

Chapter 3

Empirical Research Methodology

Chapter 1	Introduction	The background, motivation and reasoning for the study as well as the goals and outline of the study are given.
Chapter 2	Literature Study	Literature review of health care systems, chronic medication, cost, compliance, prevalence and patient profiles provide the background for the quantitative analyses
Chapter 3	Research Methodology	The research methodology followed in the study is discussed.
Chapter 4	Results and Discussion	A number of analyses are performed on the available data to establish prescribing trends, including demographic profiles, geographic distribution, utilisation, costs, providers of medication and medication compliance. The results of the empirical investigation are also reported in this chapter.
Chapter 5	Conclusions and recommendations	This chapter contains final conclusions and recommendations on chronic medication management in the private sector in South Africa.

3.1. Introduction

This study consists of two phases, as described in Chapter 1 paragraph 1.6.2.1 and 1.6.2.2. Phase one, the literature review, is documented in Chapter 2. It focuses on health care and its pharmaceutical care component and included a discussion of chronic medication and the distribution thereof. Phase two of the study consists of an empirical investigation in the form of a quantitative, retrospective, cross-sectional drug utilisation review.

This chapter contains the empirical research methodology, the procedures and rationale that were followed in quantitatively analysing medicine claims data obtained from a pharmaceutical benefit management company. It also gives insight into the data analysis to follow in Chapter 4. The empirical research objectives, both general and specific, are discussed as well as the

resulting data compilation and selection process, which includes the study design, data source and study population, study variables, measures of consumption as well as data analysis and the statistical applications performed. Limitations, validity and ethical considerations are also discussed.

3.2. General research objective

The general research objective of this study is a comparative investigation into the prescribing patterns of chronic medication in the South African private health care sector. Prescribing trends in mail order/courier and retail/community pharmacies are also investigated and compared. These trends include demographic profiles, geographic distribution, utilisation, costs, providers of medication and medication compliance.

3.2.1. Specific research objectives

The specific research objectives of the literature study are met in Chapter 2. The specific research objectives of the empirical study include the following:

- ❖ To investigate the prescribing patterns of medication in the private health care sector, stratified according to the demographic profiles of patients as well as geographical distribution
- ❖ To determine the number of chronic medication prescriptions prescribed by the various providers and further analyse demographic profiles, geographic distribution, utilisation and costs of these prescriptions
- ❖ To review the cost associated with chronic medicine claimed from the different providers (including retail and mail order pharmacies) for 2009 and 2010 and to compare originator and generic medication prescribing patterns for these pharmacy types
- ❖ To determine the medication possession ratios (MPR) of the top five chronic conditions as a proxy of patient compliance and to calculate the possible oversupply and undersupply of medication
- ❖ To determine the cost of oversupply of chronic medication based on the MPR calculations

3.3 Research design

In this study, the choice of research design is firstly based on its appropriateness to address the research question and the set objectives mentioned above and, secondly, because of the availability of data and data constraints. Panacek and Thompson (1995:139-140) describe a study design as the “general plan” for setting up and testing a specific hypothesis. The following types of research designs can be applied to any study:

- True experimental (always prospective and high scientific validity)
- Quasi-experimental (manipulation, lack of control or randomization; prospective and moderate in scientific validity)
- Non-experimental (no manipulation, generally retrospective and lower scientific validity than the other two designs)

According to this classification, the current study can be described as *non-experimental* or *observational*.

Berger *et al.* (2009:1047-1049) give the following list of different observational research designs:

- Cohort
- Cross-sectional
- Case-control
- Case-crossover
- Case-time-control
- Interrupted time series

According to Mann (2003:54), observational studies are studies where no interventions are made by the researcher. Mann (2003:54-60) describes the following three types of observational studies:

- Cohort studies

This type of study determines the incidence and natural history of a condition and can be prospective (population chosen without the outcome of interest) or retrospective (where data has been collected already and can be analysed).

- Case-control studies

Case-control studies are always retrospective in nature, where people with the outcome of interest are matched with a control group who does not have this outcome. The researcher then determines retrospectively which individuals were exposed to the treatment or the prevalence of a variable in each of the study groups.

- Cross-sectional studies

This type of study is used to determine prevalence as well as infer causation. Cross-sectional studies are the best way to determine prevalence, are relatively quick, can study multiple outcomes and do not differentiate between cause and effect or the sequence of events

According to Stats.Org (2012) a *cross-sectional study* is a type of observational study that looks at data that were collected across a whole population to provide a snapshot of that population at a single point in time. This kind of study is used to look for associations between observed properties, such as income level versus years of education or disease incidence based on geographic location. It can also be used to assess the prevalence of disease. Aldous *et al.* (2013:35) state that participants in such a study design are evaluated at one point in time and can therefore be recruited prospectively.

The data of a cross-sectional study therefore represent a set of people or cases at one point in time. It is suitable for studies that collect data on many variables from a large group of subjects, gather information on people's attitudes and behaviours, answer questions of how much, how many, who and what happened, and to begin exploratory research and identify hypotheses for future research.

Research can also be classified as quantitative or qualitative. Leedy and Ormrod (2010:135) describe qualitative research as having two main characteristics: it focuses on phenomena in natural settings (real world happenings) and the study of these phenomena, however intricate or complex. Quantitative research, on the other hand, "can be described as identifying the characteristics of a certain phenomenon and exploring possible correlations among two or more phenomena" (Leedy & Ormrod, 2010:188). This study can be deemed *quantitative*, as data were analysed and compared in order to make certain deductions and conclusions, as discussed in Chapter 5.

Furthermore, this study can be classified as a retrospective study, as events have already occurred and this data are reviewed after the medication claims have been processed. Panacek and Thompson (1995:140) describe a *retrospective* study as a study design where the events of

interest have already occurred and a prospective study as one where the events have occurred before the onset of the study.

In conclusion, a research design that best suited the needs of the study goals was selected. A quantitative, observational, cross-sectional study has been selected, and the most appropriate methodology that can be used to obtain the results is a retrospective drug utilisation review.

3.4. Drug utilisation review as a research instrument

Knapp *et al.* already stated in 1973 that the main goal of drug utilisation review (DUR) is the encouragement of optimal drug use and the provision of high-quality drug therapy as cost-effectively as possible (Knapp *et al.*, 1973:417). In 1977, the World Health Organization defined DUR as “the marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences” (WHO, 2003:8).

According to the Academy of Managed Care Pharmacy (2008) in the United States, DUR is defined as an authorized, structured, ongoing review of prescribing, dispensing and use of medication. DUR encompasses a drug review against predetermined criteria that results in changes to drug therapy when these criteria are not met. It involves a comprehensive review of patients' prescription and medication data before, during and after dispensing to ensure appropriate medication decision-making and positive patient outcomes.

Gama (2008:69) agrees by declaring that, although drug utilisation studies were used in the 1960s mainly for market-only purposes, it has evolved to include aspects of the prescribing quality of medical prescription and comparing patterns of use of specific drugs.

Presently the scope of drug utilisation studies is to evaluate the present state and future trends of the dispensing, administering and taking of medication, which includes present and future drug utilisation trends, medicine spending, suitability of prescriptions and estimating prevalence of disease (Gama, 2008:69). Wettermark *et al.* (2008:160) define DUR as “an eclectic collection of descriptive and analytical methods for the quantification, understanding and evaluation of the process of prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes.”

According to the WHO (2003) DUR and pharmacoepidemiology can provide insights into the following aspects of drug use and drug prescribing:

- **Pattern of use**, covering the extent and profiles of drug use and the trends in drug use and costs over time

- **Quality of use**, which is determined using audits to compare actual use to national prescription guidelines or local drug formularies
- **Determinants of use**, which includes user characteristics (e.g. sociodemographic parameters and attitudes towards drugs), prescriber characteristics (e.g. speciality, education and factors influencing therapeutic decisions) and drug characteristics (e.g. therapeutic properties and affordability)
- **Outcomes of use**, which are the health outcomes (i.e. the benefits and adverse effects) and the economic consequences

Wettermark *et al.* (2008:179) expand on this by listing the major areas of application of DUR as:

- To document baseline information on drug use
- To improve drug safety surveillance activities
- To assess the effectiveness of drugs
- To improve the balance of benefits, risks and costs
- To perform economic evaluations and
- To assess the effect of interventions

In this study, a DUR was used to document information on drug use and to perform economic evaluations.

According to Wertheimer (1988:155), Truter (2008:95) as well as the Academy of Managed care Pharmacy (2008), drug utilisation reviews can be performed in three different ways to assess medicine use:

- **Retrospective reviews** are conducted after the patient has received and used the medication. Retrospective studies are a systematic process that captures, reviews, analyses and interprets medicine therapy that has already been used by the patient for appropriateness by making use of data of a patient's medicine history. Real-time interventions cannot be made and this method is therefore limited (Wertheimer, 1988:95; Erwin, 1991:597).
- **Prospective reviews** occur before the patient has received the medication. Prospective studies therefore assess medicine therapy before the medicine is administered to the patient. Prospective drug utilisation review is based upon a complete drug and medical

history obtained from an interview with the patient as well as historical records. The health care practitioner can then evaluate the patient's existing therapy and prevent possible medication interactions (Truter, 2008:95).

- **Concurrent reviews** are conducted while the patient is receiving the medication. A concurrent study therefore makes intervention possible, and adaptation of a patient's medicine therapy can be made during the time he/she is receiving the medication. If a potential problem is discovered, the dispensing function is stopped until authorisation is received to continue as before or to initiate a modification or dosage correction. Such concurrent reviews prevent therapeutic misadventures (Wertheimer, 1988:155).

Retrospective DUR programmes are structured, ongoing initiatives that interpret patterns of drug use in relation to predetermined criteria and attempt to minimize inappropriate prescribing (Soumerai and Lipton, 1995:1641). Hennesay *et al.* (2003:1494) add to this definition by stating that typical ongoing retrospective DUR processes consist of medicine claims data being screened for criteria violations.

Arnold and Balu (2010:59) state that data collected from retrospective databases can also be applied in outcomes research. Examples include analysis of health care practice patterns, epidemiological analysis of disease progression, prevalence and characteristics of patient populations as well as evaluation of populations for prediction of future events, for formulary evaluation and to supplement prospective datasets. Hennesay *et al.* (2003:1499) disagrees in a sense by having found that a retrospective drug analysis had little effect on the exception rates (prescribing errors) and also on the spill-over effect (doctors correcting their prescribing behaviour). According to the Academy of Managed Care Pharmacy (2008), retrospective DUR evaluates medicine therapy after the patient has already received it and therefore has a limited ability to immediately impact patient care. Retrospective DURs do however have the ability to help identify patterns of drug utilisation that call for extra education of prescribers and patients and also to identify areas where the system is being misused and exploited, and the following categories of medicine use are generally identified by using retrospective DUR (Academy of Managed care Pharmacy, 2008):

- Abuse/misuse
- Appropriate generic use
- Drug-drug interactions and drug-disease contraindications
- Inappropriate duration of treatment

- Incorrect dosage
- Under- and overutilisation
- Therapeutic appropriateness and duplication.

In this investigation, the data used to perform the DUR are medication claims by pharmacies or dispensing doctors who dispensed prescriptions during 2009 and/or 2010 via a South African pharmacy benefit management company. The prescriptions have been dispensed and therefore this study can be deemed a retrospective DUR.

3.5. Data source

The data employed in this study were provided by a South African pharmaceutical benefit management company (PBM) in the private sector.

3.5.1. Data from pharmaceutical benefit management companies

According to Grabowski and Mullins (1997:535), PBM companies provide a variety of services designed to influence outpatient prescription drug usage and costs. In the US, PBMs are companies that administer drug benefit programmes for employers and health insurance carriers. According to a report by the Health Strategies Consultants (Richardson, 2003), PBMs contract with the following organisations to provide managed care medication benefits:

- Managed-care organisations
- Self-insured employers
- Insurance companies
- Unions
- Medicaid and Medicare-managed care plans
- The Federal Employees Health Benefits Program
- Other federal, state and local government entities

Taniguchi (1995:1915) describes a PBM's functions in the US context as follows:

- PBMs have contracts with employers, insurers, and others to provide cost-effective benefits to the members of those groups.

- PBMs can be paid a fixed amount to provide all contracted services. They may provide pharmacy services themselves (e.g. mail order prescription service is offered by Medco, one of the largest PBMs) or they subcontract with others to provide certain services.
- Full-service PBMs have the following functions:
 - establishing networks of pharmacies for use by plan members
 - processing claims electronically at the time a prescription is filled
 - maintaining a database on drug use and cost
 - using these data to generate various reports
 - encouraging the use of generic products
 - managing existing formularies
 - helping to establish customized formularies or providing a national formulary
 - providing information to support formulary guidelines (counter-detailing)
 - offering programmes where prescriptions for maintenance medications are filled less frequently (for example 6 months' supply by mail order)
 - negotiating volume-based rebates from manufacturers
 - performing drug-use review
 - developing disease management programmes based on clinical practice guidelines and measurements of patient outcome
 - evaluating outcomes by combining data on drug therapy with information about other parts of the patient's care

In South Africa, Mediscor PBM was the first PBM organisation, established in 1998, and it currently manages medical aid claims for some 1.5 million patients (Mediscor, 2012). According to their company profile, the services offered by Mediscor PBM include:

- Electronic claims processing services including gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management
- Client support services
- Fully integrated pre-authorisation service, including exception management

- Management of medicines for the Chronic Disease List (CDL), Prescribed Minimum Benefits (PMBs) and other conditions
- Medicine management in capitation environments
- On-line medicine expenditure reporting
- Supplementary services including network management, development and implementation of reference price lists, formulary management as well as price and product file management (Mediscor, 2012).

It would seem that there are several differences between the definition of PBMs in the US and in South Africa. Where PBMs in the US have full managed health care contracts with government and private medical schemes and employers (e.g. they can contract a pharmaceutical company to deliver certain medication at a reduced price for all patients on their database), the South African PBM merely processes the claim on behalf of the medical aid scheme or dispensing doctor.

The PBM who provided the data for this study manages medicine benefits on behalf of 38 medical schemes and four capitation providers. Every one of South Africa's pharmacies and 98% of all dispensing doctors are on this service provider's database (Bester & Badenhorst, 2010:i). Medicine claims data were provided from the PBM's medicine claims database for a two year period extending from 1 January 2009 to 31 December 2010. Data properties of the set of claims data used in this study are listed in Table 3.1.

Table 3.1: Applicable data properties of claims data used in this study

Data Type	Elements included
Membership	Date of birth – used to determine the age of the patient at the beginning of each year
	Gender
	Anonymous membership and independent identifier
Claims data	Province of prescriber – the postal code of the prescriber practice was assigned to a specific province
	Type of medication dispensed (originator of generic)
	National Pharmaceutical Product Interface

	(Nappi®) code
	Drug INN name
	Drug Trade name
	Quantity dispensed
	Date of treatment / claimed
	Amount paid by medical scheme
	Amount paid by patient
	Anonymous provider type identifier (courier pharmacy, retail pharmacy, dispensing GPs, dispensing specialists and other providers)

Table 3.1 illustrates that the data used contains many levels of information and this makes the database an appropriate source to be used in this study.

Motheral and Fairman (1997:346) found that randomised control trials are expensive and laborious, and they also have limited capabilities in finding solutions for real world patient populations. They therefore concluded that research using medicine claim databases is a very helpful tool in reviewing patient treatment options. Motheral and Fairman (1997:349) further emphasise that claims data is comprehensive (big data pool), can be flexible (various methodological options can be applied), is relatively inexpensive and can be analysed using very sophisticated statistical tools, making the data practical and applicable.

The International Society for Pharmacoeconomic Outcomes Research (ISPOR) supports this sentiment in naming the following advantages of using claims data in terms of outcomes (Garisson *et al.*, 2005:9-10):

- Clinical outcomes, which include biological measures of morbidity (e.g. blood pressure, cholesterol level, symptoms, and side effects) and mortality. Clinical outcome data can be found in patient registries or observational databases.
- Economic outcomes. Sources of claims or real world data are useful in providing use and cost information.
- Patient-reported outcomes/quality of life. *Patient-reported outcome* is the term adopted by the FDA and internationally to encompass any report coming directly from patients about a health condition and its treatment.

In this study, economic outcomes are a substantial focus point and the medicine claims database assist in achieving these.

3.5.2. Quality of the data

Certain validation processes have been put in place by the PBM to ensure the reliability and validity of the data used in this study (Bester, 2013):

- Gate-keeping
- Eligibility services
- Utilisation management services
- Clinical management services

Table 3.2 lists the validation criteria as applied to the data used in this study

Table 3.2: Validation criteria: PBM data

Validation process	Examples
Data integrity validation and eligibility management	• Provider validation checks • Member validation checks • Dependent code check • Duplicate medication check
Medication utilisation (active ingredient checks for each claim)	• Refill period check • Product quantity limits • Gender verification check (e.g. only females are eligible for contraceptive hormones) • Age verification check (certain medication may only be used by adults) • Product specific exclusions as required by the Scheme • General exclusions (eg. infant milk formula, etc.)
Clinical validation	• Active substance duplication check • Therapeutic duplication check • Maximum allowed dose check • Drug-drug interactions • Drug-age, drug-gender interactions • Drug-disease interactions • Drug-allergy interactions

Pricing validation	• Department of Health price file imports • Price file maintenance • Reference price application where appropriate
Formulary management	• Management of CDL and non-CDL medication as per patient benefit • Daily real-time patient benefit checks

As all the claims data used were “live” claims of 2009 and 2010, all the above checks were performed when dispensing of the medication items occurred. The PBM also has a validation test profile whereby claims are randomly generated and checked to verify that the desired claims result is achieved (Bester, 2013).

3.6 Study population

The aim and goal of this study is to determine the differences between dispensing patterns of medication in mail order and retail pharmacies, with specific regard to chronic medication in the private sector.

There are two ways of purchasing medication in pharmacies – cash and on medical aid. As all medicine medical aid claims are processed real-time and contains all patient information, medical aid claims were deemed to be the best data source for the purpose of this study. No cash claims were therefore considered. One of South Africa’s largest PBMs who is responsible for the real-time electronic interface between the pharmacy and medical aid scheme was approached to provide this data.

The total database includes all medication claims for the period 2009 and 2010. The population variables included in the data was medication claims per gender, age group and geographical area in South Africa. The number of claims, cost and demographics of patients using this medication per province were thus established. Furthermore, the benefit types of medication claimed were differentiated, i.e. chronic medication claims, acute, oncology, HIV/AIDS, OTC and other claims. The type of provider prescribing/dispensing this chronic medication was also described (e.g. dispensing doctors or courier pharmacies). Chronic medication claims include all prescribed minimum benefit conditions listed on the Chronic Disease List (CDL) and also other conditions identified as chronic by the PBM. A diagrammatic scheme of these population divisions can be found in Figure 3.1.

The prescribed minimum benefits (PMBs) were introduced in 2000 by the Council for Medical Schemes as a policy instrument for defining minimum levels of medical scheme cover that must

be provided. These minimum benefits are for the protection of members and to ensure that they are not left without care for certain major medical expenses because they cannot afford it (BHF, 2008).

According to the Board of Healthcare Funders (BHF, 2008) , PMB's in SA are minimum benefits which by law must be provided to all medical scheme members and include the provision of diagnosis, treatment and care costs for:

- any emergency medical condition, and
- a range of conditions as specified in Annexure A of the Regulations to the Medical Schemes Act (No 131 of 1998), subject to limitations specified in Annexure A. Included in this list of conditions is the list of chronic conditions.

According to McLeod (2007:121-126), PMBs can be defined as a minimum package that must be offered by all schemes. Beneficiaries must be covered in full for these conditions with no limits or co-payments. The PMB package includes the following:

- a list of 270 diagnosis-treatment pairs (DTPs) mainly offered in hospital (introduced in January 2000)
- all emergency medical conditions (defined in January 2003)
- diagnosis, treatment and medicine according to therapeutic algorithms for 25 defined chronic conditions on the CDL (introduced January 2004).
- According to the Medical Schemes Act (131 of 1998), in Annexure A of the Regulations, 26 chronic conditions are on the “chronic disease list” or CDL, and have been specified. (CMS, 2009).

CDL medications therefore include all medication used in the treatment of the following selected chronic diseases:

- Addison’s disease
- Asthma
- Bipolar affective disorder
- Bronchiectasis
- Cardiac failure
- Cardiomyopathy

- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Coronary artery disease
- Crohn's disease
- Diabetes insipidus
- Diabetes mellitus (type 1 and type 2)
- Dysrhythmia (irregular heartbeat)
- Epilepsy
- Glaucoma
- Haemophilia
- HIV/AIDS
- Hyperlipidaemia (high cholesterol)
- Hypertension (high blood pressure)
- Hypothyroidism (inactive thyroid gland)
- Multiple sclerosis
- Parkinson's disease
- Rheumatoid arthritis
- Schizophrenia
- Systemic lupus erythematosus
- Ulcerative colitis

For the purpose of this study, chronic medication includes the CDL-related medication, but also medication used to treat other chronic conditions (non-CDL conditions such as Attention Deficit Disorder (ADD), major depression, Graves' disease, eczema, psoriasis).

The chronic medication claims are divided into medicine claims made by:

- Retail pharmacies
- Courier/mail order pharmacies

- Dispensing general practitioners
- Dispensing specialists
- Other

3.6.1. Study population selection process

All data in the study were obtained from the mentioned PBM. Exclusion criteria were applied in order to select only the appropriate data over the two-year study period.

The flow and selection of data discussed in paragraph 3.6 are illustrated in Figure 3.1.

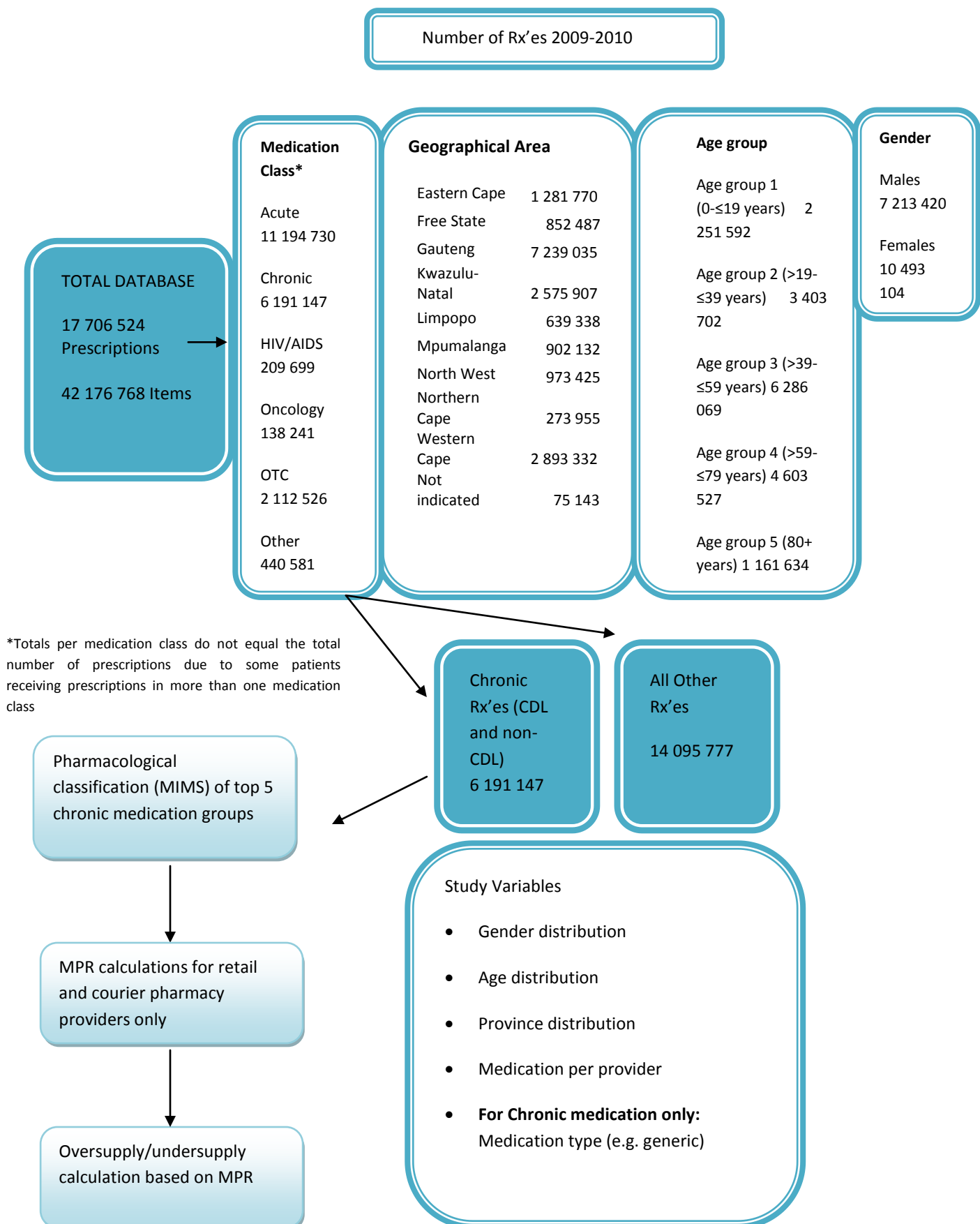


Figure 3.1: Schematic Illustration of study population and data selection

Figure 3.1 illustrates the study population selection rationale;

- All medication claims for 2009 and 2010 were selected
- Medication was classified as acute, chronic, oncology, HIV/AIDS, OTC or Other medication
- Within these medication claims, trends including demographic profiles, geographic distribution, utilisation, costs, and providers of medication were analysed
- For chronic medication specifically, additional parameters such as type of medication (i.e. generic or originator) were investigated
- For chronic medication specifically, the top five pharmacological medication groups were identified and medication possession ratios were calculated for these chronic medications for courier/mail order and community/retail pharmacies
- Based on the MPR, oversupply and undersupply were then calculated for courier/mail order and community/retail pharmacies
- The cost of the oversupply was then calculated and discussed

3.7. Study variables

In section 3.7, the study variables as applied to the study population, are discussed.

3.7.1. Age

According to the Council for Medical Schemes annual report for 2009/2010, the age group with most beneficiaries on medical schemes are between the ages of 15 and 19 years (CMS, 2011:161). The second largest age group falls between 35 and 39 years, whereas the lowest number of beneficiaries belongs to the age group 80 to 85+ years. This coincides with the Mediscor Medicines Review of 2011 which indicates that the most beneficiaries belong to the same age groups (Bester & Badenhorst, 2011:8). For the purpose of this study, the age groups will be analysed in brackets similar to that of the CMS and MMR to allow for comparison, but also rolled up into bigger age groups of 19 years per group in order to make analyses and comments that have relation to the largest age groups as a whole. The age group classifications for this study are as follows:

- Age group 1 (0-≤19 years)
- Age group 2 (>19-≤39 years)
- Age group 3 (>39-≤59 years)

- Age group 4 (>59-≤79 years)
- Age group 5 (>80 years)

3.7.2. Gender

The World Health Organization (WHO, 2007) defines sex as the biological and physiological characteristics that define men and women, and gender is defined as the socially constructed roles, behaviours, activities and attributes that society considers appropriate for men and women. In other words, male and female are sex categories and masculine and feminine are gender categories (WHO, 2007).

For the purpose of this research project, gender and sex is seen as synonyms and is used to indicate whether a prescription was prescribed for a male or female patient (as described in section 1.9.4). According to the Council for Medical Schemes report for 2009/2010, 52.1% of all medical scheme beneficiaries were female and 47.9% male (CMS, 2010:160). This trend was also investigated and compared in the dataset for this study.

3.7.3. Geographical area

The Statistical Analysis System®, SAS 9.3® (SAS Institute Inc., 2003) program was used to group all prescriber and provider practice addresses according to province. This allowed the researcher to investigate differences in the prescribing patterns of medication by the various providers according to province in South Africa. The postal code for the prescriber was captured and linked to a specific province.

3.7.4. Provider type

In this study, the focus is on distinguishing between the prescribing/dispensing patterns in retail or community pharmacies (face-to-face patient-pharmacist interaction) versus mail order pharmacies (medication sent to the patient via courier or mail service).

The flow of data that have been analysed is portrayed in Figure 3.2.

It can be noted that general analyses is done first, after which the focus is mainly on chronic medication and the characteristics of its users. Comparisons between these characteristics as well as the dispensing patterns and costs are made between retail and mail order pharmacies. Lastly, the top chronic medications are isolated and analysed to determine MPR and the associated over- and undersupply.

It can be seen that, although the main focus is comparison between *retail/community* and *courier/mail order* pharmacies in the dispensing of *chronic* medication, other providers and other medication are also initially discussed in order to provide a broader background to the dataset analysed. This is done to bring perspective to the conclusions and recommendations discussed in Chapter 5.

The provider types as listed in this study and discussed in Chapter 4 include:

- Dispensing general practitioner (GP).
- Dispensing specialist.
- Courier pharmacy.
- Retail pharmacy.
- Other providers (including, for example, practices that dispense like oncology practices or dentists, or pharmacists with appropriate dispensing licences, etc.).

3.7.5. Medication

Medication is classified using three types of distinguishing methods:

- **Medication classification per benefit category**

According to the Bester and Badenhorst (2011:5, 6), medication can be classified according to the type of medical scheme benefit that it is claimed from. These benefit categories are acute, HIV/AIDS, non-CDL chronic, oncology, OTC, other and PMB medication. As described in Chapter 1, “chronic” medication for the purpose of this study includes both non-CDL and PMB medication under one classification, namely “chronic”. The other benefit categories are classified, as indicated by Bester and Badenhorst, as acute, oncology, HIV/AIDS, OTC and other medication.

The main focus of the medication analysed in this study is on medication relating to chronic diseases (both CDL and non-CDL). In the last section of the data analysis in Chapter 4, the top five chronic diseases are selected, the chronic medication most used in these conditions are identified and possession ratios are calculated. The possession ratios for retail and courier pharmacies are then compared.

- **Pharmacological classification**

A number of classification systems are utilised to classify the medication either in the literature chapter (Chapter 2) or in the empirical investigation (Chapter 4).

- The ATC (Anatomical Therapeutic Chemical) classification code for medication (WHO, 2007) classifies medicine according to working mechanism, pharmacological therapeutic group, and indication and chemical structure. Medication are classified according to the methods in which they act and their therapeutic, pharmacological and chemical properties. Drugs are classified in groups at five different levels. (WHO, 2008).
- The MIMS (Monthly Index of Medical Specialities) classification system: classifies medicine according to its pharmacological action (Snyman, 2009). This classification system is used when the most frequently utilised medication categories are selected and described in this study. The most frequently utilised chronic medication in this study for courier/mail order and retail/community pharmacies are listed in Tables 3.3 and 3.4.

Table 3.3: Most frequently utilised chronic medication groups – courier pharmacy

MIMS Code	Pharmacological categories	N	%
7.3.8	ACE Inhibitor	365704	11.89
7.7.2	Statins	309173	10.06
16.1.1	Diuretics	242769	7.90
19.1.2	Oral antidiabetics	240095	7.81
19.3.1	Thyroid	158834	5.17
8.4.1	Platelet aggregation inhibitors	132059	4.30

Table 3.4: Most frequently utilised chronic medication groups – retail pharmacy

MIMS Code	Pharmacological categories	N	%
7.3.8	ACE Inhibitors	1245728	11.52
7.7.2	Statins	1140550	10.55
16.1.1	Diuretics	719901	6.66
19.3.1	Thyroid	662556	6.13
19.1.2	Oral antidiabetics	645796	5.97
8.4.1	Platelet aggregation inhibitors	564572	5.22

When totalling these medication groups, the most frequently utilised chronic medications are ACE inhibitors, statins, diuretics, thyroid medication and oral antidiabetics.

- The NAPPI Code (National Approved Product Pricing Index): classifies each product according to trade name, pack size, strength and manufacturer (Snyman, 2009). The NAPPI code is a well-established claiming standard for medicines and surgical products in South Africa (Medikredit, 2013) and is used as a classification system for the medicine claims database used in this study.
- The SAMF (South African Medicines Formulary): classifies agents according to pharmacological active ingredient (Gibbon, 2003).

• Type of medication

All medicine items discussed can either be classified as original medicine with generic(s) available, generic medicine items or original medicine items with no generic(s) equivalent available.

When a patent on a specific drug expires or is waived, other companies can manufacture that drug generically. A generic drug is a copy of the original drug with the same active ingredients as the original. The generic drug is sold using a different brand name than the one under which the drug was initially manufactured (Media Resource Desk, 2008). The WHO (2011) defines a generic medicine as a multisource pharmaceutical product which is intended to be interchangeable with the comparator product. It is usually manufactured without a license from the innovator company and marketed after the expiry of patent or other exclusivity rights.

An innovator pharmaceutical product is that which was first authorized for marketing on the basis of documentation of quality, safety and efficacy (WHO, 2011).

Other drugs relevant to this study are original drugs with no generic equivalent available. These drugs are either still under patent protection or drugs for which no generic substitution has been developed after the patent protection has expired.

The patient variables (age, gender, geographical area, provider type and medication) were included in a systematic way to analyse the data. Figure 3.2 portrays this.

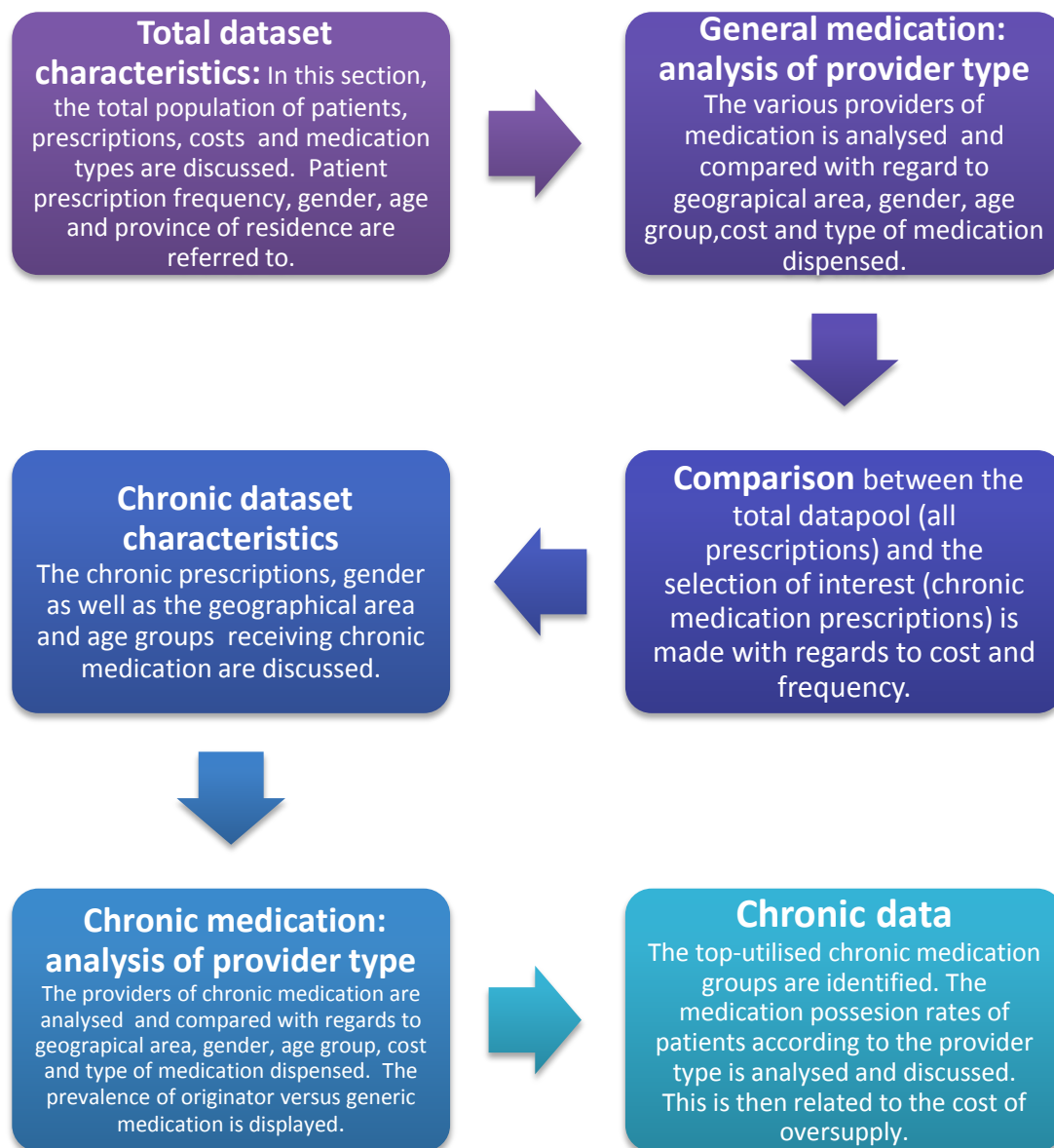


Figure 3.2 Flow of data analysis – refer to Chapter 4 (4.2 to 4.8).

3.8. Descriptive measurements

The way in which medications are utilised can be described in a number of ways such as frequency, associated cost and utilisation rates per patient.

3.8.1. Medication frequency/volume

According to Waning and Montagne (2001:20) prevalence is the number of existing cases in a defined population at a specific time. In this research project, prevalence, frequency and volume will be used as synonyms. Frequency (n) is an indication of the number of patients, medicine prescriptions or items claimed for a specific time period or for a specific group of patients (e.g. specific age group or gender). The prevalence of prescriptions and items dispensed by specific providers are also analysed.

3.8.2. Medication cost

Cost is defined by Vogenberg (2001:3) as the value of resources consumed. In this research project, cost is expressed as a rand-value. The total costs and the average costs will be used. The total cost of each prescription can also be divided into the following costs: total prescription amount (a+b), total scheme amount (a) and total patient levy (b).

3.8.2.1. Direct medicine treatment cost

According to Eisenberg (1989:2882) the different types of costs to be considered in pharmaco-economic analyses include:

- **Direct medical costs:** the costs spent directly on the illness, e.g. medicine, hospital and doctors' visits, i.e. all medical products and services.
- **Direct nonmedical costs:** any costs for nonmedical services due to illness or disease but these costs do not involve purchasing.
- **Indirect nonmedical costs:** cost of reduced productivity or potential loss of patient income. This cost includes morbidity and mortality cost (in other words, days missing from work due to morbidity, or loss of labour force due to mortality).
- **Intangible costs:** non-financial outcomes of illness, e.g. pain and suffering associated with the illness or diseases. This is difficult to quantify.
- According to Dictionary Central (2011), and Springer Reference online (Springer Reference, 2012) direct medical costs can be defined as cost for goods and services

used in the prevention, diagnosis, treatment and rehabilitation of the illness or disorder in question (e.g. cost for drugs, medical visits, hospitalization, diagnostic procedures).

In this study, only direct costs (medication costs specifically) were measured. Total costs as well as average costs were determined. The direct medicine costs were further analysed according to total prescription/item cost, medical scheme contribution and patient levy.

3.8.3. Cost-prevalence index

Cost-prevalence indices developed by Serfontein (1989:180) are indicators of the relationship between the number of medicine items prescribed or claimed and the total cost associated with these items. The following equation is used by Serfontein to calculate the cost-prevalence index:

$$\text{Cost prevalence index} = \frac{\text{Cost}(\%)}{\text{prevalence}(\%)}$$

The ratio can be used as an indicator of the relative expensiveness of chronic medicine items. The cost-prevalence index may be interpreted as follows:

- If cost-prevalence index < 1 the medicine item is considered relatively inexpensive.
- If cost-prevalence index = 1 there is equilibrium between the cost and prevalence of the medicine item.
- If cost-prevalence index > 1 the medicine item is considered relatively expensive.

Cost prevalence indices were calculated for medication dispensed by various providers in the dataset to determine relative cost of the medication groups as well as of the provider types dispensing these medications.

3.8.4. Compliance

Medication compliance (synonym: adherence) refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking. Therefore medication compliance may be defined as “the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen” (Cramer *et al.*, 2008:45). Compliance is measured over a period of time and reported as a percentage (Cramer *et al.*, 2008:45).

Zedler *et al.* (2011:584) used medication possession ratio (MPR) as an estimate of refill timeliness during the persistent period. MPR was also successfully utilised by Steiner and Prochazka (1997:113). MPR is an important indicator of refill adherence. In this study, MPR was calculated as the total days' supply *excluding* the last refill, divided by the total calendar days between the first date and the final refill dispensing date, and is expressed as a percentage. The MPR is used as a proxy of patient compliance with the medication therapy.

Compliance in this study is divided into three categories (refer to Table 2.36 in Chapter 2), namely insufficient medication use (adherence 0% to $\leq 20\%$), good medication use ($\geq 80\%$ to 110% adherence) and overuse ($\geq 110\%$). These parameters are also supported by Serna *et al.* (2010:208) and Duru *et al.* (2010:34). According to Hess *et al.* (2006) adherence can be defined as the degree to which a person's behaviour coincides with medical or health counselling. The adherence ratio can be calculated from pharmacy administrative data if the days between refills and the total days' supply are known, by using the following formula:

$$\% \text{ Adherence} = \left(1 - \frac{\text{DBR} - \text{total days supply}}{\text{DBR}} \right) \times 100$$

The formula indicates that the % adherence is related to the days between refills (DBR) and the total days' supply of medication. According to the ISPOR Work Group (Cramer *et al.*, 2008:45):

Compliance and persistence represent two constructs that are based on one's belief in the efficacy of the medication, the severity of their illness, and their ability to control it with medication. Compliance follows the initial appraisal of the health threat and behavioral changes to develop the habit of taking the medication in accordance with the physician's prescription (time, quantity, and frequency).

Cramer *et al.* (2008:45) further describe compliance and persistence as portrayed in Figure 3.3. It shows that medication compliance is seen as conformation to the recommendations by the prescriber (e.g. dosage and frequency of taking of medication).

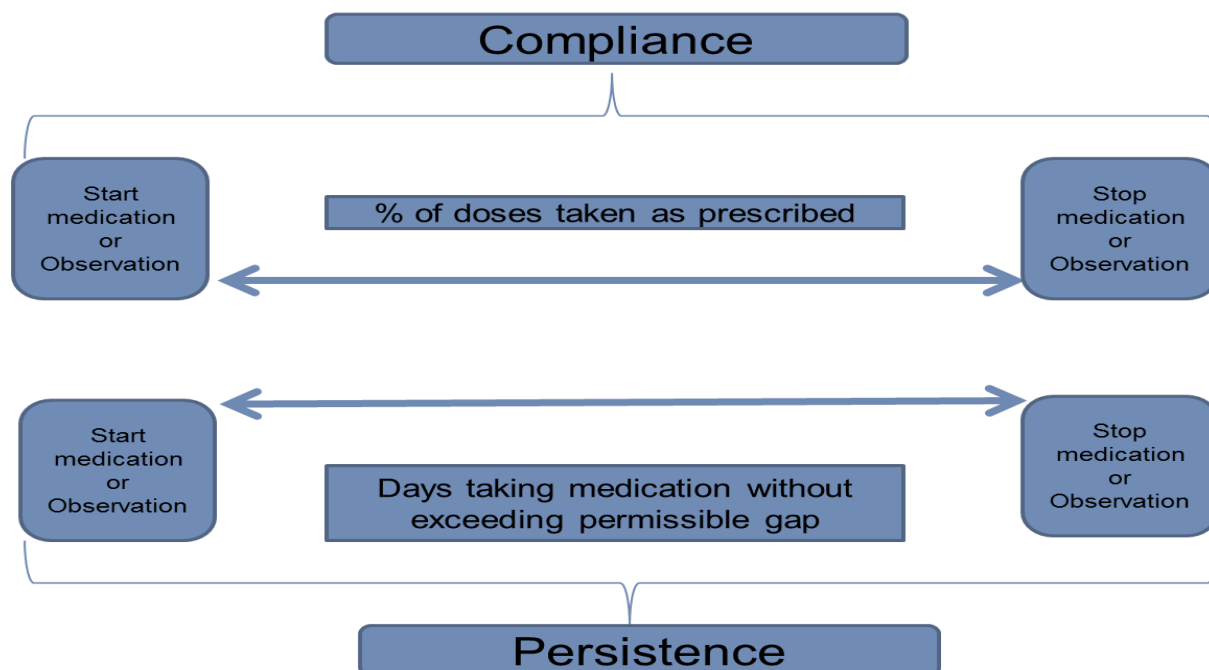


Figure 3.3: Definitions of compliance and persistence (Cramer *et al.*, 2008:45)

Compliance is measured over a period of time and reported as a percentage. Persistence, according to Figure 3.3, differs slightly in the sense that the continuous days taking medication is measured over a period of time. Karve *et al.* (2009:991) summarize the various mathematical formulas for adherence measures as portrayed in Table 3.5.

In this study, MPRs as an indication of compliance have been measured over the two-year study period for selected chronic medications. The medication possession ratios of the identified chronic medication groups were determined and compared for courier and retail pharmacies respectively

Table 3.5: Mathematical formulas for various adherence measures (adapted from Karve *et al.*, 2009:991)

Adherence measure	Formula
Medication possession ratio	Number of days' supply in index period/number of days in the study period (365 days)
Medication refill adherence	$[\text{Number of days' supply in index period/number of days in the study period (365)}] \times 100$
Continuous measure of medication acquisition	Number of days' supply/total days to next fill or end of observation period (365 days)
Proportion of days covered (PDC)	$[\text{Number of days' supply in index period/number of days in the study period (365)}] \times 100$ capped at 1

Refill compliance rate	$(\text{Number of days' supply/last claim date} - \text{index date}) \times 100$
Days-between-fills adherence rate	$[(\text{Last claim date} - \text{index date}) - \text{total days' supply/last claim date} - \text{index date}] \times 100$
Medication possession ratio, modified	$[\text{Number of days' supply}/(\text{last claim date} - \text{index date} + \text{last days' supply})] \times 100$
Continuous measure of medication gaps	Total days of treatment gaps/total days to next fill or end of observation period (365 days)
Continuous multiple interval measure of oversupply	Total days of treatment gaps (+) or surplus (-)/total days to next fill or end of observation period
Continuous, single interval measure of medication	Days' supply obtained at the beginning of the interval/days in interval

3.8.4.1. Application of MPR in this study

Medication possession ratios (MPRs) were specifically chosen to meet the end needs of this study: the calculation of the cost associated with the oversupply of medication. Inclusion criteria for the determination of MPR are as follows:

- Only patients who received the chronic medication for at least four months consecutively were included in the MPR calculation data. This serves to exclude new chronic patients who may still experience dosage or therapeutic adjustments.
- The top five most utilised chronic medication groups were identified as listed in paragraph 3.7.5.

Using data, over- and undersupply of medication could be calculated using the MPR. The calculation was based on three components:

- Number of days oversupply = total days' supply (i.e. actual days of medication received) - days between first and last refill (i.e. number of days patient was supposed to have received medication)
- Average cost per day = final cost / total days' supply
- Cost oversupply = number of days oversupply x average cost per day

Or, simplified to a single formula

Cost oversupply = average cost per day x (total days' supply – number of days patient was supposed to have received medication)

For example, say:

- the average cost of an ACE inhibitor over the period of the study was R100,
- the number of days the patient was supposed to receive the ACE inhibitors were 100 days, and
- the patient received 120 days' worth of medication,

then the cost of oversupply for a patient would be calculated as follows:

$$\begin{aligned}\text{Cost oversupply} &= \text{R}100(120-100) \\ &= \text{R}2000\end{aligned}$$

3.9. Data analysis

All data (total and target population) were analysed for two years: 2009 to 2010. The research data were analysed using a software program called the Statistical Analysis System® SAS 9.3®. Certain analyses were performed with assistance from the Statistical Consultation Services of the North-West University.

3.9.1. Statistical analysis and descriptive statistics

Doane and Seward (2007:3) define statistics as “the science of collecting, organising, and analysing, interpreting, and presenting data”, which explains why statistics is also referred to as “data science”. According to Doane and Seward (2007:5) the two principal types of statistics are descriptive and inferential statistics. Data obtained from the medical aid claims database were analysed and described using several descriptive and inferential statistical methods.

Various descriptive statistics, such as the frequency, arithmetic mean (average), standard deviation (SD), 95% confidence interval (CI) and standard error (SE) were used to describe the characteristics of the study populations within individual studies within the project.

3.9.1.1. Frequency

The frequency, symbol f , is the number of occurrences of a determinable entity per unit of time or population (Dorland's Medical Dictionary for Health Consumers, 2007).

3.9.1.2. Arithmetic mean (average)

The mean (or arithmetic average) of a set of numerical observations is the sum of observations divided by the number of observations (Devore & Peck, 2001):

$$\bar{x} = \frac{\sum x_i}{n}$$

Where:

- $\bar{x}$ = mean
- x = values of the variables
- n = the number of observations

The mean therefore represents the centre of the set of observations (Medhi, 1992:53).

3.9.1.3. Standard deviation

Marczyk *et al.* (2005:92) define standard deviation as a measure of variability indicating the average amount that scores vary from the mean. The value of the standard deviation is therefore the average distance of an observation point.

Standard deviation is calculated as follows (Lind & Mason, 1997:91-92):

$$s = \sqrt{\frac{\sum (x - \bar{x})^2}{n - 1}}$$

Where:

- s = standard deviation
- $\sum$ = sum
- x = value of any variable in the dataset
- $\bar{x}$ = mean
- n = the number of observations

3.9.1.4. Standard error

The standard deviation for the distribution of sample means is called the standard error of the mean. This indicates how much the particular mean calculated is likely to vary from one sample to another when all the samples are the same size and drawn from a random population (Leedy & Ormrod, 2010:277).

3.9.1.5. Confidence intervals

When the number of standard errors (k) is set at, for example, 95%, it means that 95% of all possible intervals under repeated sampling would contain the desired parameter. The

researcher will then have a 0.95 probability of selecting one of the samples that will contain the desired parameter (Diamantopoulos & Schlegelmilch, 2000:119).

3.9.2. Inferential statistics

Inferential statistics are used to test whether the results of the data analysis are due to relationships or random factors. Inferential statistics such as Cohen's effect sizes (d -values) can be used to describe the characteristics of the study populations within individual studies within the project. The cost-prevalence index (CPI) developed by Serfontein (1989) can also be used as an inferential statistic. These statistics are discussed below.

3.9.2.1. Statistical and practical significance

Neuman (1997:320) states that statistical significance is an indicator that the results are not likely to be due to chance factors. Statistical significance is based on p-values, where the reference probability (the p-value) is defined by the level of significance (α value). When a statistical test is performed and the attained p-value (probability) is less than the reference probability, the result is statistically significant. For this study, a result was deemed statistically significant if the p-value is smaller than 0.001.

Practical significance is determined by the d -value. According to Leedy and Ormrod (2010:285), practical significance determines whether statistical findings are useful, and calculation of the effect size (d -value) can assist in determining this "usefulness".

3.9.2.2. Effect sizes (d -values)

Effect size is the magnitude of the differences between group means or other test statistics (Marczyk *et al.*, 2005: 92). Steyn (2009:3) calculates effect size as follows:

$$d = \frac{(\bar{x}_a - \bar{x}_b)}{S_{\max}}$$

Where:

d = effect size

$\bar{x}_a$ = average medicine treatment cost of a

$\bar{x}_b$ = average medicine treatment cost of b

$S_{\max}$ = maximum standard deviation between a and b

This d -value is used to determine practical significance where the result of a statistical test was statistically significant. A d -value of 0.2 is regarded as a small significance, while a value of 0.5 is of medium significance and a value equal to or greater than 0.8 is of high significance (and practically significant), according to Cohen (1988:25).

3.9.2.3. Cramer's V

Diamantopoulos & Schlegelmilch, (2000: 199-201) describe the Cramer's V as a chi-square based adjustment (refer to section 3.9.2.5. for the definition of the chi-square test). Where the chi-square can only test independence, the Cramer's V value reflects the strength of relationships (a value of 0 means no association and a value of 1 is a perfect association). For the purpose of this study, a Cramer's V value of 0.1 is regarded as a low association, 0.3 as a medium association and a value of 0.5 is a high association that indicates practical significance.

3.9.2.4. Analysis of Variance (ANOVA)

Leedy and Ormrod (2010:282) state that the purpose of an ANOVA is to look for differences among three or more means by comparing the variances both within and across groups.

According to the *NIST/SEMATECH e-Handbook of Statistical Methods* (NIST/SEMATECH, 2012), an Analysis of Variance, or ANOVA, is used to test hypotheses concerning means when there are several populations. ANOVA is a general technique that can be used to test the hypothesis that the means among two or more groups are equal, under the assumption that the sampled populations are normally distributed. The Mathematics and Statistics Dictionary (2013) define ANOVA as a special case of multiple regression where indicator variables are used to describe the discrete levels of factor variables. The term Analysis of Variance refers not to the model but to the method of determining which effects are statistically significant.

ANOVA is also described as a procedure used when testing for differences between one or more means (Kohout & Norwood, 1981:106). The F-value is the value of the test statistic (Schlotzhauer & Littell, 1997:244). The ANOVA test determines whether there are any differences between the different groups' means. If a difference is indicated, a second analysis is performed to determine which groups most significantly influence the overall difference between the groups (Schlotzhauer & Littell, 1997:244).

3.9.2.5. Chi-square test (χ^2)

The original chi-square test (χ^2), often known as Pearson's chi-square, dates from papers by Karl Pearson in the early 1900s. The test serves both as a "goodness-of-fit" test, where the data are categorized along one dimension, and as a test for the more common "contingency table", in which categorization is across two or more dimensions (Howell, 2008:1). According to Jackson (1981:99), the chi-square test is used to test whether the proportions or event rates of two or more groups are different. It may be used to test the difference between observed frequencies (whether there is a significant or chance difference). The p -value should be ≤ 0.05 in order to be statistically significant.

According to the Business Dictionary (2013), the goodness of fit test is based on frequency of occurrence and used in determining how well the data obtained from an experiment matches the expected data. It is applicable both to qualitative attributes and quantitative variables, and helps to ensure that the experimental results are statistically significant and have not been caused by chance events.

3.9.2.6. Student's t-test (t)

The goal of the student's t -test is to determine whether there is a statistically significant difference between two means (Leedy & Ormrod, 2010:282). This definition is supported by Jackson (1981:99), who states that the student's t -test is used to determine whether the difference between the means of two groups is significantly different.

3.10. Reliability and validity of research instruments

Reliability:

Leedy and Ormrod (2010:29) define reliability as the consistency with which a measuring instrument yields a certain result when the entity being measured has not changed. Joppe (2000:1) expands on this definition:

The extent to which results are consistent over time and an accurate representation of the total population under study is referred to as reliability and if the results of a study can be reproduced under a similar methodology, then the research instrument is considered to be reliable.

Nelson (1981:42) defines reliability as the degree of consistency, accuracy and precision of a measure.

The research instrument in question for this study is the prescription claims database of one of South Africa's largest PBM companies. This dataset includes prescribed and dispensed

medication; medical scheme belonged to, monetary values of prescriptions and items, gender and age of patients as well as prescriber information. The accuracy of the data lies firstly within the “live” nature of the data – actual medication claims by providers for patient medication is recorded. Any errors therefore result in claims not being processed or processed incorrectly, which will lead to patient, provider or medical scheme complaints. Secondly, a test program is run on a daily basis to ensure that claims are processed against all the correct references and return the correct response to the submitted claim.

Validity:

Diamantopoulos and Schlegelmilch (2000:33) explain that the extent to which a particular measure is free from both systematic and random error indicates the validity of the measure. Joppe (2000:2) provides the following definition of validity in quantitative research:

Validity determines whether the research truly measures that which it was intended to measure or how truthful the research results are. Researchers generally determine validity by asking a series of questions, and will often look for the answers in the research of others.

Nelson (1981:45) agrees and adds that validity is usually assessed in terms of face, content, criteria-related or constructs validity.

The validity of this study is tested by comparing the results found in Chapter 5 to the research questions posed in Chapter 1. Furthermore, Motheral *et al.* (2003:90-96) suggest using a checklist developed by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) in order to verify the reliability and validity of results, specifically when conducting studies using a retrospective database. Table 3.6 summarises the elements discussed in the check list and the response delivered in this study to ensure that each aspect on the checklist is covered.

Table 3.6: Checklist for retrospective database studies (adapted from Motheral *et al.*, 2003:90-96).

Considerations	Aspect	Checklist question	Answer and cross reference
Data Source	Relevance	Have the data attributes been described in sufficient detail for decision makers to determine whether there was a good rationale for using this data source? Can the data be generalised and interpreted in a wider context?	Refer to paragraphs 3.5 and 3.6. The data is representative of private sector medication claims of 1.5 million patients. Medication claims are processed by the PBM used as data source. This data can therefore be generalised to the context of the greater South African private sector.
	Reliability and Validity	Have the reliability and validity of the data been described? Has the dataset been cleaned?	The datasets were tested by random data checks. Only certain data were used, e.g. non-medicine items or unpaid medication claims were removed. At MPR level, only the top 5 medication classes were used. Also refer to paragraph 5.2 and Table 3.2.
	Data linkages	Have the necessary linkages among data sources and other sites been carried out appropriately?	The medication claims data were received in a comma separator value (.csv) format and imported into the SAS® 9.3. analytical program. Identifiers were added to the imported data (e.g. courier and retail pharmacy) and the system was programmed to run the required data reports.
	Eligibility	Has the type of data to determine member eligibility been described?	In the general population dataset, eligibility was not taken into consideration and this may be a data limitation. In calculating the MPR, only patients receiving chronic medication for four consecutive months were considered and that may eliminate this limitation.

Methods	Research design	Was a data analysis plan and protocol developed a priori?	Not applicable.
Methods (cont.)	Design selection	Was a rationale provided for the selection of the particular research design?	Yes – refer to paragraph 3.3.
	Research design limitations	Has the potential limitations of the study design been addressed?	Yes – refer to paragraph 3.12.
	Treatment effect	Was a comparison group to determine the effects of an intervention properly described?	Not applicable.
Study population and variable definitions	Sample selection	Have the inclusion and exclusion criteria and steps used to derive the final sample been described?	Yes. Refer to paragraph 3.6.1 and Figure 3.1 as well as paragraph 3.8.4.
	Eligibility	Are subjects eligible for the time period over which measurement is occurring?	Patient medical scheme benefits and health plans were treated as confidential and were not available for this study. Eligibility of each patient could therefore not be confirmed. The PBM providing the data does, however, validate the data in a number of ways – refer to Table 3.2.
	Censoring	Were inclusion/exclusion criteria used to address	

		censoring and was the impact discussed?	
	Operational definitions	Are subjects and outcome criteria explicitly defined using diagnosis, drug markers, procedure codes and/or other criteria?	No diagnosis or procedure codes were used in this study but definitions relating to the outcomes can be found in paragraph 3.7.6 (medication classification) and 3.8.4 (compliance).
	Definition validity	Has a rationale been provided for definitions and criteria used and were a sensitivity analysis performed for criteria that was controversial or novel?	Yes. Refer to paragraphs 3.7 and 3.8.
Study population and variable definitions (cont.)	Timing of outcome	Is there a clear sequential relationship between the exposure and outcome?	Not applicable.
	Event capture	Are the collected data able to identify the intervention and outcomes if they actually occurred?	The database only includes medication claims (over-the-counter to schedule 6) as dispensed by the identified providers. No out-of-pocket expenses or non-medication items were therefore included.
	Disease history	Is there a link between the natural history of the disease being studied and the period of the analysis?	Not applicable
	Resource valuation	Was an exhaustive list of resources affected by the intervention defined and	In this study, only direct medication cost (direct treatment cost) was evaluated. Total medication cost, levy paid by the patient as well as medical scheme

		measured? Have resource prices been adjusted to yield a consistent valuation that reflects the opportunity cost of the resource?	contribution were analysed. No additional cost (e.g. dispensing or logistics fees) was investigated. The only inflation-related element included into the year-on-year price difference was the annual Single Exit Price (SEP) increase as allowed by the Department of Health, and this was included in the data.
Statistics	Control variables	What methods have been used to control other variables that may affect the outcome of interest?	This study has an economic basis and no clinical outcomes were measured. In the initial evaluations (Chapter 4 paragraph 4.1 to 4.6) one must be aware of inherent bias when comparing provider types. A dispensing GP, for instance, might have a lower average medication cost than a courier pharmacy due to the fact that dispensing GPs are more prone to treat acute ailments and sometimes lower LSM patients. Province of treatment will also include bias, as a courier pharmacy may dispense all its medication from one central point, therefore creating bias towards a specific province. This is taken into consideration and pointed out in the discussion of results. However, when medication possession ratios and medication oversupply were calculated, careful attention was paid to comparing chronic medication groups (like with like) between retail and courier pharmacy respectively. All confounding bias was removed and only comparisons that were found to be bias-free were performed.
Statistics (cont.)	Statistical model	Has the selection of a specific statistical model been explained?	Paragraph 3.9 contains statistical models that have been applied to the data.
	Influential	Was the sensitivity of the	The datasets were cleaned by eliminating rejected

	cases	results to influential cases evaluated?	claims and non-medication claims. The datasets were verified by random tests and also validated as explained in Table 3.2.
	Relevant variables	Were all variables identified hypothesised to influence the outcome of interest? Were all available variables included in the model?	Not applicable.
	Statistical assumptions	Was the validity of the statistical assumptions underlying the analysis investigated?	The statistical findings support the findings in the primary dataset. Statistical assumptions were supported by the Statistical Consultation Services of the North-West University.
	Multiple tests	If analysis is carried out on multiple groups, are the statistical tests adjusted to reflect this?	As the database of this study is large (17 106 524 prescription claims over the two-year period), many results were found to be statistically significant (p -values of <0.001). Using Cohen's effect sizes or d -value (Cohen, 1988:25), a d -value of greater than or equal to 0.8 was regarded as practically significant.
	Model prediction	If multivariate statistical techniques are used, how well does the model predict what was intended to predict?	Not applicable.
Discussion/Conclusion	Theoretical basis	Has a theory for the findings been provided and have other possible explanations for the findings been ruled out?	Refer to Chapter 5.

	Practical versus statistical significance	Have the statistical findings been interpreted in terms of their clinical or economic relevance?	Statistical as well as practical significance is discussed and interpreted throughout Chapter 4 and interpreted per population subgroup under discussion. Their definitions are given in paragraph 3.9.2.1.
	Generalisability	Have the populations and settings to which the results can be generalised been discussed?	Refer to Chapter 5.

3.11. Ethical aspects

The data utilised in this study is owned by and used with the permission of a pharmaceutical benefit management company. No individual patient (protection of patient confidentiality) and no medical scheme is identified from the data. All data have been used as a pool in order to identify trends and project possible patterns based on these trends. No individual medical practitioner is identified, only the speciality of the prescriber in order to identify possible prescribing trends. Each prescription record contains a reference number which links each patient, medical practice/pharmacy or medical aid scheme to line items, and this serves as a time stamp of when the transaction was adjudicated.

Permission from the North-West University Research Committee has been obtained before performing this research study. The study number allocated by the ethics committee is NWU - 0046-08-S5.

3.12. Limitations and shortcomings of this research project

The following limitations and shortcomings should be taken into account when evaluating this research project:

- All the data obtained from the pharmaceutical benefit management company database are considered to be accurate and correct.
- Data on medical aid claims, although indicative of compliance, cannot prove or disprove the patient actually taking the medication
- External validity is limited, implying that the results can only be generalised to the specific database and study population.
- Demographic data are limited to patient age and gender, province of dispensing and the provider of medication.
- Comparing the South African pharmacy market to that of Europe and other first-world countries like the US may be challenging and may not render sufficient material to do comparisons with.
- Little data on the South African pharmaceutical sector is available and statistics in terms of usage of generics, substitution percentage and perceptions of health care providers are not readily available.

- The author of this study is employed by a generics manufacturing company. As no specific analysis with regards to the brands of generics used will be done, this does not pose conflict of interest.

3.13. Proposed outline of the empirical study

The analysis will be performed as set out in Figure 3.4 to meet the specific research objectives described in paragraph 3.2.1.



Figure 3.4: Schematic representation of analysis performed to meet the study objective

3.14. Conclusions and recommendations

The conclusions and recommendations of this study with specific reference to the general and specific objectives will be discussed in Chapter 5.