# A retrospective analysis of the prescribing patterns of hipolipidaemic drugs: A pharmacoeconomic approach

**J. BLOEM**

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Dissertation submitted in partial fulfilment of the requirements for the degree *Magister Pharmaciae* at the Potchefstroom campus of the North-West University

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# *IT IS OUR LIGHT NOT OUR DARKNESS THAT MOST FRIGHTENS US*

*Our deepest fear is not that we are inadequate.*

*Our deepest fear is that we are powerful beyond measure.*

*It is our light not our darkness that most frightens us.*

*We ask ourselves, who am I to be brilliant, gorgeous, talented and fabulous?*

*Actually, who are you not to be?*

*You are a child of God.*

*Your playing small does not serve the world.*

*There's nothing enlightened about shrinking so that other*

*people won't feel insecure around you.*

*We were born to make manifest the glory of God that is within us.*

*It's not just in some of us; it's in everyone.*

*And as we let our own light shine, we unconsciously give other people permission to do the same.*

*As we are liberated from our own fear, Our presence automatically liberates others.*

MARIANNE WILLIAMSON

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# *ABSTRACT*

**Title: A retrospective analysis of the prescribing patterns of hipolipidaemic drugs: A pharmacoeconomic approach**

**Keywords:** Dyslipidaemia, hipolipidaemic medicine, prevalence, total medicine cost, generic substitution, therapeutic substitution, age, sex, generic indicator, drug utilisation review

**Background:** More than 5.5 million South Africans aged 30 years and older are at risk of chronic disease by virtue of their triglyceride levels (Maritz, 2006:101). Dyslipidaemia is common in westernized and industrialized communities (Steyn *et al*., 2000:720), especially so for South Africa, where burden of disease data show dyslipidaemia to be the second most prevalent of all the chronic conditions in the country (Council for Medical Schemes, 2006:48). It is therefore no surprise that at 3.3 per cent hipolipidaemics ranked second highest based on prevalence percentage per therapeutic group in the 2005 Mediscor medicines review on South African medical claims data (Bester *et al*., 2005:8-11). Hipolipidaemic drugs subsequently also ranked second highest for expenditure per therapeutic group, achieving a total expenditure of 5.8 per cent.

**Objective:** The purpose of this study was to characterise the usage and cost of hipolipidaemic drugs in the private health care environment in South Africa based on various categories, including age, sex, prescriber type and generic indicator.

**Methods:** A quantitative retrospective drug utilisation review was performed using dispensing records from a medicine claims database. Data for a two-year period (1 Jan. 2005 to 31 Dec. 2006) were used. Hipolipidaemic medicine usage was analysed according to five patient age strata: patients younger than 9 years, 10≤ 19 years, 20 ≤ 45 years, 46 ≤ 59 years and older than 59 years.

Basic descriptive statistics such as frequencies and arithmetic mean (average) were used to characterise the study sample, and were calculated using the Statistical Analysis System (SAS®) for Windows 9.1® program (SAS Institute Inc., 2002-2003).

**Results:** The database consisted of 19 860 593 and 21 473 062 medicine item claims for 2005 and 2006 respectively, at a total cost of R 1 893 376 921.00 (for 2005) and R2 046 944 383.00 (for 2006). Patients receiving hipolipidaemic medicine items represented about 7.2% of the

total number of patients on the database in both 2005 and 2006. About 47% of the study population in both 2005 and 2006 was female, compared to 53% males.

Hipolipidaemics represented between 3.1% (N = 19 860 593) and 3.3% (N = 21 473 062) of the total number of items claimed during the study period. The total cost of hipolipidaemics accounted for between 5.6% (N = R1 893 376 921.00) and 5.8% (N = R2 046 944 383.00) of the total cost of all medications claimed during the study period. The average cost per item of hipolipidaemics was R170.63 ± 70.19 in 2005 compared to R167.08 ± 71.93) in 2006.

HMG-CoA reductase inhibitors formed the leading therapeutic class in hipolipidaemic medicine items in all age groups on the database, except for children aged 0≤ 9 years, where the "others" group, in particular cholestyramine (Questran Lite 4 mg) was claimed more frequently. Of the items claimed for both study periods, simvastatin was the most commonly claimed, accounting for 45.35% (n = 284 232) and 46.21% (n = 325 970) respectively of the number of hipolipidaemic items claimed, at a total cost of 30.97% (n = R33 119 294.18) and 31.38% (n = R36 983 938.41) for 2005 and 2006 respectively.

Non-substitutable and generic hipolipidaemic medicine items carried the largest percentage of prevalence and cost in both study periods for both sex categories and all age groups. The majority of claims for hipolipidaemic medicine items were prescribed by general medical practitioners, followed by "other prescribers" and then by cardiologists. Only a small number of prescriptions claimed were prescribed by thoracic surgeons and even fewer by pharmacotherapists and pharmacists. Trade name products that were mostly prescribed were Lipitor and Adco-Simvastatin.

Of all the hipolipidaemic drugs utilised on the database, only three active ingredients (bezafibrate, simvastatin and pravastatin) had generic equivalents available at the time of the study. With total substitution (100%) of these three drugs with the average price of the available generic hipolipidaemic equivalents on the database, a cost saving of R1 744 462.27 or 1.63% (N = R106 943 348.53) was possible in 2005. In 2006, a total cost saving of R1 526 985.79 or 1.30% (N = R117 862 631.87) was calculated.

**Conclusion:** The study highlighted the most commonly prescribed hipolipidaemics within a sub-population of South African patients. The high average cost per prescription of hipolipidaemic drugs indicates that they are relatively expensive in comparison to other medications. Generic (and therapeutic) substitution should be investigated as potential cost-saving mechanisms in the private health care sector of South Africa.

# *OPSOMMING*


**Titel: 'n Retrospektiewe ontleding van die voorskrifpatrone van hipolipidemiese middels: 'n farmako-ekonomiese benadering**

**Sleutelwoorde:** dislipidemie, hipolipidemiese medisyne, voorkoms, totale koste van medisyne, generiese vervanging, terapeutiese vervanging, ouderdom, geslag, generiese aanwyser, medisyneverbruiksevaluering

**Agtergrond:** Meer as 5.5 milljoen Suid-Afrikaners van 30 jaar en ouer loop 'n risiko vir chroniese siektes vanweë hulle trigliseriedvlakke (Maritz, 2006:101). Dislipidemie kom algemeen in Westerse en geïndustrialiseerde gemeenskappe voor (Steyn *et al*., 2000:720), en veral in Suid-Afrika waar die oorwig van data oor siektes toon dat dislipidemie die tweede mees algemene chroniese toestand in die land is (Raad vir Mediese Skemas, 2006:48). Dit verbaas dus nie dat hipolipidemiese middels teen 3.3 persent die tweede grootste voorkoms per terapeutiese groep het in die databasis van Mediscor vir 2005 oor eise vir medisyne in Suid-Afrika nie (Bester *et al*., 2005:8-11). Hipolipidemiese medisyne is met 'n uitgawe van 5.8 persent gevolglik ook in die tweede plek vir die grootste uitgawe per terapeutiese groep.

**Doel:** Die doel van hierdie studie was om die gebruik en koste van hipolipidemiese medisyne in die private gesondheidsorgomgewing in Suid-Afrika op grond van verskillende kategorieë, waaronder ouderdom, geslag, tipe voorskrywer en generiese aanwyser, te karakteriseer.

**Metodes:** 'n Kwantitatiewe retrospektiewe studie van gebruik van medisyne is gedoen deur die voorskrifrekords uit 'n databasis van eise te gebruik. Data van 'n periode van twee jaar (1 Jan. 2005 tot 31 Des. 2006) is gebruik. Gebruik van hipolipidemiese medisyne is volgens vyf ouderdomsgroepe van pasiënte ontleed: jonger as 9 jaar, 10 ≤ 19 jaar, 20 ≤ 45 jaar, 46 ≤ 59 jaar en ouer as 59 jaar.

Basiese beskrywende statistiek, soos frekwensies en rekenkundige gemiddeld, is gebruik om die studiemonster te karakteriseer, en is met die Statistical Analysis System (SAS®) for Windows 9.1®-program bereken.

**Resultate:** Die databasis het 19 860 593 en 21 473 062 eise vir medisyne vir 2005 en 2006 onderskeidelik, met 'n totale koste van R 1 893 376 921.00 (vir 2005) en R2 046 944 383.00 (vir 2006) gehad. Pasiënte wat hipolipidemiese medisyne ontvang het, het vir sowel 2005 as 2006

7.2% van die totale aantal pasiënte in die databasis uitgemaak. Ongeveer 47% van die studiepopulasie in sowel 2005 as 2006 was vroulik en 53% manlik.

Hipolipidemiese middels het 3.1% (N = 19 860 593) tot 3.3% (N = 21 473 062) van die totale aantal items uitgemaak wat tydens die studieperiode geëis is. Die totale koste van hierdie middels was 5.6% (N = R1 893 376 921.00) tot 5.8% (N = R2 046 944 383.00) van die totale koste van alle medikasie wat tydens die studieperiode geëis is. Die gemiddelde koste van hipolipidemiese middels per item was R170.63 ± 70.19 in 2005 teenoor R167.08 ± 71.93 in 2006.

HMG-CoA-reduktaseremmers was die belangrikste klas terapeutiese hipolipidemiese middels vir alle ouderdomsgroepe in die databasis, behalwe vir kinders van 0 ≤ 9 jaar, waar die groep "ander", en veral cholestiramien (Questran Lite 4 mg), meer dikwels geëis is. Simvastatien met 45.35% (n = 284 232) en 46.21% (n = 325 970) onderskeidelik van die totale aantal hipolipidemiese middels, was die item wat in 2005 en 2006 die meeste geëis is met 'n totale koste van 30.97% (n = R33 119 294.18) en 31.38% (n = R36 983 938.41) onderskeidelik in die studieperiodes.

Nie-vervangbare en generiese hipolipidemiese medisyne het in albei studieperiodes die grootste persentasie van sowel voorkoms en koste vir albei geslagte en alle ouderdomsgroepe uitgemaak. Die meeste hipolipidemiese medisyne-items is deur algemene praktisyns voorgeskryf, gevolg deur "ander voorskrywers" en dan deur kardioloë. Slegs 'n klein aantal voorskrifte wat geëis is, is deur torakschirurge en nog minder deur farmakoterapeute en aptekers voorgeskryf. Die handelsname wat die meeste voorgeskryf was, was Lipitor en Adco-Simvastatin.

Van al die hipolipidemiese middels in die databasis, het slegs drie aktiewe bestanddele (besafibraat, simvastatien en pravastatien) ten tye van die studie generiese ekwivalente gehad. Met totale vervanging (100%) van hierdie drie middels met die gemiddelde prys van die beskikbare hipolipidemiese ekwivalente in die databasis was 'n kostebesparing van R1 744 462.27 of 1.63% (N = R106 943 348.53) in 2005 moontlik. Vir 2006 is 'n totale kostebesparing van R1 526 985.79 of 1.30% (N = R117 862 631.87) bereken.

**Gevolgtrekking:** Die studie het die mees algemeen voorgeskryfde hipolipidemiese middels vir 'n sub-populasie van Suid-Afrikaanse pasiënte uitgelig. Die hoë gemiddelde koste van hierdie middels per voorskrif toon dat hulle vergeleke met ander medisyne relatief duur is. Generiese (en terapeutiese) vervanging as moontlike meganismes vir kostebesparing in die private gesondheidsorgomgewing in Suid-Afrika moet ondersoek word.

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# *CHAPTER 1*

# *INTRODUCTION AND PROBLEM STATEMENT*

## 1.1 INTRODUCTION

This dissertation focuses on the prescribing patterns and cost of hipolipidaemic drugs in South Africa. In this chapter the problem statement, background and rationale for the study, research objective, research methodology, terms and definitions, abbreviations and the division of further chapters will be discussed. A layout of the division of chapters is given at the end of this chapter.

## 1.2 PROBLEM STATEMENT

Dyslipidaemia is common in westernised and industrialised communities (Steyn *et al.,* 2000:720), especially so for South Africa, where burden of disease data show dyslipidaemia to be the second most prevalent of all the chronic conditions in South Africa (Council for Medical Schemes, 2005:61). It is therefore no surprise that hipolipidaemics ranked second highest based on prevalence percentage per therapeutic group in the 2005 Mediscor medicines review on South African medical claims data at 3.3 per cent (Bester *et al*., 2005:8). Hipolipidaemic drugs subsequently ranked second highest for expenditure per therapeutic group, achieving a total expenditure of 5.8 per cent. Lipitor (atorvastatin) 10mg and 20mg ranked highest and second highest respectively on the top 50 list by contributing to total expenditure of 2005 in this report (Bester *et al*., 2005:8-11).

Drug utilisation review has emerged in response to the needs to control both cost and the quality of medication usage (Chrischilles *et al.,* 1996:172). The principal aim of drug utilisation research is to facilitate the rational use of drugs in populations (WHO, 2003a:9) and at the same time to reduce needless expenditure and improve the quality of care (Chrischilles *et al*., 1996:172). McMurray (1999:2) stated that pharmacoeconomic analysis of the management as well as impediment strategies for coronary heart diseases is a valuable tool for comparing the cost-effectiveness of new medical interventions allowing health care decision makers to contain cost by choosing those interventions that are most efficient. Intervention by means of medication / drugs is imperative and in the case of lowering cholesterol levels, it involves a large population of patients and potentially high costs (Johannesson *et al.,* 1997:332). Drug

utilisation review research and pharmacoeconomic studies conducted on the use of hipolipidaemics in the private health care sector of South Africa could therefore, potentially, aid in controlling the cost of hipolipidaemics, ensuring quality care and rational drug usage.

## 1.3 BACKGROUND AND RATIONALE FOR THE STUDY

Dyslipidaemia is defined as a disorder of the lipoprotein metabolism, described by an overproduction or deficiency in lipoprotein. Dyslipidaemias may manifest as an elevation of the total cholesterol (TC); or elevated low-density lipoprotein (LDL) cholesterol and triglyceride (TG) concentrations; or a decrease in the high-density lipoprotein (HDL) cholesterol concentrations in the blood (Ahmed *et al*., 1998; Berger & Marais, 2000:164).

Different types of dyslipidaemia can be identified, e.g. Type I to Type IV. These types include: dysbetalipoproteinaemia, exogenous hypertriglyceridaemia, familial hyperglyceridaemia, fat-induced hyperlipidaemia, familial hypercholesterolaemia, endogenous hypertriglyceridaemia, mixed hypertriglyceridaemia and mixed hyperlipidaemia (Anderson, 2002:845).

Familial hypercholesterolaemia (FH) is "*an autosomal dominant disorder that causes severe elevations in total cholesterol and low-density lipoprotein cholesterol*" (Citkowitz, 2006). Gender wise, the gene for FH is on the 19$^{th}$ chromosome, thus the inheritance pattern is the same for males and females although severe hypercholesterolaemia manifests earlier in males than in females. Non-familial hypercholesterolaemia, however, is more common in men younger than 55 and in women older than 55 years of age (Citkowitz, 2006).

Data that were collected by Maritz (2006:101) show that at least 1.5 million African people aged 30 years and older are hypercholesterolaemic. Familial Hypercholesterolaemia (FH) in particular, is very common in the Afrikaner (white) population group. Its prevalence is estimated to be 1:72 compared to 1:500 worldwide (Maritz, 2006:102). Older women were furthermore found to have hypercholesterolaemia more frequently than older men (Maritz, 2006:101).

The study conducted by Maritz (2006:101) indicates that more than 5.5 million South Africans aged 30 years and older carry a risk for chronic disease by virtue of their TC level. Dyslipidaemia also plays an important role in other diseases, e.g. diabetes mellitus (DM), hypertension, angina, stroke, cardiac ischemia, coronary artery disease (atherosclerosis) and pancreatitis (Kromhout, 1999:796-802).

Dyslipidaemia itself causes no symptoms though it can lead to symptomatic vascular disease (coronary artery disease and peripheral arterial disease), and high TGs (> 1000 mg/dℓ or > 11.3

mmol/ℓ) can cause acute pancreatitis (Baron; 2007:1276; Berger & Marais, 2000:168; Bhatnagar, 1998:213). High levels of LDL can cause eyelid xanthelasmas; arcus corneae; and tendinous xanthomas found at the achilles, elbow, and knee tendons and over metacarpophalangeal joints (Anon., 2005). Patients with homozygous familial hypercholesterolaemia may have the above findings plus planar or cutaneous xanthomas. Patients with severe elevations of TGs can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet (Anon., 2005). Patients with the rare dysbetalipoproteinaemia may manifest with palmar and tuberous xanthomas. Severe hypertriglyceridaemia (> 2000 mg/dℓ or > 22.6 mmol/ℓ) can give retinal arteries and veins a creamy white appearance (a condition called lipemia retinalis) (Anon., 2005). Extremely high lipid levels also give a lactescent appearance to blood plasma (Anon., 2005).

According to Gibbon (2008:164) HMG CoA reductase inhibitors (statins) are the foundation of treatment, as they are potent reducers of plasma LDL-cholesterol and have beneficial effects on HDL-cholesterol and triglycerides levels. According to Ridker *et al.* (1999:230-235) fenofibrate, gemfibrozil and niacin are the optimum treatment regimens in patients with elevated triglycerides and low HDL-cholesterol levels. Statins reduce triglycerides 30-40 per cent in general (Ridker *et al*., 1999:230-235). In patients with low HDL-cholesterol, the HDL-cholesterol will be raised 25-30 per cent with the treatment of niacin, compared to gemfibrozil, which raises HDL- cholesterol by 10-15 per cent.

A lowering (rate ratio [RR] 0.88, 95% CI 0.84-0.91; p<0.0001) in LDL- cholesterol is associated with a 12 per cent reduction in all-cause mortality; it has a 19 per cent reduction in cardiovascular heart disease (CHD) mortality and 21 per cent reduction in major vascular events (Baigent *et al.,* 2005:1273).

In developed countries such as Australia and America the treatment and prevention of cardiovascular diseases embody the highest proportion of the total health expenditure by disease group, consisting of hospitalisation and medication costs (American Heart Association, 2004). Hospitalisation contributed 45 per cent (US$109 billion ~ R907 billion)[1] of the estimated (US$241.9 billion ~ R2 trillion) spent on therapy in the United States and 46 per cent (A$2.5 billion ~ R10.8 billion) of the estimated A$5.5 billion (~R23 billion)[2] spent in Australia in 2000 to 2001.

In a recent report by Bester *et al.* (2005:8-11) conducted on South African medical claims data, hipolipidaemic drugs ranked second highest for expenditure per therapeutic group, achieving a

[1] US Dollar = R8.33 (2000 - 2001) (OANDA, 2009).
[2] Australian Dollar = R4.35 (2000 - 2001) (OANDA, 2009).

total expenditure of 5.8 per cent from a possible 74.6 per cent. Lipitor (atorvastatin) 10mg- and 20mg ranked highest and second highest respectively on the top 50 list by contributing to total expenditure of 2005 in this report (Bester *et al*., 2005:8-11).

McMurray (1999:100) stated that pharmacoeconomic analysis of the management as well as impediment strategies for coronary heart diseases is a valuable tool for comparing the cost-effectiveness of new medical interventions allowing health care decision makers to contain cost by choosing those interventions that are most efficient. Intervention by means of medication / drugs is imperative and in the case of lowering cholesterol levels, it involves a large population of patients and potentially high costs (Johannesson *et al.,* 1997:332).

A cost minimisation study that estimated the benefits of lowering cholesterol using data from the 4S-study (Scandinavian Simvastatin Survival Study) show that simvastatin therapy produced a 10 per cent decrease in length of hospital stay, a 26 per cent reduction in number of hospitalisation, a 31 per cent reduction in hospital costs and a 34 per cent reduction in total hospital days. As a result of these savings, the cost of simvastatin was reduced (Pedersen *et al.*, 1996:1796). In a treat-to-target pharmacoeconomic analysis of HMG-CoA reductase inhibitors in hypercholesterolaemia, Hilleman *et al.* (1999:536-562) showed that the most cost-effective treatment approach, was to individualise the selection of statins based on coronary risk.

Ballesteros *et al.* (2001:516) investigated the economic cost generated in one year in primary care because of inadequate (unnecessary) prescriptions of hipolipidaemic agents. It was found that the cost of inadequate prescription for hipolipidaemic drugs reached US$1.1 million (~ R9 million) for quality level one (patients whose age, risk factors, total cholesterol level and low-density lipoprotein cholesterol level were known before pharmacological intervention) and US$38 000 (~ R316 540) for level two (patients whose low-density lipoprotein levels and diet were unknown before pharmacological intervention). It was also found that 12.3 per cent of the health professionals ordered all their prescriptions inadequately. Of the total inadequate prescriptions expenditure, 20.4 per cent represented treatment initiated by family physicians and 35.3 per cent by specialists. Statins made up 78.2 per cent of the total cost and the inadequate expenditure for this therapeutic group reached US$89 000 ~ R741 370). Of the prescriptions for fibrates, 88 per cent were inadequate (Ballesteros *et al*., 2001:513).

Drug utilisation review has emerged in response to the needs to control both cost and the quality of medication usage (Chrischilles *et al.,* 1996:172). The principal aim of drug utilisation research is to facilitate the rational use of drugs in populations (WHO, 2003a:9) and at the same time to reduce needless expenditure and improve the quality of care (Chrischilles *et al*.,

1996:172). All of these can be achieved through the detection of drug interactions, contraindications, overdoses, over-utilisation and under-utilisation (Monane *et al*., 1998:51).

Based on the above discussion it is clear that treatment for lipid-deficiency in South Africa should be a very high priority with any health care organisation, and that such treatment calls for thorough and ongoing investigation and research. Drug utilisation review research and pharmacoeconomic studies conducted on the use of hipolipidaemics in the private health care sector of South Africa could, potentially, aid in controlling the cost of hipolipidaemics, ensuring quality care and providing rational drug usage.

The following questions can be formulated based on the foregoing discussion:

- What does dyslipidaemia entail and what is the significance thereof in the context of South Africa?
- What do drug utilisation review, pharmacoeconomics and managed health care entail, and what role can these play in the "rational" use of hipolipidaemic agents in the private health care sector of South Africa?

## 1.4 RESEARCH OBJECTIVES

The research of this study will include general and specific objectives.

### 1.4.1 General research objective

The general research objective of this study was to analyse the usage patterns and cost of hipolipidaemic drugs in South Africa, by utilising data from a South African Pharmaceutical Benefit Management company.

### 1.4.2 Specific research objectives

In order to achieve the general objective of the study, the following specific objectives needed attention:

- To describe and define the concepts of dyslipidaemia as well as the different types of dyslipidaemia.
- To describe the incidence and prevalence of dyslipidaemia, in worldwide countries as well as South Africa.

- To describe the pathophysiology and significance of dyslipidaemia including the risk for CVD and other diseases and the use of resources.
- To describe the diagnosis, signs and symptoms, as well as the clinical management (both non-pharmacological and pharmacological) of the disease.
- To define managed health care, describe the different types of managed health care plans and concepts within the managed health care framework as well as the application thereof in the South African health care environment.
- To define drug utilisation review and identify the different classifications of drug utilisation review and the types of drug utilisation review.
- To describe the process and units of measurement of drug utilisation review.
- To review the application of drug utilisation review in South Africa.
- To define pharmacoeconomics and the methodology of pharmacoeconomics.
- To describe the objectives of pharmacoeconomics as well the applications thereof in South Africa.
- To review evidence from pharmacoeconomical- and drug utilisation studies on the treatment of dyslipidaemia.
- To define and describe pharmacoepidemiology, the objectives, study designs as well as the application thereof.
- To define and describe evidence-based medicine, its objectives as well as the application thereof.
- To determine the prescribing patterns and cost associated with hipolipidaemic medicine within a section of the private health care sector of South Africa.
- To determine age and sex differences with regard to hipolipidaemic drug usage and cost medicine within a section of the private health care sector of South Africa.
- To determine the prevalence of original medicine items *vs*. generic medicine items for hipolipidaemic medicine within a section of the private health care sector of South Africa.
- To determine the prevalence and cost of the hipolipidaemic active ingredients based on prescribing patterns for the various age- and sex categories within a section of the private health care sector of South Africa.
- To determine the top ten hipolipidaemic trade name products for the various age- and sex categories as well as the type of prescriber within a section of the private health care sector of South Africa.
- To determine the potential cost-savings possible with generic and therapeutic substitution within a section of the private health care sector of South Africa.

## 1.5 RESEARCH METHODOLOGY

This research consisted of the literature review phase and the empirical investigation phase.

### 1.5.1 Phase 1: Literature review

According to Neuman (2003:96) a literature study (the use of relevant books, journals and articles) is conducted to express familiarity with a certain topic and to integrate what is already known in a particular field. The books and articles that were consulted for this study enclosed several fields of research, *i.e*. pharmacology (therapeutics and diseases), pharmacy practice (disease management, managed health care, drug utilisation review, pharmacoepidemiology evidence-based medicine) and economics (pharmacoeconomics).

Databases that were consulted during the literature search, included SABINET (SACat), PubMed, EBSCO Host, A-Z list of journals (NWU library), and Science Direct. Electronic search engines that were used included Yahoo (www.yahoo.com) and Google (www.google.com). Books that were used included the Merck manual, Goodman & Gilman's pharmacology, Monthly Index of Medical Specialities (MIMS), South African Medicines Formulary (SAMF), Pharmacotherapy handbook, Current Medical Diagnosis and Treatment, Textbook of Therapeutics, Clinical Pharmacy and Therapeutics, The Managed Health Care Dictionary, Managed Care - What it is and how it works, Introduction to applied Pharmacoeconomics, Case Management - A practical guide to success in managed care, Outcomes Management - Applications to clinical practice, and Fundamentals of Case Management - Guidelines for practicing Case Managers, Risk Management, Managed Care Beware, and Essentials of Managed Health Care.

The literature review is reflected in one of the chapters of this study (refer to paragraph 1.8).

### 1.5.2 Phase 2: Empirical investigation

The second phase of the research method (the empirical investigation) consisted of various elements, namely the research design, selection of the study population, data analysis, and ethical considerations (the empirical investigation is discussed in detail in chapter 3).

- Research design: a retrospective drug utilisation review was conducted on the data obtained from the database.

- Selection of the study population: The setting for the study was the private health care section of South Africa. The study population consisted of all patients on the database who had received a hipolipidaemic drug [based on MIMS classification (Snyman, 2007:12a)]. The study population was selected from data for a two-year period (starting 1 January 2005 and ending on 31 December 2006).

- Data analysis: The data were analysed by using the Statistical Analysis System® SAS 9.1® (SAS institute Inc., 2006-2007). Microsoft Word® 2000 and Microsoft Excel® 2000 were used in accordance with the SAS system for analysis and processing.

## 1.6 TERMS AND DEFINITIONS

The following terms (employed in this study) need to be explained:

- **Active ingredient**

An active ingredient is any component of a medicine item intended to provide a pharmacological activity or any other direct effect in the diagnosis, treatment, alleviation or prevention of disease, or to affect the structure or any function of the body of humans or other animals. Active ingredients include those components of the medicine item that may undergo chemical change during the manufacturing of the medicine item and that may be present in the medicine item in a modified form, intended to give the specified activity or effect (FDA, 2007).

- **Medicine item**

The term “medicine item” was used as a synonym for the term “medicine” in the study. Medicine is a substance, or mixture of substances which is accepted as being ethical by medical science and is registered with the South African Medicines Control Council, and it is to be administered or applied for the prevention, treatment or healing of an illness (Medihelp, 2007).

- **Original medicine items**

Original medicine items are the original patented pharmaceutical products (Ball *et al*., 2005). Original medicine items are generally the products that were first authorised worldwide for marketing on the basis of the documentation of their efficacy, safety and quality, according to requirements at the time of authorisation. The original product always has a brand name; this may, however, vary between countries (WHO, 2003b:116). In this study original medicine items may be classified into the following categories: Original patented drugs placed on the market for

further research ("M"), non-substitutable medicine items for which there are no generic items available ("N") and original medicine items, with available generics ("O) (refer to paragraph 4.4.3).

- **Generic medicine items**

Generic medicine items are pharmaceutical products intended to be interchangeable with the original medicine item, manufactured without a licence from the original manufacturer and marketed only after the expiry of the original patent or other exclusivity rights (WHO, 2003b:116). Generic medicine items are required to meet the same pharmacological requirements for the preparation as the original medicine item (Rognehaugh, 1998:91). In this study generic medicine items are classified in the "Y" (Yes, generic equivalent was dispensed) category (refer to paragraph 4.4.3).

- **Patient**

A patient is someone receiving medical attention, treatment, care or medication on prescription by a legal prescriber or another medical professional. The person is usually ill or has been injured and requires medical attention (OED, 2009).

- **Number of prescriptions**

A prescription is a written instruction from a legal prescriber. A "number of prescriptions", therefore, would refer to the number of written instructions from legal prescribers that were claimed during the specific study period. A prescription can contain one or more than one medicine item in South Africa.

- **Total database**

The total database consists of all the prescriptions on the database (containing all medicine items) that were issued to all patients on the database and that were claimed during the specific study periods.

- **Hipolipidaemic medicine**

Hipolipidaemic medicine includes all medicine that is used in the management of hipolipidaemic disorders, classified as pharmacological group 7.7 based on the MIMS® classification system. Hipolipidaemic agents / medicine can be divided into four categories/sub-pharmacological

groups namely: fibrates, HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors and "others" (Snyman, 2007:12a).

## 1.7 ABBREVIATIONS

The following abbreviations are applicable to the study:

LDL = Low-density lipoprotein
HDL = High-density lipoprotein
VLDL = Very low-density lipoprotein
IDL = Intermediate-density lipoprotein
TC = Total cholesterol
TG = Triglycerides
DM = Diabetes Mellitus
CVD = Cardiovascular disease
CHD = Coronary heart disease
WHO = World Health Organization
CPI = Cost Prevalence Index
NCEP = National Cholesterol Education Program
ATP III = Adult Treatment Panel III

## 1.8 DIVISION OF CHAPTERS

This study was divided into five chapters. Chapter two (literature review) focuses on dyslipidaemia, types of dyslipidaemia and deals with the analysis of usage patterns and cost of hipolipidaemic drugs as well as the contributing factor dyslipidaemia has to other diseases. An overview of the definitions, signs and symptoms, prevalence, pathophysiology and complications of the disease are discussed. The second part of the chapter focuses on managed health care, pharmacoeconomics, drug utilisation review, pharmacoepidemiology and evidence-based medicine with reference to the usage patterns and cost of hipolipidaemic drugs.

Chapter three describes the research method followed in the empirical investigation. In this chapter, a detailed description of the variables and measures used, the analysis and processing of the data, ethical aspects regarding this study and the limitations concerning this study are given.

Chapter four provides an analysis and interpretation of the research results of the empirical investigation and chapter five provides the conclusions and recommendations arrived at.

## 1.9 CHAPTER SUMMARY

In this chapter the introduction, problem statement, background and rationale for the study, research objectives, research methodology, terms and definitions, abbreviations and the division of chapters have been discussed. The following chapter will entail the literature review for dyslipidaemia, various managed health care concepts, drug utilisation review, pharmacoeconomics, pharmacoepidemiology and evidence based medicine.

# *CHAPTER 2*

# *DYSLIPIDAEMIA AND THE USE OF HIPOLIPIDAEMICS IN A MANAGED HEALTH CARE ENVIRONMENT*

This chapter provides an overview of definitions, risk factors, the pathophysiology, diagnosis and the management of dyslipidaemia. The chapter furthermore reflects on the concepts of managed care, pharmacoeconomics and drug utilisation review, evidence-based medicine and pharmacoepidemiology as well as the application thereof in the treatment of dyslipidaemia.

## 2.1 DYSLIPIDAEMIA

### 2.1.1 Introduction

Coronary heart disease (CHD) is one of the primary causes of morbidity and mortality in Western countries (Rodonki, 1999:388). About 7.2 million people die from CHD in worldwide populations every year, more than from cancer, human immune virus (HIV) and infectious causes. In the United States of America (USA) alone, 640 000 deaths can be attributed to CHD (Farnier & Davignon, 1998:4J). Mortality from CVD was the third highest cause of mortality in the world in 1999 (WHO, 1999). Three of the treatable and preventable risk factors for CHD are hypertension, dyslipidaemia, and cigarette smoking. Between 1997 and 2004, 195 people died per day because of some form of heart and blood vessel disease in South Africa (Steyn, 2007:2).

Until the mid-1990s, the importance of dyslipidaemia as a risk factor for CHD was controversial, as was the use of lipid lowering treatment (Raynor & Scarborough, 2005:154). In recent years, more emphasis has been placed on the management of cholesterol, primarily through lifestyle modifications and drug therapy (Farnier & Davignon, 1998:4J).

While the number of individuals with dyslipidaemia is difficult to estimate, a national survey of approximately 10 000 individuals aged 16 years or over in the UK found that more than 67 per cent had total cholesterol ≥ 5 mmol/ℓ (193.5 mg/dℓ) and 27 per cent had a total cholesterol:HDL-cholesterol ratio of ≥ 5.0 (Primatesta & Poulter, 2000:1322). An estimated 98.6 million adults in the USA have total blood cholesterol values of 200 mg/dℓ and higher, and of these about 34.4 million American adults have levels of 240 or above (AHA, 2009).

Risks for the development of CHD from high total cholesterol levels are high; and especially so for high risk patients; *i.e.*, people who smoke; males over the age of 45, females over the age of 55, diabetics, people with high blood pressure and people with a personal or family history of heart disease (Anon., 2008).

In the subsequent paragraph the definition of dyslipidaemia will be given as well as the main type of lipids in dyslipidaemia.

### 2.1.2 Definition of dyslipidaemia

According to Berger and Marais (2000:164) and Thornton and Holt (2000:407), dyslipidaemia is the presence of an elevation of plasma cholesterol and / or triglyceride (TGs) or a low high-density lipoprotein (HDL) level that contributes to the development of atherosclerosis and related disorders. The causes may be primary (genetic) or secondary; and the diagnosis thereof is by measuring plasma levels of total cholesterol, TGs and individual lipoproteins (Mcelroy & Chorvat, 2007; Porter & Kaplan, 2008). The main types of lipids are presented and discussed in table 2.1.

**Table 2.1: Main types of lipids (adapted from Anaizi, 2002; Walker, 2006:355)**

| Main types of lipids | |
|---|---|
| **Cholesterol** | • A steroid alcohol synthesised in the liver with variable amounts obtained from diet.<br>• Average total body cholesterol = 150g of which 90% is part of cell membrane structures.<br>• Necessary for the synthesis of steroid hormones. |
| **Triglycerides (TGs)** | • Sources: Saturated fat e.g. red meat, dairy products, coconut oil and palm oil. Unsaturated fat: omega-3: (fish oil, soybean, canola oil), omega-6: vegetable oils (corn, sunflower) and monounsaturated fat: olive oil. Trans-fatty acids: hydrogenated vegetable oils (margarine). |
| **Very low–density lipoprotein (VLDL)** (density <1 mmol/ℓ) | • Produced in the liver.<br>• Rich in triglycerides (>65%) and cholesterol (20%).<br>• Serves to transport endogenous lipids (particularly triglycerides) to extra-hepatic sites.<br>• Hydrolysed by lipoprotein lipase (LPL) to intermediate density lipoprotein (IDL) and then to low density lipoprotein (LDL). |
| **Low density lipoprotein (LDL)** (density ~ 1 mmol/ℓ) | • Product of VLDL catabolism (catalysed by LPL).<br>• Contains >60% cholesterol and accounts for >60% the total plasma cholesterol.<br>• Taken up by hepatic and extra-hepatic tissue through receptor-mediated endocytosis triggered by apolipoprotein B100 (apo B100) - LDL receptor interaction.<br>• Has a high atherogenic potential.<br>• Oxidised LDL is a major source of cholesterol for macrophages in atheromatous plaques. |

**Table 2.1: Main lipids (adapted from Anaizi, 2002; Walker, 2006:355) (continued)**

| | |
|---|---|
| **Intermediate density lipoprotein (IDL)** (density ~ 1.05 mmol/ℓ) | • Derived from both VLDL and HDL.<br>• The liver either takes up IDL particles, a process mediated by apoE or may be reduced to LDL (by losing apoE and more triglycerides). |
| **High density lipoprotein (HDL)** (density ~ 1.15 mmol/ℓ) | • Produced by extra-hepatic tissue and serves as a vehicle for the transfer of cholesterol from the peripheral tissues to the liver.<br>• HDL takes up the cholesterol liberated in the course of normal cell membrane turnover.<br>• Cholesterol esters are transferred form HDL to IDL, which are then converted to LDL or taken up by the liver directly. |

According to Wells *et al.* (2003:71) the elevated total, low-density lipoprotein cholesterol (LDL) and reduced high-density cholesterol are associated with the development of coronary heart disease. LDL accounts for 60 to 70 per cent of total serum cholesterol, and when transformed from plasma to sub-endothelial tissue, becomes oxidised (Thornton & Holt, 2000:409). This oxidation causes LDL to become cytotoxic and therefore contributes to artherosclerosis development. HDL cholesterol accounts for 20 to 30 per cent of total serum cholesterol and these levels are inversely associated with risk of coronary heart disease (CHD) (Thornton & Holt, 2000:409). VLDL is mainly composed of triglycerides and make out 10 to 15 per cent of total serum cholesterol (Thornton & Holt, 2000:409).

It can be concluded from table 2.1 that all the main lipids form part of dyslipidaemia. Dyslipidaemia, however, is classified as primary or secondary dyslipidaemia, each with its own sub-classifications. The classification of dyslipidaemia with the sub-classifications will be discussed in the subsequent paragraphs.

### 2.1.3 Classification of dyslipidaemia

Dyslipidaemia is a heterogeneous disorder with multiple aetiologies (Kromhout, 1999:798), with modern diet and lifestyle (tobacco use, obesity, high fat intake, and sedentary activity) probably being the largest contributors to the current epidemic of atherosclerosis. There are primary causes of dyslipidaemia that occur rarely and demand the attention of a consulting lipidologist; e.g., table 2.2 (Gau & Wright, 2006:449). There also are many secondary causes (table 2.3) of dyslipidaemia that may exist in clinical practice that should be addressed concurrently with initiation of pharmacotherapy.

The great majority of cases encountered during the daily practice of medicine will be secondary aetiologies of dyslipidaemia (Gau & Wright, 2006:449). A short discussion of the primary- and secondary aetiologies in the development of dislipidaemia follows subsequently.

**Table 2.2: Primary causes of dyslipidaemia (Gau & Wright, 2006:451)**

| Elevated LDL-cholesterol | Low HDL-cholesterol |
|---|---|
| • LDL receptor deficiency | • Apo A-1 deficiency |
| • Familial homozygous hyperlipidaemia | • Apo A-1 mutations |
| | • Lecithin-cholesterol acyltransferase (LCAT) deficiency (partial or complete) |
| | • Tangiers's disease |
| | • Familial hypoalpaliproteinemia |

**Table 2.3: Secondary causes of dyslipidaemia (Gau & Wright, 2006:451)**

| Elevated LDL-cholesterol | Low HDL-cholesterol |
|---|---|
| • Obesity | • Metabolic Syndrome |
| • High fat intake | • Diabetes Mellitus |
| • Hyperthyroidism | • Obesity or Weight gain |
| • Diabetes Mellitus | • Physical inactivity |
| • Nephrotic Syndrome | • Tobacco use |
| • Anabolic Steroids | • Beta Blocker therapy |
| • Progestins | • Low fat or High Polysaturated fat diets |
| • Obstructive Hepatobiliary Disease | • Anabolic Steroids |
| | • Progestins |
| | • Thiazide diuretics |

#### 2.1.3.1 Primary dyslipidaemia

Up to 60 per cent of the variability in serum fasting lipids may be genetically determined, though; expression is often influenced by interaction with environmental factors (Walker, 2006:355). Primary dyslipidaemia is a result of a confluence of factors affecting lipoprotein metabolism (Zanni & Wick, 2006) (refer to table 2.1 for the different patterns of lipoprotein distribution). Common familial disorders are classified in table 2.2 (adapted from Anaizi, 2002; Walker, 2006:355).

**Table 2.4: The different classes of primary hyperlipidaemia (adapted from Anaizi, 2002; Walker, 2006:355)**

| Class | Cause | Abnormalities* |
|---|---|---|
| **I: Familial Hyperchylomicronemia** | LPL deficiency | ⇧Chylomicrons; ⇧TGs; Pancreatitis, Diabetes Mellitus (DM) |
| **IIa: Familial Hypercholesterolemia** | LDL receptor deficiency | ⇧LDL; ⇧TC |
| **IIb: Familial Combined Hyperlipidaemia** | High Apo B synthesis + defective Apo E | ⇧VLDL, ⇧LDL, ⇧TC, ⇧TG. |
| **III: Familial dysbetalipoproteinemia** | Abnormal IDL metabolism | ⇧IDL, ⇧TC, ⇧TGs |
| **IV: Familial Hypertriglyceridaemia** | Abnormal VLDL metabolism | ⇧⇧ TGs + ⇧TC |
| **V: Familial mixed Hypertriglyceridaemia** | Abnormal VLDL & chylomicron metabolism | ⇧⇧TGs + ⇧ TC. ⇧VLDL, ⇧chylomicron; ⇔ LDL. |

* TGs = Triglycerides; TC = Total cholesterol; LDL = low-density lipoprotein; VLDL = very low density lipoprotein and IDL = Intermediate density lipoprotein; LPL = Lipoprotein lipase

The different types of primary dyslipidemias will be discussed in the following paragraphs.

#### 2.1.3.1.1 Familial hyperchylomicronemia (F.CH)

Familial hyperchylomicronemia (type I hyperlipidaemia) is a rare (1/106 births) autosomal recessive disorder caused by a complete deficiency of lipoprotein lipase or its cofactor apolipoprotein CII (apo CII), and is characterised by elevated plasma chylomicrons and triglycerides, pancreatitis, cutaneous xanthomas, and hepatosplenomegaly (Anon., 2007b; Tzotzas *et al*., 2002:185). According To Berger and Marais (2000:169), familial hyperchylomicronemia often presents itself in childhood and has various patterns of inheritance.

#### 2.1.3.1.2 Familial hypercholesterolaemia (FH)

Familial hypercholesterolemia (homozygous and heterozygous) is autosomal dominant disorders that cause severe elevations in total cholesterol and low-density lipoprotein cholesterol (Citkowitz, 2007). In this type of dyslipidaemia, the genetic abnormality is in the low-density lipoprotein receptor, which results in increased plasma low-density lipoprotein concentration (Berger & Marais, 2000:168).

Moderate hypercholesterolemia is a common finding in industrialised countries, with heterozygous FH occurring in approximately 1 per 500 persons worldwide, compared to homozygous FH, which occurs in 1 case per 1 million persons (Citkowitz, 2007). The latter type

of dyslipidaemia in adults is usually characterised by a plasma cholesterol level of more than 7.5 mmol/ℓ (LDL-cholesterol > 5) (often > 9 mmol/ℓ) before any dietary modification (Berger & Marais, 2000:168).

In South Africa, FH is prevalent mostly in European/white population groups (about 1 per cent of the population) as well as in other groups including Asians, Jews and Lebanese. Familial hypercholesterolaemia is also known to occur in the coloured and in Black populations (Berger & Marais, 2000:168).

#### 2.1.3.1.3 Familial combined hyperlipidaemia (FCH)

Familial combined hyperlipidaemia is a new inherited lipid disorder, characterised by multiple lipoprotein phenotypes - strongly associated with premature cardiovascular disease (de Graaf *et al*., 2002:46). Accordingly, in the present, FCH is the most common inherited hyperlipidaemia in humans, affecting one to three per cent of the population and up to 20 per cent of patients with premature myocardial infarction. The genetic basis of this disorder has, however, not been defined yet (Berger & Marais, 2000:170).

#### 2.1.3.1.4 Familial dysbetalipoproteinaemia

Dysbetalipoproteinemia is a genetic disorder, giving rise to severe disturbances of lipid homeostasis and premature atherosclerosis (Tremblay *et al*., 2006:203). This lipid disorder is characterised by the accumulation of abnormal β-migrating cholesterol enriched remnants of both intestinal and hepatic origin (β-VLDL) in the plasma, resulting in the elevation of plasma total cholesterol, triglycerides and apo-E. Apo E is the ligand that mediates binding of remnants to hepatic receptors involved in the clearance of these lipoproteins from the circulation (Maley & Rall, 1999:1953).

#### 2.1.3.1.5 Familial hypertriglyceridaemia

Hypertriglyceridaemia is a commonly encountered but often overlooked component of dyslipidaemia. Hypertriglyceridaemia can occur as a primary disorder due to various genetic and/or ensymatic defects and can also occur as a secondary disorder that is associated with numerous medical conditions (Haymore *et al*., 2005:17). It often presents in childhood only and has variable patterns of inheritance (Berger & Marais, 2000:169). It further presents with tuberous xanthomata, which is associated with high intermediate density lipoprotein. Depending on the severity of the lipemia, eruptive xanthoma, lipemia retinalis, epigastric pain and overt pancreatitis are variably present (Malloy & Kane, 1998:568).

### 2.1.3.2 Secondary dyslipidaemia

Although most cases of dyslipidaemia have a primary genetic pathogenesis, a significant proportion of patients have a secondary cause that can be modified (Maritz, 2003:365).

Secondary dyslipidaemia stems from various pathologies, such as endocrine disorders, untreated hyperglycaemia, hypothyroidism, nephritic syndrome, chronic renal failure, or gastrointestinal disorders (Zanni & Wich, 2006); and is characterised by normal or only minor gene defects (Berger & Marais, 2000:170). According to Berger and Marais (2000:170) the environment, underlying incidental disease, drugs and several factors may also create secondary dyslipidaemia. Some of the causes of secondary dyslipidaemia and risk factors associated therewith are summarised in table 2.5.

**Table 2.5: Causes of secondary dyslipidaemia and risk factors associated therewith (adapted from Maritz, 2003:367)**

| Secondary cause | High cholesterol (high LDL- C)* | TG excess mild to moderate (high VLDL)* | Low HDL –C* | Severe TG excess: chylomicronaemia syndrome* |
|---|---|---|---|---|
| **Diet** | • Saturated fats<br>• Caloric excess<br>• Anorexia | • Weight gain<br>• Alcohol | • Low-fat diet | • Alcohol and fat with genetic lipid disorder |
| **Drugs** | • Diuretics<br>• Glucocorticoids<br>• Cyclosporine | • Retinoids<br>• Beta-blockers<br>• Oestrogen<br>• Glucocorticoids | • Anabolic steroids<br>• Progestin's<br>• Beta-blockers<br>• Cigarettes | • Glucocorticoids<br>• Oestrogen<br>• Genetic lipid disorder |
| **Disorders of metabolism** | • Diabetes poorly controlled<br>• Hypothyroidism<br>• Pregnancy | • Type 2 diabetes<br>• Obesity<br>• Pregnancy | • Type 2 diabetes<br>• Obesity | • Diabetes poorly controlled<br>• Hypothyroidism with genetic lipid disorder |
| **Diseases** | • Nephritic syndrome<br>• Biliary obstruction | • Chronic renal failure with / without dialysis<br>• Nephritic syndrome | • Chronic renal failure with / without dialysis | • SLE (rare) |

* LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; SLE = systemic lupus erythematosus.

### 2.1.4 Incidence and the prevalence of dyslipidaemia

Data from the US National Health and Nutrition Examination Survey (NHANES) that was conducted in 1999–2000 found that 25 per cent of adults had total cholesterol greater than 5.2 mmol/ℓ or were taking a lipid lowering medication (Ford *et al.,* 2003:2185).

Data that were collected by Maritz (2006:101) show that at least 1.5 million African people aged 30 years and older are hypercholesterolaemic. This study indicates that more than 5.5 million South Africans aged 30 years and older carry a risk for chronic disease by virtue of their TC level (Maritz, 2006:101). Familial Hypercholesterolaemia (FH) is very common in the European/white population, and its prevalence is estimated to be 1:72 compared to 1:500 worldwide (Maritz, 2006:102). Older women were found to have hypercholesterolaemia more frequently than older men, in the middle age groups men and women tended to have equal rates of cholesterol and in the younger age groups, female frequency was much lower than that of the men (Maritz, 2006:101).

### 2.1.5 Pathophysiology of dyslipidaemia

Cholesterol is a lipid that is one of the primary components of cell membranes and a precursor in steroid hormone and bile acid metabolism (Thornton & Holt, 2000:409). Cholesterol, triglycerides and phospholipids are transported as lipids and apolipoproteins/lipoproteins (Wells *et al*., 2003:71). Lipoproteins divide into five categories: LDL, HDL, VLDL, chylomicrons and apolipoproteins (Thornton & Holt, 2000:409) (refer to table 2.1).

There are three main pathways responsible for the generation and transport of lipids within the body. These pathways include the exogenous pathway, the endogenous pathway, and the pathway of reverse cholesterol transport.

- **Exogenous (dietary) lipid pathway:** Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons in the epithelial cells of the intestines. Chylomicrons circulate through the intestinal lymphatic system. In the blood, circulating chylomicrons interact at the capillaries of adipose tissue and muscle cells releasing TG to the adipose tissue to be stored and made available for the body's energy needs. The enzyme lipoprotein lipase (LPL) hydrolyses the TG and free fatty acids are released. Some of the components of the chylomicrons are "repackaged" into other lipoproteins (Shepherd, 2001:E2).

- **Endogenous pathway**: The endogenous pathway involves the liver synthesising lipoproteins. TG and cholesterol esters are generated by the liver and packaged into VLDL particles and then released into the circulation. VLDL is then processed by LPL in tissues to release fatty acids and glycerol. Once processed by LPL, the VLDL becomes a VLDL remnant. The majority of the VLDL remnants are taken up by the liver *via* the LDL receptor, and the remaining remnant particles become IDL, a smaller, denser lipoprotein than VLDL. The fat of some of the IDL particles requires them to be reabsorbed by the liver (again by the LDL receptor); however, other IDL particles are hydrolysed by hepatic-triglyceride lipase to form LDL, a smaller, denser particle than IDL. LDL is the main carrier of circulating cholesterol within the body (Shepherd, 2001:E3).

- **Reverse cholesterol transport:** Reverse cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver. HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of cholesterol esters between lipoproteins.

These aforementioned discussions are illustrated in figure 2.1 (Shepherd, 2001:E3):

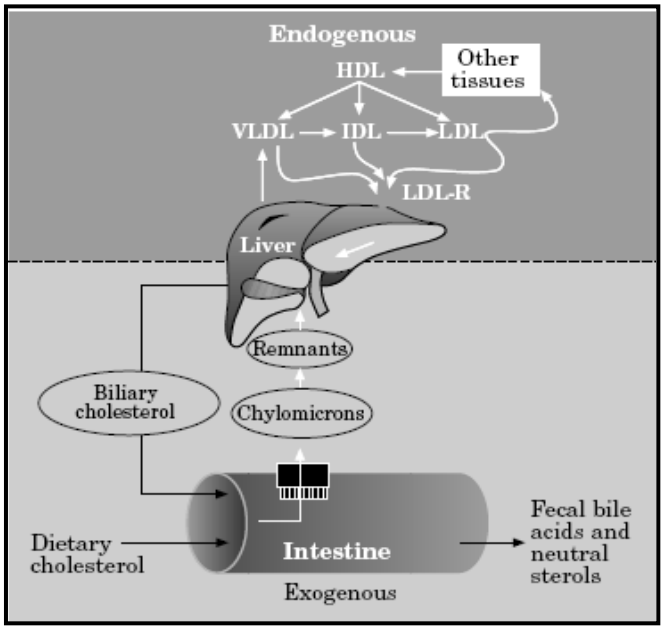


**Figure 2.1: The endogenous and exogenous lipid pathways (Shepherd, 2001:E3)**

### 2.1.6 Significance of dyslipidaemia

According to Wells *et al*. (2003:71) the elevated total, low-density lipoprotein cholesterol and reduced high-density cholesterol are associated with the development of coronary heart disease. Dyslipidaemia also carries a high risk for other diseases, as well as a risk in terms of

health care utilisation and scarce resource consumption/utilisation. These risk factors are discussed in the subsequent paragraphs.

### 2.1.6.1 Risk for the development of cardiovascular- and other diseases

HDL-cholesterol makes up 20 to 30 per cent of total serum cholesterol and plays several critical roles in maintaining a healthy vasculature and preventing cardiovascular events (Toth, 2008:488). Approximately 54 to 77 per cent of type 2 diabetics have a borderline-high to high total cholesterol (Harris, 1991:366). The rate of atherogenesis is proportional to the severity of ambient risk factors including serum cholesterol levels (Vega, 2001:1109).

There are some other factors also involved other than high LDL levels that add to the risk of developing secondary diseases from dyslipidaemia. These factors are shown in table 2.6 (Anaizi, 2002; Berger & Marais, 2000:168; Thornton & Holt, 2000:413).

**Table 2.6: Contributing risk factors**

| Positive lifestyle and behavioural factors | Positive other modifiable risk factors | Positive non-modifiable risk factors |
|---|---|---|
| • Cigarette smoking<br>• Lack in physical exercise<br>• Artherogenic diet<br>• Alcohol and Anabolic steroids (Drug abuse) | • Hypertension<br>• Obesity<br>• Diabetes Mellitus<br>• Low HDL-cholesterol<br>• Hypertriglyceridaemia | • ≥ 45 years old male<br>• ≥ 55 years old female<br>• Female without oestrogen therapy that is postmenopausal<br>• Family history of CHD<br>• Personal history of CHD |
| **Negative Risk Factors** | | |
| HDL level ≥ 1.6 mmol/ℓ | | |
| Subtract Positive Risk Factor if there is a Negative Risk Factor present | | |

Patients are placed (categorised) in one of three risk categories (table 2.6), whereby the most appropriate treatment/intervention for the patient's needs and the specific goals of that intervention are determined (Thornton & Holt, 2000:411). Patients with two or more risk factors are further stratified by evaluating their 10-year risk of developing CHD using the model Framingham 10-year risk for CHD (refer to appendix A.1).

According to Fodor *et al*. (2000:1443) the Framingham scoring system is very effective but does not apply to patients with extreme or unusual risk factors like severe hypercholesterolaemia, and also in patients with very low HDL levels. Patients with very high risk of cardiovascular disease's therapeutic management show good improvement through using the Framingham scoring system (Irons *et al*., 2002:1617).

According to Baigent *et al.* (2005:1267) a lowering in LDL-cholesterol is associated with a 12 per cent reduction in all-cause mortality; it has a 19 per cent reduction in cardiovascular heart disease mortality and a 21 per cent reduction in major vascular events.

### 2.1.6.2 Influence on health care and scarce resource utilisation

Dyslipidaemia is a significant contributor to cardiovascular morbidity and mortality in the industrialised world. This impact ensures that dyslipidaemia carries a high cost in terms of human life and health care expenditures.

In developed countries such as Australia and America the treatment or prevention of cardiovascular diseases embodies the highest proportion of the total health expenditure by disease group, consisting of hospitalisation and medication costs (AHA, 2004). Hospitalisation contributed 45 per cent (US$109 billion ~ R907 billion)[1] of the estimated (US$241.9 billion ~ R2 trillion) spent on therapy in the United States and 46 per cent (A$2.5 billion ~ R10.8 million)[2] of the estimated A$5.5 billion (~R23 billion) spent in Australia in 2000 to 2001.

According to the World Health Report of 1999, ischaemic heart disease was the leading single cause of death in the world, the leading single cause of death in high income countries, and second only to lower respiratory tract infections in low and middle income countries (WHO, 1999). In 1998 it was also the leading cause of death, with nearly 7.4 million estimated deaths a year in member states of the World Health Organization and causing the eighth highest burden of disease in the low and middle income countries (30.7 million disability adjusted life years) (WHO, 1999). It is estimated that that ischaemic heart disease will be the largest single cause of disease burden globally by the year 2020 (WHO, 1999).

There has been a rapid and significant growth in the measurement of quality of life as an indicator of health outcome in patients with coronary heart disease (Treasure, 1999:331). In the clinical course of CHD, there are many aspects that may affect a patients' quality of life. These include symptoms of angina and heart failure, limited exercise capacity of the aforementioned symptoms, the physical debility caused, and psychological stress associated with the chronic stress. Modern treatments nowadays focus not only on improving life expectancy, symptoms and functional status, but also quality of life. Thus, an improvement in health-related quality of life (HRQL) is considered to be important as a primary outcome and in the determination of therapeutic benefit (Treasure, 1999:332).

[1] US Dollar = R8.33 (2000 - 2001) (OANDA, 2009).
[2] Australian Dollar = R4.35 (2000 - 2001) (OANDA, 2009).

### 2.1.7 Diagnosis of dyslipidaemia

Wells *et al.* (2003:72) recommend that a fasting lipid profile including total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides should be measured in adults 20 years of age and older at least once every 5 years. A full serum lipoprotein profile and/or a plasma lipoprotein profile should be performed on patients that have hypercholesterolaemia (cholesterol levels greater than 5 mmol/ℓ on screening) and also have physical signs of a lipid disorder (Berger & Marais, 2000:166). Measurement of plasma cholesterol, triglyceride and HDL-cholesterol levels should be conducted after at least 12 hours of fasting, since triglycerides may be elevated in non-fasting patients (Wells *et al.,* 2003:72). Measurement should also be repeated once or more for patients with suspected elevated LDL cholesterol levels (Baron, 2007:1270).

There are appropriate and desirable levels for lipids and triglycerides as presented in table 2.7. Decisions on the type of treatment are based on a patient's LDL-cholesterol level, his or her risk factor status and the presence of known CHD or artherosclerotic disease (Baron, 2007:1274; Thornton & Holt, 2000:411). It is suggested that cholesterol is not a risk factor for CHD in patients over 75 years of age, and it is preferable for clinicians to stop screening for such patients (Baron, 2007:1272).

The National Cholesterol Education Program adult treatment panel (NCEP ATP III) that lays forth treatment options and opinions based on cholesterol and cholesterol-related diseases/sicknesses. The classification of cholesterol and triglyceride levels as based on the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines is depicted in table 2.7.

**Table 2.7: Classification of cholesterol and triglyceride levels based on NCEP-ATP III guidelines (adapted from Thornton & Holt, 2000:412).**

| Type | Desirable | Borderline | High Risk |
|---|---|---|---|
| **Total cholesterol** | < 5.2 mmol/ℓ (200 mg/dℓ) | 5.2 – 6.2 mmol/ℓ (200 – 239 mg/dℓ) | > 6.2 mmol/ℓ (240 mg/dℓ) |
| **LDL** | < 3.4 mmol/ℓ (130 mg/dℓ) | 3.4 – 4.1 mmol/ℓ (130 - 159 mg/dℓ) | > 4.1 mmol/ℓ (160 mg/dℓ) |
| **HDL** | > 1.5 mmol/ℓ (60 mg/dℓ) | – | < 0.9 mmol/ℓ (35 mg/dℓ) |
| **Triglycerides** | < 2.3 mmol/ℓ (200 mg/dℓ) | 2.3 - 4.5 mmol/ℓ (200 - 400 mg/dℓ) | 4.5 - 11.3 mmol/ℓ (400 - 1000 mg/dℓ) |

### 2.1.8 Signs and symptoms of dyslipidaemia

Dyslipidaemia itself causes no symptoms, though it can lead to symptomatic vascular disease (coronary artery disease and peripheral arterial disease) (Baron; 2007:1276; Berger & Marais, 2000:168; Bhatnagar, 1998:213). High TGs (> 1000 mg/dℓ or > 11.3 mmol/ℓ) can cause acute pancreatitis (Baron; 2007:1276; Berger & Marais, 2000:168; Bhatnagar, 1998:213). High levels of LDL can also cause eyelid xanthelasmas; arcus cornea; and tendinous xanthomas found at the achilles, elbow, and knee tendons and over metacarpophalangeal joints (Porter & Kaplan, 2008).

Patients with homozygous familial hypercholesterolaemia may also have planar or cutaneous xanthomas. Patients with severe elevations of triglycerides can have eruptive xanthomas over the trunk, back, elbows, buttocks, knees, hands, and feet (Porter & Kaplan, 2008).

Patients with the rare dysbetalipoproteinaemia may manifest with palmar and tuberous xanthomas (Porter & Kaplan, 2008). Severe hypertriglyceridaemia (> 2000 mg/dℓ or > 22.6 mmol/ℓ) can give retinal arteries and veins a creamy white appearance (a condition called lipemia retinalis) (Porter & Kaplan, 2008). Extremely high lipid levels also give a lactescent appearance to blood plasma (Porter & Kaplan, 2008; Marks *et al.*, 2003:4). The signs associated with disorders of lipoprotein metabolism are summarised according to the area it affects, in table 2.8.

**Table 2.8: Signs associated with disorders in lipoprotein metabolism (Bhatnagar, 1998:207)**

| Eyes | Skin | Systemic |
|---|---|---|
| • Corneal arcus<br>• Corneal opacities | • Xanthelasmata<br>• Tendon xanthomata<br>• Eruptive xanthomata<br>• Tubero-eruptive xanthomata<br>• Planar xanthomata<br>• Palmar xanthomata | • Aortic stenosis<br>• Ataxia<br>• Lipemia retinalis<br>• Peripheral neuropathy<br>• Hepatosplenomegaly |

### 2.1.9 Clinical management of dyslipidaemia

The South African lipid guidelines for the treatment of hyperlipidaemia are based on the revised American NCEP-ATP III guidelines (Raal, 2004:53). The ATP III guidelines recommend a two-step approach to cholesterol management with priority to attaining the goal for LDL cholesterol.

The emphasis thereafter shifts to management of the metabolic syndrome and other lipid risk factors (NIH, 2002).

After an appropriate trial of dietary therapy to reduce LDL cholesterol (~ 3 months), two additional therapeutic decisions may be required. Firstly, if the LDL cholesterol goal has not been achieved, consideration may be given to initiating drug therapy. Secondly, if the metabolic syndrome is present, additional lifestyle changes (i.e., weight reduction and increased physical activity) will be needed. Later, if lifestyle therapies do not alleviate, drug therapy for treatment of the metabolic risk factors may be required (NIH, 2002) (refer to appendix A.2 for the treatment algorithm of hyperlipidaemia).

Two treatment strategies, *inter alia* non-pharmacological treatment and pharmacological treatment, will now be discussed.

#### 2.1.9.1 Non-pharmacological treatment of dyslipidaemia

According to Berger and Marais (2000:171) one of the two key fundamentals in the management of dyslipidaemia is lifestyle modifications. The patient's lifestyle should be thoroughly assessed, with simple methods of reducing cholesterol levels and risk of CHD as the main focus (Berger & Marais, 2000:171; Raal, 2003:378).

Epidemiological and clinical trial evidence evaluating diet and CAD prevention shows that dietary strategies are effective; together with this the NCEP-ATP III has recommended a multifaceted lifestyle approach to reduce risk for CHD. This approach includes designated therapeutic lifestyle changes (TLC). Its essential features are (NIH, 2002; Raal, 2003:378):

- Reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/day).
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols and increased viscous fibres.
- Weight reduction.
- Increased physical activity.

The following model demonstrates a step by step programme of dietary therapy and therapeutic lifestyle changes (adapted from NIH, 2002).

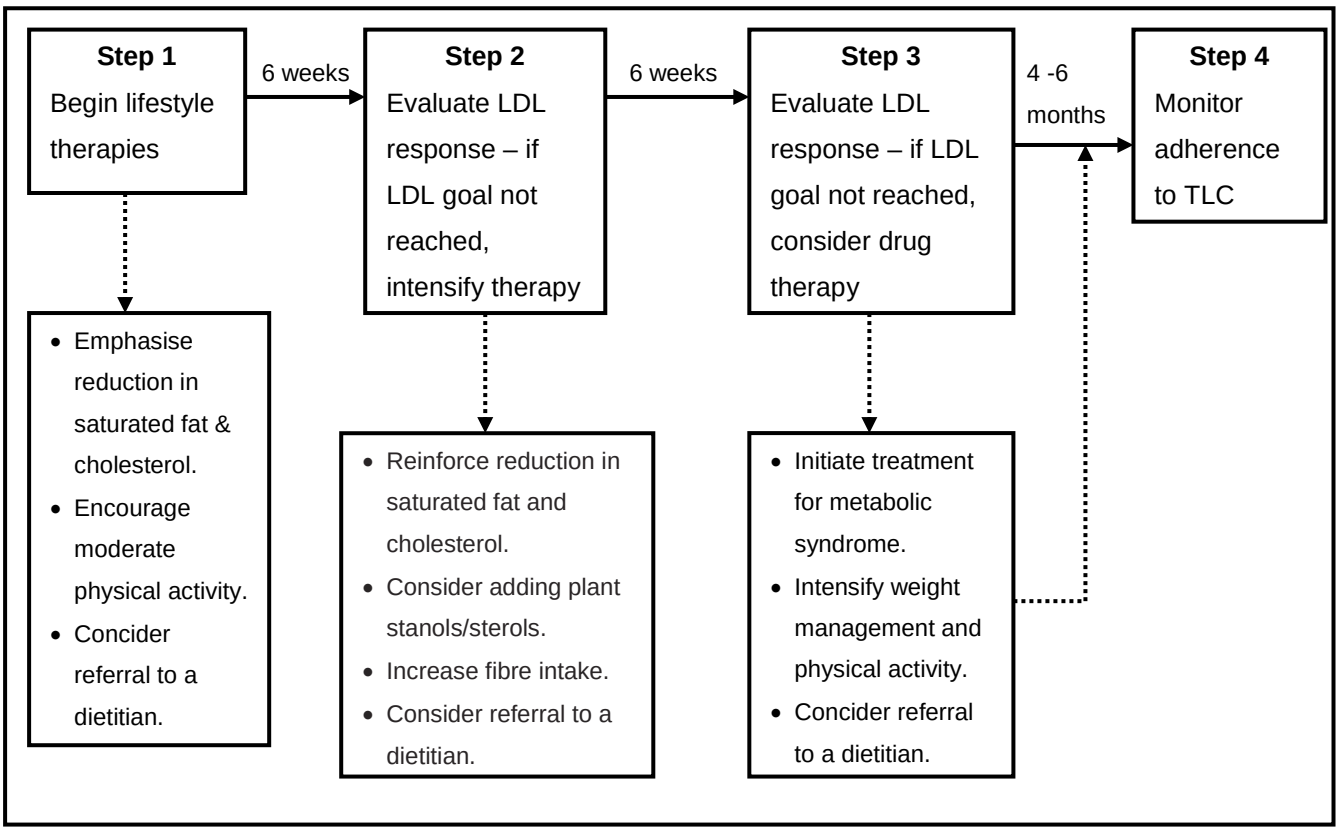


**Figure 2.2: A step by step programme of dietary therapy and TLC (adapted from NIH, 2002)**

In most patients, TLC is implemented before initiating drug therapy. However, in high-risk patients, drug therapy may be initiated simultaneously with TLC. If the patient does not achieve the LDL-cholesterol goal within 12 weeks after starting the TLC programme, then drug therapy / pharmacological treatment may be started.

### 2.1.9.2 Pharmacological treatment of dyslipidaemia

The main indication for lipid-modifying medication is to reduce cardiovascular risk. LDL cholesterol is the primary target of treatment in clinical lipid management. The use of therapeutic lifestyle changes, including LDL-lowering dietary options (plant stanols/sterols and increased viscous fibre) will usually achieve the therapeutic goal. Nonetheless, some patients' short-term and/or long-term risk for CHD will require LDL lowering medicine to reach the prescribed goal for LDL cholesterol. Drug therapy should be considered when non-pharmacological means fail to reduce the lipid levels until within the target range specified in table 2.9 (NIH, 2002; Raal, 2003:380).

**Table 2.9: Optimal fasted lipid profiles (NIH, 2002; Raal, 2003:380)**

| Type of lipoprotein | Lipoprotein level |
|---|---|
| • Total cholesterol | • </= 5 mmol/ℓ |
| • Triglycerides | • </= 1.5 mmol/ℓ |
| • HDL cholesterol | • >/= 1.2 mmol/ℓ |
| • LDL cholesterol | • >/= 3 mmol/ℓ |

There are four main classes of lipid-lowering drugs (Snyman, 2007:12a):

- Fibrates.
- HMG – CoA reductase inhibitors (Statins).
- Cholesterol absorption inhibitors (Ezetimibe).
- Others (Acipimox, cholestyramine).

In the subsequent paragraphs, the main classes of lipid-lowering drugs will be discussed.

#### 2.1.9.2.1 Fibric acid derivates / Fibrates

Newer fibrates on the market such as bezafibrate, fenofibrate and gemfibrozil are suitable for the treatment of hypercholesterolaemia especially with low HDL levels and/or increased triglyceride levels (Gibbon *et al*., 2008:169). Fibrates lower triglycerides by increasing lipoprotein lipase activity, which is responsible for the hydrolysis of triglycerides from VLDL and IDL (Thornton & Holt, 2000:420). Fibrates effectively reduce LDL levels by 10 to 15 per cent; triglycerides by up to 40 per cent, and increase HDL levels effectively by 15 to 20 per cent (Gibbon *et al*., 2008:169; Thornton & Holt, 2000:420).

Table 2.11 gives the complete layout of fibrates, including the available agents, side effects, their effects on lipids / lipoproteins, contra-indications and clinical trial results.

#### 2.1.9.2.2 HMG-CoA reductase inhibitors (statins)

When used as monotherapy, 3-hydroxy-3-methylglutaryl coenzyme A (statins) are the most potent agent to lower total cholesterol and also LDL levels (Wells *et al*., 2003:79). Statins are therefore regarded as the drugs of choice for the management of the most dyslipidaemias (primary and secondary), and they also are the most cost-effective agents (Gibbon *et al*., 2008:164; Walker, 2006:365).

Statins competitively inhibits the enzyme HMG-CoA reductase, which is the responsible enzyme in the conversion from HMG-CoA to mevalonic acid (Thornton & Holt, 2000:419). Mevalonic acid is a precursor to cholesterol in its synthesis, and when this process is inhibited it lowers the

production of cholesterol which results in an up-regulation of LDL receptors and also further reduction of freely -circulating cholesterol.

Statins were introduced in the United Kingdom in the order of simvastatin, pravastatin, fluvastatin and atorvastatin (Walker, 2006:365). The indications and relative efficacy of statins in terms of reducing total cholesterol (TC) and low-density lipoprotein cholesterol are laid out in table 2.10.

The effectiveness of statins in reducing low-density lipoprotein cholesterol concentration is highly predictable and this makes comparisons of statins easy and reliable (Stein, 2002:51c). Atorvastatin 10 mg to 40 mg/day is associated with significant greater reductions in low-density lipoprotein cholesterol than simvastatin 10mg to 40 mg/day, lovastatin 20 mg to 40 mg/day, fluvastatin 20 mg to 40 mg/day and pravastatin 20 mg to 40 mg/day (Lopez, 2002:1175). It appears that there is a possibility that all these statins would achieve greater reduction in low-density lipoprotein cholesterol levels if doses were doubled. The limiting factor, preventing doubling of doses, is an increase in hepatic toxicity and/or muscle toxicity which is observed with increased doses of these drugs (Stein, 2002:51c).

Table 2.10 gives the complete layout of HMG-CoA reductase inhibitors (statins) including the available agents and their effects on lipids / lipoproteins, contra-indications and clinical trial results.

**Table 2.10: Comparison of statins (adapted from Berger & Marias, 2000:174; Gibbon et al., 2008:165; Walker, 2006:366)**

| Drug | Indication | Daily dose | Mean TC reduction | Mean LDL reduction |
|---|---|---|---|---|
| **Atorvastatin** | • Primary hypercholesterolaemia<br>• Familial hypercholesterolaemia<br>• Mixed hyperlipidaemia | 10 mg<br>20 mg<br>40 mg<br>40 mg BD<br>80 mg BD | 28 %<br>35 %<br>40 %<br>42 %<br>46 % | 38 %<br>46 %<br>51 %<br>54 %<br>61 % |
| **Simvastatin** | • Primary hypercholesterolaemia<br>• Heterozygous & Homozygous familial hypercholesterolaemia<br>• Mixed hyperlipidaemia<br>• CHD prevention in hypercholesterolaemia | 10 mg<br>20 mg<br>40 mg<br>80 mg | 21 %<br>26 %<br>30 %<br>37 % | 28 %<br>35 %<br>41 %<br>48 % |
| **Pravastatin** | • Primary hypercholesterolaemia<br>• CHD prevention in hypercholesterolaemia<br>• Hypercholesterolaemia & CHD | 10 mg<br>20 mg<br>40 mg | 13 %<br>18 %<br>24 % | 19 %<br>24 %<br>34 % |

**Table 2.10: Comparison of statins (adapted from Berger & Marias, 2000:174; Gibbon et al., 2008:165; Walker, 2006:366) (continued)**

| | | | | |
|---|---|---|---|---|
| **Fluvastatin** | • Primary hypercholesterolaemia<br>• Mixed hyperlipidaemia<br>• CHD prevention in hypercholesterolaemia | 20 mg<br>40 mg<br>40 mg BD<br>80 mg D | 13 %<br>19 %<br>25 % | 17 %<br>23 %<br>34 % |
| **Rosuvustatin** | • Primary hypercholesterolaemia<br>• Heterozygous & Homozygous familial hypercholesterolaemia<br>• Mixed Hyperlipidaemia<br>• Hypertriglyceridaemia | 10 mg<br>20mg | 27%<br>33% | 45 %<br>52 % |
| **Lovastatin** | • CHD prevention<br>• Primary hypercholesterolaemia<br>• Familial Hypertriglyceridaemia | 10 mg<br>20 mg<br>40 mg<br>40 mg BD | 24%<br>27% | 21 %<br>27 %<br>31 %<br>42 % |

### 2.1.9.2.3 Cholesterol absorption inhibitors

Ezetimibe is a lipid-lowering drug that blocks the passage across the intestinal wall by inhibiting a newly discovered cholesterol transporter and thus it inhibits intestinal absorption of dietary and biliary cholesterol (Baron, 2007:1276). According to Gibbon *et al.* (2008:170) ezetimibe would lower LDL cholesterol by approximately 15 per cent.

Dietary and biliary cholesterol in the lumen of the small intestine is packaged into micelles that diffuse across a thin mucus layer to the surface of the intestinal epithelial cells (enterocytes) (Turley, 1999:S29). Upon reaching the enterocyte, cholesterol is released from the micelle. The cholesterol then passes through the mucosal membrane of the enterocyte by a mechanism that is thought to be mediated by a transporter within the brush border.

Soon after administration, the majority of ezetimibe and the active metabolite localise in the enterocyte brush border, with the remainder passing through the portal circulation and returning to the intestines *via* the bile (Catapano, 2001:E6). The localisation of ezetimibe in the brush border is thought to inhibit a cholesterol transport protein called Niemann-Pick C1 Like1 (NPC1L1), thus preventing biliary and dietary cholesterol from entering the bloodstream. Consequently, less cholesterol is delivered to the liver, which causes a reduction of hepatic cholesterol stores and increases clearance of cholesterol from the blood (Altman *et al*., 2004:1201; van Heek *et al*., 2000:1748).

Table 2.11 gives the complete layout of cholesterol absorption inhibitors, including the available agents, side effects, their effects on lipids / lipoproteins, contra-indications and clinical trial results.

#### 2.1.9.2.4 Others

The action of bile-acid sequestrants (cholestyramine) is primarily to bind bile acids in the intestinal lumen, with a concurrent interruption of enterohepatic circulation of bile acids, which decreases the bile acid pool size and stimulates hepatic synthesis of bile acids from cholesterol (Gibbon *et al*., 2008:167; Wells *et al*., 2003:78). This depletion of the hepatic pool of cholesterol will result in an increase in cholesterol biosynthesis and also an increase in the number of LDL receptors on the hepatocyte membrane. Therefore a directly stimulated enhanced rate of catabolism from plasma takes place and lowers LDL levels (Wells *et al*., 2003:78).

Bile-acid sequestrants or resins lower total cholesterol and LDL by 15 to 30 per cent; simultaneously increasing HDL by 3 to 5 per cent and also decreases triglycerides by 2 to 3 per cent with prolonged therapy (Thornton & Holt, 2000:422).

Table 2.11 gives the complete layout of these medicines, the available agents, side effects, their effects on lipids / lipoproteins, contra-indications and clinical trial results.

#### 2.1.9.2.5 Niacin

Niacin / Nicotinic acid was the first lipid lowering agent that was associated with a reduction in total mortality (Baron, 2007:1274). Niacin lowers both VLDL and LDL and increases HDL in pharmacological doses (1.5 g – 6 g) (Walker, 2006:369) by reducing the release of VLDL which in turn leads to decreased levels of IDL and LDL. Studies have shown that VLDL and LDL are lowered by mainly two mechanisms which include firstly, the modulation of liver triglycerides synthesis which results in increased intracellular apo B degradation, and secondly, the modulation of triglyceride lipolysis in adipose tissue (Kamanna & Kashyap, 2008:21B). By a mechanism of decreased HDL-apo A-1 catabolism, HDL half-life would be increased as well as lipoprotein (A-1) HDL subfractions, thus augmenting cholesterol efflux and reverse cholesterol transport which will cause an increase in residence time and thus allow HDL size to increase (Kamanna & Kashyap, 2008:23B).

Niacin is widely recommended as the first choice in almost all dyslipidaemias as it is very effective and inexpensive (Gibbon *et al*., 2008:168; Kamanna & Kashyap, 2008:20B). Research in hypercholesterolaemic patients show niacin to have the potential to reduce total cholesterol by up to 20 per cent (Gibbon *et al*., 2008:168; Walker, 2006:365). Niacin also has the effect when used in a full dose (3 g - 4.5 g) to lower LDL by 15 to 25 per cent, triglycerides by up to 15 per cent and increases HDL by 15 to 35 per cent (Gibbon *et al*., 2008:168; Walker, 2006:365).

Table 2.11 gives the complete layout of niacin and its derivates, the available agents, side effects, its effects on lipids / lipoproteins, contra-indications and clinical trial results.

**Table 2.11: Layout of the various drug classes, available agents, indications, its effects and side effects, contraindications and interactions (Anaizi, 2002; Berger & Marais, 2000:164-176; Gibbon *et al*., 2008:163-171; Snyman, 2007:164-170)**

| Drug class | Agents | Indications | Lipid / Lipoprotein effect | Major side-effects | Contraindications | Drug interactions | Clinical trial results |
|---|---|---|---|---|---|---|---|
| • **HMG-CoA reductase inhibitors (Statins)** | • Simvastatin<br>• Atorvastatin<br>• Fluvastatin<br>• Pravastatin<br>• Lovastatin<br>• Rosuvastatin | • Lowering of LDL and total cholesterol in dyslipidaemias<br>• Reduction of risk of cardiovascular disease | • **LDL** ↓ 18% - 55%<br>• **HDL** ↑ 5% - 15%<br>• **TG** ↓ 7% - 30% | • Myopathy<br>• Increased liver enzymes<br>• Gastrointestinal distress<br>• Headache<br>• Insomnia<br>• Skin rash<br>• Angioedema | **Absolute:**<br>• Active or chronic liver disease<br>**Relative:**<br>• Concomitant use of certain drugs | • **Alcohol:** Abuse potentiates hepatotoxicity<br>• **Warfarin:** Enhanced anticoagulant effect<br>• **Cyclosporine:** cyclosporine levels increase<br>• **Cholestyramine:** Statin should be administered 1 hour before or 4 after Colestyramine | • Reduced major coronary events<br>• CHD deaths<br>• Need for coronary procedures<br>• Stroke<br>• Total mortality |
| • **Bile-Acid Sequestrants / Resins** | • Cholestyramine | • Hypercholesterolaemia | • **LDL** ↓ 15% - 30%<br>• **HDL** ↑ 3% - 5%<br>• **TG** – No change | • Gastrointestinal distress<br>• Constipation<br>• Decreased absorption of other drugs | **Absolute:**<br>• Dysbetalipo-proteinemia<br>• TG > 400mg/dℓ<br>**Relative:**<br>• TG > 200 mg/dℓ | • **Fat-soluble vitamins:** Cholestyramine may interfere with vitamin absorption.<br>• **Absorption is reduced with:**<br>Warfarin<br>Digoxin<br>Thiazides<br>Barbiturates<br>Aspirin<br>Tetracyclines<br>Thyroxine | • Reduced major coronary events<br>• CHD deaths |

**Table 2.11: Layout of the various drug classes, available agents, indications, its effects and side effects, contraindications and interactions (Anaizi, 2002; Berger & Marais, 2000:164-176; Gibbon *et al*., 2008:163-171; Snyman, 2007:164-170) (continued)**

| Drug class | Agents | Indications | Lipid / Lipoprotein effect | Major side-effects | Contraindications | Drug interactions | Clinical trial results |
|---|---|---|---|---|---|---|---|
| • **Niacin / Nicotinic Acid** | • Nicotinic acid (niacin)<br>• Acipimox | • Hyperlipidaemia type II, III, IV & V<br>• Triglyceride-related disorders | • **LDL** ↓ 5% - 25%<br>• **HDL** ↑ 15% - 35%<br>• **TG** ↓ 20% - 50% | • Flushing<br>• Hyperglycaemia; hyperuricemia (gout)<br>• Upper gastrointestinal distress<br>• Hepatotoxicity | **Absolute:**<br>• Chronic liver disease<br>• Severe gout<br>**Relative:**<br>• Diabetes hyper-uricemia<br>• Peptic ulcer disease | • **HMG-CoA reductase inhibitors (Statins):** Enhanced risk of rhabdo-myolysis<br>• **Antihyper-tensives:** Hypotensive effect is potentiated | • Reduced major coronary events<br>• Possible total mortality |
| • **Fibric-Acid Derivatives / Fibrates** | • Bezafibrate<br>• Gemfibrozil | • Hyperlipidaemia<br>• Type IIb & type IV hyperlipidaemia (Gemfibrozil) | • **LDL** ↓ 5% - 20% (May be increased in patients with high TG)<br>• **HDL** ↑ 10% - 20%<br>• **TG** ↓ 20% - 50% | • Dyspepsia<br>• Gallstones<br>• Myopathy<br>• Unexplained non-CHD deaths in WHO study | **Absolute:**<br>• Severe renal disease<br>• Severe hepatic disease | • **Warfarin:** Increased anticoagulant effect<br>• **Statins:** Additive muscle effect<br>• **Phenytoin:** Increased level of phenytoin<br>• **Sulphonyl-ureas:** Hypogly-caemia | • Reduced major coronary events |

**Table 2.11: Layout of the various drug classes, available agents, indications, its effects and side effects, contraindications and interactions (Anaizi, 2002; Berger & Marais, 2000:164-176; Gibbon *et al*., 2008:163-171; Snyman, 2007:164-170) (continued)**

| Drug class | Agents | Indications | Lipid / Lipoprotein effect | Major side-effects | Contraindications | Drug interactions | Clinical trial results |
|---|---|---|---|---|---|---|---|
| • **Other** | • Ezetimibe | • Primary Hypercholesterola-emia | • **LDL** ↓ 17% - 25% (primary)<br>• **TG** ↓ (Minimal)<br>• **HDL** ↑ (Minimal, but up to 25 % in combination with statin) | • Headache<br>• Fatigue<br>• Gastro-intestinal disturbances<br>• Headache | • Pregnancy and lactation<br>• Children under 10 years of age<br>• Moderate to severe hepatitis | • Bioavailability decreases with cholestyramine<br>• Cyclosporin increases bioavailability | • Reduced major cornary events |

The use of lipid-lowering drugs is associated with the development of side-effects and that poses a more frequent cause of referral to the specialist. The most common side-effect is indigestion, which can be combated before initiating therapy by starting treatment alongside antacid. Other side-effects are diarrhoea, nausea, skin rash, fatigue, worsening of eczema and generalised aches and pains. When such side-effects are encountered treatment with lipid lowering drugs should be stopped for two to three weeks until the condition has been settled completely (Bhatnagar, 1998:221).

### 2.1.10 Discussion and conclusion

The following applications can be made for this study from the above-mentioned discussions:

- Dyslipidaemia can lead to coronary heart disease, which, in turn, can lead to sudden death.
- Dyslipidaemia can be classified as primary or secondary, each depending on specific signs and symptoms.
- The complications caused by dyslipidaemia are severe and should be prevented or treated aggressively.
- Treatment of dyslipidaemia can be pharmacological or non-pharmacological, with the latter being the first line of treatment.

It can be concluded that dyslipidaemia is diagnosed according to specific signs and symptoms and can be primary or secondary. The incidence of dyslipidaemia is infuenced by genetics, lifestyle habits such as lack of exercise, smoking and diet. The general aim of the management of dyslipidaemia is to reduce symptoms, risk factors, clinical course and to prevent possible complications, which in turn would have a direct influence on utilisation and cost of treatment.

### 2.1.11 Section summary

This section focused on the introduction and defining of dyslipidaemia as well as on the classification of dyslipidaemia (primary and secondary), the incidence and prevalence of dyslipidaemia, the pathophysiology, significance thereof, diagnosis, signs and symptoms together with the management of dyslipidaemia, including pharmacological and non-pharmacological treatment.

Managed health care and what it entails will be discussed in the following section.

## 2.2 MANAGED HEALTH CARE (MHC)

### 2.2.1 Introduction

Managed care has a long history. Over an extended period a hostile regulatory environment discouraged this form of organisation (Glied, 1999). However, since early 1980, managed care has grown dramatically (Glied, 1999). The growth may be due to this organisational form's relative success in responding to underlying market failures in the health care system – asymmetric information about health risks, moral hazard, limited information on quality and limited industrial competitiveness. Luiz and Wessels (2004:10) stated that South Africa is taking the USA-MHC model and changing it to fit the South African structure, but fortunately South Africa can observe the mistakes made in the USA regarding the implementation process of MHC and may choose to apply the best practices only according to that which had proved to be successful in the USA.

### 2.2.2 Definition of managed health care

Over the years many definitions of managed health care have been developed. These definitions differ in focus point and target strategy.

Powell (2000:3) defined managed health care as a collection or group of techniques used by or on behalf of purchasers of health care benefits to manage health care costs by influencing patient care decision making through case-by-case assessments of the appropriateness of care prior to its provision. In 2004, Kongstvedt (2004:285) defined managed care as "*a system of health care delivery that tries to control the cost of health care services while regulating access to those services and maintaining or improving their quality"*. Anon. (2007a) is furthermore of the opion that managed care is the enrolment of patients into a plan that makes capitated payments to health care providers on behalf of its members, thus shifting the financial risk for health care from patients and payers, to providers. The intent of this shift is to provide incentives to health care professionals to reduce their utilisation of resources, ideally through measures such as health promotion and disease prevention among the group's members.

Managed health care was defined in the Regulations published in terms of the Medical Schemes Act (131/1998) of South Africa as the "*clinical and financial risk assessment and management of health care, with a view to facilitating appropriateness and cost effectiveness of relevant health services within the constraints of what is affordable, through the use of rules-based and clinical management based programs [cit]".*

A new set of activities governing managed health care in South Africa started being used as from the 1st of January 2003 (Council for Medical Schemes, 2003:1). According to the Council for Medical Schemes (2003:19) managed care within South Africa refers to a diverse range of health care organisational strategies that are aimed at containing cost, improving access and assuring the quality of care provided to the beneficiaries of the medical schemes.

The Council of Medical Schemes (2003:3) gave some advantages of managed health care that include (but are not limited to) the following:

- To promote the use of the most cost-effective health care delivery mechanisms, thereby achieving cost reduction.
- To align the financial incentives of providers and financiers to reduce unreasonable incentives for unnecessary care.
- To strongly establish mechanisms to maintain or improve the quality of health care.
- To encourage the development of standardised treatment protocols.
- To support members in gaining access to the most suitable treatment interventions.
- To promote an integrated and holistic approach to manage the health care needs of patients.

Based on these statements it can be reasoned that managed care is a process that is used to deliver cost-effective care to patients without limiting access or quality. This can be achieved by controlled access to providers, comprehensive regulatory controls, emphasis on preventative care, risk sharing, quality and behaviour modification of both the participants and the providers.

### 2.2.3 Types of managed care plans

Defining the different types of managed care organisations (MCOs) is an ever-evolving challenge (Kongstvedt, 2004:25). It is also said that it is a generic term that describes organisations that manage and control costs and quality related to health care (Harvey & Shapiro, 1997a:270). The Integrated Healthcare Association (IHA) (2001) indicates that a broad array of health insurers, medical groups, hospitals and health systems are considered as managed care organisations. There are various types of MCOs that are being used, *inter alia* the following: health maintenance organisation (HMO), preferred provider organisation (PPO) and exclusive provider organisation (EPO) (Fincham, 2006).

### 2.2.3.1 Health Maintenance Organisations (HMOs)

An HMO is defined by Al-Assaf (1998:3) as a health care system that provides comprehensive health services to the enrolled persons living within a specific geographic region. This type of MCO provides a form of health care insurance coverage that is fulfilled by hospitals, doctors and other providers with which the HMO has a contract (Kongstvedt, 2004:26). Five different HMO models exist *i.e.* group model, staff model, network model, direct contract model and independent practice associations (IPA) which will be discussed shortly in table 2.12.

**Table 2.12: Different types of Health Maintenance Organisations (HMOs)**

| Type of HMO model | Description |
|---|---|
| • **Group model** | Group model HMO contracts with a multispeciality physician group practice to provide all physician services to the HMO members (Kongstvedt, 1997:44). These physicians are employed by the group practice and not by the HMO. The medical groups may be organised as a partnership, professional corporation, or an association; the health plan compensates the medical group for covered services at a contracted rate and arranges hospital service agreements for the inpatient or ancillary care needs (Rognehaugh, 1998:95). |
| • **Staff model** | In this closed-panel HMO, physicians are employees of the HMO (Rognehaugh, 1998:234). Accordingly all premiums and other revenues accrue to the HMO, which, in turn, compensates physicians. Very much like the group model, except the doctors are employees of the HMO. |
| • **Network model** | This type of HMO contracts with more than one physician group and may contract with single or multi-specialty groups as well as hospitals and other health care providers (Pohly, 2007). When these services are bought, network HMOs sub-capitates the primary care doctor, which in return becomes responsible for providing most of the members' care (Harvey & Shapiro, 1997b:14). |
| • **Direct contract model** | In this model the practitioners have a direct contract with the HMO but are free to see non-HMO patients. The practitioners provide services to the enrolled population. The practitioners are compensated according to a fee for service plan or on a capitation basis (Kongstvedt, 1997:47). |
| • **Independent practice association (IPA)** | The HMO contracts with a physician organisation, which in turn contracts with individual physicians, known as a delivery model. The HMO reimburses the IPA on a capitated basis; however, the IPA may reimburse the physicians on a capitated basis (Pohly, 2007). |

All the HMOs have certain specific features in common such as that they tolerate risks, have lower premiums, they are less comprehensive and also have a responsibility to deliver a certain stated service for a fixed rate to an enrolled patient (Managed Care Organisations, 2007). Members of an HMO must receive their medical treatment from specific physicians and facilities within the HMO network (Mamdami & Mamdami, 2001:96).

#### 2.2.3.2 Preferred Provider Organisations (PPOs)

Preferred Provider Organisations (PPOs) enter into contract with a private insurer and therefore particular services are rendered through an agreed combination of physicians and hospitals (Pohly, 2007; Rickel & Wise, 2000:105). Accordingly it is a health care delivery system that hold a contract with providers of medical care to provide services at discounted fees to members.

PPOs limit the size of participating provider panels and also provide incentives for their covered individuals to use these participating providers instead of other providers (Kongstvedt, 1997:38). Generally PPOs will offer more choice for the patient and will provide higher reimbursement to the providers (Pohly, 2007).

#### 2.2.3.3 Exclusive Provider Organisations (EPOs)

Wagner (1997:39) states that the EPO is very similar to the PPO. The difference, however, is that payment is provided to contracted providers only and this agreement limits beneficiaries to participating health care providers. PPOs extend their coverage to non-preferred providers as well as preferred providers and their services.

## 2.3 MANAGED HEALTH CARE AND PRESCRIBED MINIMUM BENEFITS IN SOUTH AFRICA

In South Africa there is no true form of a specific HMO currently in use. The HMO models that do exist are merely extensions of a combination of models (Serfontein, 2008).

According to the Council for Medical Schemes (CMS, 2007), South Africa currently has about sixty (60) different MCOs together with about one hundred and sixty (160) different medical aid schemes, totalling close to seven million medical schemes. From these 160 beneficiaries, there are only about 40 open to the South African public.

Prescribed minimum benefits (PMB) represent the scope of level of benefits that are available to beneficiaries as prescribed by the Medical Schemes Act (131/1998). Any benefit that is offered by the medical scheme must pay in full, without payment sharing or the use of deductibles, the diagnosis, treatment and care costs of the prescribed minimum benefit conditions. However, the co-payment or deductibles may be forced on members who have received their health care from persons other than their designated service providers (Regulations for Medical Schemes Act (Act 131/1998).

Designated health provider is defined according to the Regulations publicised for the Medical Schemes Act (Act 131/1998) as *"a health care provider or group of providers selected by the medical schemes as the preferred provider or providers to provide to its members diagnosis treatment and care in respect of one or more of the prescribed minimum benefit conditions"*.

There are three sets of prescribed minimum benefits applicable to South Africa which include (Still, 2008:115):

- A list of 271 conditions.
- The chronic disease list.
- Emergencies.

Each one of these PMB has a set of minimum treatment standards which have been published in the Regulations for the Medical Schemes Act (Act 131/1998).

The PMB system has been introduced into the South African health care system to avoid incidences where individuals are put at serious financial risk due to unfunded usage of medical services. The list of the PMB consists of disease conditions that all medical schemes are obliged to cover. In addition to that a chronic disease list (CDL) that consists of 26 chronic disease conditions has been attached. All the medical schemes are also obligated to pay for these. Hyperlipidaemia is one of the conditions listed on the CDL (Regulations for the Medical Schemes Act) (Act 131/1998).

The introduction of Prescribed Minimum Benefits aims to attain the following (Medikredit, 2009; Qualsa, 2008):

- Provide treatment access even where members do not have medical scheme coverage due to their plan benefits or limits having been exceeded/depleted.
- Avoid excess pressure on the limited resources of public hospitals as the state would have to manage these patients.
- Encourage more efficient use of the limited health care resources of the public and private sectors.

The PMB cover offered by the medical scheme should be managed under an insured benefit pool and coverage must be offered even if

- there are specified scheme exclusions;
- waiting periods apply; or
- a limit for a specific benefit has been depleted.

In order to contain costs of PMB, medical schemes may assign designated service providers and apply managed care protocols to ensure a cost-effective and efficient health care service to their members (Medikredit, 2009).

## 2.4 MANAGED HEALTH CARE CONCEPTS

Managed health care consists of certain information systems and techniques. These systems and techniques are laid out in figure 2.3.

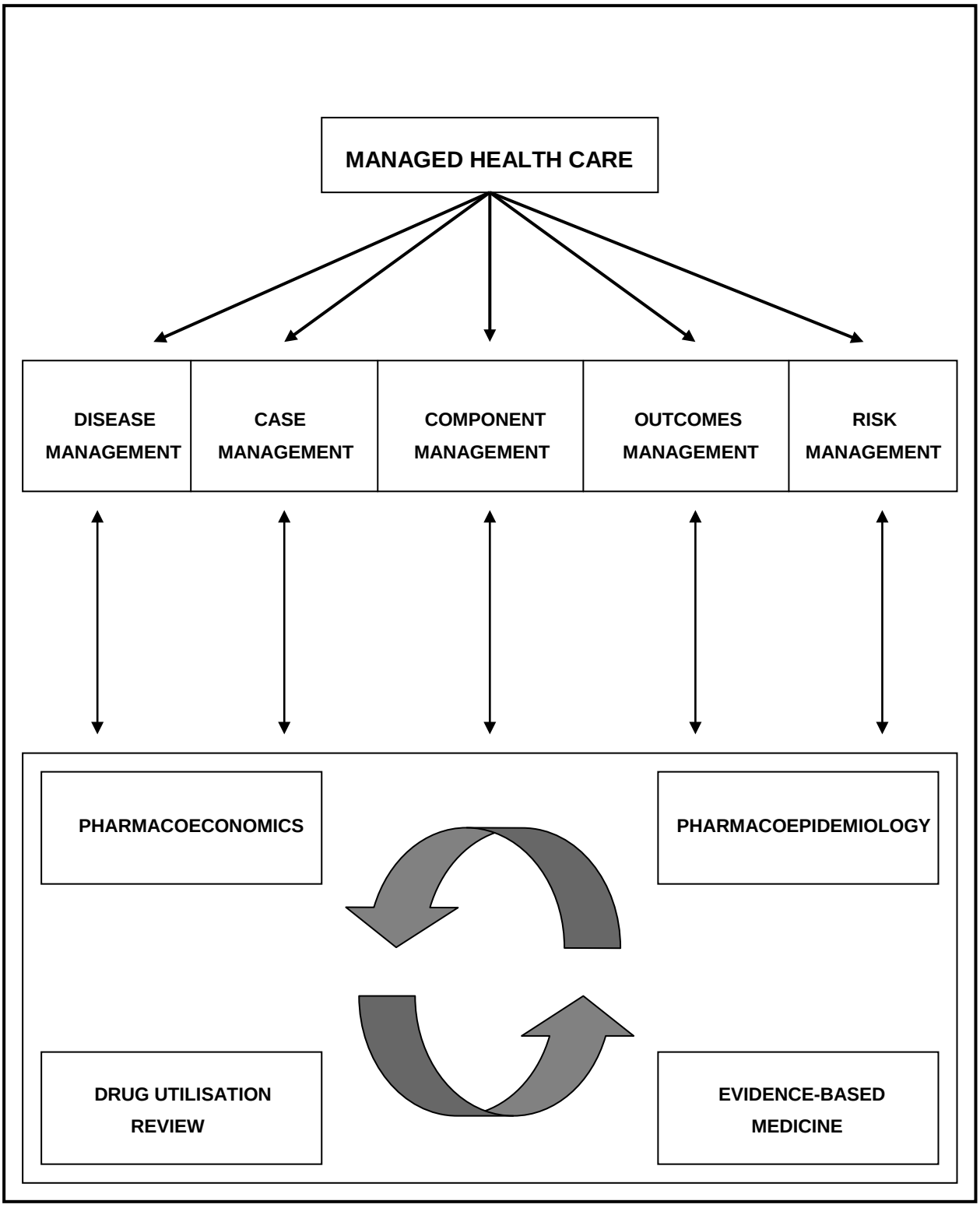


**Figure 2.3: Relationship between different concepts of managed health care (adapted from Serfontein & Hein, 1999)**

The various components of managed health care as illustrated in figure 2.7 will be discussed in the subsequent paragraphs.

### 2.4.1 Disease management

In 1996, Wynn (1996:19) stated that disease management is "*a system that integrates and coordinates all providers and facilities that ordinarily deal with the patient (i.e. physician, pharmacist, nurse, hospital, laboratory, managed-care organisation, drug manufacturer, etc.) to provide cost-effective patient care based on the clinical outcomes*". Another definition to be used is the definition of Pasternak and Harris (1996:28), which states that disease management is "*a systematic approach to a health condition or a health care intervention that organises preventative, interventional and care approaches throughout the continuum of care and which measures outcomes in terms of population, not individuals*". The latter two definitions have the same goal even though they differ in focus. Pasternak and Harris (1996:28) focus on the population where Wynn (1996:19) focuses on the patient.

Disease management is thus an approach to strategic management, using inter-disciplinary clinical terms, continuous analysis of data and cost- effective technology to improve the health outcomes of a patient or population.

In disease management, the focus may very well be on quality of care as well as overall cost. Disease management is also proactive since it focuses on the prevention aspects as well as health promotion. The goal of disease management is to decrease health care costs and utilisation over the life of the patient regardless of the short term impact or whether drug benefit costs increase as a result of more aggressive management (Olson, 2002:253). Disease management in South Africa is still at the beginning of implementation, though some guidelines have been set out for certain chronic diseases such as cholesterol / dyslipidaemia. The basic premise of disease management is that there may be a more optimal way to manage patients that could result in lowered costs, and it is possible to develop and implement a system of care that improves health outcomes (van der Merwe, 2002:24). Figure 2.4 illustrates a disease management programme for dyslipidaemia.

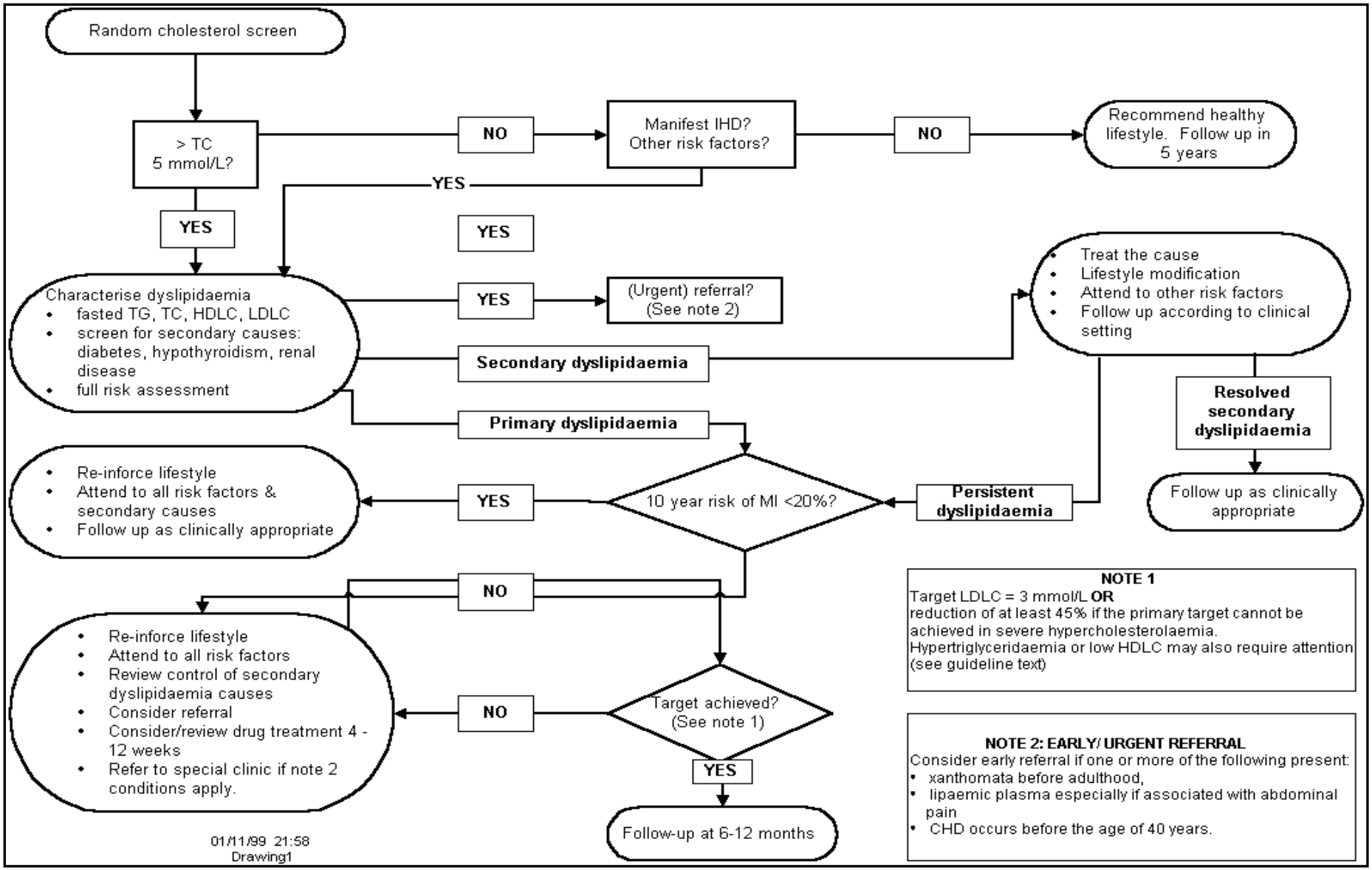


**Figure 2.4: Disease management programme for dyslipidaemia (Berger & Marias, 2000:167)**

There are three essential elements in disease management (van der Merwe, 2002:25):

- A knowledge base that quantifies the economic structure of the disease problem and describes care guidelines.
- A delivery system that co-ordinates all cares.
- A quality improvement system to audit performance against evolving standards.

Disease management should be a system of care which focuses on the patient and compartmentalisation of care should be avoided, thus providing preventative medicine rather than reactive medicine and poor patient care (McDonald *et al*., 2004:72).

McDonald *et al*. (2004:75) further state that a disease management programme aims to accomplish the following:

- Contain cost.
- Improve health outcomes.
- Reduce variations in health care.
- Improve the quality of care provided.
- Maintain or increase drug sales.

The new model for the management of disease includes population-based risk and disease assessment, systems of disease prevention and health promotion, community-based intervention and provider's network, evidence-based medicine and defined protocols of care with measurement of outcomes. The application of outcomes assessment to the practice of medicine through disease management has already begun (van der Merwe, 2002:26).

### 2.4.2 Case management

Case management originated in response to movements toward controlling the spiralling costs of health care in accident and health insurance (Siefker *et al*., 1998:3).

According to Al-Assaf (1998:3) case management is defined as "*the process by which an individual patient's care is managed by a plan to assure appropriate, cost-effective treatment in a timely approach"*. Case management is also an element of the utilisation management process and it controls the costs of health insurances (Siefker *et al*., 1998:4). It is therefore a process which assesses, plans, implements, coordinates, monitors, and evaluates options and services to meet an individual's health care needs through communication and available resources (Powell, 2000:5).

Case management is a process which is intended to assist patients in the ongoing process to improve and maintain optimum health (Fraser & Strang, 2004:32). According to Fraser and Strang (2004:32) a personalised case management process is needed since every patient has his/her own unique problems. A standard guideline should be used in every patient's specific case, though, thus case managers must use creativity to add uniqueness to each individuals case management process (Fraser & Strang, 2004:32).

### 2.4.3 Component management

Component management is a traditional approach to managing health care cost, where the individual health transaction (the doctor's consultation or procedures) is viewed as a relevant unit of service and cost. The duration of treatment, various transactions, and component categories are analysed to establish norms for unit of cost. The unit of cost of each component is then driven as low as possible through aggressive contracting, utilisation management, case management and other cost controlling techniques. Component management provided one of the very first tools for addressing the increased growth of health care costs (Tremonti, 1998).

### 2.4.4 Outcomes management

Outcomes management (OM) is the "*enhancement of physiologic and psychosocial patient outcomes through development and implantation of exemplary health practices and services, driven by outcomes assessment*" (Marcus, 2000:10). OM is a research-based process that consists of a never-ending cycle of measurement and continuous quality improvement (CQI) of clinical practice (Wojner, 2001:5). OM facilitates dissemination of health outcomes information to patients, providers, and payers of health services (Wojner, 2001:5).

South Africa has entered into an era of unprecedented growth in activity directed at the assessment of outcomes, the analysis of effectiveness and quality assurance in health care (van der Merwe, 2002:27). According to van der Merwe (2002:29), outcomes management is a technology of patient experience designed to help patients, providers and payers make rational medical care-related choices based on better insight into the effect of these choices on the patient's life and quality of life.

Outcomes management is based on the dependence of clinical standards and guidelines that doctors can use to select interventions. It is also a programme in which clinical standards and guidelines are based systematically on patient outcomes where it routinely and systematically measures the functioning and well-being of patients by means of specific clinical outcomes (van der Merwe, 2002:29).

Outcomes measurement represents an objective way to measure the end result of a health care intervention and health payers are demanding efficiency and value for their health care cost.

Table 2.13 presents different outcomes, types and examples thereof.

**Table 2.13: Types of outcomes (van der Merwe, 2002:28)**

| Outcomes | Types | Example |
|---|---|---|
| **Clinical** | • Clinical events<br>• Physiologic and metabolic measures<br>• Morbidity and mortality rates | • Blood pressure and measurement of cholesterol levels<br>• Death (cardiovascular) and all causes and complications<br>• Measures if group patients lived longer and improve in their health status |
| **Economic** | • Direct medical<br>• Indirect medical | • Hospitalisations and outpatient visits<br>• Work loss and restricted activity days |
| **Humanistic** | • Symptoms<br>• Quality of life<br>• Fuctional status<br>• Patient satisfaction<br>• Disability | • Quality of life lost, life years affected |

The addition of outcomes management to practices of health care has resulted in efforts to implement disease management programmes. These efforts are based on systematic population-based approaches in identifying patients at risk, intervening with specific programmes of care and measuring clinical and other outcomes (van der Merwe, 2002:28).

### 2.4.5 Risk management

Risk management is a term that was first coined by insurance companies in the United States during the 1960s to describe the control of expenditure on the generality of claims (van der Merwe, 2002:13).

According to Rognehaugh (1998:221) risk management is "*a health care function or discipline that executes one or more strategies to limit the organisation to the financial risk associated with delivering care; which may include the strategy of reviewing the actuarial risk of a given enrolment population toward catastrophic care, purchasing insurance or self-insuring to protect against risk, associated medico-legal factors to protect against undue risk, or organisational programs [cit] to preclude the occurrence of health events that typically lead to legal claims*". Risk management is defined by van der Merwe (2002:13) as the systematic process of

identifying and evaluating together with addressing actual risk through a well-designed programme that prevents, controls and minimises risk exposure.

The increase of medical malpractice lawsuits led the insurance companies to apply the same techniques to the health sector. Public and private health care providers developed risk management programmes to prevent injury to patients, visitors and staff to control liability of costs (van der Merwe, 2002:13).

Risk management is thus the application of skills, knowledge and risk management tools and techniques to a project in order to reduce threats to an acceptable level while maximising opportunities (Heldman, 2005:214).

### 2.4.6 Conclusion of the different instruments used in managed health care

Disease management, case management, risk management and outcomes management are different management strategies which can be used in managed health care. Wojner (2001:178) explains that the different instruments used in managed health care have a constricted relationship. Outcomes management can always be seen as the central part of the connection between the different instruments.

Disease management incorporates outcome research technology into outcomes measurement and creates management programmes. Disease management and outcomes management are separated by only a technical distinction (van der Merwe, 2002:26). Wojner (2001:178) added that case management can be seen as an opposite outcomes to disease management with outcomes management being the core, this is illustrated in figure 2.5. In this study risk management plays a part in all of the different managed care instruments.

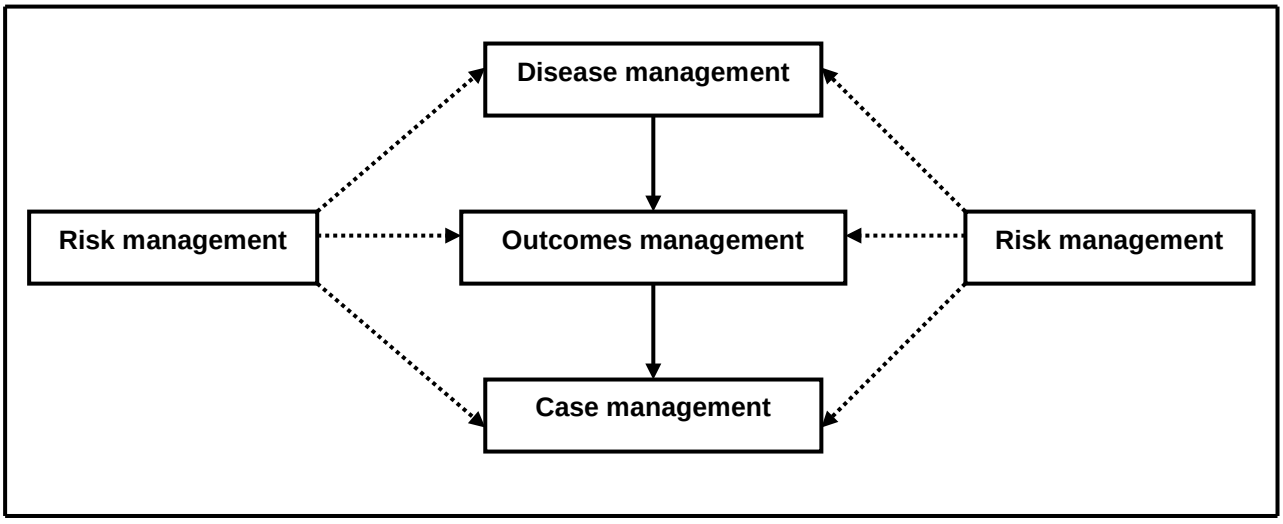


**Figure 2.5: The relationship between the health care instruments (adapted from van der Merwe, 2002:27; Wojner, 2001:178)**

In the next section the different information systems for managed health care such as drug utilisation review (DUR), pharmacoeconomics, pharmacepidemiology and evidence-based medicine will be discussed as well as the different measurement tools within the framework of these systems (refer to paragraphs 2.5.1 and 2.5.2).

## 2.5 INFORMATION SYSTEMS FOR MANAGED HEALTH CARE

### 2.5.1 DRUG UTILISATION REVIEW (DUR)

Drug utlisation review (DUR) as information system for managed health care and its measurement tools within the framework will briefly be discussed in the subsequent paragraphs.

#### 2.5.1.1 Defining drug utilisation review

Kreling and Mott (1993:415) refer to the definition of the secretary of the Health, Education and Welfare Task Force that defined DUR as a "*dynamic process aimed at the consequent improvement in the quality of health care and minimising needless expenditure*".

Drug utilisation was defined in 1977 by the World Health Organization (WHO) as the "*marketing, distribution, prescription, and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences*" (WHO, 2003a:8). A good DUR programme will look at all processes involved in the rendering of a pharmaceutical service (Serfontein & Hendriks, 2001:3).

Walters and Smart (1994:821) formulated a definition for the South African situation as follows: "*A DUR program [cit] is an authorised, structured, ongoing system for the monitoring of drug use through comparisons with specific standards and initiating of corrective action when drug-use patterns are inconsistent with these standards*". In this definition Walters and Smart neglected the cost aspect and focused on the rational medicine use. In the Republic of South Africa (RSA) the cuttings of health care cost without compromising the quality of the health care are contentious issues being addressed in both the private and public sectors (Serfontein & Hendriks, 2001:3).

DUR is a process specifically formulated to improve safe, effective and appropriate drug therapy by detecting widespread variations from prescribing drug utlilisation (Jones & Radloff, 2007:32). With this in mind, a definition for the purpose of this study can then be seen as a structured system to determine whether the usage patterns of hipolipidaemic medicine is safe, effective and appropriate in a specific sex or age group, compared to standard criteria and prescribed drug treatment.

### 2.5.1.2 Rationale for drug utilisation research

The principal aim of drug utilisation research is to determine whether the use of drugs in populations is rational or not (WHO, 2003a:9). For the individual patient, the rational use of a drug implies the prescription of a well-documented drug at an optional dose, together with the correct information, at an affordable price (WHO, 2003a:9). Without knowledge of how drugs are being prescribed and used, it is difficult to initiate a discussion on rational drug use or to suggest measures to improve prescribing habits. Information on the past performance of prescribers is the linchpin of any auditing system (Sjöqvist & Birkett, 2003:78). Drug utilisation research in itself does not necessarily provide answers, but contributes to rational use in important ways (WHO, 2003a:9).

### 2.5.1.3 The drug utilisation review process

DUR systems include an input (the health care system and data structure), the process (criteria, application, intervention and evaluation), and end with an output (specified percentage of decreased costs, hospitalisations or drugs per patient) (Jones, 1991:620).

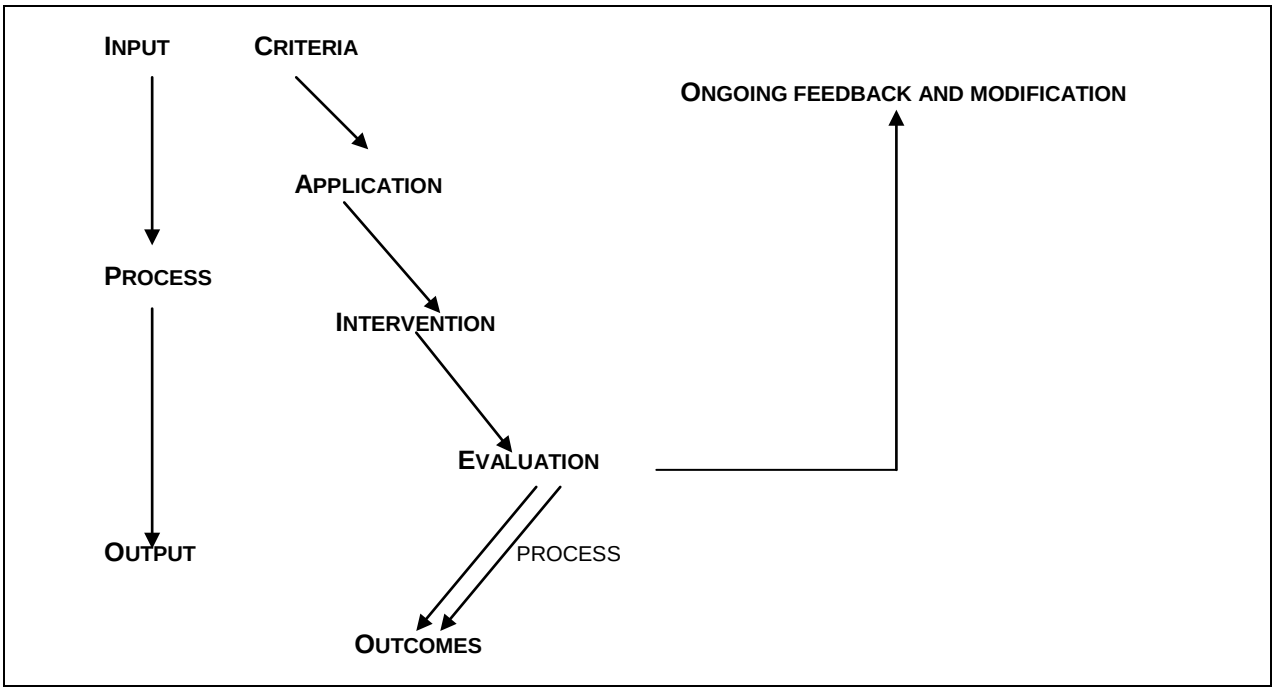


**Figure 2.6: The system's view of drug utilisation review (Jones, 1991:621)**

In the following section the classification, nature and type of DUR-studies will be discussed and related examples as applied to dyslipidaemia will be presented (refer to paragraph 2.5.1.8).

### 2.5.1.4 Classification of drug utilisation review

Drug utilisation reviews can be divided into “quantitative” or “qualitative” (Kongstvedt, 1993:154). Both of these studies as classification systems for DUR will be discussed respectively in the subsequent paragraphs.

#### 2.5.1.4.1 Quantitative drug utilisation review studies

According to Iñesta (1992:353) and Sjöqvist and Birkett (2003:80) quantitative data may be used to describe the present state and trends in drug prescribing and drug use at various levels of the health care system. Quantitative data are usually obtained from routinely collected data or from surveys (Sjöqvist & Birkett, 2003:80), and can be used to process the following (Iñesta, 1992:353; Lee *et al*., 2006:400; Sacristan & Soto, 1994:300):

- Analyse the amount of drugs consumed in a specific area.
- Identify over- and under-prescribing areas.
- Estimate the misuse of drugs.
- Compare consumption or prescribing patterns of drugs in specific areas.
- Calculate the utilisation of drugs in accordance to demographical features.
- Observe the impact of informational or regulatory activities on drug use patterns.

#### 2.5.1.4.2 Qualitative drug utilisation review studies

Qualitative studies assess the appropriateness of drug utilisation and generally link prescribing data to reasons (indications) for prescribing (Lee & Bergman, 1994:380; Sjöqvist & Birkett, 2003:80). Qualitative DUR studies include the collecting, organising, analysing and reporting of information on the rationality of drug use and can be used to accomplish the following (Kreling & Mott, 1993:416; Lee *et al*., 2006:400):

- Assess the daily dosage suitability.
- Analyse the time period of therapy.
- Identify potential drug interactions.
- Establish the most suitable dosage per indication.
- Assess the fixed combination of drugs.
- Establish an indication of use for a specific drug or non-drug regimen.

### 2.5.1.5 Nature of drug utilisation review studies

Based on their nature, drug utilisation studies are divided into prospective, retrospective and concurrent reviews which will be described in table 2.14.

**Table 2.14: The nature of drug utilisation reviews (compiled and adapted from Blackburn, 1993; Krawleski *et al*., 1994; Kreling & Mott, 1993; Wertheimer & Navarro, 1999; Powell, 2000).**

| Type | Description |
|---|---|
| **Prospective reviews** | • Prospective review has the greatest potential benefit for the patient, because it identifies drug therapy problems and corrects them before they can occur. It relies on criteria from published literature, clinical experience and basic pharmacological principles to provide an evaluation of drug therapy (Krawleski *et al*., 1994:425; Kreling & Mott, 1993:417).<br>• The Drug utilisation review (DUR) procedure is usually achieved through computer linkages between the DUR company and the network of participating pharmacies and it is accomplished through prior authorisation programmes, which require physicians to obtain approval before prescribing certain medications (Wertheimer & Navarro, 1999:379). |
| **Retrospective reviews** | • Retrospective review is a programme that is largely focused on preventing recurrence of a problem and is a structured ongoing initiative that interprets patterns of drug use in relation to predetermined criteria therefore attempt to minimise inappropriate prescribing (Hennessy *et al.*, 2003:1494; Krawleski *et al.*, 1994:431). Retrospective DUR has a number of advantages:<br>o By using a data base from a medical aid it can be performed effortlessly.<br>o Inappropriate prescribing practices can be identified and through educational interventions with the doctor these problems can be eradicated (which will lead to rational prescribing and better quality treatment for the patient).<br>o Drug therapy trends and information in certain geographical areas can be analysed and if required to, can be changed by using suitable interventions.<br>o Relatively it is an inexpensive type of DUR method with a variety of interesting applications. |
| **Concurrent reviews** | • Concurrent review concentrates on the appropriateness and correctness of the drugs prescribed while the patient is in the facility.<br>• Concurrent review is very limited and only used for patients on chronic medication and certain institutionalised patients. If the desired effect (therapeutic outcome) is not achieved, this review therefore allows for the changing of therapy (Blackburn, 1993:15; Powell, 2000:502). |

### 2.5.1.6 Types of drug utilisation review studies

There are various types of DUR studies, cross-sectional, longitudinal or continuous longitudinal and these will be described in table 2.15.

**Table 2.15: Types of drug utilisation review studies (adapted from WHO, 2003a)**

| | |
|---|---|
| **Cross-sectional studies** | • According to The World Health Organization (2003a:17) cross-sectional studies is "data, which provided a 'snapshot' of drug use at a particular time (e.g. over a year, month or a day)".<br>• Comparisons can be made with data collected over the same time period in another health facility. Such data can be drug-, problem-, indication-, prescriber-, or patient-based.<br>• A cross-sectional study can measure drug use or be criterion-based to assess drug use in relation to guidelines or limitations (WHO, 2003a:17).<br>• A cross-sectional study can be carried out before and after an educational or any other intervention (WHO, 2003a:17). |
| **Longitudinal studies** | • According to the WHO (2003a:17) longitudinal data is a necessity to public health authorities to study the trends in drug use.<br>• This data can be on total drug use as obtained through a database or it can be on a statistically valid sample of pharmacies / medical practices (WHO, 2003a:17).<br>• Data used in longitudinal studies are often obtained from cross-sectional surveys, and although data collection is a constant and continuous process, the practices and patients surveyed are constantly changing (WHO, 2003a:17).<br>• Prescribing trends of individual practitioners and practices cannot be obtained from longitudinal data. |
| **Continuous longitudinal studies** | • Continuous longitudinal data can be collected at individual practitioners and patient levels (WHO, 2003a:17). Through a unique identifier claims databases are able to follow individual patients.<br>• Information about concordance with treatment based on the period among prescriptions, co-prescribing, duration of treatment and prescribed daily doses (PDDs) can be provided through continuous longitudinal data (WHO, 2003a:17). |

### 2.5.1.7 Drug utilisation review units of measurement

The units of measurement used in DUR will be discussed in table 2.16.

**Table 2.16: Units of measurement in drug utilisation review (compiled and adapted from Sjöqvist & Birkett, 2003; WHO, 2003a)**

| | |
|---|---|
| **Defined daily dose (DDD)** | • The WHO (2003a:38) defines DDD as "*the assumed average maintenance dose per day for a drug used for its main indication in adults*."<br>• The defined daily dose is a unit of measurement and does not necessarily agree with the recommended or prescribed daily dose (PDD) (Sjöqvist & Birkett, 2003:83).<br>• The doses for individual patients and patient groups will often differ from the DDD and have to be based on individual characteristics (e.g. age and weight) as well as pharmacokinetic and pharmacogenetic considerations.<br>• The DDD is often a compromise based on a review of the available information about doses used in various countries (WHO, 2003a:38).<br>• The DDD may even be a dose that is seldom prescribed, because it is an average of two or more commonly used dose sizes (WHO, 2003a:38). |

**Table 2.16: Units of measurement in drug utilisation review (compiled and adapted from Sjöqvist & Birkett, 2003; WHO, 2003a) (continued)**

| | |
|---|---|
| **Prescribed daily dose (PDD)** | • According to The World Health Organization (2003a:38) PDD can be defined as "*the average dose prescribed according to a representative sample of prescriptions.*"<br>• Studies of prescriptions or medical-/ pharmacy records can establish the PDD.<br>• PDD does not necessarily reflect actual drug utilisation since the patient does not always take all the prescribed medication that has been dispensed (Sjöqvist & Birkett, 2003:84). |
| **Cost** | • According to the WHO (2003a:39) drug use can be expressed in terms of costs. Cost figures are appropriate for an in general analysis of expenditure on drugs.<br>• International comparisons based on cost parameters can be misleading and have limited value in the evaluation of drug use (WHO, 2003a:39).<br>• Long-term studies are difficult due to fluctuations in currency and changes in prices (Sjöqvist & Birkett, 2003:83; WHO, 2003a:40).<br>• When cost data are used, an increase in the use of cheaper drugs may have little influence on the total level of expenditure on drugs, while a shift to more expensive drugs is more noticeable (WHO, 2003a:40). |
| **Other units for presentation of volume** | • Grams of active ingredient.<br>• Number of tablets.<br>• Number of prescriptions (WHO, 2003a:39). |

### 2.5.1.8 Application of drug utilisation reviews to the use of statins

Numerous studies have been conducted using drug utilisation review on hipolipidaemics. Examples of such studies are outlined in table 2.17.

**Table 2.17: Examples of drug utilisation studies on hipolipidaemic medicine items**

| Author & Year | Description | DUR classification, type and nature | DUR measurement unit | Outcome |
|---|---|---|---|---|
| Hartz *et al*. (2007) | Estimates for all statins consumed in Norway, with focus on atorvastatin *vs* simvastatin. | Cross-sectional and longitudinal; quantitive and qualitative; prospective / longitudinal | PDDs; DDDs; number of prescriptions | Atorvastatin and simvastatin were dispensed in 79 – 87% of all statin users, and the proportion was significantly higher in the high consumption county. The estimated PDDs were higher than the DDDs, up to twice the DDD for atorvastatin. The high consumption county had the highest PDD for simvastatin (25.9 mg) and atorvastatin (21.9 mg), and more users received tablets in the upper range of available strengths. Continuity of therapy was similar in the three counties in Norway. |

## Table 2.17: Examples of drug utilisation studies on hipolipidaemic medicine items (continued)

| | | | | |
|---|---|---|---|---|
| Tabata *et al*. (2007) | Determine and define the renoprotective effect of preoperative statin use in coronary artery bypass grafting. | Retrospective cohort; longitudinal; quantitative | Number of prescriptions; DDDs | The statin group had a lower incidence of new renal insufficiency than the non-statin group (1.6% *vs* 3.9%, odds ratio 0.39, 95% confidential interval 0.18 to 0.82). Multivariate logistic regression analysis including all patients also showed that preoperative statin use (odds ratio 0.54, 95% confidence interval 0.30 to 0.99) was significantly associated with low incidence of new postoperative renal insufficiency. In conclusion, preoperative statin use may be renoprotective after coronary artery bypass grafting. |
| Savoie & Kazanjian (2001) | Study on the utilisation of lipid-lowering drugs in men and women in Canada. | Retrospective; longitudinal; quantitative | Number of prescriptions | The results indicated that, 74.7 per cent of individuals on statins had no reported history of coronary heart disease. Women without coronary heart disease formed 23.1 per cent of statins recipients and were aged 70 and over. Only 15.3% of men with CHD had been prescribed a statin. Based on the systematic review, 88.7% of the utilisation of statins in this Canadian province was not supported by the results of the systematic review. Considering baseline lipid-levels does not substantially alter these findings. This study concludes that statins prescribing practices need to be realigned with research evidence. This implies refocusing utilisation away from women and the elderly, towards men with CHD. |
| Straus *et al*. (1999) | Use of a tiered review for evaluation of appropriate drug use of HMG-CoA reductase inhibitor therapy. | Longitudinal; quantitative and qualitative; concurrent review | PDDs; DDDs; number of prescriptions | The pharmacy reviewer judged 57 (48%) of the 118 high-dose cases and 47 (47%) of the 100 standard-dose cases to be questionable; these were subsequently reviewed by the physician reviewer, who found that 43 (75%) of the 57 questionable high dose cases and 38 (81%) of the 47 questionable standard-dose cases involved suboptimal prescribing practices. Overall, the physician's review determined that 36% of the high-dose cases and 38% of the standard-dose cases reviewed involved suboptimal prescribing practices. |
| Raymond *et al*. (2007) | The purpose of this research was to measure prevalent and incident statin use in the population of British Columbia from 1996 to 2004 across specific patient characteristics (sociodemographic and clinical). | Quantitative and qualitative; continuous longitudinal studies; retrospective review | PDDs; DDDs; number of prescriptions | Prevalent use (1996-2004) and incident use (1999-2004) of statins in an entire population have increased dramatically. Although many statin users (60.19%) had evidence of medical conditions that indicate appropriate statin use, 39.91% of users were at low risk for cardiovascular disease, and therefore the benefit of statins in this group remains small. |

**Table 2.17: Examples of drug utilisation studies on hipolipidaemic medicine items (continued)**

| | | | | |
|---|---|---|---|---|
| Cooke & Hammerash (2006) | The objective of this study was to evaluate the treatment of dyslipidemia in patients with CHD and determine if sex differences exist. | Retrospective, quantitative and qualitative | Number of claims (dianostic codes) | The majority of CHD patients from a Maryland-based health maintenance organization had elevated LDL-C values, despite a lipid-lowering prescription rate of 68.6%. A significant gap in dyslipidaemia treatment in these CHD patients remained, particularly for women. |

Most DUR studies as respected in table 2.17 have been done in retrospect with PDDs and DDDs as the unit of measurement. Looking at the outcomes as reported in table 2.17, it is clear that DUR is very effective in the health care environment and provides valuable answers.

### 2.5.1.9 Drug utilisation review in South Africa

The National Drug Policy of South Africa (1996) has some specific aims, policies and strategies that include the following:

- Drug selection: To promote the rational choice of drugs and associated items to be used in South Africa, in accordance with the Essential Drugs concept. Essential drugs are drugs that are required to treat the majority of conditions that are prevalent in a country in a cost-effective and efficient manner. The concept does not imply that no other drugs are useful, but that these drugs are the most needed for the health care of the majority of the population. They should therefore be available at all times, in adequate amounts and in the proper dosage forms (Department of Health, 1996:18).

- Procurement and distribution: To ensure an adequate supply of effective and safe drugs of good quality to all people in South Africa. Standard Operating Procedures (SOP) will be developed with practical guidelines to cover all administrative procedures to manage and control effectively the storage and distribution of drugs (Department of Health, 1996:18)

- Rational use of drugs: To promote the rational prescribing, dispensing and use of drugs by medical, paramedical and pharmaceutical personnel and to support the informed and appropriate use of drugs by the community (Department of Health, 1996:18).

These aims are combined in the definition of drug utilisation of the WHO. Drug utilisation reviews may be used to reach these aims of the National Drug Policy.

Venter (2009) stated that millions of DURs are annually performed in South Africa by PBMs. Examples of DUR studies conducted on hipolipidaemic medicine items in South Africa are presented in table 2.18:

**Table 2.18: Examples of drug utilisation studies on hipolipidaemic medicine items performed in South Africa**

| Author & Year | Description | DUR classification, type and nature | DUR measurement unit | Outcome |
|---|---|---|---|---|
| Truter & Kotze (1996) | To estimate average prescribed daily doses (PDDs) for selected hipolipidaemics available on the South African market, compared to the estimated PDDs with established DDDs and international dosage ranges. To investigate the age and sex of the hipolipidaemic users. | Retrospective drug utilisation study using data from an organisation. | PDDs and DDDs. | The PDDs used in the patient population studied were within locally and internationally acceptable dosage ranges, but were generally lower than established DDDs for lipid-lowering drugs. Prescription differences occured between female and male patients and between age groups with regard to chronic medication. |
| Truter & Kotze (1997) | To investigate the variability of prescribed daily doses (PDDs) with respect to sex and age categories in the usage of simvastatin in South Africa. | Retrospective drug utilisation study using prescription data from various medical schemes.. | PDDs and DDDs. | Average PDDs were in all cases lower than the DDD of 15mg, except for females aged 30 to 39 years. In almost all sex and age categories, a dose of 10mg was the median as well as the mode and the standard deviation of the PDD for females and males decreased age the age of 40 to 49 years. Variation existed in the dosage regimen of simvastatin which depended on a multitude of factors, such as the severity of the disease state, sex and age. |

Both these studies were conducted in retrospect with PDDs and DDDs as the unit of measurement.

### 2.5.1.10 Conclusion to drug utilisation review

There is a definite and compelling need for drug utilisation in South Africa. Drug utilisation research is a multidisciplinary activity and the results of drug utilisation studies can be used for various purposes. It can, for example, be a part of an academic investigation, a management initiative or an audit of the performance of a drug or group of drugs. Drug utilisation research is a valuable component of quality assurance for medicine usage. It should thus be formally recognised and encouraged, and the necessary infrastructure for this type of research needs to be established in South Africa.

According to Sacristan and Soto (1994:299) the concomitant use of drug utilisation review with pharmacoeconomics can result in improved cost-effective utilisation of medicines and a better utilisation of pharmacoeconomic methods, both of which contribute to a more rational use of drugs. This in turn, can help to achieve at least one of the economic objectives of the National Drug Policy for South Africa, namely the promotion of the cost-effective and rational use of drugs (Truter, 1997:20).

The concomitant use of drug utilisation review with pharmacoeconomics can result in a more cost-effective utilisation of medicines and a better utilisation of pharmacoeconomic methods, both of which contribute to a more rational use of drugs (Sacristan & Soto, 1994:299). Pharmacoeconomics and its contents will be discussed in the subsequent paragraphs.

### 2.5.2 PHARMACOECONOMICS

#### 2.5.2.1 Introduction

Pharmacoeconomics is particularly relevant when managing the health of a group or a population and any organisation that makes use of pooled resources to pay for the health services e.g. managed health care organisations, government programmes and insurance plans (Vogenberg, 2001:2).

The proportion of prescriptions costs paid for by public financed schemes has been increasing steadily and there are also concerns about the quality of prescribing patterns as well as the effectiveness of many drugs, with some preparations having little or even no proven therapeutic value (Robays, 1999).

The treatment of coronary heart diseases places a substantial financial burden on health care resources (McMurray, 1999:100). This is because the cost of coronary heart disease is the sum of three components: (1) the medical resources used to treat the illness, (2) the non-medical resources associated with it, and (3) lost productivity due to illness (Larson, 1996:46). As a result, pharmacoeconomic analysis of the management and impediment strategies for coronary heart diseases is a valuable tool for comparing the cost-effectiveness of new medical interventions allowing health care decision makers to contain cost by choosing those interventions that are most efficient (McMurray, 1999:100). This is imperative especially because intervention to lower cholesterol levels with drugs involves large populations of patients and potentially high costs (Johannesson *et al*., 1997:332).

Economics of health care includes not merely an assessment of the cost of a new therapy, but also an assessment of its overall economic and clinical impact. The discipline of pharmacoeconomics is developed to fulfil this role (Li, 2003:192).

### 2.5.2.2 Defining pharmacoeconomics

Pharmacoeconomics identifies, measures and compares costs and consequences of medicine therapy to health care systems and the society (Carriere & Huang, 2001:19; Sanchez, 2005:1). Cantor (2002:S29) furthermore stated that pharmacoeconomics is an interdisciplinary science that incorporates elements from pharmacies, clinical medicines, clinical epidemiology, statistics, psychology, economics and ethics. More recently, Jones (2006:96) described pharmacoeconomics as an evidence-based approach that assesses whether the additional benefits associated with a medicine or medicine therapy are worth the additional costs associated with the treatment.

Pharmacoeconomics can thus be seen as a simultaneous comparison of medicines against alternative treatments (medicine based or non-medicine based) with reference to both the costs and outcomes.

### 2.5.2.3 Objectives of pharmacoeconomics

The primary objective of pharmacoeconomic analysis is to identify measures and compare the costs and consequences of pharmaceutical interventions (Venturini & Johnson, 2002). A pharmacoeconomic study is thus intended to apprise the decision maker (whether it is the patient, family, provider, a third party payer, or the policy maker) about the balance between the cost and effects of a new health care practice in comparison with an established method (Rajagopalan *et al*., 1996:1298).

Health care costs are increasing rapidly and the ageing of populations in developed countries has contributed significantly to the need for consideration of effectiveness in the evaluation of any health care treatment, especially in pharmaceuticals (Li, 2003:192). The ultimate objective of pharmacoeconomic evaluation is to compare costs and outcomes of alternative regimens, ideally by generating a single index or cost-outcome ratio (Li, 2003:194). This ratio can be generated by using the process as shown in figure 2.7.

A properly constructed pharmacoeconomic evaluation will provide valuable insights that will allow for the selection of options representing the best value for money, without compromising the quality of care that will be received (Li, 2003:199).

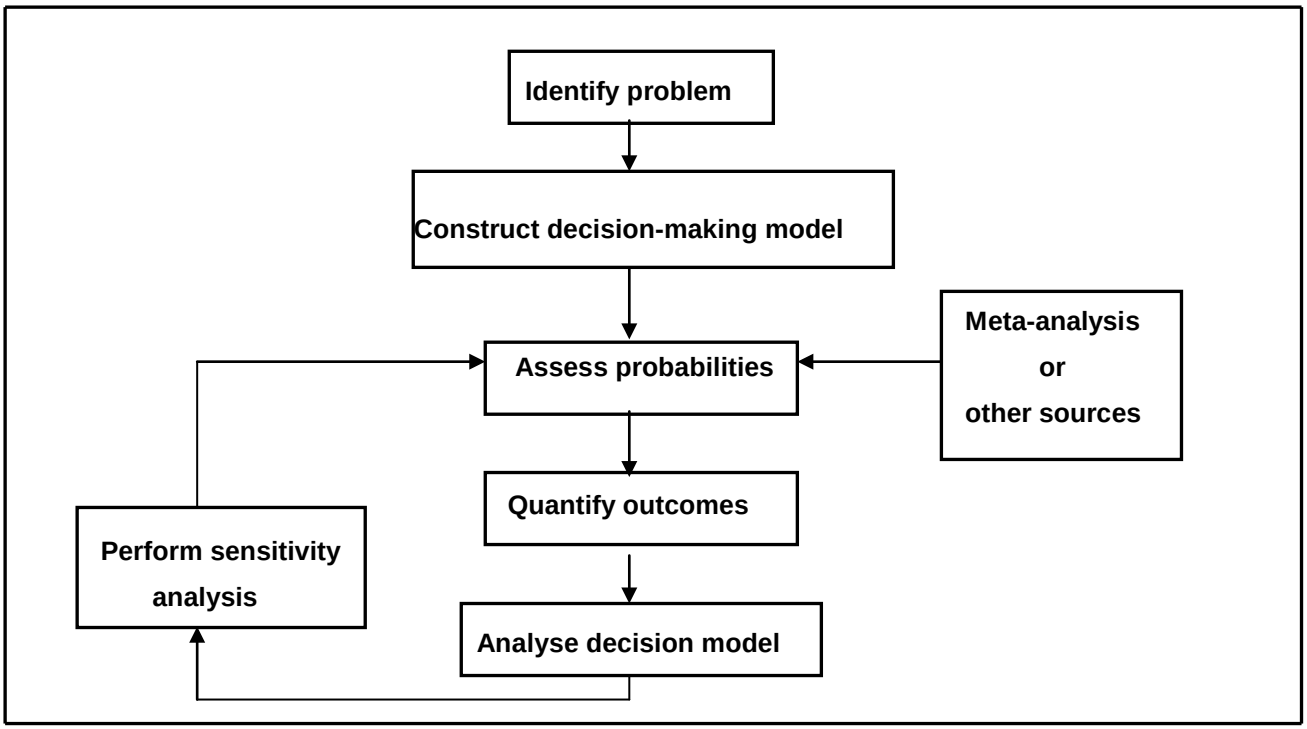


**Figure 2.7: Overview of the process of pharmacoeconomic evaluation (Li, 2003:194)**

In accordance with the pharmacoeconomic evaluation by Li (2003:194), the WHO (2000) formulated the following main steps in conducting a pharmacoeconomic evaluation:

- Define the economic question and the perspective of the study.
- Determine the treatments that need to be evaluated.
- Choose the study design.
- Identify, measure and value the costs of the alternative treatments.
- Identify, measure and value the benefits associated with the alternative treatments.
- Adjust costs and benefits for differential timing.
- Measure the incremental costs and benefits.
- Combine costs and benefits and analyse the results.
- Test the sensitivity of the results.

#### 2.5.2.4 Application of pharmacoeconomics

The proper application of a pharmacoeconomic model in clinical medicine would necessitate a multidisciplinary approach that requires expertise and inputs from clinical medicine practitioners, biostatistics and psychometrics, among others. Li (2003:192) is also of the opinion that a properly conducted pharmacoeconomic evaluation will provide valuable insight for clinicians to allow them to choose from the options that represent the best value-for-money without compromising the quality of care delivered.

Pharmacoeconomics has been lauded to be of great value in the following areas of health care delivery:

- To improve public and individual health through improved rational decision making.
- To determine relative values among alternative therapies.
- To improve system resource allocation.
- To determine whether interventions work in practice.
- To assess whether the care is of high quality.
- To assess new diagnostic tests.
- To determine whether a programme represents good value-for-money (Li, 2003:194).

To date, the most successful application of the principles of pharmacoeconomics is in the areas of purchase decision, subsidy decision, establishing practice standards and the assessment of technologies (Li, 2003:192).

#### 2.5.2.5 Methodology of pharmacoeconomics and cost-analysis

The term cost-analysis is used widely and is therefore sometimes abused (Beyea & Nicoll, 1999:1). Cost analysis is a process that examines cost-related aspects of a specific clinical process or event (Beyea & Nicoll, 1999:1). Accordingly, cost-analysis is performed to provide information that will help decision makers determine how a resource or resources will be allocated. Expenses may include direct and indirect costs and outcomes and benefits may be reflected by clinical measures or financial calculations based on the projected benefit of outcome.

There are different methodologies that exist in a pharmacoeconomic analysis such as cost-benefit analysis (CBA), cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA) (Walley *et al*., 2004:108). In table 2.19 the different methodologies and the criteria for selecting different methodologies are compared.

In subsequent paragraphs examples of the application of pharmacoeconomic studies as related to dyslipidaemia/hyperlipidaemic will be given (refer to paragraph 2.5.2.6).

**Table 2.19: Different methodologies and criteria for selecting pharmacoeconomic study methods (compiled from Chang & Nash, 1998:13; Walley *et al*., 2004:108)**

| Method of evaluation | Aim of evaluation | Costs and benefits |
|---|---|---|
| • **Cost-benefit analysis (CMA)** | Comparison of different programmes with different outcomes. | Costs and benefits are measured in pecuniary units to determine a cost benefit ratio. |
| • **Cost-minimalisation analysis (CMA)** | Comparison of similar therapies producing essentially identical outcomes. | The cost is measured for additional cost to therapy A relative to therapy B. |
| • **Cost-effectiveness analysis (CEA)** | Comparison of different therapies resulting in clinically different patient outcomes. | Measures the cost per life saved, cost per patient cured or cost per life year gained. |
| • **Cost-utility analysis (CUA)** | Comparison of similar therapies affecting quality of life. | Measures cost per Quality Adjusted Life Years (QALY) gained. |
| • **Cost-of-illness evaluation** | Compares prevention / treatment options. | Estimates the cost of a defined population. |

A discussion of these methods of pharmacoeconomics will follow subsequently.

#### 2.5.2.5.1 Cost-benefit analysis (CBA)

Cost-benefit analysis (CBA) is a type of clinical economic evaluation of the outcomes of a programme or an intervention (Carriere & Huang, 2001:19). CBA measures both the costs and the benefits in monetary terms by net benefits (total benefits - total cost) or by benefits-to-cost ratio (total benefits/total cost) (Bungay & Sanchez, 2003:32; Carriere & Huang, 2001:19).

According to Bungay and Sanchez (2003:32), in a CBA, the benefits acquired from a programme or an intervention, and all the costs of providing that programme or intervention are identified and converted into equivalent dollars in the year in which they will occur.

The consequences of CBA should be measured as the willingness-to-pay of the individuals who bear the consequences (Barner & Rascati, 2003:115; Carrier & Huang, 2001:19). These consequences include direct and indirect benefits such as explained below (Bootman *et al*., 1996:63):

- Direct benefits

  Direct benefits include the portion of averted costs currently borne that are associated with spending for health services; they represent potential savings in the avoided use of health resources (Bootman *et al*., 1996:63).

- Indirect benefits

  Indirect benefits include the potential increased earnings of productivity gains that would not have been possible without the particular health care programme (Bootman *et al*., 1996:63).

There are five steps in conducting a CBA and they are depicted in figure 2.8.

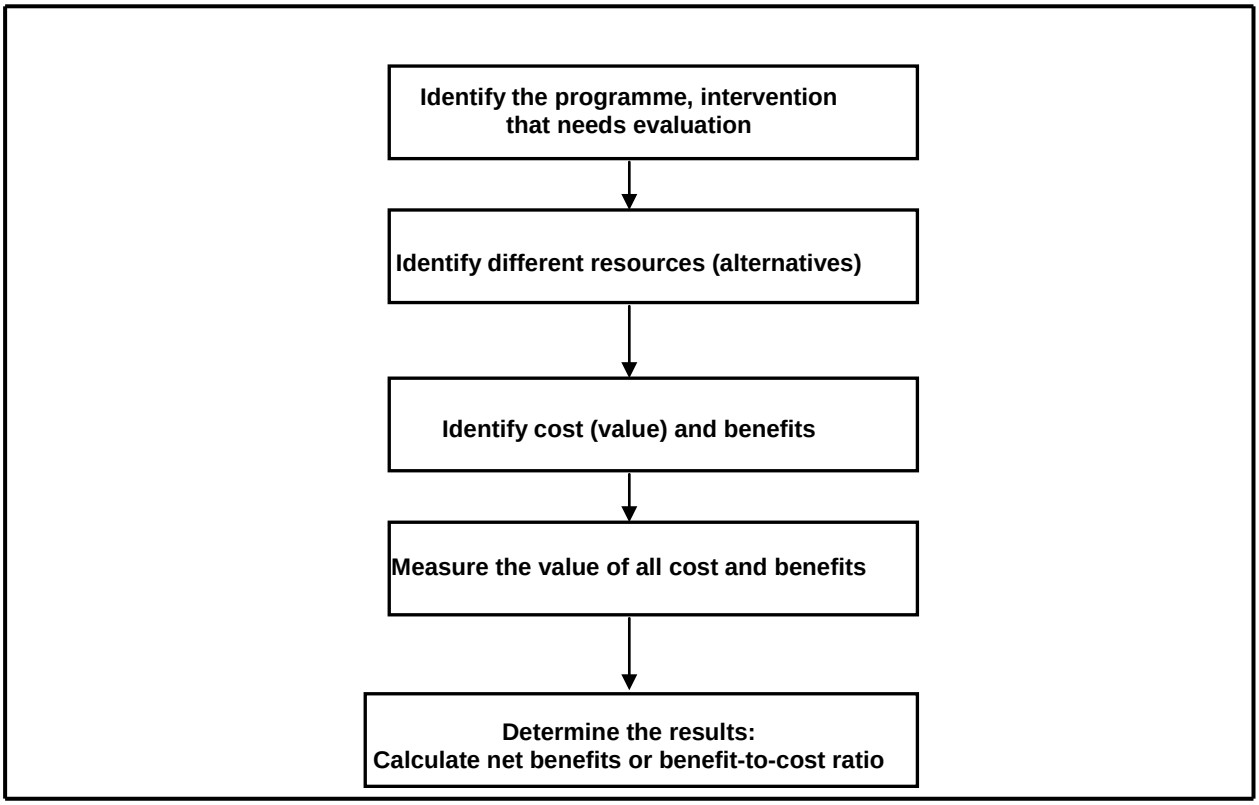


**Figure 2.8: Steps in conducting a cost-benefit analysis (Barner & Rascati, 2003:120; McGhan & Kitz, 1996:65)**

#### 2.5.2.5.2 Cost-minimisation analysis (CMA)

CMA is a technique designed to identify the preferred choice among possible alternatives with equivalent outcomes or consequences by examining the cost associated with each of those alternatives (Carriere & Haung, 2001:19). According to Bungay and Sanchez (2003:32) cost-minimalisation analysis is used to compare two or more treatment alternatives that are both equal in efficacy, and treatment alternatives are measured in monetary terms.

#### 2.5.2.5.3 Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis (CEA) compares the costs of medical interventions based on their effectiveness, in monetary terms. The effectiveness is determined independently and is measured in terms of clinical meaningfulness (e.g., life years gained) (Strom & Kimmel, 2006:474).

After a CEA an incremental cost-effectiveness ratio is calculated as in figure 2.9.

$$\text{ICER} = \frac{\text{(Cost of treatment A) – (Cost of treatment B)}}{\text{(Effectiveness of treatment A) – (Effectiveness of treatment B)}}$$

**Figure 2.9: Formula for an incremental cost-effectiveness ratio (Venturi & Johnson, 2002)**

The results express the cost that - on average - needs to be sustained to obtain "an additional success" if treatment A is chosen instead of B (e.g., cost per avoided recurrence, cost to avoid a complication, cost to avoid an adverse event, etc.) (Venturini & Johnson, 2002).

According to Edejer *et al*. (2003:5) CEAs have two main uses namely:

- CEA of a wide range of interventions can be performed to inform a specific decision maker.
- CEA of a wide range of interventions can be performed to provide general information on the relative costs and health benefits of different technologies or strategies, which contribute through multiple channels to a more informed debate on resource priorities.

The steps in performing a CEA are described in figure 2.10.

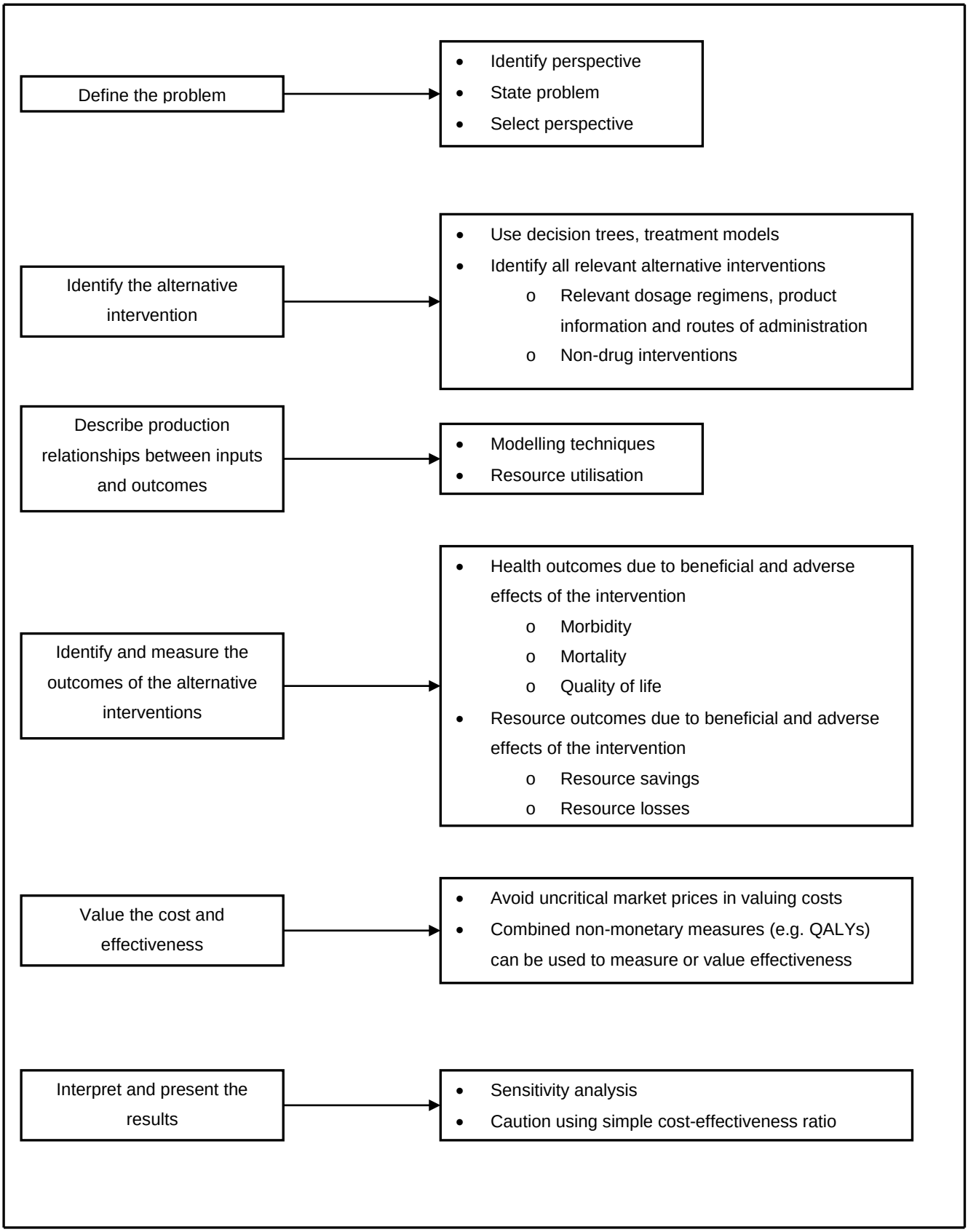


**Figure 2.10: Steps in performing cost-effectiveness analysis (Bootman *et al*., 1996:80)**

After performing a CEA there are four possible results as illustrated in Figure 2.11.

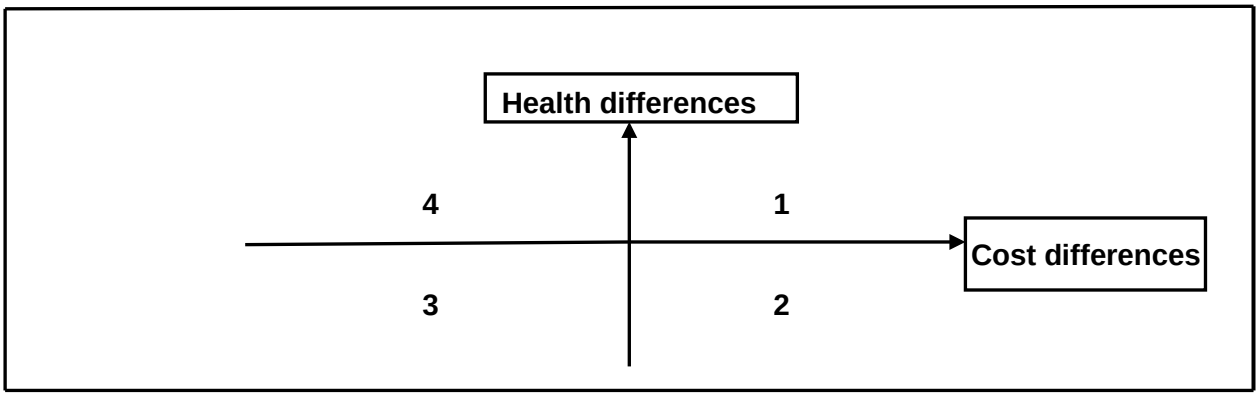


**Figure 2.11: Four possible results of a cost-effectiveness analysis (Walley *et al*., 2004:112)**

In figure 2.11 the four quadrants represent the following (Walley *et al*., 2004:112):

- **1** = the new treatment is more effective and more expensive.
- **2** = the new treatment is less effective and more expensive.
- **3** = the new treatment is less effective and less expensive.
- **4** = the new treatment is more effective and less expensive.

#### 2.5.2.5.4 Cost-utility analysis (CUA)

Cost-utility analysis (CUA) is an economic tool in which the intervention or cost of a treatment alternative is expressed in monetary terms and the outcomes or consequences in terms of patient preference or quality-adjusted-life-years gained (QALYs) (Bungay & Sanchez, 2003:33). CUA is controversial because it is difficult to place a value on health status or on an improvement in health status as perceived by different individuals or societies (WHO, 2003a:27). CUA can compare cost, quality and quantity of patient years (Bungay & Sanchez, 2003:33).

Health-related quality of life is a specific area of investigation within the field of health services and quality of life (Bungay & Sanchez, 2003:40). Quality of life (QoL) is the description of aspects or areas of physical, social and emotional health that are important and relevant to the patient (Strom & Kimmel, 2006:478).

#### 2.5.2.5.5 Cost-of-illness analysis (COI)

Bungay and Sanchez (2003:32) refer to cost-of-illness as an examination of the overall costs (direct and indirect) of a particular disease in a specific or defined population. These costs of an

illness can be used to determine the value of a treatment or a prevention strategy.
The following costs are examined in a cost-of-illness study:

- Direct costs - direct costs are the responsibility of the health care system, community and family in directly addressing the problem (Jefferson *et al*., 2000:18).

    - Direct non-medical costs - the costs caused by the illness, disease or need to seek medical care (Strom & Kimmel, 2006:474).
    - Direct medical costs - the costs included in providing medical care (Strom & Kimmel, 2006:474).

- Indirect costs - these costs do not stem directly from the transactions for services (Strom & Kimmel, 2006:474). These costs are made up from productivity losses due to the illness or disease (Jefferson *et al*., 2000:18).

- Intangible costs - these are costs of pain, suffering, grief and loss of leisure time (Jefferson *et al*., 2000:18).

### 2.5.2.6 Application of pharmacoeconomics on hipolipidaemics

Numerous studies on the application of pharmacoeconomics with hipolipidaemic agents have been conducted. Examples of such studies are presented in table 2.20.

**Table 2.20: Pharmacoeconomic studies on hipolipidaemics**

| Author & Year | Description | Study population | Type of study | Measuring unit | Outcomes / Foundings |
|---|---|---|---|---|---|
| Chaiyakunapruk *et al*. (2000) | The pharmacoeconomic impact of HMG-CoA reductase inhibitors (statins) in type II diabetes mellitus. | Patients with type II diabetes mellitus. | Cost-effectiveness analysis. | Measures the cost per life saved, cost per patient cured or cost per life year gained. | In the secondary prevention, statins have been shown to be well-tolerated, efficacious and cost-effective means of reducing cardiovascular risk. |
| Hilleman *et al*. (1999) | A population - based treat - to - target pharmacoeconomic analysis of HMG-CoA reductase inhibitors in hypercholesterolaemia. | Patients who is on HMG-CoA reductase inhibitors in Omaha, Nebraska. | Cost of illness. | Estimates the cost of a defined population. | The most cost-effective treatment approach is to individualise the selection of statins based on coronary risk and it was further recommended that atorvastatin and fluvastatin should be available in the national formulary. |

## Table 2.20: Pharmacoeconomic studies on hipolipidaemics (continued)

| | | | | | |
|---|---|---|---|---|---|
| Crouch (2000) | To determine the effective use of statins to prevent coronary heart disease. | Middle-aged patients with CHD (secondary prevention) | Cost-benefit analysis. | Pecuniary units to determine a cost benefit ratio. | Lipid-lowering therapy is relatively cost-effective compared with other interventions. In middle-aged patients with CHD (secondary prevention), the estimated cost per year of life saved as a result of statin therapy is between $4,500 and $14,000. The cost for primary prevention of CHD with a statin in middle-aged patients is about $20,000 to $40,000 per year of life saved. These figures compare with a cost of $40,000 per year of life saved for haemodialysis and $70,000 per year of life saved for coronary artery bypass surgery for one-vessel coronary disease. |
| Pedersen *et al*. (1996) | To estimate the benefits of lowering cholesterol using data from the 4S (Scandinavian simvastatin survival study). | A group of 4444 patients with coronary heart disease in Scandinavia, aged between 35 and 70 years. | Cost-minimisation analysis. | The cost is measured for additional cost to therapy A relative to therapy B. | Simvastatin therapy, produced a 10 per cent decrease in length of hospital stay, a 26 per cent reduction in number of hospitalisation events, a 31 per cent reduction in hospital costs and a 34 per cent reduction in total hospital days. As a result of these savings the cost of simvastatin was reduced. |
| Attansio *et al*. (2001) | To compare the average annual maintenance costs for simvastatin and atorvastatin in hipolipidaemic patients. | Patients being treated with statin therapy in Western Europe countries. | Cost-minimisation analysis. | The cost is measured for additional cost to therapy A relative to therapy B. | There was no significant difference between groups in the percentage of patients reaching their LDL-cholesterol goal over the study period (80% for simvastatin-treated patients versus 89 per cent for atorvastatin-treated patients. However, the cost of maintaining a similar percentage of patients at their appropriate LDL-cholesterol levels was significantly lower in the simvastatin group compared to the atorvastatin group in 13 of the 17 countries assessed. In the remaining 4 countries, there was a cost advantage for simvastatin, but it did not reach statistical significance. |

**Table 2.20: Pharmacoeconomic studies on hipolipidaemics (continued)**

| | | | | | |
|---|---|---|---|---|---|
| Johannesson *et al*. (1997) | To evaluate the cost-effectiveness of treatment with simvastatin in male and female patients with coronary heart disease aged 35 – 70 years of age. | Male and female patients aged 35 – 70 years of age with coronary heart disease | Cost-effectiveness analysis. | Measures the cost per life saved, cost per patient cured or cost per life year gained. | Simvastatin was cost-effective in patients with coronary heart disease among both men and women at the ages (from 35 to 70 years) and with cholesterol levels (< 5.2mmol/ to >6.2mmol/ℓ). |
| Huse *et al*. (1998) | To calculated the cost-effectiveness of HMG-CoA reductase inhibitors (Statins) in both primary and secondary prevention of cardiovascular heart diseases. | Patients at risk of cardiovascular heart diseases on HMG-CoA reductase inhibitor (statin) therapy. | Cost-effectiveness analysis. | Measures the cost per life saved, cost per patient cured or cost per life year gained. | Statins (simvastatin, fluvastatin, atorvastatin, lovastatin, pravastatin) included in the study were cost-effective in prevention of cardiovascular heart diseases and atorvastatin was the most cost-effective. |
| Tonkin *et al.* (2006) | Determining the cost-effectiveness on lipid-lowering therapy with statins (pravastatin) in patients with previous coronary syndromes aged 65 - 74 years of age. | Patients with previous coronary syndromes aged 65 – 75 years of age. | Cost-effectiveness analysis. | Measures the cost per life saved, cost per patient cured or cost per life year gained. | All cause mortality was lowered by 4.3 per cent in the older patients compared to a reduction of 2.3 per cent in younger patients. |

From the discussion depicted in table 2.20, most of the pharmacoeconomic studies evaluated HMG-CoA reductase inhibitors (statins), more specifictly pravastatin, simvastatin and atorvastatin. Also from table 2.20, most of these were CEA pharmacoeconomic studies.

### 2.5.2.7 Application of pharmacoeconomics in South Africa

In 2006 Jones (2006:96) stated that the full implementation of pharmacoeconomics in South Africa would not properly take place for the next two to five years since the full implementation would also require the development of capacity-building within the Department of Health and the industry. However, pharmacoeconomics is currently growing in South Africa since the International Society of Pharmacoeconomics and Outcomes Research South Africa (ISPOR) has been established in South Africa in May 2007 with the following objectives (ISPOR, 2008):

- To provide an environment and opportunity where researchers, health care practitioners and decision makers can share their views at a national and international level.
- To serve as a neutral forum in bringing together researchers, health care practitioners, and decision makers interested in pharmacoeconomics, the pharmaceutical industry, health-related organisations, public health and academia.
- To act as a facilitator together with improving the implementation of educational programmes in pharmacoeconomics and outcomes research for all members of the health care community.

#### 2.5.2.8 Conclusion to pharmacoeconomics

Bruckner *et al*. (2000) came to the conclusion that pharmacoeconomics does not give one the correct answer, nor does it take away the use of common sense, it merely introduces one to the necessary scepticism and aids in the process of decision making. Pharmacoeconomics is thus not about saving money, but rather on focusing on how to spend money so that money is saved in the process to gain advantage in reaching the endpoint.

Pharmacoepidemiology will be discussed in the subsequent section.

### 2.5.3 PHARMACOEPIDEMIOLOGY

In the subsequent paragraphs, the introduction to pharmacoepidemiology, the definition thereof and the objectives and methods of pharmacoepidemiology will be dicussed.

#### 2.5.3.1 Introduction to pharmacoepidemiology

Epidemiology is the study of the occurrence and transmission of diseases in human population and therefore epidemiological studies of drug use make use of the methods and statistical measures to study the occurrence and distribution of drug use and its associated problems (Waning & Montagne, 2001:1-2). Pharmacoepidemiology is derived from the Greek words *(pharmakon, epi, demos and logos)* meaning the study of poison (drugs/medicine) in a population (Chauvin *et al.,* 2002:455). It sums up two different areas: pharmacology (the study of interactions between drugs and living organisms) and epidemiology (Ley, 2001:386).

#### 2.5.3.2 Defining pharmacoepidemiology

Pharmacoepidemiology is defined according to Chauvin *et al.* (2002:455) as "*the application of epidemiological reasoning, methods and knowledge to the study of the uses and effects*

*(beneficial and adverse) of drugs within a large consumer population*". *A* more recent and clearer definition of pharmacoepidemiology was put forward by the World Health Organization (2003a:8) as the study of the use and effects / side-effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes.

Strom (2006:3) defines pharmacoepidemiology as the study of the use and effects of medicine in large numbers of people. Pharmacoepidemiologal studies have the ability to find associations between a drug/drug class and one or more clinical events that had been missed under the strictly controlled conditions of therapeutic trials (Fautrel, 2004:175).

Pharmacoepidemiological studies often make useful contributions to our knowledge about effectiveness and safety, because unlike clinical trials, they assess drug effects in large, heterogenous populations of patients over longer periods of time (WHO, 2003a:9). With the rapidly growing use of epidemiological techniques, came the recognition of pharmacoepidemiology as a new discipline (Bergman, 2001:31).

#### 2.5.3.3 Focus and objectives of pharmacoepidemiology

Initially the basic focus of pharmacoepidemiology was on the safety of individual drug products (pharmacosurveillance), but now it also includes studies on their beneficial effects (WHO, 2003a:9). As a result, pharmacoepidemiology focuses on pharmaceutical care outcomes and the identification of potential and realised drug-related problems. Though it has been used to examine drug epidemics, it can also be used to study illicit drug use. The idea of pharmacoepidemiology is to measure the source, diffusion, use and effects of drug use in a population and to determine the frequency and distribution of drug use outcomes in that population (Waning & Montagne, 2001:4).

Stewart (1978:122) indicates that pharmacoepidemiology has the following objectives:

- Assess medicine use patterns.
- Document prescriber physicians' prescribing habits.
- Assess toxicity of chronic medications.
- Monitor a patient using medication.
- Monitor why medicine is being used.
- Perform drug cost analysis.
- Document clinical efficacy of medicines.
- Collect information on new uses of a medicine.

- Alert health care systems of possible medicine-related problems.

### 2.5.3.4 Pharmacoepidemiological study designs and research methods

A brief description of the different pharmacoepidemiological study designs and research methods will now be discussed in table 2.21.

**Table 2.21: Different pharmacoepidemiological study designs and research methods**

| Type of pharmacoepidemiological study | Description of the type of pharmacoepidemiological study |
|---|---|
| • **Cross-sectional study** | A prevalence survey of health and illness in the population at one point in time (Waning & Montagne, 2001:5). |
| • **Case-control study** | A retrospective analysis comparing subjects with the condition (referred to as cases) to those without it (referred to as controls) with respect to possible risk of getting the disease or causative factors for the diseases (Strom, 2006:19; Waning & Montagne, 2001:5). |
| • **Cohort study** | An incidence study that is usually prospective or longitudimal. This incidence study follows a population free of health problems over time, examining subsequent development of problems and factors associated with them (Strom, 2006:19; Waning & Montagne, 2001:5). |
| • **Clinical trials** | An experimental approach that tests the value of a new treatment or intervention and compares it with the standard treatment or a placebo. This investigator controls the therapy that each participant receives (Strom, 2006:21; Waning & Montagne, 2001:5). |
| • **Case reports** | These are reports of events that are observed in patients and not in groups. It describes a single patient who was exposed to a drug and who experienced an adverse outcome (Strom, 2006:18). |

Based on the aforementioned discussions, Chaunvin *et al*. (2002:456) presented the types of epidemiological studies as illustrated in figure 2.12.

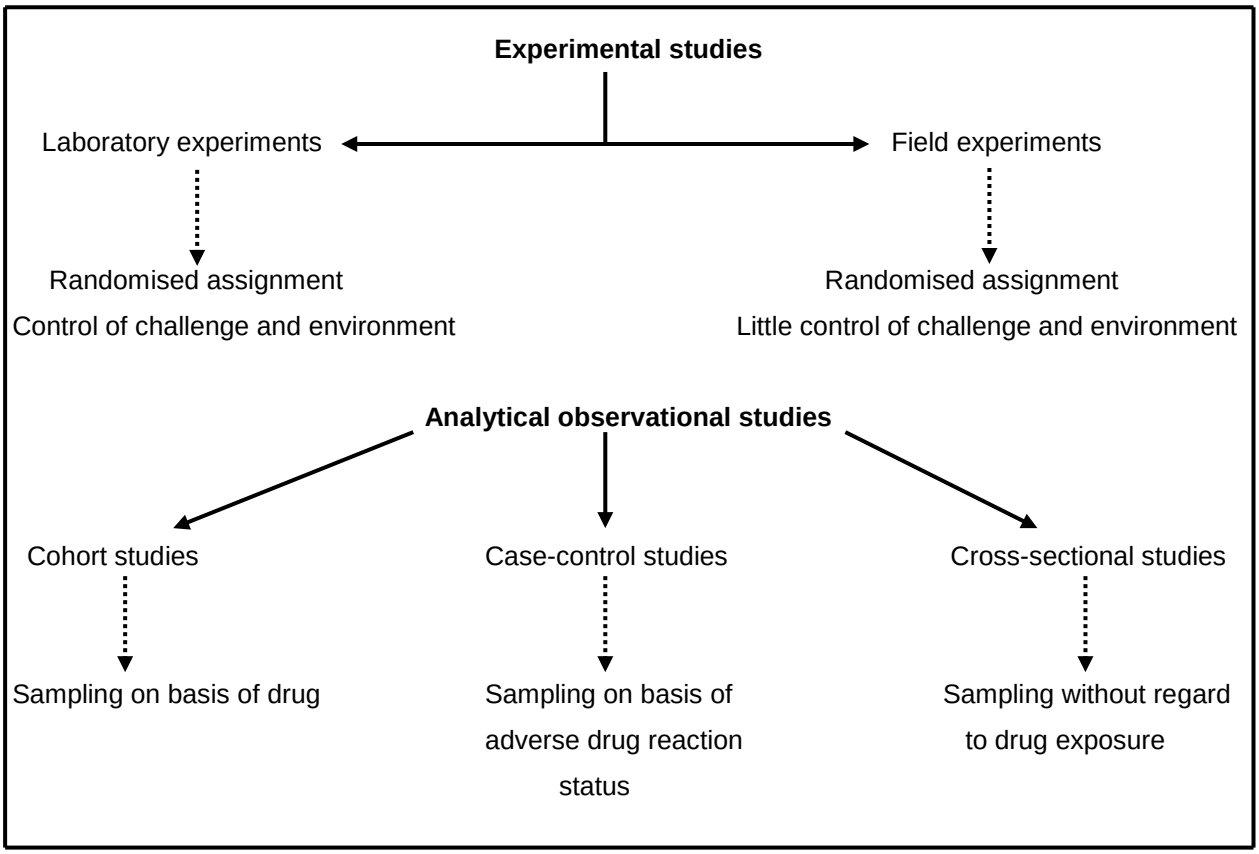


**Figure 2.12: Types of epidemiological studies (Chauvin *et al.,* 2002:456)**

### 2.5.3.5 Application of pharmacoepidemiology

In a population-based, case-control study by Meier *et al.* (2000:3205) whose objective was to determine whether statins, fibrates, or other lipid-lowering drugs were associated with reduced bone fracture risk, it was found that current exposure to statins is associated with a decreased risk of fractures in individuals aged 50 years and older.

Eaton *et al.* (2002:1389) quantified the effect of statins on 1-year mortality, hospitalisations and decline in physical functions among patients with cardiovascular disease aged 65 and older in nursing homes. In this retrospective cohort study it was found that the prevalence of statins was 2.6 per cent. Statin use was varied according to gender, age, comorbid condition, medication use, and cognitive and physical function. It was concluded that statin therapy improved clinical outcomes; including reduction in 1-year all cause mortality. Statin therapy also decreased death and hospitalisation in older population groups presenting with cardiovascular diseases.

A pharmacoepidemiological investigation into the drug management of four chronic disease states in South Africa was conducted by Truter in 1999 (also refer to table 2.15).

In the subsequent section, evidence-based medicine will be discussed.

### 2.5.4 EVIDENCE-BASED MEDICINE

Evidence-based medicine remains a much debated topic for clinicians, purchasers, planners and the public (van der Merwe, 2002:11). Dickersin *et al*. (2007:334) stated that the term 'evidence-based medicine' was coined in 1991 by a group at McMaster University, Ontario, and it arose from a confluence of events and changes in culture.

#### 2.5.4.1 Defining the concept evidence-based medicine

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients, which means integrating individual clinical evidence with the best available clinical external evidence obtained from systematic research (Bedenoch & Heneghan, 2002:1; van der Merwe, 2002:11). Dickersin *et al*. (2007:334) define evidence-based medicine as a part of the health care practice that is based on integrating knowledge which is gained from clinical expertise, research evidence and the patients' values and circumstances.

It can thus be concluded that evidence-based medicine is part of an integrated health system which gains knowledge from the analytical clinical research of evidence, which they use for formulating standard criteria for patient treatment.

#### 2.5.4.2 Objectives and steps in evidence-based medicine

Since evidence-based medicine arose from a confluence of events and changes in culture, Dickersin *et al*. (2007:334) further state that there is a growing recognition which includes the following:

- The systematic synthesis of dependable information on a topic has greater value than conventional reviews.
- Tragedy can result from paying attention to poor quality evidence instead of good quality evidence.
- Results in many individual studies can be explained with bias, and randomised clinical trials are now recognised as the study design that is best suited for avoiding bias in questions of intervention effectiveness.
- Medical literature is growing exponentially.
- Clinicians need information and they do not get enough from the sources they use.

- Undesirable gaps and variation may or do exist in practice.

There are 5 steps in the evidence-based medicine process according to Meyrs (2002:47) namely: formulation of a clear clinical question about the patient's problem, searching the literature for relevant clinical questions, evaluating the evidence for its validity and usefulness, implementing useful findings in clinical practice and evaluating the entire process. These steps can be explained with the usage of the three-loop cycle as illustrated in figure 2.13, which will be discussed subsequently.

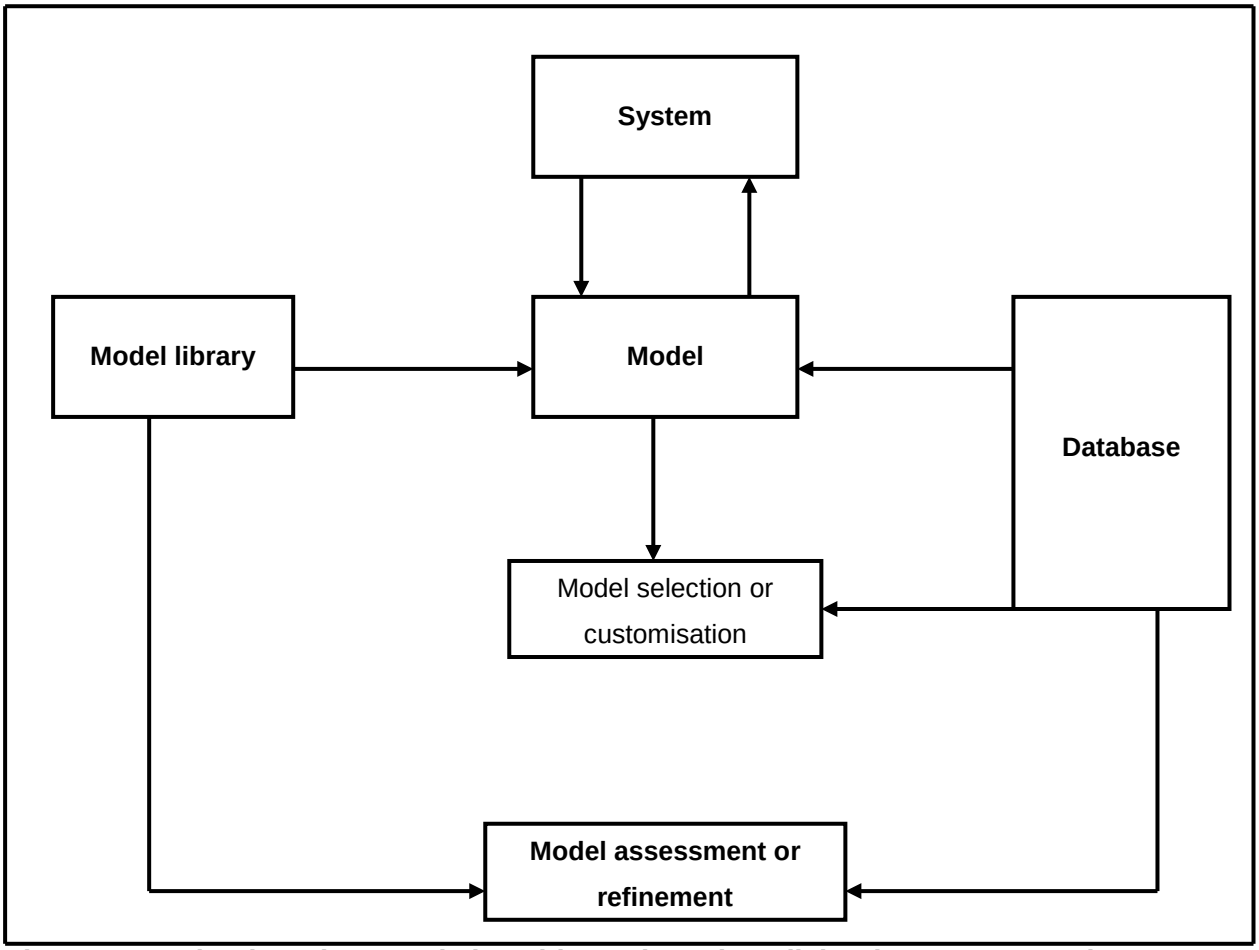


**Figure 2.13: The three-loop cycle in evidence-based medicine (Meyrs, 2002:48)**

- **Formulating a clear clinical question about a patient's problem (Step 1)**

The clinical question can be related to the specific diagnosis, prognosis, treatment, iatrogenic harm and the quality of care. The question must be specific and must contain the following three essential aspects (Meyrs, 2002:61):

  - The type of patient.
  - The clinical intervention.
  - The clinical outcome.

- **Searching the literature for relevant clinical articles (Step 2)**

This is done in order to find the most relevant studies in the literature on the internet or on the database. The evidence, however, must be concrete and medically correct (Meyrs, 2002:61).

- **Evaluating the evidence for validity and usefulness (Step 3)**

With this step it is essential to ensure that the evidence is valid for clinical use, and if this article is relevant the clinicians can rely on the content to provide guidance for an intervention (Meyrs, 2002:61).

- **Implementing useful findings in clinical practice (Step 4)**

The founded evidence can be implemented into the health care sector; the clinician can then implement it into the patient's care protocol which can be used as a guideline for future care programmes (Meyrs, 2002:61).

- **Evaluating the entire process (Step 5)**

The evidence-based medicine process as a whole should be re-evaluated regularly to determine shortcomings, thus the process will regularly be updated and improved (Meyrs, 2002:61).

#### 2.5.4.3 Evidence-based medicine in South Africa and the future

Evidence-based medicine has not yet been fully implemented in South Africa, though some studies have been done with great findings and results which proved that implementation of evidence-based medicine in South Africa can lead to improved quality of care, as well as improved cost of care. Craig *et al*. (2001:254) state that evidence-based medicine as part of a health care organisation has three tasks for the future namely:

- To implement the evidence summaries in the clinical practice.
- To continuously develop and update the systematic reviews or evidence-based guidelines in their area of knowledge.
- To encourage patients to take part in studies of treatment, diagnosis and prognosis on which the medical practice is based.

## 2.6 CHAPTER SUMMARY

In this chapter the following aspects were discussed: dyslipidaemia, managed health care, drug utilisation review (DUR), pharmacoeconomics, pharmacoepidemiology and evidence-based medicine. These discussions correlate with general and specific goals and aims of this study as had been presented previously.

Chapter 3 will provide a gereral layout of the empirical investigation of this study.