo, 2009).

The mainstay of non-drug treatment is diet and physical activity (WHO, 2017). Moreover, the choice of specific oral anti-hyperglycaemic agents is predicated on their effectiveness in lowering glucose, extra-glycaemic effects that may reduce long-term

complications, safety profiles, tolerability, ease of use, and expense (Nathan, Buse, Davidson, Ferrannini, Holman, Sherwin, & Zinman, 2009).

2.8.4.1 Non-pharmacological treatment

Lifestyle interventions can prevent or delay some cases of T2DM and thus reduce the huge economic burden of diabetes. Many of these interventions are cost-effective and/or cost-saving, even in developing countries. Nonetheless, these interventions are not yet widely used (IDF, 2015).

Exercise

This type therapy is based on maintaining optimum body weight, weight reduction may be necessary if the patient is over weight (Barbara & Ruthanna, 2011). Weight loss effectively lowers glycaemia and exercise improves the coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity (Nathan *et al.,* 2009). Insulin resistance has also been proven to improve with weight reduction (American Diabetes Association, 2014). Moderate intensity exercise of 225-420 minutes per week will decrease weight with 5-7.5 kg. Exercise increases glucose metabolism by increasing the sensitivity of the insulin receptors. Exercise is beneficial in both T2DM and type 1 DM resulting in the reduction of both morbidity and mortality (Labuschagne *et al*., 2017).

Diet

Recommended diets include carbohydrates that are more complex, adequate proteins as well as maintaining low cholesterol and low lipid level. Increased fiber with meals appears to reduce surges in blood sugar associated with food intake (Barbara & Ruthanna, 2011). Carbohydrate intake should be monitored for glycaemic control. Whole grains, legumes, low fat milk, vegetables and fruits should form part of carbohydrate intake instead of refined carbohydrates. The type of fat (saturated, monosaturated and polysaturated) is of more importance than total fat intake. Saturated fats should be limited and trans fatty acids avoided. Two weekly servings of fatty fish are recommended to reduce risk factors for cardiovascular disease (CVD). Furthermore, ten to twenty percent of the total energy should come from proteins, with the emphasis on vegetable rather than animal protein. Artificial sweeteners are allowed. Sodium intake should be restricted if the patient also has hypertension (<

2300 mg/day). Alcohol may be used in moderation as it increases the risk for hypoglycaemia when used with pharmacological agents such as insulin or secretagogues (Labuschagne *et al*., 2017).

2.8.1.1. Pharmacological treatment

Drugs that are used in the treatment of DM include Sulfonylureas, Biguanide, Alpha-glucosidase Inhibitors and Thiazolidinedione's (Ripsin, Kang & Urban, 2009). The incorrect use of these drugs can lead to conditions such as hypoglycemia, headache, dizziness, weakness, gastrointestinal disturbances with nausea (SAMF, 2012). The choice of specific anti-hyperglycemic agents as first line or additional therapy is predicated on their effectiveness in lowering glucose, extra-glycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense (Nathan *et al*., 2009)

Biguanides

Metformin is the commonly used biguanide drug available worldwide. Its major effect is to decrease hepatic glucose output and lower fasting glycaemia (Nathan *et al*.,2009). Metformin monotherapy is not usually accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with pre-diabetic hyperglycemia (Ripsin *et al*., 2009). The major non-glycemic effect of Metformin is either weight stability or modest weight loss, in contrast with many of the other blood glucose-lowering medications (Nathan *et al*., 2009).

Sulfonylureas

Sulfonylureas have remained one of the major therapies for T2DM since they were first introduced in the 1950s (Holman, 2006). Sulphonylureus are Insulin secretagogues and induce insulin release by binding to receptors on the pancreatic β-Cell-K ATP channel 2. The β-Cell-K ATP channel is a hetero-octamer, containing a potassium channel and a sulfonylurea receptor (SUR1). When Sulfonylureas bind to SUR1-receptors it leads to glucose-independent closure of the potassium-channel, membrane depolarisation, the opening of calcium-channels, and the release of stored insulin in the cytoplasmic storage granules (Labuschagne *et al*., 2017).

The major adverse side effect is hypoglycemia, which can be prolonged and life threatening, but such episodes, characterized by a need for assistance, coma, or seizure, are infrequent (Nathan *et al*., 2009). They are categorized into 2 generations namely, first and second generation. First generation Sulphonylureus: Chlorpropramide; Second-generation Sulphonylureus: Glibenclamide, Gliclazide, Glimepiride and Glipizide (Gangji, Cukierman, Gerstein, Goldsmith & Clase, 2007).

Alpha- glucosidase inhibitors

This class of compounds works by delaying intestinal carbohydrate absorption, reducing postprandial glycaemia, and helping to manage diabetes. In addition, they also have an insulin-sparing effect, leading to an increase in incretin hormones, glucagonlike peptide-1, and inhibiting the postprandial release of gastric inhibitory polypeptide (GIP), and lastly helping in the reduction of body weight (Labuschagne *et al*., 2017). The major adverse side effect is hypoglycaemia, which can be prolonged and life threatening, but such episodes, characterized by a need for assistance, coma, or seizure, are infrequent (Nathan *et al*., 2009). The only available drug from this class in South Africa is Acarbose.

Thiazolidinediones (TZDs)

Thiazolidinediones increases the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin (Hevener, Olefsky, Reichart, Nguyen, Bandyopadyhay, Leung, Watt, Benner, Febbraio, Nguyen & Folian, 2007). They appear to have a more durable effect on glycaemic control, particularly compared with Sulfonylureas (Kahn *et al*., 2006). TZDs are peroxisome proliferator-activated receptor gamma (PPARγ) agonists; they elicit their effect by decreasing blood glucose through improvement of target cell sensitivity to insulin. They have beneficial effects on insulin sensitivity by regulating the transcription of several genes in glucose and lipid metabolism (Labuschagne *et al*., 2017). The available drug commonly used from this class in South Africa is Pioglitazone.

Insulin

Insulin is a hormone secreted by beta cells of Langerhans in the pancreas (Fu, Gilbert & Liu, 2013). It is required in many patients with DM– all patients with DM type 1, patients with gestational diabetes, many patients with T2DM and other forms of

diabetes. Insulin therapy has beneficial effects on triacylglycerol and HDL cholesterol levels, especially in patients with poor glycaemic control (Nathan *et al*., 2009)

Insulin remains the most effective agent to reduce the blood glucose levels. Insulin therapy and glycaemic targets should be individualized to the patient and accompanied by an education program and regular home blood glucose monitoring. The Incorrect use of insulin or overdose can lead to Hypoglycaemia this is the most common and most serious complication of insulin treatment (SAMF, 2012).

2.9 THE GUIDELINES FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

According to South African Standard Treatment Guidelines 2015 set by the South African Society for Metabolism, Diabetes and Endocrinology (SEMDSA) and subsequently adopted by the South African Department of Health, Metformin, if not contraindicated and if tolerated, it is the preferred and most cost-effective initial agent. It is added to the combination of dietary modifications and physical activity. It is the minimum effective therapy for T2DM.

If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve or sustain the glycaemic goals, a second agent is then added. This second agent may be either a sulphonylureus, or basal insulin. If a combination of two agents fails to lower Haemoglobin A1c (HbA1c) to target, a third agent is added. The preferential sequence of agents to use is metformin, followed by the addition of sulphonylureus, followed by the addition of basal insulin (Nathan *et al*., 2009). If the combination of two oral agents and basal insulin fails to lower HbA1c to target, or if other reasons to adjust therapy exist, then intensified insulin therapy in consultation with a specialist is required (either twice daily pre-mix, or basal-bolus therapy) and the sulphonylureus is discontinued (Inzucchi, Bergenstal, Buse, Diamant, Ferrannini, Nauck, Peters, Tsapas, Wender & Matthews, 2012). In South Africa, secondary failure of oral agents occurs in about 5–10% of patients annually.

2.10 THE GLOBAL BURDEN OF DIABETES MELLITUS

Diabetes prevalence is globally increasing, and South Africa is no exception. The estimation of the current and future burden of DM are important to allocate community and health resources and to plan and prioritize their health programmes (Hall, Thomsen, Henriksen & Lohse, 2011). WHO has estimated that 422 million adults were living with DM in 2014 globally. It also indicated that the global prevalence of DM has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population (WHO, 2017).

Shaw, Sicree & Zimmet (2010) have estimated the number of people worldwide with DM for the years 2010 and 2030. They were using studies from 91 countries to calculate age- and sex-specific DM prevalence, which were applied to national population estimates, to determine national DM prevalence for all 216 countries for 2010 and 2030. Their findings indicated that the world prevalence of DM among adults (aged 20–79 years) will be 6.4%, affecting 285 million adults, in 2010, and will increase to 7.7%, and 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with DM in developing countries and a 20% increase in developed countries.

Another study has estimated the prevalence of DM in sub Saharan Africa within which South Africa falls under. They conducted a systematic literature review of papers published on DM in Sub-Saharan Africa 1999-March 2011, providing data on DM prevalence and economic impact. Their results indicated that T2DM accounts for over 90% of DM in Sub-Saharan Africa (Hall *et al*., 2011).

Moreover, Guariguata, Whiting, Hambleton, Beagley, Linnenkamp & Shaw (2014), in their study titled: Global estimates of DM prevalence for 2013 and projections for 2035 conducted a literature search of studies reporting the prevalence for DM for 2013 and 2035. They found that in 2013, 382 million people had DM and estimated that this number is expected to rise to 592 million by 2035. They also found that most people with DM live in low and middle income countries.

The conservative South African estimate is that 7% of adults, aged 20–79 years, have DM. More than half (61.1%) of the 2.3 million people with DM in South Africa (SA), were undiagnosed. Urban and migrant populations have higher DM prevalence rate (Labuschagne *et al*., 2017).

The new estimates of DM prevalence in adults confirm the large burden of DM, especially in developing countries (Guariguata *et al*., 2014). WHO (2017) indicated that DM caused 1.5 million deaths in 2012 and the majority of people with DM are affected by T2DM.

2.11 SUMMARY

In this chapter, an overview of studies relevant to this study were provided. It started by providing different definitions of polypharmacy by several studies. Types of polypharmacy, the causes and then the consequences polypharmacy were briefly discussed. It further illustrated how the economic cost of polypharmacy was determined in available literature. A look into DM and its management was also covered. The next chapter will provide a clear outline of the methodology that was adopted in this study.

CHAPTER 3
METHOD

3.1 INTRODUCTION

This chapter presents the methodology used in this study. It will first layout the study design and the study site. Furthermore, it will state the study population, study period and the pilot study. It will continue by discussing the sample selection, the data collection instrument, data entry and analysis as well as reliability and validity. It will conclude by laying out the ethical considerations that were undertaken before the study.

3.2 STUDY DESIGN

This research was a quantitative study, providing the numeric description of the economic cost of polypharmacy whereby the financial burden of polypharmacy was retrospectively measured using descriptive statistics. A retrospective study is a study that uses existing data that have been recorded for reasons other than research (Brink, 2012). The study was conducted using T2DM outpatient files with polypharmacy from the outpatient section of the pharmacy. The prescriptions that were used from the files were from January 2016 to December 2017.

3.3 STUDY SITE

The study was conducted at Mankweng Hospital which is a government funded tertiary hospital. Mankweng Hospital is in a mountainous area called Mankweng that is approximately 27 km east of the city of Polokwane (Figure 3.1). It serves patients from Magoshi included, inter alia, Kgoshi Mothapo, Kgoshi Mothiba, Kgoshi Molepo, Kgoshi Dikgale, Kgoshi Sophia Mamabolo and Kgoshi Mamabolo of Segopje; these are rural areas (Mohapi, 2014). Patient files were obtained from the Medical Records unit or the pharmacy of the hospital.

Adapted from https://maps.afrigis.co.za, 2018

Figure 3.1: Mankweng Map

3.4 STUDY POPULATION

The population of this study was T2DM patients who are identified to have polypharmacy. These are patients taking or having a prescription of 2 or more medications for the management ofT2DM.

3.5 STUDY PERIOD

The study period for this study was 2 years. Only prescriptions of within January 2016 to December 2017 were evaluated.

3.6 PILOT STUDY

The pilot study was conducted in 10% of the sample size to determine validity, to confirm if it was reliable and if it answered the research question.

3.7 SAMPLE SELECTION

A consecutive sample of patients with T2DM managed at Mankweng Hospital during the 2-year period of the study were selected. The sample size was calculated based on the prevalence rate of 12.5% diabetes mellitus (Sahadew, Singaram & Brown 2016), sampling error of 5% and 95% confidence interval, a sample size of 162 T2DM patients was required for the study. The sample size was calculated based on the formula below:

$$n = \frac{Z^2 p(1-p)}{e^2}$$ Where,

n is the sample size,

Z is the confidence interval (95% CI)

p is the prevalence of type 2 diabetes (i.e. 12.5%) (Sahadew *et al*., 2016)

e is the sampling error (5%).

A convenient sampling method was used because the files of T2DM patients can be accessed on a day in which the patient comes for review of therapy and then collect the medications at the outpatient section of the pharmacy. A patient comes for review after five months so chances of seeing that file again was after five months unless if the patient was not well controlled and needed monitoring more frequently. The other part of the sample was retrieved in the records with the assistance of staff working at records. A list of T2DM patients was obtained from the OPD register and then taken to the records for retrieval. Among the retrieved files a convenience sampling method was also applied as only the files with polypharmacy were chosen.

Inclusion and exclusion criteria

Inclusion criteria

The inclusion criteria for this study was T2DM patients from the outpatient section whose prescriptions were dispensed. Only prescriptions of within January 2016 to December 2017 with two or more items per prescription for the management of T2DM were evaluated.

Exclusion criteria

The exclusion criteria for this study was the Inpatient files. Any file with insufficient information particularly about the diagnosis of the patient was also not considered.

Any file that had no polypharmacy within the study period.

3.8 DATA COLLECTION INSTRUMENTS

Data was recorded in a data sheet which was designed using Microsoft excel. The data sheet enabled recording of information that was divided into three sections namely the demographic information, the diagnosis profile and treatment information (Appendix 1).

The demographic information included the age and gender whereas the diagnosis profile included the time of diagnosis, the presence of complications and comorbidities. Moreover, the treatment information included the number of medications, names of medications, number of repeats and the type of polypharmacy while the economic cost section included the pack size dispensed, the unit cost.

3.9 DATA ENTRY AND ANALYSIS

The demographic information from the patient file such as age and gender were retrieved from the file. The diagnosis profile such as year of diagnosis, presence of complications and co-morbidities was also recorded. Furthermore, the treatment information such as the number of medications and the number of repeats. Lastly the economic cost information of the patient's medications such the pack size of the dispensed medication was also recorded.

Data collected was entered on MS Excel™ spreadsheets on a daily basis and then transferred to SPSS version 25 for analysis, where the descriptive statistic such as minimum, maximum and percentages were evaluated. The independent t-test analysis was used to determine the statistical significance ($p<0.05$). The test compared the two variables namely the medical cost of polypharmacy in hospital using drug prices from the purchase invoice from Mankweng Hospital and in retail pharmacies using drug prices from the Drug Prices registry (Appendix 3). Standard therapeutic treatment for

diabetes mellitus was used as control, which means the cost of the minimum effective treatment for T2DM that can control sugar levels was used as an independent variable. The statistical analysis included means (M), standard deviations (SD) and the degree of freedom (*df*).

The pharmacy purchase invoices were used to retrieve the costs of antidiabetic medicines for the years 2016 and 2017 and the costs were tabulated (Appendix 2). And the background calculations of the cost of each regimen per month was done in excel, taking into consideration the strength and the quantity of medication dispensed. Moreover, the calculated cost of each regimen was entered on SPSS to do the descriptive analysis.

3.10 RELIABILITY AND VALIDITY

Since the data collection instrument was self-designed by the researcher, it needed to be validated to confirm if it was answering the research question and it was reliable. The pilot study was conducted in 10% of the sample size to determine validity, to confirm if it is reliable and if it answers the research question.

3.11 ETHICAL CONSIDERATIONS

Study approval

The Senior Degree Committee (SDC) reviewed the proposal before the actual submission to the Faculty's Higher Degree Committee (FHDC). Furthermore, the proposal was also submitted to Turfloop Campus Research and Ethics Committee (TREC) for ethical clearance to conduct the study.

The letter for permission to conduct the study at the hospital together with the clearance letter obtained from the TREC (Appendix 4) was submitted to the Limpopo Department of Health for approval. The Department of Health provided the permission certificate (Appendix 5). Then the permission certificate together with the consent form was submitted to the Pharmacy Manager and the Records Manager of the hospital to further provide a consent to retrieve the files. Following the study, data will be stored securely for a period of not less than five years and discarded appropriately.

Anonymity

No personal data such as identity number or full names of the patient were retrieved from the patient file. The study was as anonymous and unlinked as possible.

3.12 SUMMARY

This chapter presented the methodology used in this study. It has laid out the study design and the study site. Furthermore, it has stated the study population, study period and the pilot study. It continued by discussing the sample selection, the data collection instrument, data entry and analysis as well as reliability and validity. It concluded by laying out the ethical considerations that were under taken before the study. The results of the data collected over the 2 years' study period, will be presented in Chapter four.

CHAPTER 4
RESULTS AND DISCUSSION

4.1 INTRODUCTION

In this chapter, the results will illustrate the participants' demographics which consist of the number of participants, patients age, years of diagnosis and the regimen the patients are on. The other aspects of this research will be shown in graphs tables and charts following the statistical analysis method(s) used. The data will describe the financial costs and burden incurred by patients for their therapy as per objectives of the study.

4.2 PATIENT DEMOGRAPHICS

The number of patient files checked for the study period for this study was over 300 however the total number of files with polypharmacy identified was 128. The number of files used for pilot study was 13 which was not included in the total sample of 115 evaluated in this study. This sample size is statistically acceptable. The demographic information that was collected for this study was patient gender and age. The demographics are to tell us whether there is a relationship between the different age groups or among males and females when it comes to polypharmacy prevalence as well as the polypharmacy financial burden. Other demographic data regarding race, income, employment, education and marital status could not be determined as there was no direct patient contact and the record file did not include this information.

Table 4.1: Patient population by gender

Gender	Population (n)	Percentage
Male	37	32.2
Female	78	67.8
Total	115	100.0

In this study the majority (67.8%) of files that were selected and met the requirement of the selection criteria belonged to female patients while male patient was only 32.2%. This was an indication that type 2 diabetes mellitus is more prevalent in females than males and it also meant that polypharmacy is more prevalent in females among patients who are diagnosed with type 2 diabetes. The stats listed above in Table 4.1 was supported by surveys done in the year 2009 in Limpopo and Mpumalanga, the survey confirmed that prevalence of diabetes affects about 50% of the adult female population (Mayosi, Flisher, Lalloo, Sitas, Tollman, & Bradshaw, 2009). Moreover, these results diverge with the ones found in a study where the cost of diabetic care was investigated whereby their respondents were 59% male and 41% female (Shrestha, Lohani, Angdembe, Drattarai & Bhattarai, 2013).

Table 4.2: Patient population by age group

Age groups	Number of patients	Percentage
30 – 40	1	1
41- 50	13	11
51- 60	46	40
61- 70	36	31
71+	19	17
Total (n)	115	100

The table 4.2 above indicates that the least number of participants were of the age group of 30-40 years (1%) this may be because this disease is mostly detected or diagnosed at a later stage of life where complications starts to prevail (American Diabetes Association, 2014) but also because polypharmacy is associated with the old age group (Dutta & Prashad, 2015); whereas the majority of the participants were from the age group of 51- 70 years (71%). The age group of 71 years or older accounted for 17%. This means that polypharmacy is more prevalent in patients of the age group of 51-60 years old and less prevalent in patients falling under the age group of 30-40 years of age. This is because age itself is a risk factor of comorbidities and risk factors associated with T2DM (Gadsby *et a*l.,2011). These results concur with the study where cost of diabetes care was investigated and found that 70% of their respondents belonged to the age group of 46-60 years (Shrestha *et al*., 2013). DM being a chronic illness tends to affect older age groups. The results also concur with a study where majority of respondents belonged to the age group of 46-60 years which happens to be the economically productive age group this means that DM affects the

economically active member of the family more often, which may be the principal breadwinner thereby pushing the whole family into a vicious cycle of worsening health and poverty (Shresha *et al*., 2013).

Diabetes mellitus was ranked number two cause of death in South Africa (Bateman, 2017). Diabetes is expected to take an increasingly large financial toll in the future, particularly on older adults and on working-age adults (Boyle, Thompson, Gregg, Barker & Williamson, 2010). It is evident in this study that most participants, with DM were between the age group of 51-60 years. Polypharmacy associated with the management of type 2 DM is a well-known risk factors for adverse drug reactions, which commonly cause adverse clinical outcomes that results in more costs of health care in older diabetic patients (O'mahony, O'sullivan, Byrne, O'connor, Ryan and Gallagher, 2015).

Table 4.3 below shows the distribution of gender based diagnosis for the 115 patients' files reviewed

Table 4.3: Patient population by age group vs gender

Age groups	Patient gender		Total
	Male	Female	
30 – 40	1	0	1
41- 50	4	9	13
51- 60	14	32	46
61- 70	14	22	36
71+	4	15	19
Total	37	78	115

The results indicate that male patients that experienced polypharmacy associated with the management of type 2 DM were not young adults. However, the age group with more prevalence was between 51-60 years, which represented the majority in both males and females who are still in the working age group. The second age group that had prevalence of polypharmacy was 61-70 years which accounts for 31% of the total population, of which males accounts for 31% and females accounts for 69% this is due to the fact that type 2DM is an age-related condition. Nineteen (19) of the

participants were above the age of 70 years and out of them 79% were females and 21% were males.

Figure 4.1 below illustrate the relationship between the financial burden of polypharmacy and the time of diagnosis. It also assists in noting the time in which majority of patients were diagnosed with the condition.

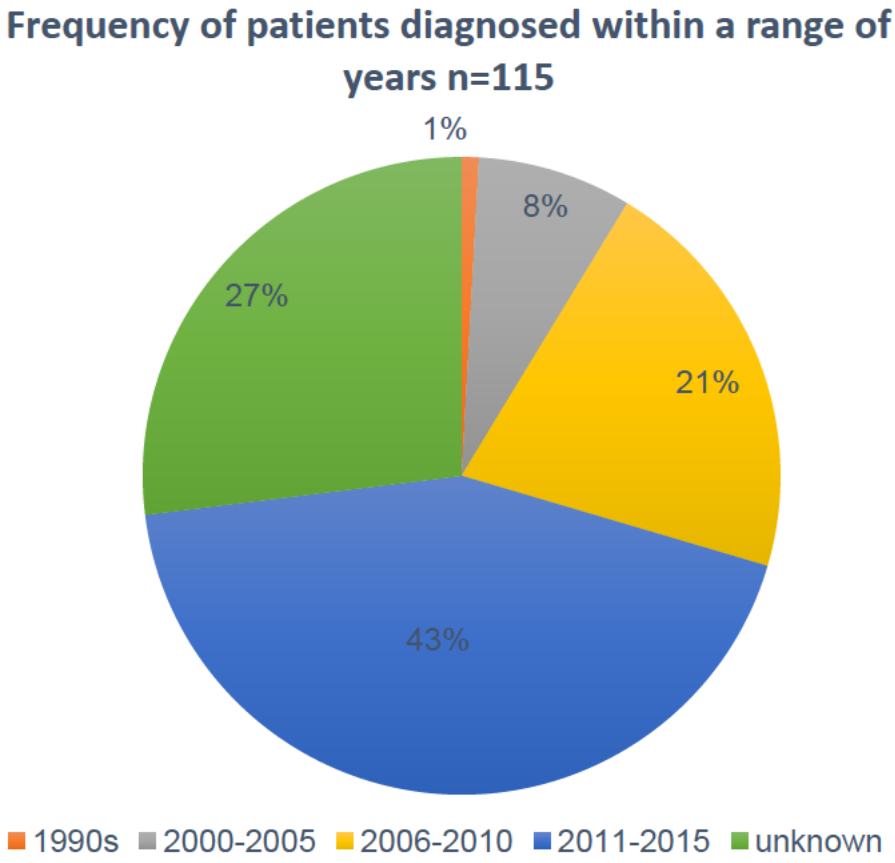

Figure 4.1: Patient population by year of diagnosis n=115

The trend of diagnosis of type 2 diabetes mellitus is increasing with years. 1% of patients were diagnosed in the 1990s, 8% of the population were diagnosed in the years 2000-2005. This means that least of the participants had diabetes for 10 years or more and the reason for that may be due to death of other patients due to complications, other co-morbidities or adverse drug reactions due to polypharmacy. furthermore 21% of patients were diagnosed in the years 2006- 2010 and majority of participants (44%) of the population were diagnosed in the years 2011- 2015. This means that the onset of diabetes was 5 years or less in majority of the participants. The diagnosis year for 27% of the population is unknown. That is the second most

portion of the participants and the reason for that was patients may have lost the file due to misplacement by the records department and therefore opening a new file with insufficient information

The results above diverge from data by Shresha *et al*., 2013 that revealed that total direct cost per annum for a diabetic patient with 16 to 20 years of illness (diagnosed long time ago) was approximately 161% higher than the diabetic patient with illness duration of 1 to 5 year whom were recently diagnosed.

Table 4.4: Distribution of patient gender by diagnosis year

Year of diagnosis	Patient gender		Total
	Male	Female	
1990s	0 (0%)	1 (0.9%)	1
2000-2005	2 (1.7%)	7 (6.1%)	9
2006-2010	10 (8.7%)	14 (12.2%)	24
2011-2015	16 (13.6%)	34 (29.6%)	50
Unknown	9 (7.8%)	22 (19.1%)	31
Total	37	78	115

The table above shows a cross tabulation of the gender of patients and the range of years in which these patients were diagnosed. Looking at the table the results indicates that for all the years of diagnosis females were always leading in numbers than males. Only one patient among the study population was diagnosed in the 1990s. Most patients were diagnosed between the years 2011-2015 which accounted for 43% of the total population of which 68% were females and 32% were males.

The figure below shows the distribution of patients by the year in which they were diagnosed and their age group.

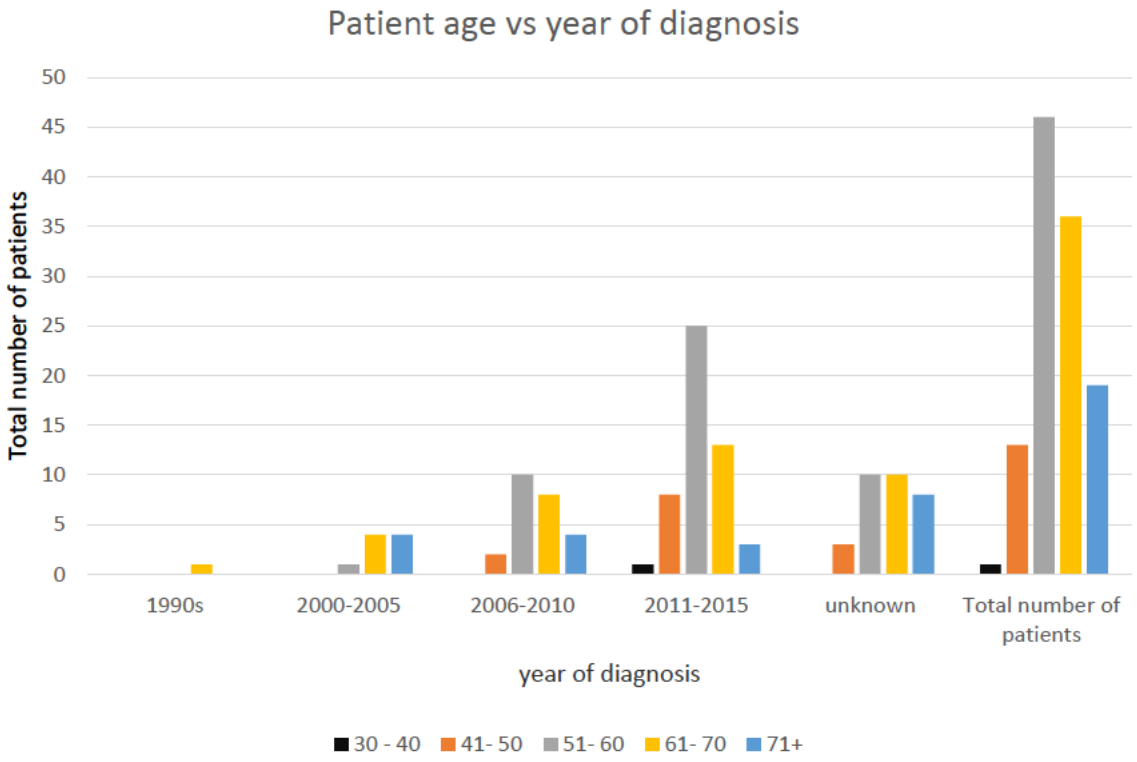

Figure 4.2: Patient population by year of diagnosis

The results from the above figure shows that the 1 patient who was diagnosed in the 1990s was of the age group of 61-70 years whereas out of 9 patients who were diagnosed within the years 2000-2005 none of them was falling under the age groups of 30 - 50 years, equal number of patients were falling under the age groups of 61-70 and 70+ years and only 1 patient was falling under the age group of 51-60 years. Majority of patients were diagnosed within the years 2011-2015 and half of their number were 51 to 60 years of age. Those that their files had no diagnosis date or year, equal numbers (10 patients) of them were falling between the age group of 51-60 as well as 61-71 years.

The figure below shows the identified prescription regimen for type 2 diabetes mellitus at Mankweng Hospital for the years 2016 and 2017.

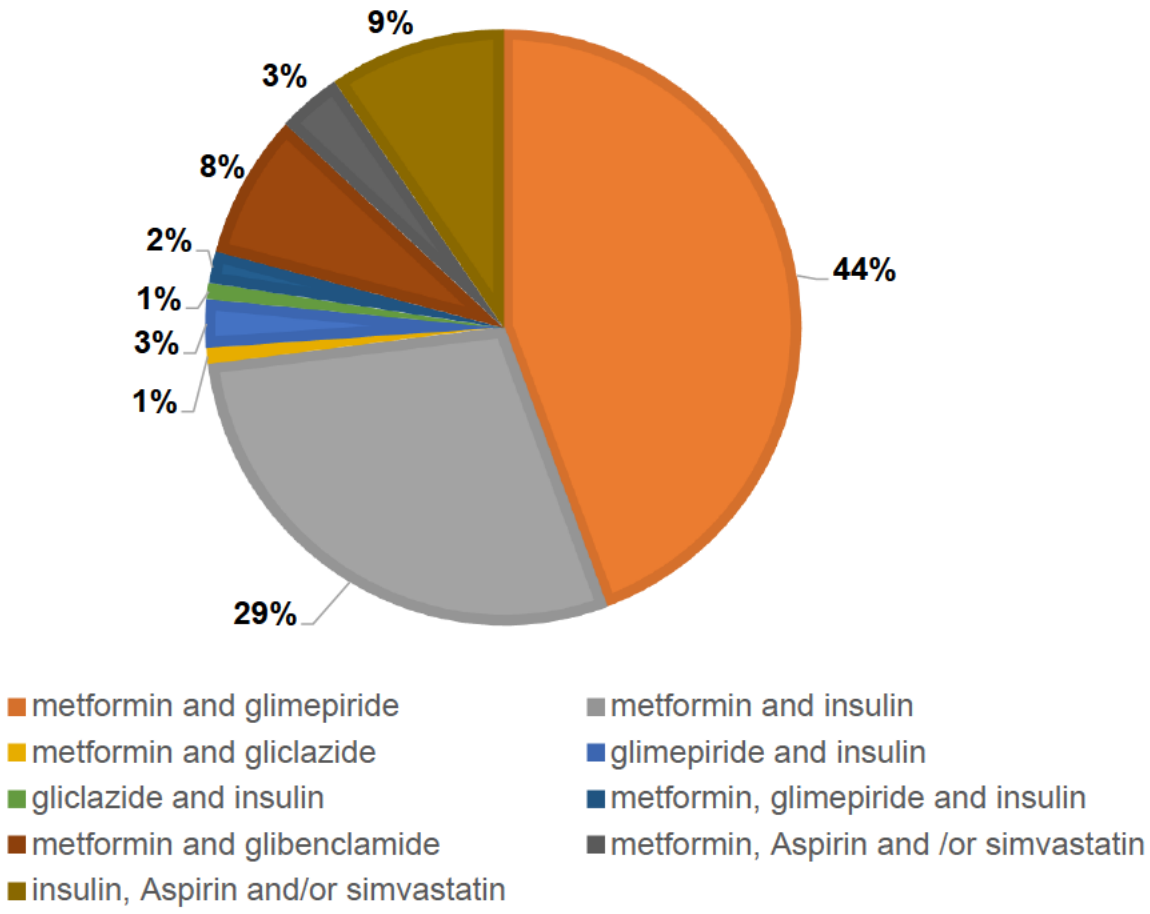

Figure 4.3: The treatment regimens of the patients during the study period n=115.

The figure stipulates that most patients (44%) were on metformin and glimepiride regimen followed by metformin and insulin regimen (29%). However, least of the population was on Gliclazide and Insulin regimen (1%), metformin and Gliclazide (1%) regime as well as Metformin, Glimepiride and insulin regimen (2%). These results concur with a study done in Johannesburg, South Africa on treatment gaps found in the management of type 2 DM where they found that the majority of patients were prescribed a combination of one oral hypoglycaemic agent together with insulin which was 38.9% followed by those who are on a combination of orals which accounted for 25.9% of the study population (Pinchevsky, Butkow, Chirwa & Raal, 2017).

This means that besides glimepiride other sulphonylureus are less considered during prescribing and dispensing or it means that there is a high prevalence of secondary failure of oral agents particularly the sulphonylureus than the documented 5-10% in the standard treatment guidelines of South Africa. This further means that the standard treatment guideline itself is not followed thoroughly by the prescribers and dispensers since well the second most prescribed regimen for the participants is an insulin containing regimen which is supposed to be the third line treatment regimen.

Metformin remains a frequent drug of choice in the regimen presented. That is because metformin is recommended as a first-line treatment option for type 2 DM. Metformin aids in reducing glycaemic levels, helps with weight-loss and is associated with fewer hypoglycaemic episodes, whilst still being lower in cost when compared to other oral treatment options in Hospital settings. Metformin is advantageous compared to sulfonylurea monotherapy in terms of cardiovascular mortality. Unless contraindicated, metformin remains the drug of choice, in addition to suitable lifestyle modification (Labuschagne *et al*., 2017)

The figures below show the change in frequencies of patients on each regimen as collected from the files over the two-year study period.

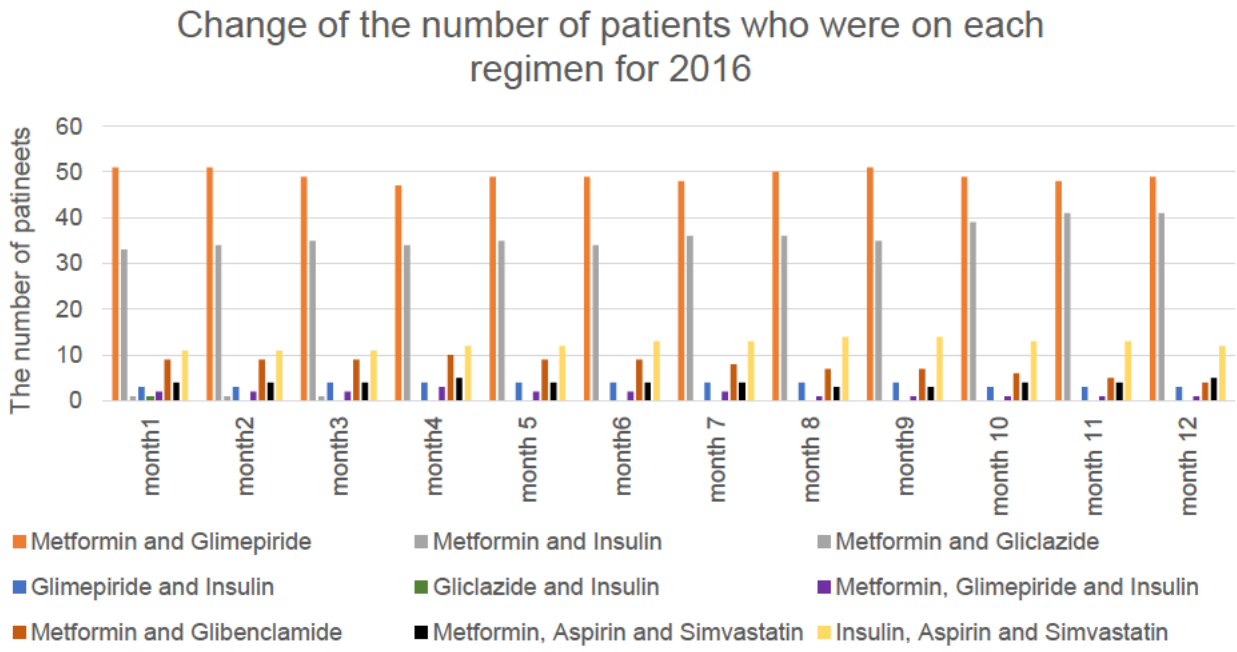

Figure 4.4: Change of frequency of patients on a regimen for 2016.

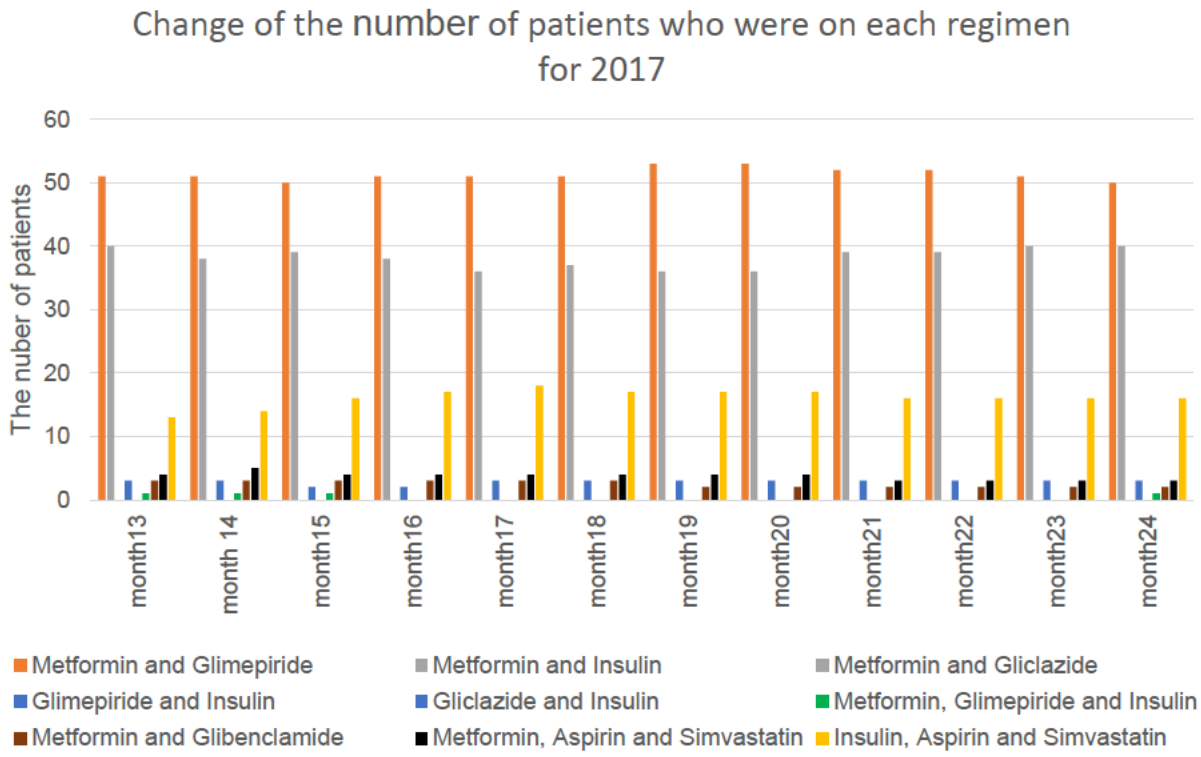

Figure 4.5: Change of frequency of patients on a regimen for 2017.

The figures indicate change in frequency of patients on a regimen over the years 2016 and 2017. It shows a trend of treatment switches for patients who are considered to be on polypharmacy for management of type 2 DM. The 1st Month is January 2016 and month 24th is therefore December 2017. The diagram indicates that metformin and insulin as well as metformin and glimepiride remained the highly consumed regimen amongst them all. However, the trend shows that whenever metformin and glimepiride consumption declined the metformin and insulin consumption increases, as stipulated from the graph from month 9 to month 14. The consumption of the regimen consisting of Insulin, Aspirin and Simvastatin shows an increase over the months as the slope is escalating. As for other regimen the consumption was high in the early 2016 and then it declined in month 8 and then remained constant from there.

Looking at the plot there is no significant difference or change or rather switching of regimen on the patients. This therefore would mean that the regimens that these patients are on are very much individualised and patients are responding well or would mean that a copy and paste of a script is done and therefore even the dispensing of

similar medications is done without proper screenings and recommended tests as per guidelines on these patients. A study done in Kwazulu-Natal, South Africa has found that compliance of the guidelines for the management of type 2 DM by health care workers occurred in only 4.2% of the patient files that were reviewed (Rampersad, Rangiah & Kendon, 2018).

4.3 FINANCIAL BURDEN QUANTIFICATION

Figure 4.5 below shows the framework used during the calculations and analysis of the costs of drug regimen considered as polypharmacy for the management of type 2 DM. The prices of medicines were obtained from the pharmacy purchase requests at the hospital following the 2017 purchases. The pricing schedule for 2017 was used in costing for both 2016 and 2017 and please note that there might be a slight pricing difference between 2016 and 2017 but this slight price difference cannot bring a significant difference to the study findings. The estimates of the retail costs were calculated using prices obtained from the national medicines price updated in 2018, whereby the prices included the maximum dispensing fee charged per medicine (Medicines price registry, 2018). The maximum possible cost per regimen was influenced by the maximum dose, frequency and quantity of medicines supplied to the patients per month. This study employed the cost of illness approach during analysis, focusing only on the direct medicines cost for a portion of patients who are diagnosed with type 2 DM and having polypharmacy in their prescription as per the definition of polypharmacy in this study.

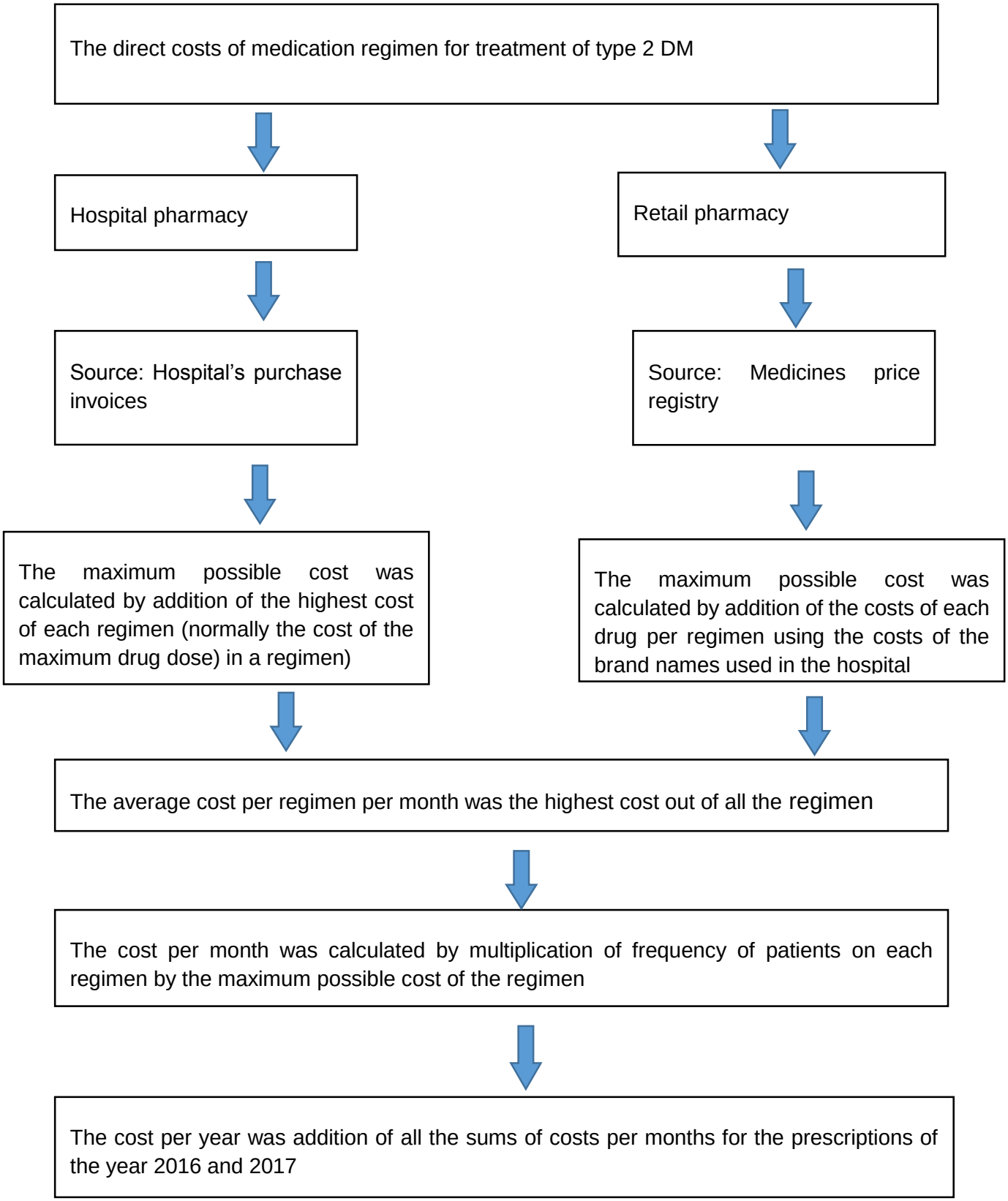

Figure 4.6: The calculations framework for the quantification of the costs

The maximum cost per regimen per month in the hospital pharmacy.

The cost per regimen is the maximum possible cost of the regimen calculated using the drug cost from the purchase invoices from Mankweng Hospital pharmacy for the year 2017. Based on frequency of the individuals on the regimens per month (Appendix 6), the total cost per regimen per month was calculated and the average monthly cost of each regimen was generated.

Table 4.5: The average costs per regimen per month per patient for 115 patients

Drug regimen	Cost per regimen(ZAR)	Average 2016(ZAR)	Average 2017(ZAR)
Metformin and glimepiride	22.23	943.98	920.05
Metformin and insulin	111.43	3646.68	3594.57
Metformin and gliclazide	28.04	5.01	5.72
Glimepiride and insulin	97.82	301.61	288.80
Gliclazide and insulin	103.63	16.04	18.33
Metformin, glimepiride and insulin	115.74	132.95	135.41
Metformin and glibenclamide	28.62	154.00	147.38
Metformin, aspirin and simvastatin	30.59	104.88	106.75
Insulin, aspirin and simvastatin	106.18	1204.64	1164.37

The hospital spends a minimum of R22.23 per patient per month due to polypharmacy associated with the management of T2DM, with a maximum of R115.74. However, in 2016 the hospital spent an average of R3646.68 on metformin and insulin which is the costliest regimen as well as R5.01 on metformin and Gliclazide which is the least costly

regimen. This average cost per regimen for 2016 (Mean= 71.59, SD= 1176.63, N= 115) was expected to be less than the average cost per regimen for 2017(Mean= 723.31, SD= 1158.33, n=115). The difference was not statistically significant t (16) =2.12, p=0.06.

The results indicate that insulin is the mainstay therapy for T2DM at the hospital even when the literature refer to this type of diabetes as non-insulin dependent. It can be deduced from this results that the hospital spent a lot on the insulin containing regimen than other regimens for the two years of study. According to Kirigia, Sambo, Sambo & Barry (2009) the economic burden of diabetes mellitus in the WHO African region reported that insulin consumes 35.4% of the total cost of the direct cost of diabetes generally, indicating that this is a usual practice in the management of the condition.

In 2017 the hospital spent an average of R3594.57 on metformin and insulin, R5.72 on metformin and Gliclazide which was still the least costly regimen. Five regimens out of nine had insulin and three of them fall in top 5 of the most costly regimen among the regimens.

The study findings indicate that the least costly regimen was metformin and Gliclazide. as well as Gliclazide and insulin. This is because this regimen is less prescribed than others. The reason why Gliclazide containing regimen are less prescribed may be because it is less preferred by the prescribers. A systematic review and meta-analysis of the efficacy and hypoglycemic safety of Gliclazide versus other insulinotropic agents reported that Gliclazide significantly reduced HbA1c with no difference regarding hypoglycemia risk. Compared with other sulfonylureas, HbA1c reduction with gliclazide was not significantly different, but hypoglycemia risk was significantly lower (Chan & Colagiuri ,2015).

The annual cost per regimen

The annual cost for each year is the sum of all the monthly costs per regimen (Appendix 6) which is the product of the number of patients on the regimen for that month and the maximum possible cost for that regimen.

Table 4.6: The total annual costs per regimen for 2016 and 2017

Drug regimen	Annual cost 2016(ZAR)	Annual cost 2017(ZAR)
Metformin and glimepiride	13137.93	13693.68
Metformin and insulin	48249.19	51034.94
Metformin and gliclazide	84.12	0
Glimepiride and insulin	4206.26	3325.88
Gliclazide and insulin	103.63	0
Metformin, glimepiride and insulin	2354.80	462.96
Metformin and glibenclamide	2633.04	858.60
Metformin, aspirin and simvastatin	1468.32	1376.55
Insulin, aspirin and simvastatin	15820.82	20492.74

Figure 4.6 below translates the above table to give a clear illustration of the difference between the annual costs of each regimen for the year 2016 and 2017. The annual cost per regimen for 2016 (Mean= 9784.23, SD=15489.59, n=115) was expected to be lower than the annual cost per regimen for 2017 (Mean=10138.37, SD=16959.01, n=115). The difference was not statistically significant.

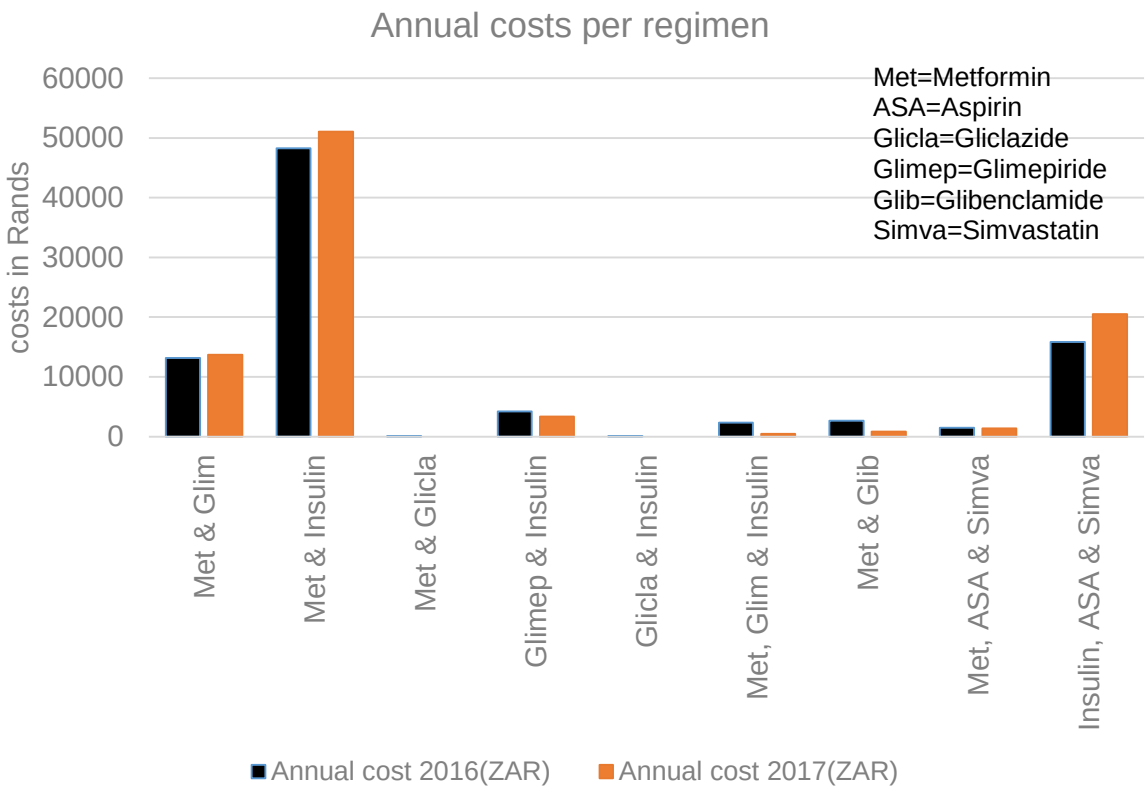

Figure 4.7: The Annual costs per regimen in 2016 and 2017

The annual costs for each year is the sum of all the monthly costs per regimen which is the product of the number of patients on the regimen for that month and the maximum possible cost for that regimen. The table indicates that the regimen that costs a lot than others is metformin and insulin which has an approximate annual cost of R50000.00 and then it is followed by the regimen consisting of insulin, aspirin and simvastatin that has an annual cost ranging from R15000.00 to R20000.00. Both the regimens consist of an insulin which is one of the expensive treatment options for both types of diabetes mellitus.

Table 4.6 and figure 4.6 above indicate that for both years 2016 and 2017 the highest costly regimen was metformin and insulin followed by insulin, aspirin and simvastatin, then metformin and glimepiride. It is clearly visible that the costs for these regimens increased from year to year. The cost for other regimens decreased from 2016 to 2017. The cost for the regimen consisting of metformin, aspirin and simvastatin remained constant. However, the least costly regimen was metformin and Gliclazide as well as Gliclazide and insulin. On the diagram it can also be deduced that these regimens

were not at all prescribed or dispensed in the year 2017. The regimen costs were high in 2017 as compared to 2016.

The total cost of polypharmacy

The total cost of polypharmacy was calculated as the sum of the monthly costs for each regimen considering the frequencies of patients on the regimen by the maximum possible cost of that regimen using medication costs obtained from the pharmacy purchase request having tender prices for the year 2017. The tables below show the findings.

Table 4.7: The total cost of regimens for the study period.

Drug regimen	Annual cost 2016	Annual cost 2017	Total cost
Metformin and glimepiride	13137.93	13693.68	26831.61
Metformin and insulin	48249.19	51034.94	99284.13
Metformin and gliclazide	84.12	0	84.12
Glimepiride and insulin	4206.26	3325.88	7532.14
Gliclazide and insulin	103.63	0	103.63
Metformin, glimepiride and insulin	2354.8	462.96	2817.76
Metformin and glibenclamide	2633.04	858.60	3491.64
Metformin, aspirin and simvastatin	1468.32	1376.55	2844.87
Insulin, aspirin and simvastatin	15820.82	20492.74	36313.56
Total cost	88058.11	91245.35	179303.50

The table above shows the total costs for each identified regimen for the study period years. This shows clearly that the costliest regimen was metformin and insulin which costed R99 284.13 followed by insulin, aspirin and simvastatin that costed R36313.56 over these two years. The regimen that was less costly over the years was metformin and Gliclazide which costed only R84.12. The cost of these polypharmacy regimens increased from R88058.11 in 2016 to R91245.35 in 2017. Furthermore, the total cost of these treatment regimens over the study period was R179 303.50 for the 115 patients who were found to be having polypharmacy. This means that the average cost per patient per year is R1 559.16 and R129.93 per month for the management of

T2DM patients who are on polypharmacy. The variance for annual cost of 2016 (Mean=17611.62, SD= 30 223.93, n=115) was assumed to be equal to the annual cost for 2017 (Mean=18249.07, SD=30223.93, n=11). The difference was not statistically significant.

The annual cost is lower than the cost of polypharmacy reported by Santibanez-Beltran and others 2013 in their study that was considering the three dimensions namely, consultation of family medicine, pharmacy use and medications where they found the annual cost of polypharmacy in the elderly to be $ 2201.17 (R30453.80) per patient out of a population of 131. Where they went on and estimated the cost in 1000 patients where they found the cost of polypharmacy to be $ 2 201 170 (R30453797.09) (Santibáñez-Beltrán *et al*., 2013).

These results stipulate that the treatment regimens that consisted of oral antihyperglycemics were less costly than the regimens consisting of an insulin over the years which means that the regimens consisting of this drug were either less used or the cost of insulin itself was high yet T2DM is said to be a non- insulin dependent DM (American Diabetes Association, 2014).

Although it has been acknowledged that polypharmacy imposes a high financial burden, the reality is in case where the hospital has run out of stock or cannot supply enough for the month, the patients then must concede the costs by buying at retail pharmacies. The report estimates that the economic cost of diabetes in Sub-Saharan Africa in 2015 totaled $19.5 billion. More than half of this economic cost (56%, $10.8 billion) was on accessing diabetes treatment, including medication and hospital stays and one half of these costs were out of pocket (paid for by the patients), putting a huge financial burden on people with diabetes (International Diabetes Federation, 2015).

The incurred costs in retail pharmacies

The table below shows the cost per regimen, that is the maximum possible cost of a regimen which was calculated by addition of the average price for four generics of the drug that makes a regimen prescribed in the hospital where by the cost of the highest dose of those particular drugs were used (Appendix 7). The cost estimates presented here are encountered by patients in cases where the hospital has run out of stock when they have to then incur the costs by buying at retail pharmacies.

Table 4.8: The maximum possible cost per regimen per patient per month

Drug regimen	Cost per regimen (ZAR)
Metformin and glimepiride	384.42
Metformin and insulin	666.16
Metformin and Gliclazide	276.38
Glimepiride and insulin	851.44
Gliclazide and insulin	743.40
Metformin, glimepiride and insulin	951.01
Metformin and Glibenclamide	275.59
Metformin, aspirin and simvastatin	265.22
Insulin, aspirin and simvastatin	732.24

The table clearly indicates that the highest costly regimen was the one consisting of metformin, Glimepiride and Insulin with the cost of R951.01. That is the maximum possible cost the patients must pay in retail to get that prescribed regimen. Meanwhile the least costly regimen is the one consisting of Metformin, Aspirin and Simvastatin with the cost of R265.22, however it is still the maximum possible cost that a patient should pay for that specific regimen. That is the minimum possible cost the patient must pay in retail to get that prescribed regimen. It can also be stipulated from the table that the regimen consisting of insulin as one of the drugs are the top 5 costliest regimens of them all.

Table 4.9: The possible annual cost per regimen for 2016 and 2017.

Drug regimen	Annual cost 2016 (ZAR)	Annual cost 2017 (ZAR)
Metformin and glimepiride	246797.60	236802.70
Metformin and insulin	315093.70	305101.30
Metformin and Gliclazide	829.14	0
Glimepiride and insulin	39166.24	28948.96
Gliclazide and insulin	743.40	0
Metformin, glimepiride and insulin	19971.21	3804.04
Metformin and Glibenclamide	26181.05	8267.70
Metformin, aspirin and simvastatin	13791.44	11934.90
Insulin, aspirin and simvastatin	118622.90	141322.30

The table above shows the annual costs per regimen for the retrospective study years of 2016 and 2017. The costs were calculated by multiplication of the frequency of prescription regimen by the maximum possible costs per regimen as shown in the previous table. The annual costs are viewed at the retail prices perspective so as to see the real transparent cost of polypharmacy as compared to the cost of polypharmacy in the hospital/government point of view as the prices are negotiated tender prices. So, it is clearly indicated on the table that for the 115 patient files that were investigated, the highest costly regimen is the one consisting of metformin and insulin with the total annual cost of R315093.70 in 2016 and decreased to R305101.30 in 2017. The annual cost for 2016 (Mean=R86799.63, SD=R116865.86) was expected to have an equal variance of the annual cost for 2017 (Mean=R81797.99, SD= R117249.43). The difference was not statistically significant p=0.5 at 95% confidence interval.

Table 4.10: The possible total cost of polypharmacy incurred by patients buying at retail pharmacies.

Drug regimen	Annual cost 2016 (ZAR)	Annual cost 2017 (ZAR)	Total costs (ZAR)
Metformin and glimepiride	246797.60	236802.70	483600.30
Metformin and insulin	315093.70	305101.30	620195
Metformin and Gliclazide	829.14	0	829.14
Glimepiride and insulin	39166.24	28948.96	68115.2
Gliclazide and insulin	743.40	0	743.40
Metformin, glimepiride and insulin	19971.21	3804.04	23775.25
Metformin and Glibenclamide	26181.05	8267.70	34448.75
Metformin, aspirin and simvastatin	13791.44	11934.90	25726.34
Insulin, aspirin and simvastatin	118622.90	141322.30	259945.20
Total costs	781196.70	736181.90	**1517379**

The table above indicates the possible total cost of polypharmacy incurred by patients buying at retail pharmacies in cases where the hospital has run out of stock for the 115 patients . It is indicated on the table that the annual cost of polypharmacy ranges from R730000.00 to R780000.00 for the 115 patients. Moreover, the total cost of polypharmacy for the two retrospective study periods is R1517379.00. This means that approximately one and half million rand were spent on polypharmacy associated with the management of T2DM patients for only

115 patients. Almost half (R620195) of that amount of money is spent on the regimen consisting of Metformin and Insulin.

The cost of polypharmacy was found to be R179303.10 for the two retrospective study years using the costs of drugs from the purchase invoices of the Hospital. However, the cost that was calculated using the retail costs was found to be R1517397.00. For the same group of study subjects. Both the costs indicate that polypharmacy associated with the treatment of T2DM imposes a high financial burden both on the publicly funded institutions as well as on patients.

On average the hospital spends R779.57 per annum on a patient that is considered to be on polypharmacy on the management of T2DM, meanwhile the patient will spend R6597.38 on these same medications per annum if the medications are out of stock at the Hospital. As it was indicated that majority of the patients were between the ages of 51-60. These are the elderly patients who depends on social grant for survival and the fact that they attend the public hospital for health care it means that they cannot afford. With that being said, these costs are a lot for the patients.

Comparing the costs by patients at a government hospital and at retail pharmacies.

Table 4.11: The comparison of the maximum possible cost of each regimen and their difference.

Drug regimen	Government costs (ZAR)	Retail costs (ZAR)	Difference (ZAR)
Metformin and glimepiride	22.23	384.42	362.19
Metformin and insulin	111.43	666.16	554.73
Metformin and Gliclazide	28.04	276.38	248.34
Glimepiride and insulin	97.82	851.44	753.62
Gliclazide and insulin	103.63	743.40	639.77
Metformin, glimepiride and insulin	115.74	951.01	835.27
Metformin and Glibenclamide	28.62	275.59	246.97
Metformin, aspirin and simvastatin	30.59	265.22	234.63
Insulin, aspirin and simvastatin	106.18	732.24	626.06

Table 4.11 above shows the difference between the costs of same regimen in retail pharmacies as compared to that of the public hospital. The percentage difference between the two costs ranged from 82% to 94 % with higher costs being that of the retail pharmacies. The regimen cost for government (Mean=R71.59, SD=R42.29) was expected to be lower than the regimen cost for retail (Mean=R571.76, SD=R271.62) assuming that they have an equal variance. The difference was statistically very significant t (16) = 2.11, p=0.000026 (1 tail).

In case of stock out in hospital, patients tend to obtain their medication from retail pharmacies. Diabetes does not only impose high costs of treatment on families, it also affects their ability to pay for this treatment through the loss of income of the diabetic member because of the loss of working hours or even employment in some instances due to the disease (Hall *et al*., 2011).

Table 4.12: The comparison of the total annual cost of each regimen between the hospital and retail prices.

Drug regimen	Annual cost 2016(ZAR) in public	Annual cost 2016 (ZAR) in retail	Annual cost 2017(ZAR) in public	Annual cost 2017 (ZAR) in retail
Metformin & glimepiride	13137.93	246797.60	13693.68	236802.70
Metformin and insulin	48249.19	315093.70	51034.94	305101.30
Metformin & gliclazide	84.12	829.14	0	0
Glimepiride & insulin	4206.26	39166.24	3325.88	28948.96
Gliclazide and insulin	103.63	743.4	0	0
Metformin, glimepiride and insulin	2354.80	19971.21	462.96	3804.04
Metformin & glibenclamide	2633.04	26181.05	858.60	8267.70
Metformin, aspirin & simvastatin	1468.32	13791.44	1376.55	11934.90
Insulin, aspirin & simvastatin	15820.82	118622.9	20492.74	141322.30
Total	88058.11	781196.70	91245.35	736181.90

Table 4.13: Independent t-Test: Two-Sample Assuming Equal Variances for the year 2016 comparing retail and public annual costs.

	Annual cost 2016(ZAR) in public	Annual cost 2016 (ZAR) in retail
Mean	9784.23	86799.63
Variance	240206384.7	13658329850
P value (one-tail)	0.03	
P value (two-tail)	0.06	

Table 4.14: Independent t-Test: Two-Sample Assuming Equal Variances for the year 2017 comparing retail and public annual costs.

	Annual cost 2017(ZAR) in public	Annual cost 2017 (ZAR) in retail
Mean	10138.37	81797.99
Variance	287607867.2	13747428162
P value (one-tail)	0.04	
P value (two-tail)	0.08	

Table 4.12, 4.13 and 4.14 above show the comparison of the annual costs of the treatment regimen in public hospital and in retail for the years 2016 and 2017. The total annual cost for all regimens for each year are also projected. Looking at the total

costs there has been an increase in the costs of regimens over the years. It should be noted that the same unit prices were used for both years. The vast difference in the costs between the hospital costs and the retail costs is shocking considering that the patients are supposed to concede those costs in cases where medications are unavailable at hospitals. Statistically, the difference is significant in both years because in 2016 t (16) = 2.12, p=0.03 (1 tail) and in 2017 t (16) =2.12, p=0.04 (1 tail) meaning that the P value is less than 0.05 in 95% confidence interval.

Table 4.15: The comparison of the total cost of each regimen in a government hospital and in retail pharmacy for the whole study period.

Drug regimen	Total costs in public hospital	Total cost in retail pharmacy
Metformin and glimepiride	26831.61	483600.30
Metformin and insulin	99284.13	620195
Metformin and gliclazide	84.12	829.14
Glimepiride and insulin	7532.14	68115.20
Gliclazide and insulin	103.63	743.40
Metformin, glimepiride and insulin	2817.76	23775.25
Metformin and Glibenclamide	3491.64	34448.75
Metformin, aspirin and simvastatin	2844.87	25726.34
Insulin, aspirin and simvastatin	36313.56	259945.20
Total	179303.50	1517379.00

Table 4.15 above indicates the total cost of polypharmacy that is associated with the management of T2DM for the 115 patients between a government hospital and a retail pharmacy costs perspective. It is indicated on the table that the cost of polypharmacy for the whole study period is R179303.50 in government and R1517379.00 in retail for the 115 patients. This means that approximately R2 million is spent on polypharmacy associated with the management of type 2 diabetes mellitus patients for only 115 patients. The total cost of polypharmacy looking at each regimen individually and adding them all together for the public and retail assuming that the variance is equal it was hypothesized that the retail costs (Mean=R303475.76, SD=R480115.84) will be higher than the public (hospital) costs (Mean=R35860.80, SD=R58945.15). The difference was statistically significant t (16) = 2.11, p=0.04 (1 tail).

This concurs with a Tanzanian study that estimated that the total cost for outpatient care for all diabetic patients US$2.7 million (R37,15 million), of which insulin accounted for two-thirds of the expenditure (Hall *et al*., 2011). It concurs with it because this study then means that for 1000 patients who are considered to be on polypharmacy for the management of T2DM, the costs of polypharmacy for 2 consecutive years is estimated to be around R15 million.

For the same group of study subjects. Both the costs indicate that polypharmacy associated with the treatment of T2DM imposes a high financial burden both on the publicly funded institutions as well as on patients. On average the hospital spends R779.58 per annum per patient that is considered to be on polypharmacy on the management of T2DM. This is lower as compared to that reported by a South African study that investigated the cost of hyperglycemic emergency admissions in South Africa over a two-month period in 2005 and reported an average cost of R5309.00 per admission (Pepper, Burch, Levitt & Cleary, 2007). It is also lower than an estimated total economic cost of diabetes (direct and indirect) in the WHO's Africa region in 2000 which was US$ 8836 (R123024.66) per person per year (Kirigia *et al.,* 2009). Meanwhile this study also found that a patient will spend R6597.30 on these same medications per annum if the medications are out of stock at the Hospital. This proves that despite the government subsidies, the out-of-pocket expenditure borne by patients and their families is almost one-third of the total cost. This is out of the reach

of most of our patients, who belong to the lower socio-economic class and often have no income (Hall *et al*., 2011).

The reason for our lower costs is because this study only looked at the direct medical costs particularly drug regimen costs of diabetes. In other studies, the direct medical costs are further subdivided into cost for consultations, medical instruments such as the glucometer and strips as well as the laboratory tests costs (Kirigia *et al*., 2009).

As it was indicated that majority of the patients from this study were adults of the age group of 51-60 years. This is an age group of the working class and the reduction of the economic activity through disease and disability due to diabetic complications affects both the household and the national economy. When the national economy is affected therefore the supply of the health care services will be affected hence shortage of medicines. This is supported by Hall *et al.,* (2011), as they reported that the burden of T2DM is disproportionately borne by people of working age which is the age group most profoundly affected by other comorbidities such as Hypertension, Arthritis and HIV. The fact that they attend the public hospital for health care it means that they cannot afford.

It is critical for policymakers to highlight the importance of introducing early and cost-effective interventions for primary and secondary prevention of T2DM because an increasing prevalence of diabetes among the economically active, and the high prevalence of diabetic complications and low survival rates, will negatively impact economic development, and in turn the health budget at the national level. Information on the cost of diabetes, including the cost of the complications is needed to emphasize the impact this lifestyle disease has on the economy in the south African context (Hall *et al*., 2011).

Studies like this that provide accurate projections of diabetes financial burden are essential to policymakers to plan for future health care needs and costs. This is the first study that attempted to quantify the financial burden of polypharmacy associated with the management of T2DM in South Africa, however it is narrow as compared to available studies of the financial burden of diabetes as it did not look at aspects such as general use of health resources such as human resource and hospital stays and lost productivity. Its looked at the direct drug costs and their impact on the government as well as the patient.

Available studies highlighting the high cost of diabetes in terms of its economic burden and cost to society has been helpful in health policy debates and decision-making (International Diabetes Federation, 2016). Knowledge of the costs of diabetes enhance the understanding of the importance of addressing health care and prevention issues associated with diabetes by relevant authorities.

The financial burden of DM is enormous in the world and it has turned out to become a chief public health problem because a great share of the healthcare expenditure has been spent on the treatment of its associated morbidity and mortality. DM is very costly to manage because of its chronic nature and severity of complications (Shreshra, 2013). Awareness of the importance of active monitoring and management of diabetes has become more widespread; however, adherence to recommended practices remains low (Sloan, Bethel, Ruiz, Shea &and Feinglos 2008).

4.3 SUMMARY

The frequencies of the data collected have been presented, analysed and have been thoroughly discussed in this chapter. The comparison of the quantification of the financial burden of polypharmacy both in the public and retail sectors has been shown in a form of tables and have been discussed. The next chapter will provide a summary of the results and therefore present the conclusion for the overall study. It will also outline the suggested recommendations that the researcher has for the study and detail limitations that occurred during the data collection period.

CHAPTER 5

SUMMARY, CONCLUSION AND RECOMMENDATIONS

5.1 INTRODUCTION

This chapter aims to provide a summary of the findings of this study and therefore provide a conclusion based on the results found. It will further outline the recommendations by the researcher based on the results found as well as the limitations encountered during data collection.

5.2 SUMMARY OF RESULTS

The study population for this study was 115 type 2 diabetic patients who were considered to be on polypharmacy. The distribution of the population by gender revealed that 68% of females were on polypharmacy as compared to 32% of males. The results also showed that majority of participants accounting 71% of the population were falling within the age group of 51-70 years, meanwhile the least number of participants accounting 1% of the population were falling between the age group of 30-40 years.

Polypharmacy imposes a high burden on the costs of the management of type 2 DM as compared to patients who are on monotherapy with which the average cost per month for the management of type 2 DM is R31.17 in public which is R374.04 annually.

The total cost of the treatment regimen for the two years' study period was found to be R179 303.50 in hospital and the possible cost of polypharmacy was found to be R1 517 379.00 in retail for the 115 patients. This means that the average cost per patient per year is R1 558.18 and R129.93 per month in hospitals but R6 597.30 per year and R549.78 per month in retail for the management of type 2 DM patients who are on polypharmacy. These numbers are 4 times higher than patients who are on monotherapy.

5.3 CONCLUSION

This study aimed to provide research data on costs associated with polypharmacy in the management of type 2 DM in hospital settings in South Africa. It intensively scrutinised the cost of polypharmacy associated with treatment and management of type 2 DM in a public funded rural hospital over 2 years' retrospective period. A comparison of the costs from the government with the retail pharmacies was done and it can therefore be concluded that polypharmacy imposes a high financial burden on the management of type 2 diabetic patients.

The appreciation and understanding of the amount of cost in real terms by health professionals and decision makers, can add value to processes of budget allocations to pharmaceutical services. Furthermore, the disease management can be rationalised along patient comfort and safety as well as through a thorough cost-benefit analysis. This should be done where possible to minimise incidences of drug tolerance that may result from poor adherence to treatment and irrational prescribing to save costs.

5.4 RECOMMENDATIONS

The following recommendations are made based on the results of the study:

Preventative programs for type 2 DM need to be prioritized.

- The results discussed above emphasize the need for preventative approaches to the diabetic population. Health care workers must start reinforcing implements of promoting diabetes awareness in communities. This includes recognition of diabetes risks both in children and in adults.
- The non-pharmacological management of type 2 DM is the mainstay of therapy and prevention. So pharmacist and Doctors needs to emphasize more on those rather than dispensing a lot of medications to patients.

Clinicians intervention

- Doctors and pharmacist should work together to optimize the quality of care for patients with type 2 DM but also consider the cost aspect when prescribing and dispensing treatment regimen for a patient.
- The patient's prescriptions must be reviewed and rationalised on a monthly basis in line with recent lab results and the progress of the patients, clinicians must avoid copy and paste of the previous prescription.
- The standard treatment guidelines need to be reviewed and amended to reduce the number of preventative medications a patient is taking for DM complications rather than dealing with the condition heads on.

Government intervention

- The government needs to review and increase the taxation of products regarded as risk factors for the development of type 2 DM such as tobacco (cigarettes), alcohol and sugar beverages such as cold fizzy drinks and juices for the benefit of the community at large and as a means of raising funds for the management of this lifestyle disease.

5.5 LIMITATIONS OF THE STUDY

This study is narrow when comparing it to the cost of illness studies available on literature. It was limited to calculating direct drug costs which may seem little with a naked eye.

Information such as the income bracket of the patient and whether they have medical aid or not could not be retrieved from the file as most of the files could not provide such information. The researcher feels like it would have been more informative and relevant to compare the cost of polypharmacy in relation to the income bracket of the patient as well as the paying entity for those medications.

Analysing costs of medicines were challenging and the SPSS as well as excel could provide the analysis of frequencies. A better software could have been useful for better understanding of costs analysis.

5.6 CLOSURE

This study allowed the researcher to determine that polypharmacy imposes a huge financial burden on the government and on the patient and therefore on South Africa at large. The results of this study can be used by healthcare professionals to be aware of the economic cost of polypharmacy on type 2 diabetic patients who also have other co-morbidities to take care of. The results can also be used by the pharmacy team at the study site to put systems in place for interventions that will impact positively on polypharmacy. As DM was ranked number 2 leading cause of death in SA mainly due to its complications, more research is needed to address prescribing trends and implementations of preventative measures for diabetic patients across the country and a broad study on the economic impact of polypharmacy needs to be done. The opportunity for further research following this study is significant as the health care system in SA is currently going through a transition to a National Health System.

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APPENDICES

Appendix 1: The data collection tool

THE FINANCIAL BURDEN OF POLYPHARMACY IN TYPE 2 DIABETIC PATIENTS AT MANKWENG HOSPITAL, LIMPOPO PROVINCE					
SECTION 1: DEMOGRAPHIC INFORMATION					
GENDER					
AGE					
	TIME OF DIAGNOSIS		CO-MOBIDITIES		
SECTION 2: DIAGNOSIS PROFILE					
SECTION 3: TREATMENT					
DATE:	REPEATS:		DATE:	REPEATS:	
NAME OF DRUGS	STRENGTH	QUANTITY	NAME OF DRUGS	STRENGTH	QUANTITY
COMPLICATIONS			**COMPLICATIONS**		
ADDITIONAL INFORMATION:					

SECTION 3: TREATMENT CONT''					
DATE:	REPEATS:		DATE:	REPEATS:	
NAME OF DRUGS	STRENGTH	QUANTITY	NAME OF DRUGS	STRENGTH	QUANTITY
COMPLICATIONS			**COMPLICATIONS**		
DATE:	REPEATS:		DATE:	REPEATS:	
NAME OF DRUGS	STRENGTH	QUANTITY	NAME OF DRUGS	STRENGTH	QUANTITY
COMPLICATIONS			**COMPLICATIONS**		

Appendix 2: The drug prices from Mankweng Hospital Pharmacy Purchase Invoices.

DRUGS	2016 COSTS	2017 COSTS
METFORMIN 850MG 84S	R14.63	R17.92
METFORMIN 850MG 56S	R9.38	R11.80
METFORMIN 850MG 28S	R5.38	R6.76
METFORMIN 500MG 56S	R8.93	R8.93
METFORIMIN 500MG 84S	R12.50	R12.50
GLIMEPIRIDE 1MG 30S	R2.69	R2.53
GLIMEPIRIDE 2MG 30S	R3.81	R3.58
GLIMEPIRIDE 4MG 30S	R4.60	R4.31
PROTAPHANE PEN	R41.39	R26.03
PROTAPHANE VIAL	R25.53	R31.22
ACTRAPID PEN	R41.39	R26.03
ACTRAPID VIAL	R25.53	R31.17
ACTRAPHANE PEN	R37.76	R26.03
ACTRAPHANE VIAL	R25.53	R31.12
GLICLAZIDE 80MG 56S	R18.275	R12.75
GLICLAZIDE 80MG 28S	R10.12	R10.12
GLICLAZIDE 80MG 112S	R37.30	R37.30
GLIBENCLAMIDE 5MG 28S	R4.05	R4.00
GLIBENCLAMIDE 5MG 56S	R6.05	R6.05
GLIBENCLAMIDSE 5MG 84S	R7.80	R7.80
GLIBENCLAMIDE 5MG 100S	-	R10.70
SIMVASTATIN 10MG 30S	R4.26	R5.56
SIMVASTATIN 20MG 30s	R6.75	R7.22
ASPIRIN 300MG 14s	R4.00	R5.45

Appendix 3: the drug prices from the retail prices retrieved from Medicines Price Registry website.

Drug name	Brand 1	Brand 2	Brand 3	Brand 4	Brand 5
Metformin	R129.25	R95.69	R95.74	R89.39	R87.77
Glimepiride	R246.83	R263.07	R294.03	R312.55	R307.79
Gliclazide	R257.84	R218.57	R190.12	R108.93	R108.57
Glibenclamide	R26.67	R58.69	R226.44	R413.18	R155.14
Insulin	R396.55	R462.60	R480.74	R666.39	R826.68
Simvastatin	R59.90	R60.93	R65.38	R162.61	R223.03
Aspirin	R73.01	R183.4	R0	R0	R0

Appendix 4: TREC certificate, ethics approval

University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 4029, Fax: (015) 268 2306, Email:Abdul.Maluleke@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE CLEARANCE CERTIFICATE

MEETING:	**31 August 2017**
PROJECT NUMBER:	**TREC/348/2017: PG**
PROJECT:	
Title:	The financial burden of polypharmacy in type 2 diabetic patients at Mankweng Hospital, Limpopo Province
Researcher:	Ms G Mothapo
Supervisor:	Mr RM Tshitake
Co-Supervisor:	Mr TL Manyama
School:	Health Care Sciences
Degree:	MPHARM in Pharmacy Practice

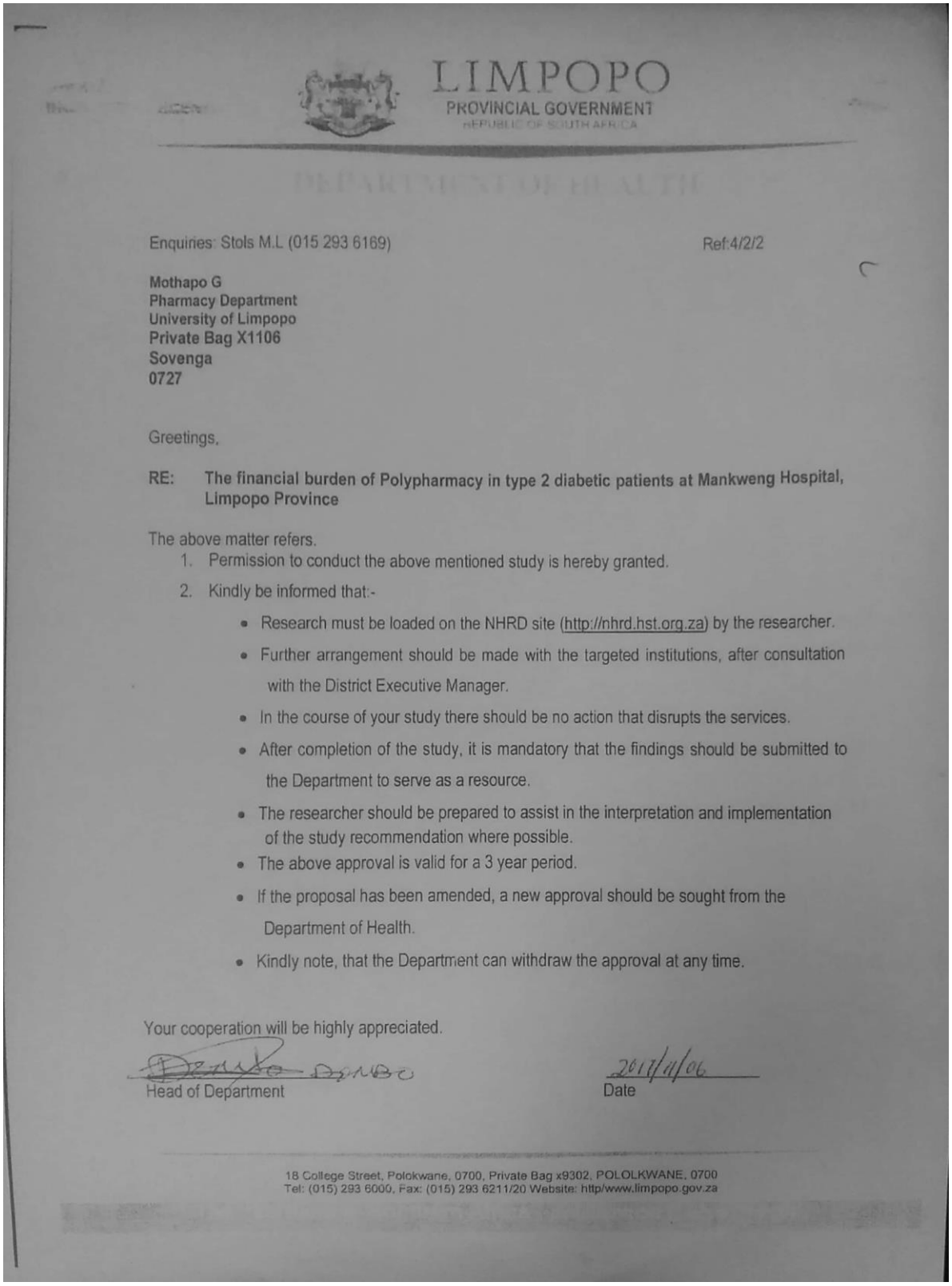
PROF TAB MASHEGO
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:
i) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**
ii) **The budget for the research will be considered separately from the protocol.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Finding solutions for Africa

Appendix 5: Department of Health Approval letter



LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

Enquiries: Stols M.L (015 293 6169) Ref:4/2/2

Mothapo G
Pharmacy Department
University of Limpopo
Private Bag X1106
Sovenga
0727

Greetings,

RE: **The financial burden of Polypharmacy in type 2 diabetic patients at Mankweng Hospital, Limpopo Province**

The above matter refers.

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions, after consultation with the District Executive Manager.
   - In the course of your study there should be no action that disrupts the services.
   - After completion of the study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 3 year period.
   - 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.

Head of Department

2011/11/06
Date

18 College Street, Polokwane, 0700, Private Bag x9302, POLOLKWANE, 0700
Tel: (015) 293 6000, Fax: (015) 293 6211/20 Website: http/www.limpopo.gov.za

Appendix 6: calculations of hospital prices using prices from the purchase invoices of Mankweng Hospital.

Drug regimen	Metformin & glimepiride	Metformin & insulin	Metformin & Gliclazide	Glimepiride & insulin	Gliclazide & insulin	Metformin, glimepiride & insulin	Metformin & Glibenclamide	Metformin, aspirin & simvastatin	Insulin, aspirin & simvastatin
Cost per regimen	22.23	111.43	28.04	97.82	103.63	115.74	28.62	30.59	106.18
Month 01	51	33	1	3	1	2	9	4	11
Cost 01	1133.73	3677.19	28.04	293.46	103.63	231.48	257.58	122.36	1167.98
Month 02	51	34	1	3	0	2	9	4	11
Cost 02	1133.73	3788.62	28.04	293.46	0	231.48	257.58	122.36	1167.98
Month 03	49	35	1	4	0	2	9	4	11
Cost 03	1089.27	3900.05	28.04	391.28	0	231.48	257.58	122.36	1167.98
Month 04	47	34	0	4	0	3	10	5	12
Cost 04	1044.81	3788.62	0	391.28	0	347.22	286.2	152.95	1274.16
Month 05	49	35	0	4	0	2	9	4	12
Cost 05	1089.27	3900.05	0	391.28	0	231.48	257.58	122.36	1274.16
Month 06	49	34	0	4	0	2	9	4	13
Cost 06	1089.27	3788.62	0	391.28	0	231.48	257.58	122.36	1380.34
Month 07	48	36	0	4	0	2	8	4	13
Cost 07	1067.04	4011.48	0	391.28	0	231.48	228.96	122.36	1380.34
Month 08	50	36	0	4	0	1	7	3	14
Cost 08	1111.5	4011.48	0	391.28	0	115.74	200.34	91.77	1486.52

Month 09	51	35	0	4	0	1	7	3	14
Cost 09	1133.73	3900.05	0	391.28	0	115.74	200.34	91.77	1486.52
Month 10	49	39	0	3	0	1	6	4	13
Cost 10	1089.27	4345.77	0	293.46	0	115.74	171.72	122.36	1380.34
Month 11	48	41	0	3	0	1	5	4	13
Cost 11	1067.04	4568.63	0	293.46	0	115.74	143.1	122.36	1380.34
Month 12	49	41	0	3	0	1	4	5	12
Cost 12	1089.27	4568.63	0	293.46	0	115.74	114.48	152.95	1274.16
Month 13	51	40	0	3	0	1	3	4	13
Cost 13	1133.73	4457.2	0	293.46	0	115.74	85.86	122.36	1380.34
Month 14	51	38	0	3	0	1	3	5	14
Cost 14	1133.73	4234.34	0	293.46	0	115.74	85.86	152.95	1486.52
Month 15	50	39	0	2	0	1	3	4	16
Cost 15	1111.5	4345.77	0	195.64	0	115.74	85.86	122.36	1698.88
Month 16	51	38	0	2	0	0	3	4	17
Cost 16	1133.73	4234.34	0	195.64	0	0	85.86	122.36	1805.06
Month 17	51	36	0	3	0	0	3	4	18
Cost 17	1133.73	4011.48	0	293.46	0	0	85.86	122.36	1911.24
Month 18	51	37	0	3	0	0	3	4	17
Cost 18	1133.73	4122.91	0	293.46	0	0	85.86	122.36	1805.06
Month 19	53	36	0	3	0	0	2	4	17

Cost 19	1178.19	4011.48	0	293.46	0	0	57.24	122.36	1805.06
Month 20	53	36	0	3	0	0	2	4	17
Cost 20	1178.19	4011.48	0	293.46	0	0	57.24	122.36	1805.06
Month 21	52	39	0	3	0	0	2	3	16
Cost 21	1155.96	4345.77	0	293.46	0	0	57.24	91.77	1698.88
Month 22	52	39	0	3	0	0	2	3	16
Cost 22	1155.96	4345.77	0	293.46	0	0	57.24	91.77	1698.88
Month 23	51	40	0	3	0	0	2	3	16
Cost 23	1133.73	4457.2	0	293.46	0	0	57.24	91.77	1698.88
Month 24	50	40	0	3	0	1	2	3	16
Cost 24	1111.5	4457.2	0	293.46	0	115.74	57.24	91.77	1698.88

Appendix 7: Calculations of monthly costs per regimen using retail prices

Drug regimen	Metformin & glimepiride	Metformin & insulin	Metformin & Gliclazide	Glimepiride & insulin	Gliclazide & insulin	Metformin, glimepiride & insulin	Metformin & Glibenclamide	Metformin, aspirin & simvastatin	Insulin, aspirin & simvastatin
Cost per regimen	384.42	666.16	276.38	851.44	743.4	951.01	275.59	265.22	732.24
Month 01	51	33	1	3	1	2	9	4	11
Cost 01	19605.42	21983.28	276.38	2554.32	743.4	1902.02	2480.31	1060.88	8054.64
Month 02	51	34	1	3	0	2	9	4	11
Cost 02	19605.42	22649.44	276.38	2554.32	0	1902.02	2480.31	1060.88	8054.64
Month 03	49	35	1	4	0	2	9	4	11
Cost 03	18836.58	23315.6	276.38	3405.76	0	1902.02	2480.31	1060.88	8054.64
Month 04	47	34	0	4	0	3	10	5	12
Cost 04	18067.74	22649.44	0	3405.76	0	2853.03	2755.9	1326.1	8786.88
Month 05	49	35	0	4	0	2	9	4	12
Cost 05	18836.58	23315.6	0	3405.76	0	1902.02	2480.31	1060.88	8786.88
Month 06	49	34	0	4	0	2	9	4	13
Cost 06	18836.58	22649.44	0	3405.76	0	1902.02	2480.31	1060.88	9519.12
Month 07	48	36	0	4	0	2	8	4	13
Cost 07	18452.16	23981.76	0	3405.76	0	1902.02	2204.72	1060.88	9519.12
Month 08	50	36	0	4	0	1	7	3	14

Cost 08	19221	23981.76	0	3405.76	0	951.01	1929.13	795.66	10251.36
Month 09	51	35	0	4	0	1	7	3	14
Cost 09	19605.42	23315.6	0	3405.76	0	951.01	1929.13	795.66	10251.36
Month 10	49	39	0	3	0	1	6	4	13
Cost 10	18836.58	25980.24	0	2554.32	0	951.01	1653.54	1060.88	9519.12
Month 11	48	41	0	3	0	1	5	4	13
Cost 11	18452.16	27312.56	0	2554.32	0	951.01	1377.95	1060.88	9519.12
Month 12	49	41	0	3	0	1	4	5	12
Cost 12	18836.58	27312.56	0	2554.32	0	951.01	1102.36	1326.1	8786.88
Month13	51	40	0	3	0	1	3	4	13
Cost 13	19605.42	26646.4	0	2554.32	0	951.01	826.77	1060.88	9519.12
Month 14	51	38	0	3	0	1	3	5	14
Cost 14	19605.42	25314.08	0	2554.32	0	951.01	826.77	1326.1	10251.36
Month 15	50	39	0	2	0	1	3	4	16
Cost 15	19221	25980.24	0	1702.88	0	951.01	826.77	1060.88	11715.84
Month16	51	38	0	2	0	0	3	4	17
Cost 16	19605.42	25314.08	0	1702.88	0	0	826.77	1060.88	12448.08
Month 17	51	36	0	3	0	0	3	4	18
Cost 17	19605.42	23981.76	0	2554.32	0	0	826.77	1060.88	13180.32
Month 18	51	37	0	3	0	0	3	4	17
Cost 18	19605.42	24647.92	0	2554.32	0	0	826.77	1060.88	12448.08

Month 19	53	36	0	3	0	0	2	4	17
Cost 19	20374.26	23981.76	0	2554.32	0	0	551.18	1060.88	12448.08
Month 20	53	36	0	3	0	0	2	4	17
Cost 20	20374.26	23981.76	0	2554.32	0	0	551.18	1060.88	12448.08
Month 21	52	39	0	3	0	0	2	3	16
Cost 21	19989.84	25980.24	0	2554.32	0	0	551.18	795.66	11715.84
Month 22	52	39	0	3	0	0	2	3	16
Cost 22	19989.84	25980.24	0	2554.32	0	0	551.18	795.66	11715.84
Month 23	51	40	0	3	0	0	2	3	16
Cost 23	19605.42	26646.4	0	2554.32	0	0	551.18	795.66	11715.84
Month 24	50	40	0	3	0	1	2	3	16
Cost 24	19221	26646.4	0	2554.32	0	951.01	551.18	795.66	11715.84