Burden of rheumatoid arthritis in the private health sector: medicine cost and comorbidities

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Dissertation submitted in fulfilment of the requirements for the degree *Master of Pharmacy* in Pharmacy Practice at the Potchefstroom Campus of the North-West University

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Graduation May 2018

Student number: 23465174

ACKNOWLEDGEMENTS

My sincerest gratitude is for my supervisor, Prof JR Burger, for her excellent guidance, support, extraordinary expertise and effort which helped me to pursue excellence. She inspired me by setting a remarkable example. Words cannot describe how grateful I am towards Prof Burger. Thank you for your great amount of patience, your devoted attention and your advice at any time of any day, Prof.

I would furthermore like to express my sincere appreciation to the following people:

Prof MS Lubbe, in her capacity as co-supervisor, for her assistance, guidance and valuable time spent on data analyses and throughout the rest of this study.

Dr R Joubert, in her capacity as co-supervisor, for her assistance and advice throughout this study.

Mrs A Naudé, in her capacity as assistant supervisor, for her support and advice throughout this study.

Mrs M Cockeran for her expertise and the time she spent on the statistical analysis for manuscript one.

Ms A Bekker for her assistance regarding data analysis.

Mrs H Hoffman for the time she spent on proofreading chapter one, the literature review and reference list with utmost attention to detail.

Mrs A Potgieter for her fast and thorough assistance with the language editing of this study.

Mrs E Oosthuizen for her assistance with the technical editing of this study, her kind and encouraging words, administrative support and willingness to help with anything and everything.

The Pharmaceutical Benefit Management Company for providing the data for this study.

The North-West University for financial and technical support.

Jo-Ancóbe, Danelle and Mavis, thank you for lending shoulders and ears on days that seemed too long. I am thankful for the friendships that we developed.

Laurendt, my love, thank you for all the support throughout these two years. A special thanks for all your help regarding the interpretation and explanation of the statistics of the study, offered with so much love and patience. Although it did not always seem that way, your optimism and kind words of encouragement in times of despondence were much appreciated.

My mom and dad, Annelise and Neels, I am immensely grateful for the opportunity you granted me, with the grace of our Heavenly Father, to pursue a masters degree. Thank you for your love and support and for always believing in me. My brother Córne, thank you for the sincere interest you showed in my work.

My friend Marietha, a special thanks for your endearing words of encouragement shared over every, much needed cup of coffee.

Above all, praise and glory to our Heavenly Father for all the blessings I receive and for His unfailing love and grace that restore my faith. He gave me strength to persevere with excellence. My God, my anchor.

PREFACE

This dissertation was conducted in article format. The dissertation is divided into four chapters. Chapter 1 provides an outline of the study and sets out the problem statement, research aims and objectives, and the method followed to conduct the empirical investigation. Chapter 2 is a comprehensive literature review to fulfil the literature objectives stated for this study. Chapter 3 contains the results of the empirical investigation, written as two manuscripts and additional paragraphs. The final chapter concludes this study, highlighting the study's limitations and strengths and making recommendations for future research. The reference list and annexures are available at the end of the dissertation.

The manuscripts were prepared for submission to the journals below for publication:

- Rheumatology international
- Value in health regional issues

Both manuscripts and their reference lists were written according to the author guidelines specified by each respective journal (Annexures E and F). The complete reference list of the dissertation is, however, compiled according to the Harvard referencing style of the North-West University.

The supervisor and co-supervisors of the study acted as co-authors in the manuscripts. The contributions of each author for both manuscripts are subsequently outlined.

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 1

The contributions of each author regarding manuscript 1, **"Chronic disease list conditions in patients with rheumatoid arthritis in the private healthcare sector of South Africa"**, were as follow:

Author	Role in study
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Prof MS Lubbe (Co-supervisor)	Co-supervision of study and manuscript concept Data and statistical analysis Revising and approval of the final manuscript version
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Mrs M Cockeran (Statistician)	Data and statistical analysis Verifying the results from the statistical analysis Revising and approval of the final manuscript version

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of N Olivier.

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Prof MS Lubbe

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Mrs M Cockeran

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 2

The contributions of each author regarding manuscript 2, **"Antirheumatic prescribing patterns and direct medicine costs in the South African private health sector"**, were as follow:

Author	Role in study
Ms N Olivier	Planning and designing of the study Data and statistical analysis Interpreting the results Manuscript writing
Prof JR Burger (Supervisor)	Supervision of study and manuscript concept Data and statistical analysis Guidance and interpretation of the results Revising and approval of the final manuscript version
Prof MS Lubbe (Co-supervisor)	Co-supervision of study and manuscript concept Data and statistical analysis Revising and approval of the final manuscript version
Dr R Joubert (Co-supervisor)	Co-supervision of study and manuscript concept Revising and approval of the final manuscript version
Mrs A Naudé (Assistant supervisor)	Guiding of the study and manuscript concept Revising and approval of the final manuscript version

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of N Olivier.

Prof JR Burger

Prof MS Lubbe

Dr R Joubert

Mrs A Naudé

ABSTRACT

Title: Burden of rheumatoid arthritis in the private health sector: medicine cost and comorbidities

Keywords: burden of disease, comorbidity, direct medicine treatment cost, medicine claims data, medicine utilisation, prevalence, rheumatoid arthritis, South Africa

The purpose of the study was to determine the prevalence of rheumatoid arthritis (RA) and associated comorbidities, as well as to investigate antirheumatic prescribing patterns, direct medicine treatment cost and the impact of comorbidities on the total annual direct medicine cost per patient diagnosed with RA in the private healthcare sector of South Africa. The study consisted of two phases: a literature review and an empirical investigation. The objective of the literature review was to provide an overview of RA, including the burden of the disease (i.e. its prevalence, comorbidities and economic impact). The empirical investigation (a drug utilisation review (DUR) study) followed a quantitative, non-experimental (descriptive), cross-sectional design. Retrospective medicine claims data provided by a South African Pharmaceutical Benefit Management (PBM) company for the period 1 January 2014 to 31 December 2014 were analysed. Data for a total of 4 352 patients with an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis code for RA (e.g. M05, M06 and M08) in conjunction with a claim for medicine paid from a patient's prescribed minimum benefits (PMBs) was analysed.

Patients with RA represented 0.5% of the total number of beneficiaries registered on the database during 2014 (N = 838 618). A total of 3 016 (69.3%) patients had RA and at least one other chronic disease list (CDL) condition. The gender ratio of female to male was 3:1 in the study population as a whole and also in both respective disease groups (i.e. patients with RA only and patients with RA and other coexisting CDL conditions). The study population had a mean age of 60.32 ± 14.29 years (95% CI 59.90-60.75); however, patients with RA and other CDL conditions (mean age 63.59 ± 12.26; 95% CI 63.15-64.02) were meaningfully older than those patients with RA only (mean age 52.96 ± 15.76; 95% CI 52.11-53.80). Hypertension was the most prevalent CDL condition, recorded in 47.5% of RA patients. Other CDL conditions that coexisted with RA the most often were hyperlipidaemia (25.9%), hypothyroidism (19.7%), type 2 diabetes mellitus (11.4%), asthma (7.8%), cardiac failure (3.8%), glaucoma (2.5%), dysrhythmias (2.2%), epilepsy (2.1%) and bipolar mood disorder (1.9%). The odds of having cardiovascular disease (CVD) risk factors (i.e. a combination of hyperlipidaemia, hypertension and type 2 diabetes mellitus) co-occur with hypothyroidism were 2.5 times lower among men than among women.

The total annual direct medicine treatment cost of RA summed to R59 264 203.68 for the study population in 2014. The mean (median) cost per medicine item for patients with RA only was

R746.36 ± 3 846.09 (R127.21) whereas that for patients with RA and coexisting CDL conditions was R623.27 ± 3 494.73 (R130.33); as such, there was no practical significant difference in the mean cost per medicine item for patients with RA only and for those with RA and coexisting CDL conditions (Cohen's $d < 0.1$). The drugs representing the 90% drug utilisation (DU90%) segment for phase one treatment were celecoxib (26.6%), meloxicam (24.4%), prednisone (20.5%), diclofenac (7.7%), etoricoxib (7.3%), piroxicam (2.9%) and diclofenac/misoprostol (2.2%), these drugs accounting for 92.8% of the total annual medicine cost. The DU90% for phase two treatment consisted of methotrexate (26.5%), prednisone (14.7%), sulphasalazine (10.2%), chloroquine (9.8%), meloxicam (8.9%), celecoxib (7.2%), diclofenac (3.8%), leflunomide (3.2%), etoricoxib (3.0%), naproxen/esomeprazole (1.3%), betamethasone (1.2%) and methylprednisolone (1.2%), these drugs accounting for only 34.7% of the total annual medicine cost.

Rheumatoid arthritis patients with coexisting hypertension generated the highest total annual direct medicine treatment cost among patients with RA and other coexisting CDL conditions at R9 124 831.15, accounting for 15.4% of the total cost of RA for 2014. However, analysis showed no practical significant difference in the mean cost per item of patients with RA only (R746.36 ± 3 846.09) and those with RA plus hypertension (R544.38 ± 2 983.08) (Cohen's $d < 0.1$). The presence of coexisting CDL conditions showed no practical significant impact on the total direct medicine cost of RA in patients from the study population.

In conclusion, this study established base-line estimates of the prevalence of RA and coexisting CDL conditions and of the direct medicine treatment costs, and investigated antirheumatic medicine prescribing patterns of patients with RA in a section of the private healthcare sector of South Africa.

UITTREKSEL

Titel: Las van rumatoïede artritis in die private gesondheidsektor: medisynekoste en komorbiditeite.

Sleutelwoorde: siektelas, komorbiditeit, direkte medisynebehandelingskoste, medisyne-eisedatabasis, medisyneverbruik, voorkoms, rumatoïede artritis, Suid-Afrika

Die doel van die studie was om die voorkoms van rumatoïede artritis (RA) en geassosieerde komorbiditeite te bepaal, asook om die antirumatiese voorskryfpatrone, direkte medisynebehandelingskoste en invloed van komorbiditeite op die totale jaarlikse direkte medisynekoste per pasiënt wat gediagnoseer is met RA in die private gesondheidsorgsektor van Suid-Afrika te ondersoek. Die studie het twee fases behels: ’n literatuurstudie en ’n empiriese ondersoek. Die doel van die literatuurstudie was om ’n oorsig van RA te verskaf, insluitend die siektelas (d.i. die voorkoms, komorbiditeite en ekonomiese impak). Die empiriese ondersoek (‘n medisyneverbruiksevalueringstudie (“DUR”)) het ’n kwantitatiewe, nie-eksperimentele (beskrywende) dwarssneestudie-ontwerp gevolg. Medisyne-eisedata vir die periode 1 Januarie 2014 tot 31 Desember 2014 wat vanaf ’n Suid-Afrikaanse Farmaseutiese Voordele Bestuursmaatskappy verkry is, is retrospektief ontleed. Data vir ’n totaal van 4 352 pasiënte met ’n Internasionale Statistiese Klassifikasie van Siektes en Verwante Gesondheidsprobleme, 10de Hersiening (“ICD-10”-kode) vir RA (bv. M05, M06 en M08) en ’n medisyne-eis wat uit hul voorgeskrewe minimum voordele betaal is, is ontleed.

Pasiënte met RA het 0.5% van die totale getal geregistreerde begunstigdes op die databasis in 2014 (N = 838 618) verteenwoordig. ’n Totaal van 3 016 (69.3%) pasiënte het RA en ten minste een ander kroniese siektelys (“CDL”) toestand gehad. Die verhouding vrouens tot mans was 3:1 vir die studiepopulasie as geheel en ook binne elke afsonderlike siektegroep (d.i. pasiënte met slegs RA en pasiënte met RA en meegaande CDL toestande). Die studiepopulasie se gemiddelde ouderdom was 60.32 ± 14.29 jaar (95% CI 59.90-60.75); pasiënte met RA en ander CDL toestande (gemiddelde ouderdom 63.59 ± 12.26; 95% CI 63.15-64.02) se ouderdom was egter betekenisvol hoër as dié van pasiënte met slegs RA (gemiddelde ouderdom 52.96 ± 15.76; 95% CI 52.11-53.80). Hipertensie was die CDL toestand wat die meeste voorgekom het en in 47.5% van die RA pasiënte gedokumenteer is. Ander meegaande CDL toestande met ’n hoë voorkoms sluit in hiperlipidemie (25.9%), hipertiroïdisme (19.7%), tipe 2 diabetes mellitus (11.4%), asma (7.8%), hartversaking (3.8%), gloukoom (2.5%), disritmieë (2.2%), epilepsie (2.1%) en bipolêre gedragsversteuring (1.9%). Die waarskynlikheid dat risikofaktore vir kardiovaskulêresiektes (d.i. ’n kombinasie van hiperlipidemie, hipertensie en tipe 2 diabetes mellitus) en hipotiroïdisme saam voorkom, was 2.5 keer laer onder mans as onder vrouens.

Die totale jaarlikse direkte medisynebehandelingskoste vir RA vir die studiepopulasie in 2014 het R59 264 203.68 beloop. Die gemiddelde (mediaan) koste per medisyne-item vir pasiënte met slegs RA was R746.36 ± 3 846.09 (R127.21) terwyl dié vir pasiënte met RA en meegaande CDL toestande R623.27 ± 3 494.73 (R130.33) beloop het; aanduidend van geen praktiese betekenisvolle verskil in die gemiddelde koste per medisyne-item tussen pasiënte met slegs RA en diegene met RA en saambestaande CDL toestande nie (Cohen se d < 0.1). Medisyne wat die 90% medisyneverbruiksegment ("DU90%") vir fase een van die behandeling verteenwoordig het, sluit in selekoksib (26.6%), meloksikaam (24.4%), prednisoon (20.5%), diklofenak (7.7%), etorikoksib (7.3%), piroksikaam (2.9%) en diklofenak/misoprostol (2.2%), en was vir 92.8% van die totale jaarlikse medisynekoste verantwoordelik. Die DU90% vir fase twee van die behandeling sluit in metotreksaat (26.5%), prednisoon (14.7%), sulfasalasien (10.2%), chlorokien (9.8%), meloksikaam (8.9%), selekoksib (7.2%), diklofenak (3.8%), leflunomied (3.2%), etorikoksib (3.0%), naproksen/esomeprasool (1.3%), betametasoon (1.2%) en metielprednisoloon (1.2%), en was vir slegs 34.7% van die totale jaarlikse medisynekoste verantwoordelik.

Rumatoïde artritis pasiënte met meegaande hipertensie het die hoogste totale jaarlikse direkte antirumatiese medisynebehandelingskoste onder pasiënte met RA en ander meegaande CDL toestande beslaan, teen R9 124 834.15, wat vir 15.4% van die totale koste van RA in 2014 verantwoordelik was. Ontleding het egter getoon dat daar geen prakties betekenisvolle verskil in die gemiddelde koste per item vir pasiënte met slegs RA (R746.36 ± 3 846.09) en pasiënte met RA en hipertensie (R544.38 ± 2 983.08) was nie (Cohen's d < 0.1). Die teenwoordigheid van meegaande CDL toestande het geen prakties betekenisvolle invloed gehad op die totale direkte antirumatiese medisynekoste van RA pasiënte in die studiepopulasie nie.

Ten slotte, hierdie studie het basislynberamings verskaf van die voorkoms van RA en saambestaande CDL toestande, van die direkte medisynebehandelingskoste, en het antirumatiese medisynevoorskryfpatrone ondersoek van pasiënte met RA in die private gesondheidsorgsektor van Suid-Afrika.

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LIST OF ABBREVIATIONS AND ACRONYMS

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
AICAR	Amino-imidazolecarboxamide ribonucleotide
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
ANOVA	Analysis of variance
APC	Antigen presenting cell
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body mass index
CBC	Complete blood count
CD	Cluster differentiated
CDAI	Clinical disease activity index
CDC	Centers for Disease Control and Prevention, United States of America
CDL	Chronic disease list
CI	Confidence interval
CMS	Council for Medical Schemes
COPD	Chronic obstructive pulmonary disease

COX	Cyclo-oxygenase
CRP	C-reactive protein
CVD	Cardiovascular disease
CXR	Chest X-ray
DALY	Disability-adjusted life years
DAS-28	Disease activity score in 28 joints
DGA	Physician global assessment
DMARDs	Disease modifying antirheumatic drugs
DoH	Department of Health
DUR	Drug utilisation review
DU90%	90% Drug utilisation segment
ED	Emergency department
ESR	Elevated sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GDP	Gross domestic product
HAQ	Health assessment questionnaire
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-DRβ1	Human leukocyte antigen-D related β1

HRCT	High resonance computed tomography
HRQoL	Health-related quality-of-life
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
Ig	Immunoglobulin
IL	Interleukin
IM	Intra-muscular
INF-ɣ	Interferon-gamma
IQR	Interquartile range
JAK	Janus kinase
MHC	Major histocompatibility complex
MS	Multiple sclerosis
MTX	Methotrexate
MRI	Magnetic resonance imaging
NAPPI	National Pharmaceutical Product Interface
NEC	Not elsewhere classified
NHRPL	National Health Reference Price List
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases, United States Department of Health and Human Services
NOS	Not otherwise specified
NRAS	National Rheumatoid Arthritis Society, United Kingdom

NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OR	Odds ratio
PBM	Pharmacy benefit management
PFT	Pulmonary function tests
PGA	Patient global assessment
PMB	Prescribed minimum benefits
PO	By mouth
QALY	Quality-adjusted life years
QoL	Quality-of-Life
QUEST-RA	International Quantitative Standard monitoring of patients with rheumatoid arthritis
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SARAA	South African Rheumatism and Arthritis Association
SARS	South African Revenue Service
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified disease activity index
SEP	Single exit price

SJC	Swollen joint count
SLE	Systemic lupus erythematosus
SPERA	Standard Protocol to Evaluate Rheumatoid Arthritis
TJC	Tender joint count
TNFα	Tumour necrosis factor alpha
URI	Upper respiratory tract infections
VAS	Visual analogue scale
VAT	Value added tax
WHO	World Health Organization
YLD	Years lived with disability
YLL	Years of life lost

LIST OF DEFINITIONS

Active erosive disease

For a disease to qualify as an active erosive disease, (i) a cortical break needs to be present on the radiographs of both hands and feet in any of the following locations: the proximal interphalangeal joints, the metacarpophalangeal joints, the wrist (considered as one joint) and the metatarsophalangeal joints; and (ii) a minimum of three of these separate joints needs to be affected (Van der Heijde *et al.*, 2013:479).

Acute phase response

This term defines a pathophysiological defence mechanism which is present in both acute and chronic inflammation. This defence mechanism causes a change in the serum concentration of certain proteins/biomarkers, the latter being able to act as either pro- or anti-inflammatory agents after tissue damage has occurred (Neto & de Carvalho, 2009:421).

Anti-citrullinated protein antibody

Anti-citrullinated protein antibodies (ACPAs) are auto-antibodies that attack an individual's own peptides and proteins that are citrullinated. They are commonly found in patients with RA, which also makes them useful alternatives for sensitive and specific biological markers in the diagnosis of RA, such as the rheumatoid factor (RF) (Szekanecz *et al.,* 2008:26).

Burden of disease

'Burden of disease' can be defined as the overall impact of a health problem and refer to, among other, incidence, prevalence, cost of illness, morbidity and mortality (De Lissovoy, 2007:1047). The 'societal burden of disease' is often measured as quality-adjusted life years (QALYs) or disability-adjusted life years (DALYs) (De Lissovoy, 2007:1046; Econex, 2009:1). On the other hand, the 'economic burden of disease' measures the total cost on the overall economy, categorised under three major components: direct medical care costs, direct nonmedical costs and indirect costs (Santerre & Neun, 2010:66).

Chronic disease

Chronic diseases are also known as 'non-communicable diseases', generally progress slowly with long-lasting effect and are not contagious/transmissible (Bobrow & Ehrlich, 2014:248). These diseases cannot be prevented by vaccines or cured with medication treatment (World Health Organization (WHO), 2014).

Chronic Disease List (CDL)

The CDL of South Africa comprises of 26 chronic/non-communicable diseases and HIV (human immunodeficiency virus)/AIDS (acquired immunodeficiency syndrome). These are diseases for which a patient's medical scheme, by law, not only has to cover medication costs, but also the costs of physicians' consultations and tests associated with the condition (Council for Medical Schemes (CMS), 2017a).

Comorbidity

'Comorbidity' may be defined as 'coexisting diseases"', 'multiple pathology', or 'multi-morbidity', all of these terms referring to the simultaneous presence of several acute or chronic diseases in an individual, without any mention or identification of an index disease (Valderas *et al.,* 2009:358). On the other hand, the term 'comorbidities' may also signify diseases which co-occur at a significantly higher rate than expected by chance alone, these diseases being alternatively defined as 'co-occurring diseases', 'concomitant diseases' or 'disease clustering' (Meghani *et al.*, 2013:2). For the purposes of this study, the term 'comorbidity' describes a medical condition that is present at the time of, or after, diagnosis of an index disease, without implying that the coexisting medical condition is an outcome of the index disease (Ording & Sørensen, 2013:200).

Cost

The cost of a product or service is the monetary value of the resources consumed in its production or delivery; thus, it can be defined as the magnitude of resources consumed, which includes labour, equipment and supplies (Larson, 2005:48).

Cost driver

Cost drivers can be described as any factor(s) that influence the cost of an activity; an activity is resource demanding and a resource is costly (Touré, 2017). Both price and volume influence expenditure on medicines (Gray, 2009:16).

Direct medical costs

Those costs associated directly with a healthcare intervention, including the costs of medical tests, -examinations, -treatment and -supplies, staff time, accommodation and, overheads, as well as capital costs (Elliott & Payne, 2005:47; Santerre & Neun, 2010:66).

Erosion score

A method that was developed to describe the severity of radiologic abnormalities in the hands and wrists of patients with RA, through the administration of scores (Gladman & Chandran, 2011:77).

Fibromyalgia

Fibromyalgia is classified as a chronic neurosensory disorder that result in widespread intermittent muscle pain and joint stiffness in different parts of the body, as well as intermittent fatigue (Gale Encyclopedia of Medicine, 2008a).

Gout

Gout is a form of acute arthritis that usually has a sudden onset of symptoms which go away after five to 10 days; however, recurrence is common for this condition (Gale Encyclopedia of Medicine, 2008b). Abnormal high levels of uric acid circulate in the blood, causing urate crystal deposition in joint tissues. This leads to severe pain and inflammation mainly in the big toe, but it may also affect the heel, ankle, hand, wrist, elbow or spine (Dictionary for the Health Sciences, 2011:374).

Index disease

An 'index disease' is defined as a condition or core mechanism with a relatively large impact on the development of a comorbidity, its course and outcomes (Meghani *et al.*, 2013:3).

Indirect costs

Costs that result from a reduction in the work productivity of a patient due to illness, death or implementation of treatment. This include opportunity costs of the patient, e.g. time taken off from work, time and money spent going to health providers (Elliott & Payne, 2005:47; Santerre & Neun, 2010:66).

International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

The ICD-10 is the 10th revision of the coding system developed by the WHO to translate written medical descriptions into standard codes. These codes inform medical schemes with regard to treatment received by their members for specific conditions, in order to settle claims correctly (CMS, 2017b).

Mono-arthritis

By definition, mono-arthritis is inflammation that occurs in one joint at a time and can be caused by many factors, such as infection, crystal deposition, trauma, neoplasm and hormonal changes (Scutellari *et al.*, 1995).

Oligo-arthritis

Inflammation that involves two to three joints separately (Scutellari *et al.*, 1995).

Osteoporosis

A deficit of mineral components in the body, especially calcium, that causes bone to become increasingly porous and brittle (i.e. bone density reduction), resulting in a higher incidence of fractures (Wells *et al.,* 2015:16).

Poly-arthritis

An inflammatory disease that is commonly induced by RA. It usually involves five or more joints, either simultaneously or in a chronological order, and causes pain, stiffness, swelling, tenderness and loss of function (Dictionary of Nursing, 2008).

Prescribed minimum benefits (PMBs)

"A set of defined benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected" (CMS, 2017c).

Professional fee

The fee that a pharmacist has the right to charge for one or more of the services delivered in one or more of the various categories of the pharmacy, as amended in the Pharmacy Act (Act 53 of 1974), subject to certain guidelines provided and approved by the South African Pharmacy Council (South Africa, 2010).

Psoriatic arthritis

'Psoriatic arthritis' is an autoimmune disease which affects the whole body, causing permanent joint and tissue damage due to inflammation. Approximately 42% of patients who suffer from psoriasis (i.e. a common chronic skin condition involving rapid skin cell growth that forms thick, silver, itchy scales) develop psoriatic arthritis (Arthritis Foundation, 2016).

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a chronic autoimmune, inflammatory disease that manifests itself symmetrically in multiple joints of the body, affecting the synovial membrane of these joints and possibly also affecting other organs. Erosion of the cartilage and bone causes irreversible joint deformity (Wells *et al.,* 2015:26).

Rheumatoid factor (RF)

Rheumatoid factors are proteins, also known as auto-antibodies in RA, that are produced by the immune system and whose presence may indicate a diagnosis of RA (Handa, 2003:190).

Seronegative spondylo-arthropathy

“A heterogeneous group of inflammatory rheumatic diseases (e.g. ankylosing spondylitis, Reiter's syndrome, enteropathic arthritis, psoriatic arthritis, Behçet's disease and juvenile idiopathic arthritis) with predominant involvement of axial and peripheral joints and inflammation at the site of insertion of tendons and ligaments to bone (enthesitis) with high incidence of human leukocyte antigen (HLA) -B27, but negative RF tests” (Tidy, 2014).

Single exit price (SEP)

In South Africa, the SEP is an indication of the maximum price that may be charged for a specified medicine product, determined by the manufacturer, that includes the logistics fee and value added tax (VAT) (South Africa, 2012:10).

Systemic lupus erythematosus (SLE)

‘Systemic lupus erythematosus’ is chronic, autoimmune collagenosis (Dictionary for the Health Sciences, 2011:463). Researchers have found that 15% of RA patients also develop SLE (Icen *et al.,* 2008:56). Lupus cause more serious life-threatening and complicated inflammatory scars affecting internal organs (e.g. the kidneys, brain and heart) and large areas of the skin (Dictionary for the Health Sciences, 2011:463).

CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 Introduction

This chapter includes the background and problem statement, research aims and objectives, research methodology applied, data source and analysis, criteria for the study population and ethical considerations applicable to this study. Chapter one concludes with the division of the contents of the following chapter.

1.2 Background and problem statement

Rheumatoid arthritis (RA) is an autoimmune disease in which the body's own healthy tissues are attacked by the immune system due to undesirable self-antigen activation (Widmaier *et al.,* 2011:661). Aletaha *et al*. (2010:2570) define RA as *"a chronic inflammatory disease characterised by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality".* This autoimmune disease is progressive, characterised by symmetric poly-articular joint involvement and associated with systemic effects (Wells *et al.,* 2015:26). Although the main aetiology is still unknown, it seems to involve a complicated interplay between genetic and environmental factors (Choy, 2012:v3).

'Burden of disease' generally refers to the total, cumulative outcome (including, e.g., cost, health and social aspects) of a defined disease or a variety of pernicious diseases in terms of the impairment it causes in a community (Hessel, 2008:94). Some of the most common symptoms of RA such as pain, functional disability, fatigue and depression are related to substantial quality-of-life (QoL) reductions (Lundkvist *et al*., 2008:S51). For at least 50% of RA patients, these consequences make it difficult to hold down full-time employment within 10 years of the onset of the disease (World Health Organization (WHO), 2016). According to Lundkvist *et al.* (2008:S51), there is a paucity of accurate data on the burden of RA as a disease in South Africa compared to other countries.

Rheumatoid arthritis is one of the most common chronic inflammatory joint diseases with an average global prevalence estimated at about 0.5%-1.0%. This average also applies to developed countries, but varies between 0.3%-0.5% in the case of developing countries (Osiri & Sattayasomboon, 2013:608; WHO, 2016). Lundkvist *et al.* (2008:S49) indicate a higher prevalence in the United States and northern Europe than in southern Europe and developing countries. Bester *et al.* (2016:220) estimate the prevalence of RA in South Africa to be 0.7%; however, it should be noted that they used less sensitive criteria (i.e. that of the American College of Rheumatology (ACR), 1987) than the new 2010 ACR criteria or the European League against Rheumatism (EULAR) criteria (see Annexures B and C). A study conducted by Rothmann (2015:157) on medicine claims data from the private

health sector in South Africa, identified 0.36% (n = 3 688) individuals that had RA, contributing to the total patient population (N = 1 029 699) on the database for the year 2012. The South African Rheumatism and Arthritis Association (SARAA) documented the prevalence of RA as being the highest (n = 1 582; 64%) among ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis diagnosis (N = 2 481) in the private health sector of South Africa during 2015 (Van Duuren, 2017). According to Bester *et al*. (2016:219), the number of patients presenting with RA in South Africa will increase in the future.

Despite RA normally being observed in patients between the ages of 35 and 50 years, the onset of the disease may occur at any age (Beers *et al.,* 2006:283). The prevalence of the disease generally rises with increasing age until approximately 70 years (Woolf & Pfleger, 2003:649). Rheumatoid arthritis is more prevalent in women than in men, with a gender ratio that varies from 2:1 to 3:1 (Alamanos & Drosos, 2005:133). However, the inequality in the gender ratio seems to decrease with an increase in age (Suta *et al.,* 2015:221). Generally, more women are diagnosed with RA at a younger age than are men, giving rise to the perception that RA is more severe in females than males, when in fact it is actually the result of a longer period of disease and not greater intensity or severity (Kvien *et al.,* 2006:215). Although disparities with regard to a possible link between ethnicity and the presence of RA have been accumulating over the past years, it is known that members of all ethnic groups may be affected (CDC, 2017; McBurney & Vina, 2012:464).

In patients with an early onset of disease (i.e. before the age of 45 years), disability becomes more severe than in those patients who have a later onset of disease (i.e, ≥70 years) (Woolf & Pfleger, 2003:650). Early effective RA therapy can suppress inflammation before irreversible joint destruction occurs, but unfortunately this opportunity only exists for a short period of time (Bester *et al.*, 2016:221). According to Boonen and Severens (2011:S7), the average time period until surgery is necessary is 10 years after disease onset; however, delay in treatment and increased erosion scores intensify the need for surgery. Ledingham (2016) emphasised the importance of early detection and referral after serious delays in referrals and appointments for assessment by rheumatology specialists were identified. Early identification and aggressive treatment of RA is therefore important in reducing the costs that are incurred later on with the detrimental progression of the disease (Boonen & Severens, 2011:S7).

The introduction of highly effective treatment alternatives such as methotrexate, leflunomide and biologics has dramatically improved the long-term prognosis of RA; however, the development of comorbidities may decrease the QoL and lifespan of RA patients (Dougados *et al.,* 2014:62). Even though these patients commonly present with an average of one to two comorbid conditions, the risk of developing these additional diseases is still overlooked and/or poorly understood by the public and by policymakers (Grøn *et al.,* 2014:871; Michaud & Wolfe, 2007:885; National Rheumatoid

Arthritis Society (NRAS), 2012:2). In addition, as stated by Osiri and Sattayasomboon (2013:608), developing countries lack information on comorbidities in patients with RA. The number of changes in treatment regimens due to drug interactions, medical costs, disability and mortality is directly proportional to the number of comorbidities that a RA patient has (Michaud & Wolfe, 2007:886).

Mosby's Medical Dictionary (2009a) defines the term comorbidity as "*two or more coexisting medical conditions or disease processes that are additional to an initial diagnosis*". According to Meghani *et al.* (2013:2), Feinstein introduced the term in 1970 to indicate a "*distinct additional clinical entity*" occurring in the presence of an index disease. The term 'index disease' refers to the main condition under study that has a relatively large impact on the development, course and outcome of the comorbidities present (Meghani *et al.,* 2013:3; Ording & Sørensen, 2013:200). Various terms have often been used interchangeably to denote the concept of comorbidity, causing confusion with regard to the correct terminology (Ording & Sørensen, 2013:200). On the one hand, 'coexisting diseases', 'multiple pathology' and 'multi-morbidity' all refer to the simultaneous presence of several acute or chronic diseases and/or medical conditions within an individual, without any mention or identification of an index disease (Meghani *et al.,* 2013:2; Valderas *et al.,* 2009:358). On the other hand, 'co-occurring diseases', 'concomitant diseases' and 'disease clustering' signify diseases that co-occur at a significantly higher rate than expected of chance alone (Meghani *et al.*, 2013:2). Ording and Sørensen (2013:200) state that the term 'comorbidity' should describe medical conditions that are present at the time, or after, diagnosis of an index disease, without implying that the coexisting medical conditions are an outcome of the index disease. The association of comorbidities with RA, in this case classified as the index disease, may be due to three possible factors, namely the pathogenesis of RA itself, the effect of medications used for treating RA, and mere coincidence (Osiri & Sattayasomboon, 2013:608).

As a result of chronic inflammation, cardiovascular disease (CVD) is known to be one of the most common comorbidities observed in RA patients, these patients facing an almost six times higher risk of a silent myocardial infarction than members of the general population do (Boonen & Severens, 2011:S4). Malignancies (specifically lymphoma and pulmonary and skin cancers), chronic anaemia, gastro-intestinal ulcers, osteoporosis and depression are among the comorbid conditions more commonly associated with RA (Osiri & Sattayasomboon, 2013:608). Al-Bishri *et al.* (2013:13) observed additional conditions such as hypertension (35.9%), diabetes (30.9%), osteoporosis (25.8%), dyslipidaemia (19.4%), peptic ulcer disease (10.0%), hypothyroidism (9.0%), chronic liver disease (8.0%) and ischemic heart disease in 340 RA patients in Saudi Arabia.

The economic burden of RA is substantial to the patients, the healthcare system and society (Rat & Boissier, 2004:518). Generally speaking, the economic burden of any medical condition is a measurement of the total cost that weighs on the overall economy, this total cost being the sum of

sub-costs categorised into three major classes: direct medical care costs, direct non-medical costs, and indirect costs (Santerre & Neun, 2010:66). Direct costs in healthcare are directly associated with the treatment, diagnosis, prevention and/or management of a disease, whereas indirect costs result from a decrease in work productivity due to treatment, the outcomes of the disease or death (Lundkvist *et al.*, 2008:S52). Indirect costs are known to be the most important cost drivers in RA due to early retirement resulting from decreased work capacity (Lundkvist *et al*., 2008:S52). Recent increased utilisation of expensive biologics has, however, resulted in a dramatic shift in the costs incurred and in the management of the disease (Chaudhari, 2008:38). According to Hodkinson *et al.* (2013:583), the cost of therapy is still relatively low in patients receiving non-biologic disease modifying anti-rheumatic drugs (DMARDs), but increases rapidly when biologics are utilised as alternative treatment. An analysis of medicine claims data from the private health sector of South Africa dating from 2005 to 2008 showed that the average cost per medicine item increased with 1000% from R128.45 ± 155.93 to R1 477.88 ± 3 134.39 when treatment with biologics was initiated (Roux, 2010:227). Patients who are diagnosed with RA have direct medical costs that are two to three times higher than those of their peers who are not diagnosed with the disease (Baser *et al.*, 2013:2578; Lambert, 2001:961). Biologics (i.e. specialty medicine) are regarded as major cost driving products in the private health sector of South Africa (Bester *et al.*, 2015:4). For the purposes of the empirical investigation of this study, the researcher will focus on the direct medicine costs of RA patients only.

According to Michaud *et al.* (2003:2761) key clinical factors to consider when predicting the future cost of RA treatment are functional disability and comorbidity. The NRAS (2012:7) states that there is no accurate estimate of how much expenditure is due to the treatment of comorbidities associated with RA. Osiri and Sattayasomboon (2013:608) documented total annual direct medical costs of RA patients with comorbid conditions as being two times higher, on average, than those of RA patients without comorbid conditions for the period of 2008 to 2009. When only RA-related medication costs were considered, the patients with comorbid conditions still incurred 1.12 times higher costs (R12 286.68 *vs.* R10 922.43)[1] than those patients without comorbidities. They concluded, however, that it was not the comorbidities posing a major economic burden, but rather RA itself.

In South Africa, RA is one of 26 chronic/non-communicable diseases that are all included in the chronic disease list (CDL) of South Africa (Refer to Annexure A) (Council for Medical Schemes (CMS), 2017a). These CDL conditions are stipulated as qualifying for prescribed minimum benefits (PMBs), meaning that the patient's medical scheme, by law, not only has to cover the cost of medication, but also that of physicians' consultations and tests associated with the condition (CMS,

[1] Average currency rate for 2009 (US Forex Inc., 2017); $1:R8.4213

2017c). The South African Medical Schemes Act (131 of 1998) included PMBs as one of medical schemes' features to ensure that all members are continuously provided with predetermined, affordable health service standards, irrespective of their benefit option (South Africa, 1998).

It is important to recognise that RA is a systemic disease with possible consequences such as the development of other diseases/comorbidities, even though joint damage may be controlled (Cutolo *et al.,* 2014:479). Devoted attention to this population is critical for optimal disease and healthcare cost management, since patients with multiple chronic conditions suffer from suboptimal health outcomes and incur higher healthcare costs (Parekh *et al.,* 2011:461). Villaverde *et al.* (2014) state that future research is needed to determine which comorbid condition(s) poses the highest economic burden and has the greatest impact on the costs of RA as a disease. Data and literature based on RA medicine costs in South Africa are limited, necessitating studies that measure and evaluate the cost of treatment, a contributing factor to the economic burden of RA (Lundkvist *et al.,* 2008:S54; Tarr *et al.,* 2014). In conclusion, the full burden of a disease must be understood before the value of interventions can be assessed (Boonen & Severens, 2011:S3).

1.3 Research questions

Recent research suggests that the prevalence and treatment cost of RA and associated comorbidities are yet unknown in South Africa. For this reason, the following questions regarding the burden of RA were formulated for this study:

- What is the prevalence of RA on a national and international level?
- What types of comorbidities are present in patients diagnosed with RA and what is their prevalence?
- What is the total medicine cost (i.e. indirect and direct) for patients with RA internationally as well as nationally?
- What is the impact of comorbidities on the total annual medicine cost (i.e. indirect and direct) for patients with RA?

1.4 Research aim

The purpose of this study was to determine the prevalence of RA and associated comorbidities, as well as to investigate antirheumatic prescribing patterns, direct medicine treatment costs and the impact of comorbidities on the total annual direct medicine cost for patients diagnosed with RA in the private healthcare sector of South Africa.

1.5 Research objectives

The aim of this study was achieved by means of conducting a literature review and an empirical investigation. The objectives of both these parts of the study are detailed in the subsections below.

1.5.1 Literature review

The literature review's objectives were to:

- Conceptualise RA to form a better understanding of the pathogenesis of the disease.
- Describe the prevalence of RA and associated comorbidities (i.e. type and description), nationally as well as internationally.
- Determine the impact of comorbidities on the total medicine treatment cost (i.e. direct and indirect) of RA.

1.5.2 Empirical investigation

The empirical investigation's objectives were to:

- Establish the prevalence of RA as well as comorbidities associated with RA from the medicine claims database.
- Evaluate antirheumatic medicine prescribing patterns in RA patients and estimate the total annual direct medicine cost of RA.
- Determine the impact of comorbidities on the total direct medicine treatment cost of RA patients per year.

1.6 Research methodology

A two-dimensional research procedure consisting of a literature review and an empirical investigation was followed in order to answer the research questions stated above.

1.6.1 Literature review

Chapter two contains the literature review of which the broad focus area was to determine the burden of RA as a disease (i.e. the prevalence of the disease and additional comorbidities, as well as the impact of these comorbid conditions on the total direct medicine cost per patient per year). The purpose of the literature review was to gain perspective regarding the findings of other studies. Different databases were used to conduct the search for literature, which was gained from books,

websites and journals. Search engines that were used include Google Scholar, EBSCOhost, Scopus and Science Direct. The web pages of organisations such as the WHO, World Bank, and Arthritis Foundation of South Africa were also used. Specific keywords and phrases that were used on their own and in combination with others include ‘rheumatoid arthritis’, ‘prevalence’, ‘treatment cost’, ‘burden of disease’, ‘extra-articular manifestations’, ‘comorbidity’, ‘direct costs’ and ‘indirect costs’.

1.6.2 Empirical investigation

The most appropriate research design to address the given research problem was a quantitative, non-experimental (descriptive), cross-sectional drug utilisation review (DUR), analysing medicine claims data retrospectively.

Quantitative research relies on numerical data to test the relationship between given variables (Maree & Pietersen, 2016:171). A quantitative study design can take one of two forms, namely experimental and non-experimental. Since there was no manipulation of the variables in this study, the approach can be defined as non-experimental (Brink *et al*., 2012:9). Non-experimental research can further be classified as either descriptive or correlational. In the context of medical claims data analysis, descriptive studies would set out to quantify the extent of the burden of a disease in a population, using a cross-sectional survey or cohort study design (Morroni & Myer, 2014:79). In cross-sectional studies, the data of various participants is examined at one point in time (Brink *et al*., 2012:115).

In motivation of the chosen research design, a fuller description of the nature of this type descriptive study and the DUR used for data analysis will be supplied in the following paragraphs.

1.6.2.1 Data analysis

Cross-sectional studies are most appropriate for the determination of disease prevalence and for the simultaneous assessment of the disease outcomes and disease exposures — by estimation of the odds ratios (ORs), the association between the disease outcome and disease exposure can be determined (Setia, 2016:261). Data for 2014 was used, therefore the study is considered to make use of retrospective analysis. Conducting retrospective studies is relatively inexpensive as various outcomes can be studied from data that is already available (Mann, 2003:56).

According to the WHO, (2003a:8) a DUR such as this study specifically emphasises the social, medical and economic outcomes within a society that result from the marketing and distribution of medication. ‘Drug utilisation research’ is described as "*an eclectic collection of descriptive and analytical methods for the quantification, the understanding and the evaluation of the processes of*

prescribing, dispensing and consumption of medicines, and for the testing of interventions to enhance the quality of these processes" (Wettermark *et al*., 2008:159).

A DUR may be useful in ensuring and/or enhancing appropriate medicine utilisation at a patient level, and has numerous other favourable aspects. Listed below are a few examples of such aspects (Academy of Managed Care Pharmacy, 2009; Truter, 2008:95; WHO 2003a:9; WHO, 2003b:85):

- It is a relatively inexpensive method which can be employed to identify associations, adverse or beneficial, between medicine treatment and diseases.
- The method is easy to use since therapy is reviewed on an administrative database after the patient has received treatment.
- It enables researchers to identify inappropriate prescribing practices such as under- or over-utilisation of medicine, non-formulary medicine use and incorrect drug dosages.
- It can be used to determine the extent to which generic equivalents are used. This information regarding generic substitution may be utilised in attempts to reduce medicine expenditures.
- It can be used to compare current treatment guidelines with actual drug use or prescribing patterns. This information may help to identify the educational needs of healthcare providers (e.g. prescribing doctors or nurses).
- The 90% drug utilisation segment (DU90%), i.e. the medicine that accounts for 90% of all prescriptions at different levels (e.g. the prescriptions of a specific prescriber or a group of prescribers, hospitals or region) can be identified. The DU90% is an indicator of the quality of prescribing patterns.

Drug utilisation research can provide prescribers or decision makers in managed healthcare organisations with valuable information, enabling them to optimise drug therapy by correcting and/or preventing repetitive, incongruous medicine utilisation (WHO, 2003a:9).

1.6.2.2 Data source and -fields

Data for this study was obtained from the nationally representative medicine claims database of a well-known South African Pharmaceutical Benefit Management (PBM) company.

Private healthcare financing in South Africa is generally delivered through medical schemes. The PBM company that provided the data for this project has a well-established client base and provides services to 1.7 million beneficiaries from medical schemes registered in South Africa, Namibia and

Botswana; health insurance providers; labour union sick funds; and capitation management clients. Currently, the database of the PBM company contains longitudinal data consisting of medicine claims of patients for more than 40 clients, processing almost 200 thousand real-time claims per day. This database represents an average of 11% of the overall private health sector (CMS, 2017e).

The data fields that were extracted from the database include:

- prescription number
- encrypted patient member and dependant numbers
- gender of patient
- patient's date of birth
- quantity of the medicine items prescribed
- drug's trade name
- National Pharmaceutical Product Interface (NAPPI) code
- date the prescription was filled
- diagnosis code
- active ingredient
- single exit price (SEP)
- value added tax (VAT)
- professional fee
- patient co-payment
- schemes contribution
- total cost

1.6.2.4 Target and study population

Every RA patient who received medicine treatment and was an active member of any South African medical aid scheme, included in the PBM database during 2014, was considered as the target population of this study. The study population consisted of all patients who met the inclusion criteria (see Table 1.1). The data was filtered by means of the application of exclusion criteria.

1.6.2.5 Inclusion and exclusion criteria

The inclusion and exclusion criteria that were applied in the study are listed in Table 1.1.

Table 1.1: Inclusion and exclusion criteria for the study

Inclusion Criteria	Exclusion Criteria
Study period: Only claims submitted between 1 January 2014 and 31 December 2014 were included. Age: All patients of any age receiving treatment for RA were included. Gender: Both males and females were included. Diagnosis code: All patients with a diagnosis code for RA (e.g. ICD-10 codes M05.0, M05.1, M05.2, M05.3, M05.8, M05.9, M06.0, M06.1, M06.2, M06.3, M06.4, M06.8, M06.9 and M08.0), in conjunction with a claim for medicine to be paid from their PMBs were included.	Incomplete data fields for age, gender and diagnosis code.

1.6.2.6 Data analysis plan

The data analysis was done in such a manner as to meet the specific objectives set out for the empirical investigation.

The study variables included independent and dependent variables. An independent variable influences other variables, thus causing change and contributes to a particular outcome, whereas a dependent variable is the outcome variable, reflecting the effect of or response to the independent variable (Brink *et al.,* 2012:90). The variables included in the data analysis plan are described in Table 1.2 and categorised as independent/dependent in Table 1.3.

Table 1.2: Variables included in the data analysis plan

Variables	Description
Age	The patient's age was determined from the patient's date of birth using the Statistical Analysis System (SAS) 9.4® software programme (SAS Institute Inc., 2012-2012).
Gender	For the purposes of this research project, only patients whose gender group (i.e. male or female) was known, were included.
Prevalence	In this research project, 'prevalence' and 'frequency' were used as synonyms. It is an indication of the number of patients within a specific group (e.g. gender, disease group, treatment phase or comorbidities).
Active ingredient of medicine	Individual products were identified using NAPPI codes. The latter codes are unique, scheme-recognised codes that are nationally used to electronically identify claims for all pharmaceutical, surgical and healthcare products in South Africa (MediKredit, 2016). These codes provide information on the manufacturer, registration, strength and dosage of the product (CMS, 2003:16).
Disease group	Patients were divided into two disease groups based on patient diagnosis: disease group 1 = patients with RA only; disease group 2 = patients with RA plus ≥1 CDL condition.
CDL conditions	Refer to the conditions that are included in the South African CDL (Annexure A). The medication used for the treatment of each chronic condition was identified from the corresponding treatment algorithms for each chronic condition. The frequency of the CDL conditions was an indication of the number of comorbidities per patient in disease group 2.
Treatment phase	Different phases were identified according to the therapeutic algorithm for RA (refer to Figure 2.3). Treatment phase 1 = non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids only Treatment phase 2 = NSAIDs, corticosteroids, and DMARDs or biologics The different types and numbers of medicine items, the number of patients, gender, CDL conditions and direct medicine cost per phase were determined.
Cost	Cost is the value of resources consumed, expressed as South African rand values. The following costs were calculated in this project: total cost per patient per disease group total cost per patient per treatment phase total cost per patient per CDL condition (the 10 most prevalent) Medicine item cost including patient and scheme contribution, professional fee, SEP and VAT.

A summary of the data analysis plan is provided in Table 1.3.

Table 1.3: Data analysis plan summary

Objectives	Measurement	Variables		Statistical analysis		
		Independent	Dependent	Descriptive	Inferential	Significance
Establish the prevalence of RA by age and gender (Disease group 1)*	Total number of patients with RA	-	Number of patients	Frequency (%)	-	-
	Descriptive analysis of mean age of patients in Disease group 1	Number of patients	Age	*Age follows normal distribution:* Mean ± SD, 95% CI *Age follows skew distribution:* Median IQR	-	-
	Gender distribution of patients in Disease group 1	Gender	Number of patients	Frequency (%)	Chi-square	Cramér's *V*
	Difference in mean age by gender of patients in Disease group 1	Gender	Age	*Age follows normal distribution:* Mean ± SD, 95% CI *Age follows skew distribution:* Median IQR	Student *t*-test	Cohen's *d*

Objectives	Measurement	Variables		Statistical analysis		
		Independent	Dependent	Descriptive	Inferential	Significance
Establish the prevalence of RA by age and gender (Disease group 1)*	Number of patients in Disease group 1 per treatment phase†	Treatment phase	Number of patients	Frequency (%)		-
	Gender distribution of patients in Disease group 1 in each treatment phase	Gender	Number of patients	Frequency (%)	Chi-square	Cramér's *V*
	Difference in mean age by gender of patients in Disease group 1 in each treatment phase	Gender Treatment phase	Age	Mean ± SD, 95% CI	*Difference in age by gender in each treatment phase:* Student *t*-test *Difference in age by gender across treatment phases:* Two-way ANOVA	Cohen's *d*
Establish the prevalence of RA/CDL condition by age and gender (Disease group 2)**	Total number of patients with RA/CDL condition (Disease group 2)		Number of patients	Frequency (%)	-	-

Objectives	Measurement	Variables		Statistical analysis		
		Independent	Dependent	Descriptive	Inferential	Significance
Establish the prevalence of RA/CDL condition by age and gender (Disease group 2)**	Descriptive analysis of age of patients in Disease group 2	Number of patients	Age	*Age follows normal distribution:* Mean ± SD, 95% CI *Age follows skew distribution:* Median IQR	-	
	Gender distribution of patients in Disease group 2	Gender	Number of patients	Frequency (%)	Chi-square	Cramér's *V*
	Difference in mean age by gender of patients in Disease group 2	Gender	Age	*Age follows normal distribution:* Mean ± SD, 95% CI *Age follows skew distribution:* Median IQR	Student *t*-test	Cohen's *d*
	Number of patients in Disease group 2 per treatment phase	Treatment phase	Number of patients	Frequency (%)		-

Objectives	Measurement	Variables		Statistical analysis		
		Independent	Dependent	Descriptive	Inferential	Significance
Establish the prevalence of RA/CDL condition by age and gender (Disease group 2)**	Gender distribution of patients in Disease group 2 in each treatment phase	Gender	Number of patients	Frequency (%)	Chi-square	Cohen's *d*
	Difference in mean age by gender of patients with RA in each treatment phase	Gender Treatment phase	Age	Mean ± SD, 95% CI	*Difference in age by gender in each treatment phase:* Student *t*-test *Difference in age by gender across treatment phases:* Two-way ANOVA	-
Establish the association between CDL conditions (number and type) in Disease group 2 and age and gender	Number of comorbidities per patient (Disease group 2)	CDL conditions (diagnosis)	Number of patients	Frequency (%) *Number of CDL conditions follows normal distribution:* Mean ± SD, 95% CI *Number of CDL conditions follows skew distribution:* Median IQR		

Objectives	Measurement	Variables		Statistical analysis		
		Independent	**Dependent**	**Descriptive**	**Inferential**	**Significance**
Establish the association between CDL conditions (number and type) in Disease group 2 and age and gender	Association between number of comorbidities per patient and gender	Gender Treatment phase	Number of comorbidities per patient	Frequency (%) Mean ± SD, 95% CI Count data	Spearman's correlation/ Poisson regression	
	Association between number of comorbidities per patient and age	Age Treatment phase	Number of comorbidities per patient	Frequency (%) *Number of CDL conditions follows normal distribution:* Mean ± SD, 95% CI *Number of CDL conditions follows skew distribution:* Median IQR	Poisson regression	
	Type of comorbidities (top 10) (Disease group 2)		CDL conditions (diagnosis)	Frequency (%)	-	-

Objectives	Measurement	Variables		Statistical analysis		
		Independent	Dependent	Descriptive	Inferential	Significance
Establish the association between CDL conditions (number and type) in Disease group 2 and age and gender	Difference in type of comorbidities (top 10) per treatment phase	Treatment phase	CDL conditions (diagnosis)	Frequency (%)	Chi-square	Cramér's *V*
	Association between comorbidity type (top 10) and gender	Gender	CDL conditions	Age-adjusted odds ratio	Multinomial regression	
Determine the impact of comorbidities on the total direct antirheumatic medicine treatment cost of RA patients.	Total cost of treatment per year	Disease group Treatment phase CDL conditions (top 10)	Total treatment cost per year	Frequency (%) Mean ± SD, 95% CI Median		
Cost analysis of the influence of VAT, SEP and dispensing fee on direct RA-related treatment cost		Medicine item cost (active substances)	Total cost per item Patient contribution Scheme contribution SEP VAT Dispensing fee	Frequency (%) Mean ± SD, 95% CI Median		

*Disease group 1: patients with RA only

**Disease group 2: patients with RA plus ≥1 CDL condition

†'Treatment phase' implies phases based on treatment algorithm, i.e. NSAIDs and corticosteroids only (Phase one) vs. NSAIDs, corticosteroids, and DMARDs or biologics (Phase two).

1.7 Statistical analysis

The analysis of data for the purposes of the empirical investigation was done with the Statistical Analysis System (SAS) 9.4® software (SAS Institute Inc., 2002-2012) and Statistical Package for the Social Sciences (IBM SPSS® 22).

1.7.1 Descriptive statistics

Descriptive statistics enable the researcher to organise a set of measurements according to different techniques in order to summarise data obtained from a sample in a simple, meaningful way (Mendenhall *et al.,* 2013:4). These statistics can also be used to predict an outcome in the presence of a particular variable (Heiman, 2011:21).

Frequencies (n) interpreted as percentage (%) values, arithmetic means, medians, standard deviations (SDs) and 95% confidence intervals (Cls) are the five groups of descriptive statistics that were used for the interpretation of the different variables included in this study (i.e. age, gender, number of patients with RA, number of patients with RA and coexisting CDL conditions, number and type of active ingredients, total cost per medicine item and total direct medicine cost per year).

1.7.2 Inferential statistics

Inferential statistics become useful to the researcher when methods are needed to draw conclusions from a set of data (Swanepoel *et al.,* 2010:4). These methods enable the researcher to interpret the statistics of a small sample to a large population (Brink *et al.,* 2012:190). A statement made about a population parameter is called a statistical hypothesis, which can be deemed either valid or invalid by means of statistical inference (Swanepoel *et al.,* 2010:243). Two types of inferential statistical tests are available: parametric (e.g. *t*-tests, analysis of variance (ANOVA), Tukey's tests, and correlation and regression statistics) and nonparametric (e.g. chi-square) (Brink *et al*., 2012:190-192).

1.7.2.1 Two sample *t*-test

This type of test is also known as an 'independent *t*-test' or 'student's *t*-test' and can be used to determine whether a statistically significant difference exists between the means of two independent samples, with an approximately normally distributed dependent variable within each sample group (Brink *et al.,* 2012:191; Heiman, 2011:262). Independent samples are two separate groups, for example an experimental group and a control group (Brink *et al.,* 2012:191). The formula for the calculation of the independent *t*-test is (Swanepoel *et al.,* 2010:262):

$$t = \frac{\overline{x_1} - \overline{x_2}}{\sqrt{\frac{s_1^2}{n_1} + \frac{S_2^2}{n_2}}}$$

where:

$n_1 \; and \; n_2$: sample sizes

$\overline{x_1} - \overline{x_2}$: sample means

$s_1^2 \; and \; S_2^2$: sample variances

1.7.2.2 Two-way analysis of variance

The two-way ANOVA is used when there is one dependent variable and two independent variables (called 'factors', illustrated in all possible combinations) (McDonald, 2014). When comparing the population means of more than two groups, the test can be used to determine the effects of several independent variables on the dependent variable or the interaction between these independent variables (Heiman, 2011:319; Swanepoel *et al.,* 2010:315). An ANOVA generates an F-ratio test statistic that indicates the level of significance (i.e. the *p*-value) (Carr, 2012:157). The overall sample mean of all the Y_{ij}s can be denoted by (Swanepoel *et al.,* 2010:320):

$$\bar{Y} = \frac{1}{n_{TOT}} \sum_{i=1}^{g} \sum_{j=1}^{n} Y_{ij}$$

The sample means of the Y_{ij} within each group is denoted by:

$$\bar{Y}_i = \frac{1}{n}\sum_{j=1}^{n} Y_{ij}\,, i = 1.2\ldots, g$$

where:

Y_{ij}: recorded value of the j-th element in the i-group, $i = 1,2,\ldots, g$ and $j = 1,2,\ldots, n$

g: number of groups that will be studied

n: number of individual elements in each group (assuming all are equally large)

n_{TOT}: total number of individual elements in the study ($n_{TOT} = ng$)

1.7.2.3 Tukey's honestly significant difference

Tukey's honestly significant difference (HSD) is a post hoc comparison performed after ANOVA tests. An ANOVA can only indicate to the researcher that a significant difference exists among two or more of the group's means (Brink *et al.,* 2012:191). Tukey's HSD test is then conducted to determine which specific means differ significantly from one another (Heiman, 2011:293). The formula for the calculation of Tukey's HSD is (Heiman, 2011:308):

$$HSD = (q_k)\left(\sqrt{\frac{MS_{wn}}{n}}\right)$$

where:

MS_{wn}: computed from ANOVA

q_k: studentised range statistic

k: number of levels in the factor

n: number of scores in each level of the factor

1.7.2.4 Pearson correlation coefficient

Any correlation coefficient measures the strength of the linear relationships between variables; in the case of Pearson's correlation coefficient, both variables are measured on a ratio/interval scale (Brink *et al.,* 2012: 188; Pietersen & Maree, 2016:264). The symbol r denotes Pearson's correlation coefficient, with a minimum of -1 and a maximum of +1 indicating a positive or negative relationship (Heiman, 2011:147; Pietersen & Maree, 2016:265). A positive relationship indicates that the variables are directly proportional to one another; a negative relationship indicates an inverse relationship between the variables (Brink *et al.,* 2012:189). The Pearson correlation coefficient is defined as (Heiman, 2011:148):

$$r = \frac{N(\sum XY) - (\sum X)(\sum Z)}{\sqrt{[N(\sum X^2) - (\sum X)^2][N(\sum Y^2) - (\sum Y)^2]}}$$

where:

Z_X: sum of variable X

Z_Y: sum of variable Y

N: number of pairs

1.7.2.5 Spearman's correlation coefficient

Seen as the nonparametric alternative to Pearson's correlation coefficient, Spearman's correlation coefficient describes the linear relationship between two ordinal variables, measured by rank scores (Heiman, 2011:151). It makes no assumption about the distribution of the two variables; the sample is denoted by r_s, the values being the same as for *r* in Pearson's coefficient, and the corresponding population parameter is indicated by p_s (Pietersen & Maree, 2016:267). The Spearman rank-order correlation coefficient is represented as (Heiman, 2011:152):

$$r_S = 1 - \frac{6(\sum D^2)}{N(N^2 - 1)}$$

where:

D: difference between the two ranks in each X–Y pair

N: number of pairs of ranks

1.7.2.6 Poisson regression

Poisson regression is used to predict on grounds of an independent variable a dependent variable (i.e. the response, outcome, target or criterion variable) that consists of 'count data' (i.e. data that is ≥ 0, e.g. number of new cases) (Heiman, 2011:161). The linear relationship between variable x and variable y is mathematically expressed by the following estimated regression function (Swanepoel *et al.,* 2010:115):

$$\hat{y} = a + bx$$

where:

a: y-intercept of the linear regression line

b: gradient of the linear regression line

x: independent variable

1.7.2.7 Multinomial regression

Multinomial logistic regression is a predictive analysis where multiple independent variables are considered simultaneously as the outcome of one dependent variable (Heiman, 2011:179). The strength of the relationship between the sum of the independent variables and the dependent variable is indicated by the correlation coefficient *multiple R* (Heiman, 2011:179). The multiple regression equation for k independent variables is defined as (Swanepoel *et al.,* 2010:297):

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_k x_k + \varepsilon$$

where:

y: dependent variable

$x_1, x_2, .., x_k$: independent variables

$\beta_0, \beta_1, .., \beta_k$: unknown regression coefficients

ε: error term

1.7.2.8 Chi-square test

The two-way chi-square test is used to determine, on grounds of contingency tables, whether two nominal variables are independent or dependent in order to test the significance of the association between the two variables (Pietersen & Maree, 2016:275). Datasets that are presented as frequencies are usually compared using the chi-square test (Brink *et al.,* 2012:191). With nominal variables, the participants are divided into two or more different categories (Heiman, 2011:352). Testing the hypothesis for the chi-square test involves comparing observed data with the expected data (Pietersen & Maree, 2016:276). The following equation demonstrates how the chi-square distribution is calculated (Heiman, 2011:354):

$$X_n^2 = \sum \left(\frac{(f_o - f_e)^2}{f_e} \right)$$

where:

X_n^2: chi-square distribution

f_o: observed counts

f_e: expected counts

The degrees of freedom are calculated as follows (Heiman, 2011:360):

$$df = (r - 1)(c - 1)$$

where:

r: number of rows

c: number of columns

From these values, the *p*-value can be computed to establish whether the difference between the observed and the expected values are statistically significant or not, indicating independence or dependence between the variables (Heiman, 2011:360).

1.7.2.9 Odds ratio

The association between an exposure and an outcome can be measured with an OR. It can calculate the odds of an event occurring in the presence of a particular intervention, and compare it to the odds of the event occurring in the absence of that intervention (McHugh, 2009:120). "*The OR can also be used to determine whether a particular exposure is a risk factor for a particular outcome, and to compare the magnitude of various risk factors for that outcome*" (Szumilas, 2010:227). The following equation can be used to calculate the OR (Rice, 2006:526):

$$OR = \frac{P(disease/exposed)/[1 - P(disease/exposed)]}{P(disease/unexposed)/[1 - P(disease/unexposed)]}$$

where:

P: probability that event occurs

$1 - P$: probability that event does not occur

The following guideline values were used for the interpretation of ORs (Szumilas, 2010:227):

1 = exposure does not affect odds of outcome

>1 = exposure associated with higher odds of outcome

<1 = exposure associated with lower odds of outcome

1.7.3 Analysis of effect size

Effect size is the "*magnitude of the difference between groups"*, this being the main finding of a quantitative study (Sullivan & Feinn, 2012:279). Hypothesis testing only indicates a statistical significance (i.e. the *p*-values); effect sizes are able to indicate a practical significance irrespective of the sample size (Pietersen & Maree, 2016:233). Cohen's *d*-value, Cramér's *V* and ORs were used in this study to indicate the effect size of statistically significant results.

1.7.3.1 Cohen's *d*-value

Cohen's *d*-value is used to compare the mean, standardised difference between two groups (Cohen, 1988:24). Cohen's *d*-value can be calculated as follows:

$$d = \frac{\bar{x}_1 - \bar{x}_2}{\sigma}$$

where:

$\bar{x}_1$: group 1 mean

$\bar{x}_2$: group 2 mean

σ: biggest standard deviation between the two groups

The following guidelines exist for the interpretation of the magnitude of the *d*-values (Pietersen & Maree, 2016:234)*:*

0.2 = small effect

0.5 = medium effect

0.8 = large effect

A Cohen's *d*-value ≥ 0.8 was considered to be practically significant.

1.7.3.2 Cramér's *V*

Cramér's *V* can be calculated to measure the importance/strength of a significant association between nominal variables, as indicated by a chi-square test, for cross-tables of any size (Jones, 2008:280; Pietersen & Maree, 2016:234). As a variation of the phi coefficient, the result of the two statistic tests are similar — when there is no association between the two variables, Cramér's *V* equals 0 and generally has a maximum value of 1 (Jones, 2008:280). As a post-test, Cramér's *V* is calculated after the chi-square test with the following equation (Zaiontz, 2017):

$$V = \sqrt{\left(\frac{X^2}{n(k-1)}\right)}$$

where:

X^2: chi-square statistic

n: sample size

k: number of rows or columns in the table

The effect size of Cramér's *V* is interpreted according to the following guidelines (Pietersen & Maree, 2016:234):

0.1 = small effect

0.3 = medium effect

0.5 = large effect

A Cramér's *V* value ≥ 0.5 was considered to be practically significant.

1.7.3.3 Effect size of odds ratio

The following equation can be used to calculate the OR as an effect size:

$$Effect\ size = \frac{OR}{\pi/\sqrt{3}}$$

The guideline values used for the interpretation of ORs as effect sizes were (Steyn, 2012:52):

1.38 = small effect

2.25 = medium effect

3.64 = large effect

An OR ≥ 3.64 was considered to be practically significant.

1.7.3.4 Beta coefficient exponentiation

For any type of relationship, the Exp(β) is an indication of how well the count data fits the observed data (Swanepoel *et al.,* 2010:119). The Exp(β) is interpreted as ORs for the predictors ($0 \leq \beta < 1$), where:

0 = practically significant

1 = no effect

1.8 Ethical considerations

Anonymity and confidentiality were at all times maintained. Information on the identity of the beneficiaries, medical schemes, service providers and prescribers was removed by the PBM company before data was received and analysed. The PBM company assures integrity, validity and reliability of the data with certain validation processes, such as: data integrity validation, administration of eligibility criteria and drug utilisation reviews. The PBM company ensures appropriate and cost effective therapy via benefits for chronic medicine, management of exclusion lists, reference price list design and implementation, PMB including ambulatory care services (i.e. designated service providers and formularies) and an online medication management system (Medscheme, 2015). The data was, however, checked for outliers and duplications before analysis via random data checks.

Confidentiality agreements were signed by the researchers with the Panel of Directors of the PBM company in order to obtain permission to use their data for the purpose of research only. The Health Research Ethics Committee of the North-West University approved the study (NWU-00179-14-A1;

refer to Annexure D). This study was categorised as a minimal risk study as the benefits outweighed the risks.

1.9 Chapter summary

This chapter included the background to the study, the problem statement, research aims and objectives, a summary of the research methodology applied, a description of the data source and analysis as well as the criteria for the study population, and finally the ethical considerations that were taken into account. It was established that RA is a costly disease to treat, especially where administration of certain DMARDs and biologics is needed, and that comorbid conditions can have a definite effect on the cost of treatment. The following chapter entails a comprehensive literature review aimed at increasing the understanding of RA as a disease and of the burden inflicted upon patients diagnosed with this disease and other comorbid conditions.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

In this chapter, an overview of RA, including the burden of the disease (i.e. prevalence, comorbidities and economic impact), will be provided.

2.2 Definition

Rheumatoid arthritis is autoimmune of nature and categorised as a “chronic inflammatory disease” (Widmaier *et al.,* 2011:661). Excessive inflammation in RA patients causes damage to connective tissue in the joints (i.e. synovial membrane) and deterioration of cartilage, leading to severe disability (Aletaha *et al.,* 2010:2570; Widmaier *et al.,* 2011:661). Rheumatoid arthritis is a progressive and debilitating disease that may affect several organ systems that result in the development of comorbidities and increased mortality rates (Choy, 2012:v3; Rindfleisch & Muller, 2005:1037).

2.3 The immune system and rheumatoid arthritis

The immune system’s main function is to protect the host from infinite pathogenic microbes, toxicities and allergens that have the ability to threaten normal homeostasis within the body (Chaplin, 2010:S3). The immune system comprises two components known as the ‘innate immune response’ and the ‘adaptive immune response’, which interact in synchrony as a “self-nonself” differentiation mechanism (Mayer, 2016). This mechanism of “self-nonself” differentiation refers to the phenomenal ability of the immune system to discern between the body’s own cells and pathogens (e.g. bacteria, viruses, fungi) or infected cells in order to detect and eliminate potentially harmful non-self molecules from the body (Mayer, 2016). Pathogens that breach the anatomic barriers, known as the body’s first-line of defence (e.g. skin, cornea, respiratory and gastrointestinal tract mucosa), can trigger either one of the immune responses (Delves, 2017a). The innate immunity has the ability to respond immediately to any foreign substance or pathogen, without requiring any pre-exposure or recognition of the antigen to be effective (Widmaier *et al.,* 2011:632). This ‘naturally’ existent, innate immunity is inherited from the mother due to Immunoglobulin G (IgG) antibodies, which are transported *via* the placenta, and also Immunoglobulin A (IgA), which is found in the breast milk of nursing mothers (Sanders *et al.,* 2010:827). The adaptive immune system, on the other hand, develops after exposure to pathogens and thereafter respond upon recognition of specific antigens identified by memory B-cells that previously triggered an immune response (Delves, 2017a; Widmaier *et al.,* 2011:643). Antigens are viral, microbial or any other type of foreign protein/pathogen that is capable of inducing an immune response that is followed by lymphocyte activation and antibody production (Mellors, 2006). As such, an antigen is any molecule that the host does not recognise (Widmaier *et*

al., 2011:641). Figure 2.1 provides a simple illustration of the two different immune system responses and its components (adapted from Widmaier *et al.,* 2011:632).

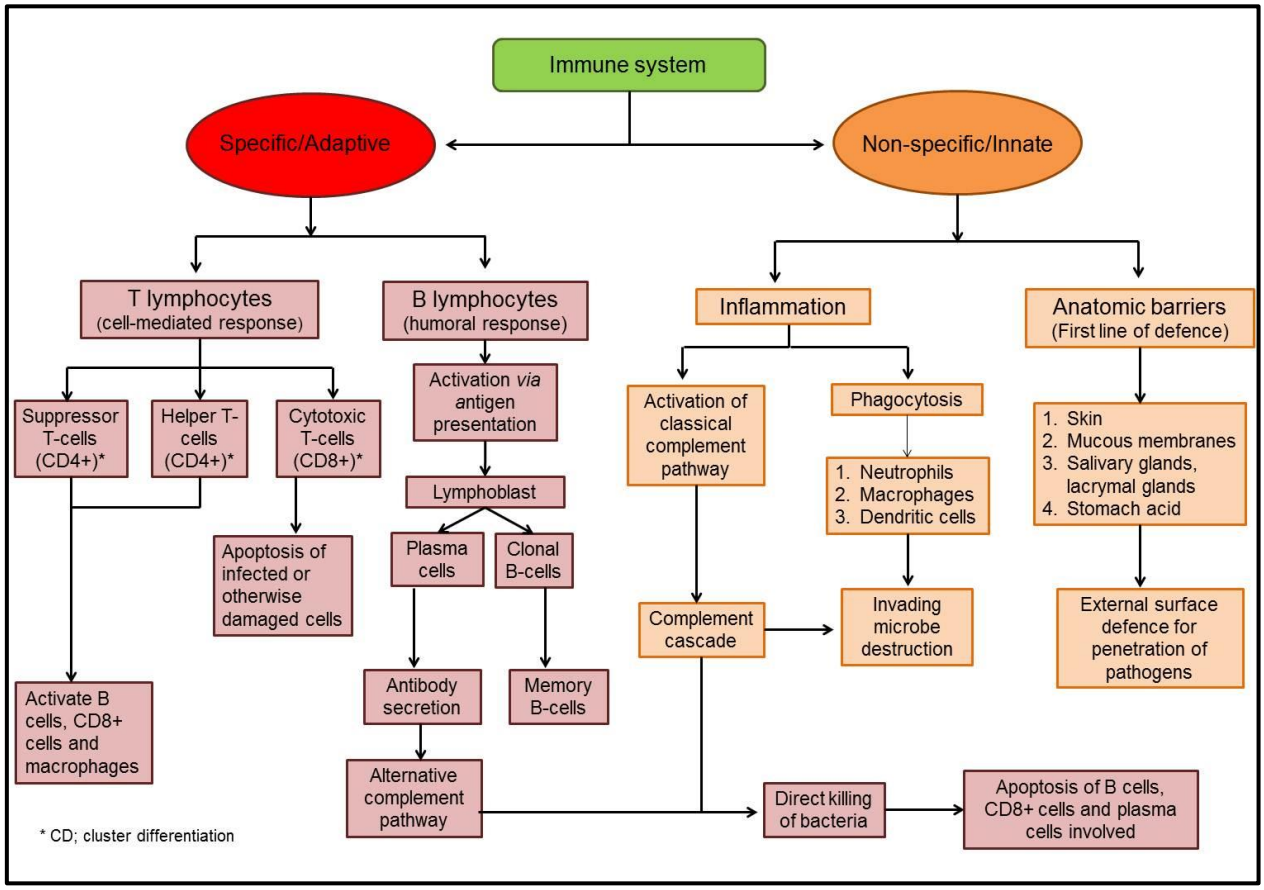

Figure 2.1: Components of the immune system responses

The development of a healthy immune system requires successful activation[2], regulation[3], and resolution[4] (Beers *et al.,* 2006:1320). Our self-regulating immune system reacts upon invasion of pathogens only in order to prevent healthy tissue destruction (Sanders *et al.,* 2010:828). Rheumatoid arthritis is considered an autoimmune disease, meaning the patient's immune system is unable to distinguish between the body's own healthy tissues and antigens, resulting in a reaction where produced antibodies destroy normal, healthy tissue (Boissier *et al.,* 2012:222; Dictionary for the Health Sciences, 2011:591).

Autoimmunity primarily manifests due to the presence of auto-antibodies which may arise even years before onset and clinical manifestation of the disease (Smolen & Redlich, 2014:511). Antibodies (i.e.

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2 I.e. antigen recognition and elimination by circulating antibodies.
3 Suppressor/regulatory T-cells cause immunosuppression to resolve exaggerated responses.
4 I.e. the apoptosis of activated cytotoxic T-cells to prevent cellular content spillage.

immunoglobulins) are present on the surface of B-cells and/or secreted from plasma cells, which serve as binding receptors for any circulating antigen, 'tagging' them as targets to be destroyed (Delves, 2017b; Widmaier *et al.,* 2011:651). Auto-antibodies are defined as those immunoglobulins that form and react against an antigenic constituent of the host's own tissues (Mosby's Medical Dictionary, 2009b). The production of two characteristic auto-antibodies, commonly associated with RA — anti-citrullinated protein antibody (ACPA) and an unusual group of anti-IgG (i.e. rheumatoid factors (RFs)) — leads to the formation of IgG-anti-IgG complexes in joint fluid circulations (Boissier *et al.,* 2012:222; Mellors, 2006). Table 2.1 displays the five major classes of immunoglobulins found in the human body and their immune functions (Schroeder & Cavacini, 2010:S48).

Table 2.1: The five major classes of immunoglobulins and their immune functions

Immunoglobulin class	Immune function
IgM	Also called 'natural antibodies', which are associated with specific humoral immune responses and act as a first-line of defence. They perform immunoregulatory functions and are therefore seldom responsible for autoimmune diseases or pathogenesis, however, auto-antibody reactions are possible.
IgG	Predominant isotype present in the body. Contributes directly to an immune response that includes elimination of toxins and viruses. Pathogenic auto-antibodies have the tendency to arise from somatically mutated, high affinity IgG populations.
IgD	The purpose of immunoglobulin D (IgD) is still unclear and its role in any of the vital antibody effector mechanisms is unknown.
IgA	Critical for protection of mucosal surfaces from toxins, viruses and bacteria *via* direct elimination or surface binding prevention. As such, high serum levels are found in mucosal surfaces, genito-urinary tracts and in secretions, including saliva and breast milk. Almost 50% of the protein in colostrum (i.e. the 'first milk' during breastfeeding) consists of IgA.
IgE	Very low immunoglobulin E (IgE) serum circulating concentrations are associated with allergic reactions, hypersensitivity and the response to parasitic worm infections.

T-cells contain antigen receptors that are remarkably similar to those of immunoglobulins, but cannot combine with the antigen unless it is first bound to the major histocompatibility complex (MHC) proteins in humans (Castro *et al.,* 2015:30). The latter is also known as human leukocyte-associated antigens (HLA) and is located on chromosome 6 (Dictionary for the Health Sciences, 2011:466). The MHC is in theory the genetic markers of 'biological self', since no individual has the same MHC proteins as another (Widmaier *et al.,* 2011:646). The MHC molecules are divided into the following three main categories (Delves, 2017c; Dictionary for the health sciences, 2011:467; Tizard, 1995:92; Widmaier *et al.,* 2011:646):

- class I MHC molecules (present at the surface of all nucleated cells);
- class II MHC molecules (mainly found on the surface of macrophages, B-cells and other dendritic cells) — responsible for- and specialised to present antigen peptides to the T-cell receptors; and
- class III MHC molecules — code for complement proteins as a result of microbial invasion protection.

Nucleated cells that are infected with intracellular antigens (e.g. viruses) are presented to activated cytotoxic (cluster differentiated (CD) -8+) T-cells with the help of class I MHC molecules on the cell surface, to destroy or kill the infected cells (Beers *et al.,* 2006:1321; Dictionary for the health sciences, 2011:467). However, extracellular antigens must first be processed into peptide fragments and presented at the surface of class II MHC molecules to be recognised by helper (CD4+) T-cells (Beers *et al.,* 2006:1321; Dictionary for the Health Sciences, 2011:467). Rheumatoid arthritis has been associated with components of the class II MHC molecules that encode a set of alleles at the human leukocyte antigen-D related β1 (HLA-DRβ1) gene locus (Gough & Simmonds, 2007:453).

In cases of RA, due to persistent inflammation caused by the aforementioned abnormal degenerative autoimmune response, various joint lining tissues are damaged and eventually the joints itself are also affected (Copstead & Banasik, 2005:1281). The key mechanism of this inflammatory cascade includes, among other, the over-production and over-expression of tumour necrosis factor alpha (TNFα), which in turn result in other pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1 (IL-1) that persistently drive both synovial inflammation and joint destruction (Scott *et al.,* 2010:1094). Poor management of long-term disease cause destructive erosion of cartilage and adjacent bone cortex that leads to complete and irreversible loss of joint integrity (Rindfleisch & Muller, 2005:1037). Initially, smaller joints such as the metacarpophalangeal and proximal interphalangeal joints of the hands, and the metatarsophalangeal joints of the feet, elbows, wrists, knees and ankles are more commonly and symmetrically involved (Altman, 2015).

2.3.1 Aetiology of rheumatoid arthritis

Although autoimmune reactions are clearly involved in this disease, the precise aetiology of RA still remains unknown and not fully understood. Evidence, however, suggests that there may exist a complicated interplay between genetic and environmental factors that increases the development of clinical manifestations (Kourilovitch *et al.,* 2014:26). A brief description of these and other factors that may increase susceptibility to RA follows in the subsequent paragraphs.

2.3.1.1 Genetic factors

Heritability of RA and the risk of developing the disease are estimated at an average of 30% to 50% for ACPA-positive disease, but is lower for ACPA-negative disease, with an average of 20% (Boissier *et al.,* 2012:222; Scott *et al.,* 2010:1096). A family history of RA increases the risk of disease development up to three to five times (Smolen *et al.,* 2016). Pathogenesis of the disease that implicates genetics as the basis is further confirmed by observations of RA concordance amongst monozygotic twins, with a five-fold greater risk for disease development in such twins compared to dizygotic twins (Pratt *et al.,* 2009:37).

It has been established that the HLA-DRβ1 gene is the main genetic susceptibility locus for RA, since 80% of patients carry the HLA-DRβ1*04[5] cluster (Choy, 2012:v3). Several human leukocyte HLA-DRβ1 alleles that share an amino acid sequence at the peptide binding site (i.e. the shared epitope) have been identified within the DRβ1*04[5] and DRβ1*01[5] loci as risk factors for ACPA-positive RA development (Luban & Li, 2010:284). Although the precise contribution of this sequence to RA is unknown, it has been proposed that the shared epitope binds to citrullinated peptides, which results in the production of ACPAs or RFs, consequently referred to as "seropositive disease" (Arthritis Foundation, 2015). Citrullination can be defined as the post-translational conversion within a protein of the amino acid arginine, into the non-standard residue citrulline, this conversion being catalysed by the enzyme peptidyl arginine-deiminase in the presence of calcium (Lam, 2006). Macrophages in lung tissue are activated during cigarette smoking, which induces apoptosis and causes calcium concentrations to increase, leading to peptidyl arginine-deiminase mediated citrullination (Pratt *et al.,* 2009:40). These auto-antibody biomarkers seem to play a vital role in the initiation of an inflammatory response within auto-immune diseases (Luban & Li, 2010:284). The presence of the shared epitope is considered to be a risk factor for a more severe, destructive RA prognosis as well as for the development of comorbidities such as cardiovascular disease (CVD), fatigue and other systemic manifestations (Klareskog *et al.,* 2009:659; Kurkó *et al.,* 2013:172).

In 2005, the *PTPN22* allele, located on chromosome 1, was confirmed as the second most important non-HLA susceptibility gene identified in ACPA-positive RA and codes for tyrosine phosphatase, which performs the role of T- and B-cell activation (Klareskog *et al.,* 2009:661; Pratt *et al.,* 2009:38). Anti-citrullinated protein antibody-negative disease involves different HLA alleles (e.g. HLA-DRβ1*03[5]), interferon regulatory factors (e.g. interferon response factor 5) and lectin-binding proteins (e.g. C-type lectin domain family 4 member A), which are not yet well-established genetic factors, but appear to be just as important as those involved in ACPA-positive disease and therefore call for further investigation (McInnes & Schett, 2011:2206). Pratt *et al.* (2009:40) state that the synovium

[5] Numbers following the asterisk represent the allele group (Delves, 2014c).

of a patient with ACPA-positive RA is characterised by denser lymphocyte infiltrations, resulting in more progressive joint destruction compared to more extensive fibrotic changes perceptible in ACPA-negative RA.

According to Kvien *et al.* (2006:214) genetic markers and gender also seem to play an interacting role in the development of RA, suggesting hormonal influences in the pathogenesis of the disease. A population-based case-control study by Doran *et al.* (2004:213) examining the relationship between the use of oral contraceptives or oestrogen replacement therapy and the risk of developing RA, indicated that oral contraceptive exposure in earlier years decreased the risk of developing RA. Furthermore, in conditions where oestrogen and/or progesterone reach excessively high levels (e.g. during pregnancy) it seems to act as a protective mechanism against development of RA (Karlson *et al.,* 2004:3463). More substantial evidence with regard to the precise mechanism is still, however, required (Ngo *et al.,* 2014:355). An "immunological shift" is observed in women during pregnancy to prevent foetal rejection, inflammatory responses are reduced and anti-inflammatory responses increased (Robinson & Klein, 2012:263). De Vries *et al.* (2003:1763) also found that the susceptibility of RA development in females relative to males decrease with increasing numbers of shared epitope alleles within an individual. This evidence, and the fact that females have a higher occurrence of the disease compared to men, may confirm the possible role of hormonal factors in RA susceptibility (Alamanos & Drosos, 2005:134).

2.3.1.2 Environmental factors

Suta *et al.* (2015:220) indicates that the majority of environmental factors that may increase susceptibility to RA are unknown, but their contribution to disease onset seems to be highly significant. Research indicates that the main environmental factors increasing the risk of RA development are related to smoking and alcohol consumption (Kourilovitch *et al.,* 2013:26). However, a study conducted by Maxwell *et al.* (2010) confirmed that moderate alcohol intake resulted in a dose-dependent decrease in the risk of RA development, as well as an inverse association between frequency of consumption and disease severity. Another Swedish prospective cohort study analysed the association between the consumption of alcohol and incidence of RA among women; the researchers also concluded that moderate intake of alcohol reduced the risk of RA development (Di Giuseppe *et al.,* 2012). These findings may be attributed to the fact that moderate alcohol consumption has obvious anti-inflammatory effects by means of lowering IL-6 (pro-inflammatory cytokine) and C-reactive protein (CRP) (i.e. biological marker of inflammation) (Szabo, 2007:S51; Volpato *et al.,* 2004:610).

A two-fold increased risk for RA development in men is a result of long-term smoking, such a history being especially related to seropositive RA, which will persist even after smoking cessation (Boissier

et al., 2012:223; Kvien *et al.,* 2006:214). Smoking seems to be an important risk factor for citrullination of synovial proteins, and is dose-dependently associated with ACPA production in RA patients with shared epitope alleles (Ally & Visser, 2010:21; Luban & Li, 2010:285). Smokers that carry duplicates of the shared epitope have as high as a 21-fold increased risk for developing RA due to ACPA production compared to non-smokers without shared epitope alleles (Boissier *et al.,* 2012:223). Another study found a 36.11-fold increase in the risk of the development of ACPA-positive RA in patients who smoke and also carry duplicates of the shared epitope, whereas the risk of ACPA-negative RA development increased 12.29-fold (Bang *et al.,* 2010:375).

Occupational exposure to silica and mineral oils and also region of birth (which determines the extent of exposure to air pollution and insecticides) contribute to an increase in susceptibility for RA development (Arthritis Foundation, 2017; Kourilovitch *et al.,* 2014:26). Stolt *et al.* (2005:584) investigated the impact of silica exposure on the development of RA and found a two-fold increase in disease incidence among men aged 18 to 49 years, and a 2.5-fold increase among men aged 50 to 70 years. The results were especially associated with men in occupations that involve rock drilling and crushing of stones. Silica, asbestos and silicon are all derived from the same chemical group that causes inflammation *via* production of pro-inflammatory cytokines (e.g. IL-1β, IL-6, IL-8 and TNFα), which result in auto-antibody production such as RF, antinuclear antibodies and ACPA (Speck-Hernandez & Montoya-Ortiz, 2012).

2.3.1.3 Other factors

On-going research has identified, but not yet fully investigated, other factors that may trigger RA disease onset and development, including breastfeeding, birth weight, obesity, the body's response to physical or emotional trauma, socioeconomic status, intake of three or more cups of coffee per day (particularly decaffeinated), and diets high in red meat but low in vitamin C (Arthritis Foundation, 2017; Symmons, 2013).

Although the reason is unclear, the risk of developing RA is higher in infants with a birth weight of more than four kilograms compared to infants with a birth weight that is less than three kilograms (Jacobsson *et al.,* 2003:1069). Panagiotakos *et al.* (2005) investigated the association between chronic inflammation and obesity; their results suggested that the participants who had more visceral fat exhibited increased CRP levels of up to 53%, their TNFα levels were 30% higher, their amyloid A levels showed a 26% increase, their white blood cell count increased by 17% and their IL-6 levels were 42% higher compared to participants who had normal body fat distribution. The adipocyte derived pro-inflammatory cytokines that are released from adipose tissue may lead to systemic inflammation, which is a possible gateway to the development of various diseases, including RA (Lu *et al.,* 2014:1914). A higher prevalence of RA among patients with a low socioeconomic status may

be an indication that access to treatment and specialised healthcare is unaffordable for these patients (Jacobi *et al.,* 2003:571).

2.3.2 Pathogenesis of rheumatoid arthritis

The multifaceted pathogenesis of RA involves antigen-activated CD4+ T-cells, B-cells and the interaction of pro-inflammatory cytokines that play dominant roles in the activation of an immune response and the pathophysiology of RA (Choy, 2012:v3). 'Cytokines' is a collective term for protein messengers secreted by immune cells in order to regulate cell function and mitosis in both innate and adaptive immune responses (Widmaier *et al.,* 2011:634). However, according to Ally and Visser (2010:19), this responsibility of the cytokines to regulate cellular function, *via* promotion or suppression of inflammation, is disturbed in RA and they therefore persistently act as pro-inflammatory cytokines instead.

Despite the various unknowns, chronic joint inflammation is a common hallmark of RA and also the origin of joint damage perceptible in this autoimmune disease (Rindfleisch & Muller, 2005:1038). Various contributing factors (e.g. infection, genetic/environmental factors, autoimmune reaction) may cause the production of auto-antibodies, such as RFs or ACPA in some patients, that lead to the activation of an immune response (Choy, 2012:v4; Wells *et al.,* 2015:26). In reaction, dendritic cells, macrophages and B-cells present the antigens to helper T-cells (CD4+), hence the secretion of cytokines followed by activation of B-cells, cytotoxic T-cells (CD8+), NK-cells and macrophages (Widmaier *et al.,* 2011:635). The inflammatory process is localised in the synovium (i.e. synovitis occurs) as the space between the joints is infiltrated with the aforementioned inflammatory cells (Hitchon & El-Gabalawy, 2011:107). Neo-angiogenesis and poor lymphangiogenesis are characteristic features of this condition, which cause limitations with regard to cellular egress (McInnes & Schett, 2011:2205). The synovium acts as an inn-keeper that regulates the movement of lymphocytes and macrophages that produce multiple pro-inflammatory cytokines, such as chemokines, TNFα's, various interleukins and interferons, and colony-stimulating factors (Beers *et al.,* 2006:283; Boissier *et al.,* 2012:226).

As time progresses, the chronically inflamed synovial tissue starts to grow irregularly (i.e. proliferation of endothelial cells takes place), which induces invasive pannus tissue development (Rindfleisch & Muller, 2005:1038). Tumour necrosis factor alpha, IL-1 and IL-6 pro-inflammatory cytokines are predominant in the initiation and continuance of inflammation, which stimulates the erosion of cartilage and osteoclast-mediated bone absorption (Beers *et al.,* 2006:283; Wells *et al.,* 2015:26). The characteristic shift of RA towards the T-helper-1 and T-helper-17 phenotype (described as a pro-inflammatory state) seems to impair cartilage reparation due to alterations during collagen synthesis with the overproduction of interferon-gamma and insufficient production of T-

helper-2 cytokines, which are involved in cartilage repair (Boissier *et al.,* 2012:226). Furthermore, apoptosis and deprivation of chondrocytes from cartilage cause destruction of surface cartilage with end results that include loss of joint space and motion, ankylosis, joint subluxation, tendon contractures and chronic deformity (McInnes & Schett, 2011:2214; Wells *et al.,* 2015:26).

2.3.3 Clinical presentation

The onset and presentation of RA signs and symptoms are insidious and development of early RA can take up to weeks or even months (Ally & Visser, 2010:19). Approximately 30% of patients experience a sudden, but severe onset of symptoms such as myalgia and systemic complications, this being more commonly seen in older age groups (Jeffery, 2014:231).

Patients normally present with prodromal, nonspecific systemic symptoms which include generalised fatigue and malaise, anorexia and low-grade fever. These symptoms progress to joint symptoms such as pain, morning stiffness that lasts at least 45 minutes and arthralgia, all indicating the development of synovitis (Beers *et al.,* 2006:286; Wells *et al.,* 2015:26). Since joint pain may commonly occur from day to day, Handa (2003:190) emphasises that the clinician has to carefully assess and determine the exact source of pain in order to differentiate arthralgia from arthritis. Swelling that is caused by osteoarthritis (OA) can be distinguished from the swelling of RA with careful palpitation of the joints; a joint affected by RA is described as feeling “spongy/doughy”, warm and may be erythematous in contrast to a joint affected by OA, which feels like a “firm knob” enlargement (Ruffing & Bingham, 2016).

Even though RA has many symptoms, a symmetrical pattern of poly-articular joint involvement involving five or more joints (highly variable) is the most typical clinical presentation and characteristic of this disease (Wells *et al.,* 2015:26). Involvement of any joint is possible, although the axial skeleton (excluding the upper cervical spine) is rarely affected, the most commonly affected joints being the wrist, index and middle metacarpophalangeal joints (Beers *et al.,* 2006:284). Early in the disease, virtually all RA patients experience pain and disability as flares, alternating with phases of remission (Boissier *et al.,* 2012:226). Since RA is characterised as a systemic disease, it is evident that the excessive inflammation over a long period of time will affect organs and areas of the body apart from the joints themselves (Cojocaru *et al.,* 2010:287).

Choy (2012:v4) states that RA is associated with articular and extra-articular manifestations, also referred to as systemic effects, since a United States pharmacy claims data analysis showed that 47.5% (N = 16 752) of RA patients suffered from at least one extra-articular[6] manifestation (e.g.

[6] Any condition or symptom that is indirectly linked to the locomotor system, are described as extra-articular manifestations in RA (Cojocaru *et al*., 2010:287).

rheumatoid nodules, vasculitis, pericarditis, osteoporosis, anaemia, fatigue, depression). Extra-articular manifestations are serious conditions and although they are less common, patients presenting with extra-articular RA should receive intensive therapy and be regularly monitored (Ally & Visser, 2010:19).

The subcutaneous rheumatoid nodule is known as the most common extra-articular lesion which occurs in 20-30% of the patients, especially among seropositive RA patients (Ruffing & Bingham, 2016). This lesion is present on extensor tendon surfaces, elbows, and fingers, as well as in the antebrachium, metacarpophalangeal and proximal interphalangeal joints, occiput, back and heel, and even at internal sites such as the heart and lungs (Jeffery, 2014:233; Ruffing & Bingham, 2016). According to Cojocaru *et al.* (2010:287) and Wilke (2010), other systemic effects that occur more commonly include:

- anaemia (decreased red blood cells);
- Felty's syndrome (decreased white blood cells, associated with an enlarged spleen);
- interstitial lung disease (causing shortness of breath);
- pericarditis (causing chest pain);
- coronary artery disease (especially with constant erythrocyte sedimentation rate (ESR) and increased CRP levels — RA is an independent risk factor);
- scleritis and episcleritis (inflammation of the white part in the eye);
- Sjögren's syndrome (degeneration of the salivary and lachrymal glands, causing dryness of the mouth and eyes); and
- vaculitis (inflammation of the blood vessels leading to necrosis and ultimately damage in the nerves, skin and other organs).

2.3.4 Diagnostic criteria

Arthritis can be differentiated into inflammatory vs. non-inflammatory disease. According to Handa (2003:191), inflammatory arthritis, such as RA, is characterised by marked morning stiffness that lasts longer than 30 minutes, elevated ESR and pain that improves with gentle movement of the joints. Non-inflammatory arthritis is characterised by mild morning stiffness that lasts less than 30 minutes, pain which worsens on joint movement, and normal acute phase response (i.e. alterations

in serum concentrations of certain biomarkers after tissue damage) (Handa, 2003:191). The conditions in each category are illustrated in Figure 2.2 (adapted from Handa, 2003:191).

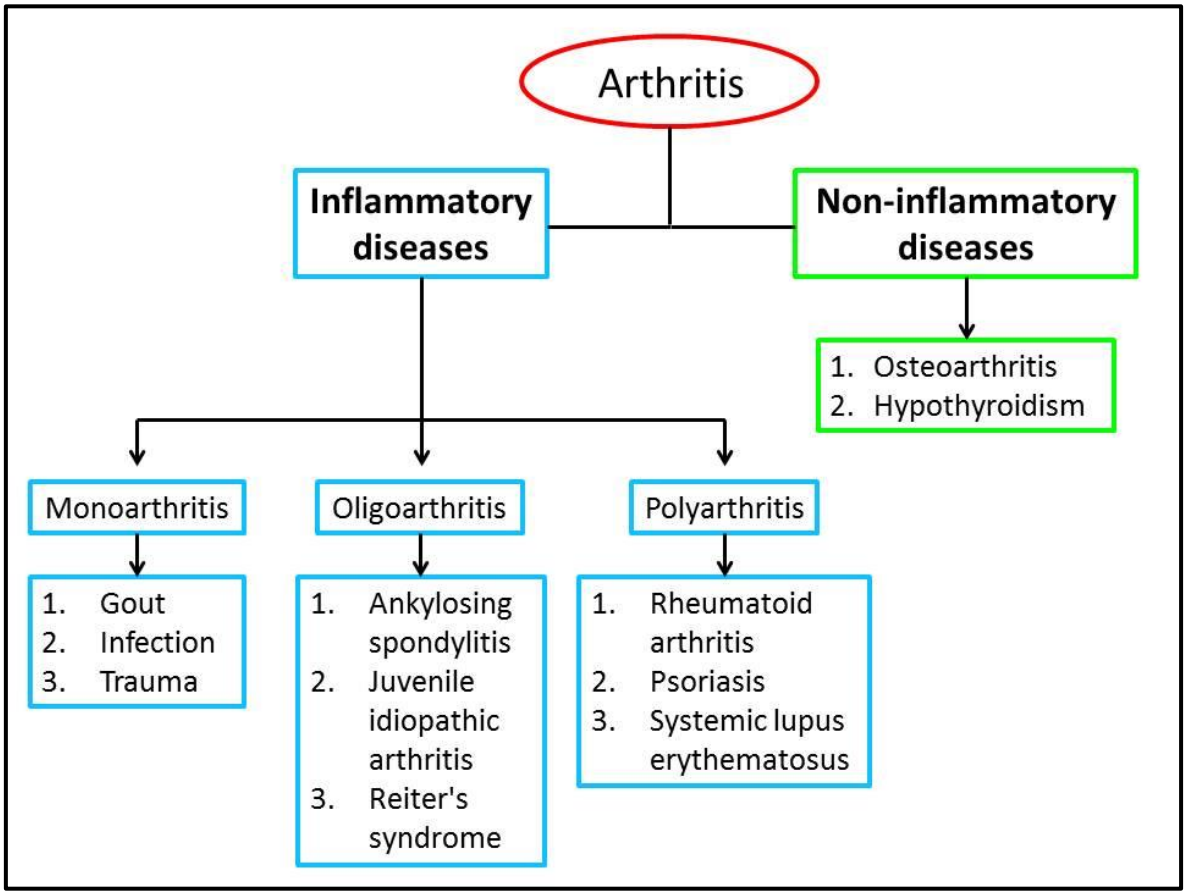


Figure 2.2: Classification of inflammatory and non-inflammatory diseases

Primarily, RA is entirely a clinical diagnosis (Handa, 2003:190). It may be difficult to obtain a definite diagnosis early in the disease (Rindfleisch & Muller, 2005:1039), but Kourilovitch *et al.* (2014:27) state that the ACR/EULAR proposed new diagnostic criteria in 2010 that allows early stage classification of RA in order to improve disease prognosis (see Annexure C).

Although the criteria might be helpful to identify patients, it remains difficult to establish a clear diagnosis in any individual, since there is not a single diagnostic test or feature that is pathognomonic for RA, and therefore diagnosis should rather be made upon recognition of a pattern in the signs and symptoms (Wilke, 2010). Screening tests and biological markers are available to provide diagnostic certainty for RA, but there still exists 15-20% of patients who are seronegative (i.e. RF is absent) (Handa, 2003:190). Rheumatoid factors are one of the most common auto-antibodies detectable in blood samples of RA patients (Boissier *et al.,* 2012:222). Although the majority of patients originally present as seronegative, approximately 80% seroconvert (i.e. become seropositive for RF) (Nielson

et al., 2012). High levels of RF can indicate a tendency toward more aggressive disease and possibly lead to the development of extra-articular/systemic complications (Arthritis Foundation, 2015).

Another biological marker and auto-antibody known as ACPA reportedly has a similar sensitivity as RF (i.e. the sensitivity of ACPA is 67% and that of RF is 69%), but has a higher specificity for RA development (i.e. the sensitivity of ACPA is 95% and that of RA is 85%) (Kourilovitch *et al.,* 2014:28). In many patients, both RF and ACPA may precede the clinical manifestation of RA, but these auto-antibodies can also occur in many other conditions (e.g. Sjögren's syndrome and chronic infectious diseases such as endocarditis, tuberculosis and hepatitis B), rendering them poor screening tests for RA (Arthritis Foundation, 2015; Mellors, 2006).

Other blood tests that are commonly used in the diagnosis of RA are the ESR and CRP tests, which are helpful measures of inflammation in the joints (Snyder & Taylor, 2016). The ESR indicates a degree of inflammation based on how rapidly red blood cells settle within one hour; whereas CRP is produced in the liver when inflammation occurs anywhere in the body, and thus represents a more accurate measure of inflammation than the ESR (NRAS, 2013).

Radiography or X-rays remains the first choice of imaging in the diagnosis and follow-up of RA, even though visualisations of erosions are not detectable early in the disease (National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), 2016). Radiographic findings characteristic of RA include peri-articular osteopenia, loss of joint space and marginal erosions of the joints (Wilke, 2010). Magnetic resonance imaging (MRI) is more sensitive and provides more accurate assessments that are able to detect articular inflammation and erosions earlier in the disease to confirm early initiation of DMARD therapy (Altman, 2015). According to Basu *et al.* (2011), the level of peptidyl arginine-deiminase enzyme activity decreases considerably along with ACPAs and RFs after six months of DMARD treatment, thus indicating peptidyl arginine-deiminase enzyme as a useful additional biomarker in monitoring disease progression.

In conclusion, it should be emphasised that if patients present with symptoms of bilateral, symmetrical, inflammatory disease, or polyarthritis affecting hand joints for a period that exceeds six weeks, a diagnosis of RA should be considered (Beers *et al.,* 2006:284).

2.3.5 Treatment guidelines

According to Rindfleisch and Muller (2005:1039), joint destruction or radiographic progression presents within a few weeks of symptom onset. Since there is only a small window of opportunity to halt or decrease the disease progression of RA, early diagnosis, referral and treatment is of the essence for a positive prognosis and minimal radiological joint damage (Ally & Visser, 2010:19). As

stated by Cummins *et al.* (2015:326), the best clinical practice is that a patient is referred to a rheumatologist within six weeks of symptom onset.

Therapy of patients with inflammation entails two primary objectives: first, relief of symptoms such as pain and discomfort in order to maintain function; second, modification of the disease progression by slowing or restricting the tissue damaging process to halt irreversible joint destruction and deformity (Furst *et al.,* 2012:636).

The ultimate goal of RA therapy is to achieve complete remission in addition to controlled disease activity, minimal pain, maintenance of QoL and the ability to execute daily activities, delay of disability by slowing the destruction of the joints, and the management of possible systemic complications (Rindfleisch & Muller, 2005:1040; Wells *et al.,* 2015:27). Anderson *et al.* (2012:640) state that disease remission can be considered a realistic goal for patients, given the dramatic improvement of drugs used in the treatment of RA. Whilst there are unfortunately still several patients who struggle to sustain remission, more aggressive treatment approaches and biological DMARDs increase the ability to slow disease progression and provide total symptomatic relief (Gower, 2016). According to Bester *et al.* (2016:223), all RA patients should either be in remission or achieve at least lower disease activity, which requires intensive monthly evaluation of patients who are initiated on DMARD therapy. Table 2.2 indicates the three validated scores currently used in South Africa for the calculation of disease activity at each visit (adapted from Bester *et al*., 2016:223).

Table 2.2: Disease activity formulas and categories

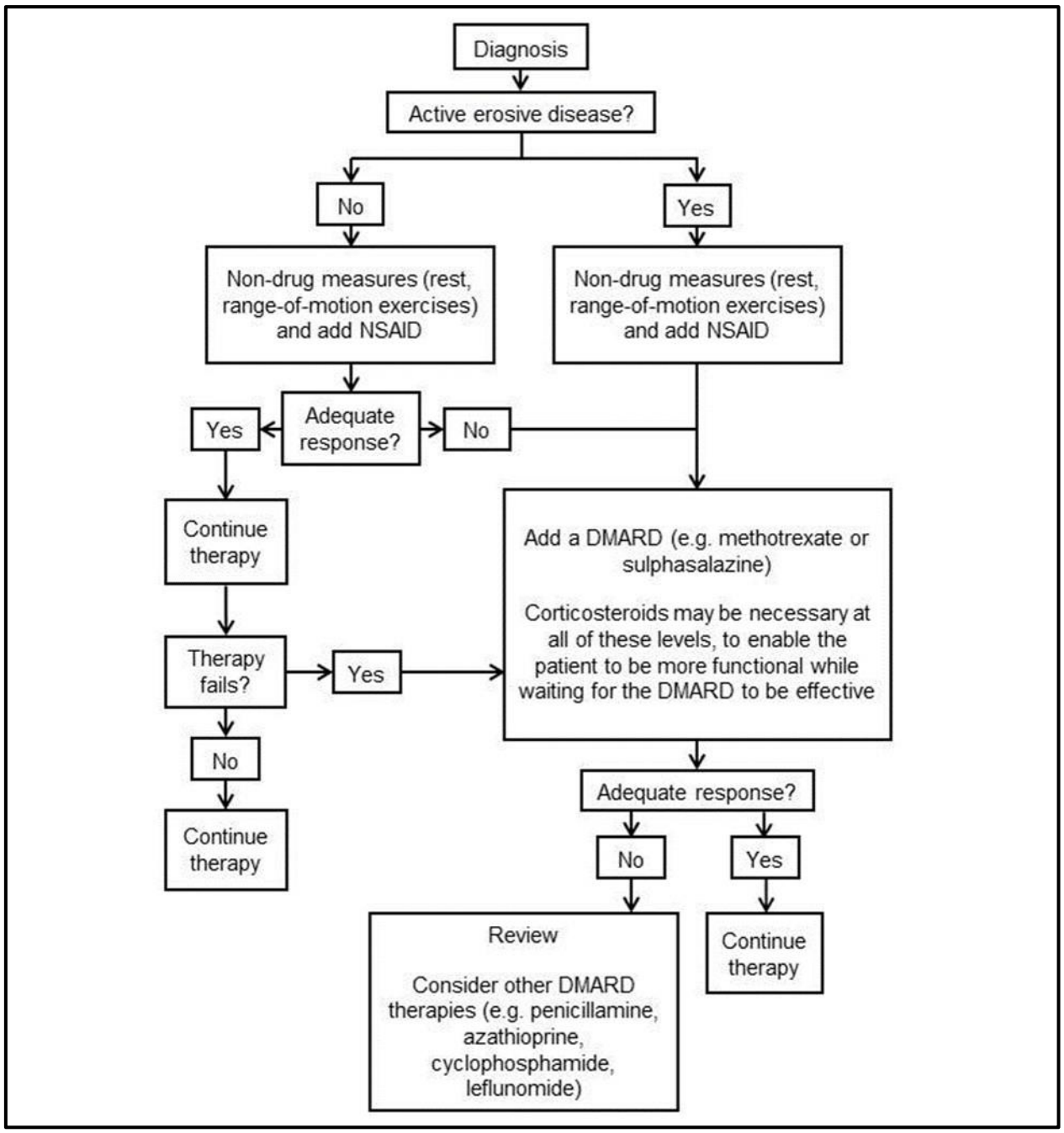
Index	Formula	Remission	Disease activity		
			Low	Moderate	High
SDAI	TJC + SJC + PGA (cm) + DGA (cm) + CRP (mg/dL)	≤ 3.3	≤ 11	≤ 26	> 26
CDAI	TJC + SJC +PGA (cm) + DGA (cm)	≤ 2.8	≤ 10	≤ 22	> 22
DAS-28	0.56 x √TJC + 0.28 x √SJC + 0.7 x ln(ESR) +0.014 x PGA (mm)	≤ 2.6	≤ 3.2	≤ 5.1	> 5.1

SDAI = simplified disease activity index; TJC = tender joint count; SJC = swollen joint count; PGA = patient global assessment; DGA = physician global assessment; CRP = C-reactive protein; CDAI = clinical disease activity index; DAS-28 = disease activity score in 28 joints; ESR = erythrocyte sedimentation rate.

DMARD therapy should be increased until low disease activity (SDAI ≤ 11) or remission (SDAI ≤ 3.3) is achieved.

Optimal RA treatment requires a comprehensive programme that combines medical, social and emotional support for the patient, including options such as medication, reduction of joint stress, physical and occupational therapy, and surgical interventions (Ruffing & Bingham, 2016).

To provide continuous, more affordable healthcare in the private sector of South Africa, a defined set of benefits, namely PMBs, was designed. These PMBs were listed according to the Medical Schemes Act (131 of 1998) to provide all medical scheme members with specific, predetermined health services (CMS, 2017c). According to the CMS (2017c), PMBs assign the responsibility to the medical schemes to cover the costs associated with the diagnosis, treatment and care of any emergency condition and 270 specified medical conditions (defined in the Diagnosis Treatment Pairs list, which includes 26 chronic/non-communicable conditions and HIV/AIDS defined in the CDL (see Annexure A). In deciding whether a condition qualifies as a PMB, doctors follow a diagnosis-based approach in which they should only give attention to the symptoms and not to how the condition was contracted (CMS, 2017c). Rheumatoid arthritis is one of the conditions specified on the CDL for which patients' medical schemes not only have to cover medication, but also the physicians' consultation fees as well as the cost of the tests related to the condition (CMS, 2017a). For the purpose of this study, any comorbidity that coexists with RA and is listed as one of the 27 diseases on the CDL will be included for investigation. The minimum standards for the treatment of a chronic condition such as RA are captured in what is known as benchmark 'therapeutic algorithms'. Medical schemes are obliged to provide treatment that is not inferior to these algorithms (CMS, 2017a). This obligation helps to manage risks and ensure appropriate predetermined standards of healthcare. The therapeutic algorithms are published in the *Government Gazette*: "Regulations made in terms of the Medical Schemes Act, 1998 (Act No. 131 of 1998); therapeutic algorithms for chronic conditions". Figure 2.3 depicts the algorithm for RA treatment in South Africa (South Africa, 2003).



For the disease to qualify as an 'active erosive disease', (i) a cortical break needs to be present on the radiographs of both hands and feet in any of the following locations: the proximal interphalangeal joints, the metacarpophalangeal joints, the wrist (considered as one joint) and the metatarsophalangeal joints; and (ii) a minimum of three of these separate joints needs to be affected (Van der Heijde *et al.*, 2013:479). NSAID = non-steroidal anti-inflammatory drugs; DMARD = disease modifying antirheumatic drugs

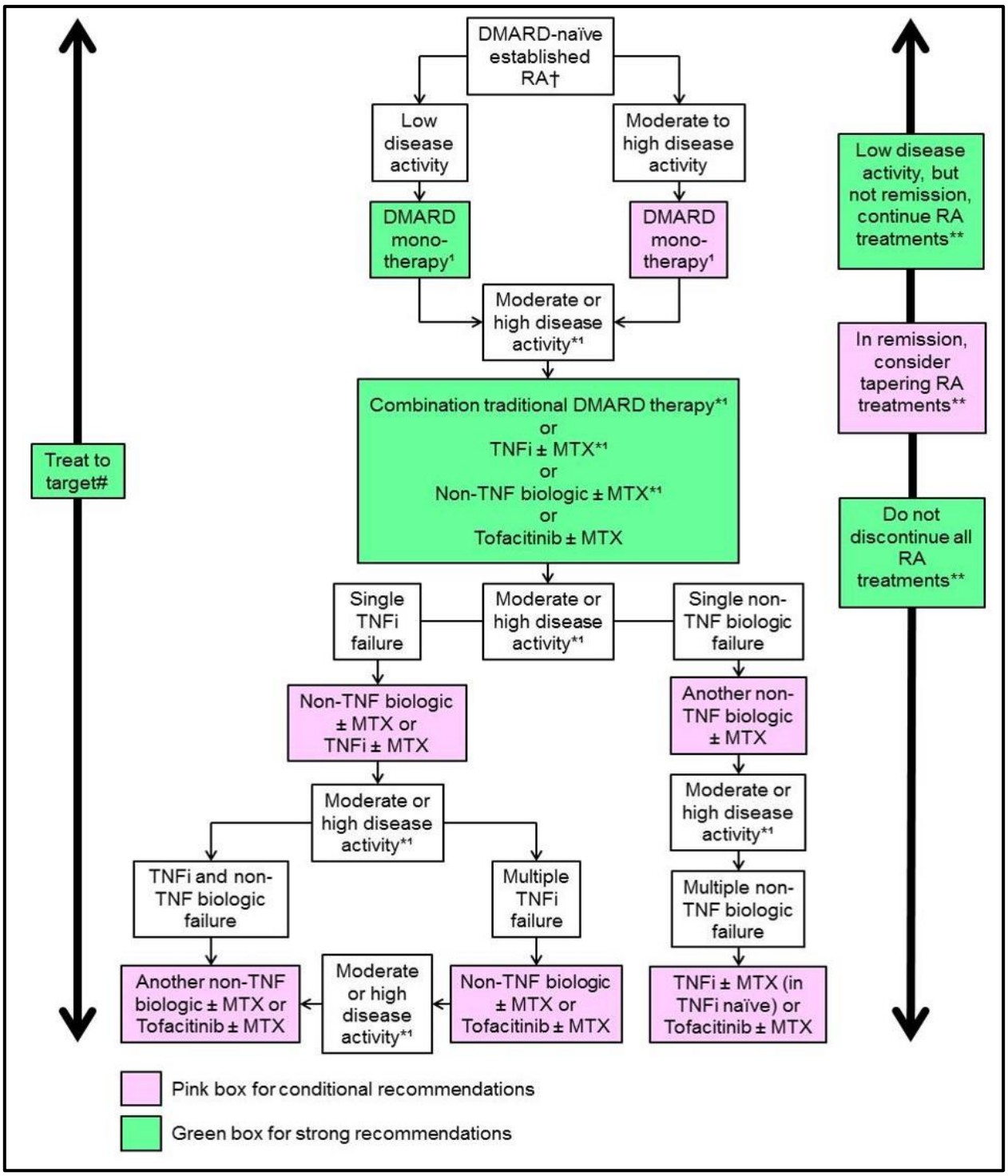
Figure 2.3: South African therapeutic algorithm for rheumatoid arthritis

According to Snyman (2012:61), the therapeutic algorithm should be read in context with the standard ICD-10 codes. If a patient has a PMB condition such as RA, ICD-10 codes become very important in terms of the identification of the condition in patient claims (CMS, 2017b). If the wrong ICD-10 codes are provided, services approved as PMBs might be paid from the wrong benefit account, or it might not be paid at all if the patient's day-to-day or hospital benefit limits are exhausted (CMS, 2017b). In Table 2.3 a summary is provided of all the ICD-10 codes for the therapeutic algorithm of RA (Snyman, 2012:32).

Table 2.3: Standard International Statistical Classification of Diseases and Related Health Problems 10th Revision codes for rheumatoid arthritis

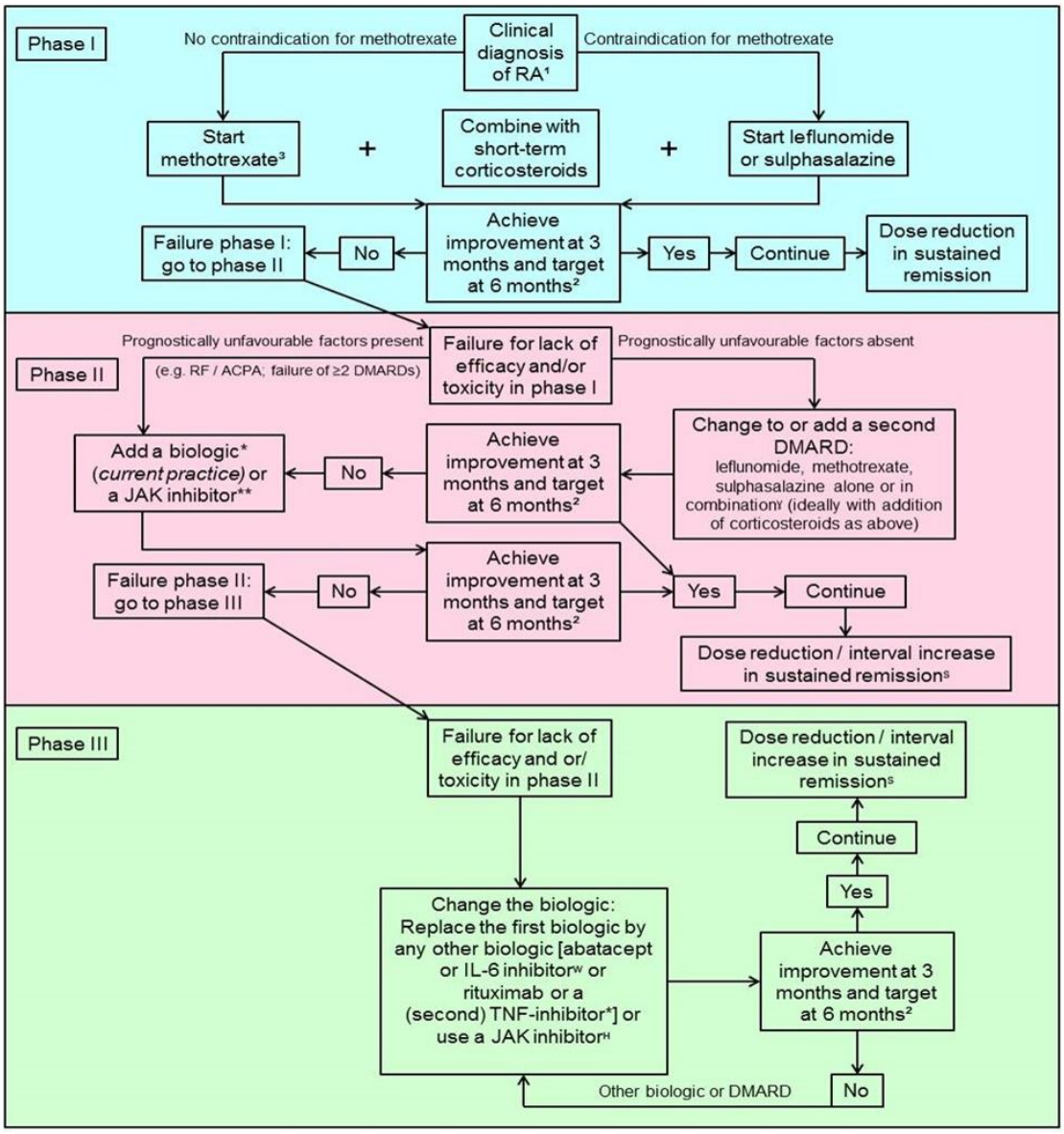
Classification	Sub-classification	Description
M05		Seropositive RA
	M05.0	Felty's syndrome
	M05.1	Rheumatoid lung disease (J99.0*)
	M05.2	Rheumatoid vasculitis
	M05.3	RA with involvement of other organ systems
	M05.8	Other seropositive RA
	M05.9	Seropositive RA, unspecified
M06		Other RA
	M06.0	Seronegative RA
	M06.1	Adult-onset Still's disease
	M06.2	Rheumatoid bursitis
	M06.3	Rheumatoid nodule
	M06.4	Inflammatory poly-arthopathy
	M06.8	Other specified RA
	M06.9	RA, unspecified
M08	M08.0	Juvenile RA

Figures 2.4 and 2.5 depict, respectively, the therapeutic algorithms of the ACR and the EULAR's recommendations for the management of RA, in comparison to the South African treatment algorithm in Figure 2.3 (Singh *et al.*, 2016:10; Smolen *et al.,* 2017:968).



†Established RA is defined as disease duration ≥6 months, or meeting the 1987 ACR classification criteria (see Annexure B). *Consider adding low-dose corticosteroids (≤10 mg/day of prednisone/equivalent) in patients with moderate or high RA disease activity when starting traditional DMARDs and in patients with DMARD or biologic failure. [1]Also consider short-term corticosteroid use (<3 months' treatment) for RA disease flares. #Treatment target should ideally be low disease activity or remission. **Tapering denotes scaling back therapy (reducing dose or dosing frequency), not discontinuing it and if done, must be conducted slowly and carefully. MTX = methotrexate; TNFi = tumour necrosis factor inhibitor.

Figure 2.4: American College of Rheumatology therapeutic algorithm for established rheumatoid arthritis



[1]2010 ACR/EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to the ACR/EULAR definition or, if remission is unlikely achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]Methotrexate should be part of the first treatment strategy; while combination therapy of DMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other DMARDs. *TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved biosimilar), abatacept, IL-6 inhibitors, or rituximab; in patients who cannot use DMARDs as co-medication, IL-6 inhibitors and JAK inhibitors have some advantages. **Current practice would be to start with a biologic (in combination with methotrexate or another DMARD) because of the long-term experience compared to JAK inhibitors. [Y]The most frequently used combination comprises methotrexate, sulphasalazine and hydroxychloroquine. [S]Dose reduction or interval increase can be safely done with all biologics with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture this good state upon re-institution of the same biologic. [W]Efficacy and safety of biologics after JAK inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [H]Efficacy and safety of a JAK inhibitor after insufficient response to a previous JAK inhibitor is unknown. JAK = janus kinase; IL-6 = interleukin-6; DMARD = disease modifying antirheumatic drugs; TNF = tumour nercrosis factor.

Figure 2.5: European League against Rheumatism therapeutic algorithm for management of rheumatoid arthritis

Phase I of both the ACR and EULAR algorithms immediately starts treatment with monotherapy, consisting of a conventional DMARD (e.g. methotrexate, sulphasalazine, leflunomide) or a DMARD in combination with antimalarial drugs (e.g. hydroxychloroquine) and short-term, low-dose corticosteroids until the DMARDs become effective. The South African algorithm, on the other hand, initiates treatment with NSAIDs and non-pharmacological interventions such as rest and exercise only. Following this approach in the management of RA may narrow the window of opportunity to halt the disease progression and cause further joint destruction, since it is recommended that DMARD therapy be started as soon as possible (Smolen *et al.,* 2005:171).

Phase II is more or less the same for all three algorithms: the South African algorithm now starts treatment with DMARDs; ACR and EULAR either combine the initial DMARD with another DMARD or change it, whilst a biologic agent (e.g. tofacitinib, abatacept, rituximab) is added in certain conditions such as high disease activity or where treatment targets are not achieved. Low dose corticosteroids are still recommended in each algorithm at this phase as a form of adjunctive therapy in order to promote the functionality of patients while awaiting DMARD efficacy.

Phase III of the ACR and EULAR algorithms continues to combine and/or alternate between DMARDs and biologics, depending on the success of the treatment — it remains a trial-and-error process to find the optimal RA treatment for every individual patient. The South African algorithm states that only another conventional DMARD should be considered in the case of inadequate response to the medication used in phase II; no recommendation of any biologic for treatment has been made. Bester *et al.* (2016:224) state that commencement of biological treatment in South Africa is only considered after at least three conventional DMARD therapies have failed, although this recommendation has not yet been added to the South African algorithm.

2.3.6 Pharmacological treatment

There are currently three general therapeutic drug classes that are used in the treatment of established RA: (1) NSAIDs/selective cyclo-oxygenase-2 (COX-2) inhibitors; (2) corticosteroids; and (3) DMARDs (Lee & Kavanaugh, 2003:811). Disease modifying antirheumatic drug therapy consists of two groups, which include non-biologic DMARDs (usually designated “DMARDs”) and several biologic DMARDs (designated “biologics”) (Furst *et al.,* 2012:643). These therapies are discussed in the following paragraphs.

2.3.6.1 Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs are analgesic, reduce inflammation and stiffness and provide relatively rapid symptomatic relief, but have no impact on the progression of the disease and therefore should only be used as adjunctive therapy (Wells *et al.,* 2015:28). Effective doses of aspirin

may have serious side effects and are therefore no longer used in RA treatment, although lower doses of ≤ 325 mg/d may be administered simultaneously with another NSAID for its antiplatelet cardio-protective effect (Beers *et al.,* 2006:286). However, this dose of aspirin may seem high compared to Vandvik *et al.* (2012:e638S) who suggest a low-dose aspirin of 75-100 mg per day for people 50 years and older as prophylactic treatment of CVD. Table 2.4 displays the recommended dosage regimens for NSAIDs used in the treatment of RA (Altman, 2015; Rossiter *et al.,* 2016).

Table 2.4: Recommended dosage regimens for non-steroidal anti-inflammatory drugs

Drug	Usual dosage	Maximum recommended daily dosage
Non selective		
Diclofenac	Short-term therapy: 50 mg t.i.d/75 mg b.i.d. Long-term therapy: 100-150 mg/d sustained release	150 mg
Etodolac	300–500 mg PO b.i.d.	1 200 mg
Fenoprofen	300–600 mg q.i.d.	3 200 mg
Flurbiprofen	100 mg b.i.d. or t.i.d.	300 mg
Ibuprofen	400–800 mg q.i.d. Long-acting tablets: 1 600 mg single dose at night	3 200 mg
Indomethacin	25 mg t.i.d. (maintenance dose), increased to 200 mg/d sustained release if needed Night pain/morning stiffness: 100 mg of total dose at bedtime	200 mg
Ketoprofen	50–75 mg q.i.d., 200 mg/d sustained release	300 mg
Lornoxicam	12 mg/d in 2 to 3 divided doses	12 mg
Meclofenamate	50 mg t.i.d. or q.i.d.	400 mg
Nabumetone	1000–2000 mg/d in one dose or divided doses	2 000 mg
Naproxen	250 mg b.i.d., if necessary increase to 500–1000 mg/d in two divided doses Maintenance dose = minimum effective dose	1 500 mg
Oxaprozin	1200 mg/d	1 800 mg
Piroxicam	20 mg/d or divided doses	20 mg
Sulindac	150–200 mg b.i.d.	400 mg
Tolmetin	400 mg t.i.d.	1 800 mg

Drug	Usual dosage	Maximum recommended daily dosage
COX-2 specific		
Celecoxib	100-200 mg/d or b.i.d.	400 mg
Etoricoxib	90 mg/d	120 mg
Meloxicam*	7.5–15 mg/d Deep IM, 7.5–15 mg/d for maximum of 3 days	15 mg

mg/d = milligrams per day; b.i.d. = two times daily; t.i.d. = three times daily; q.i.d. = four times daily; PO = by mouth; COX = cyclooxygenase; IM = intra-muscular

*COX-2 specificity for this drug is unclear

The difference between NSAIDs and COX-2 inhibitors is attributable to their pharmacological pathway to the inhibition of the inflammatory process: NSAIDs inhibit non-specifically both COX-1 and COX-2 iso-enzymes, while COX-2 inhibitors specifically inhibit COX-2 (Lee & Kavanaugh, 2003:813). The dose of these medications may be increased every two weeks (i.e. the rate for maximal response with NSAIDs) until the desired outcome is reached, but should not exceed the maximum recommended daily dosage (Altman, 2015) (refer to Table 2.4).

2.3.6.2 Corticosteroids

Corticosteroids have prompt and dramatic effects, with anti-inflammatory as well as immunosuppressive properties that have the ability to slow bone erosion (Furst *et al.,* 2012:650). Unfortunately, long-term use diminishes their clinical benefit because of serious adverse effects, therefore they are prescribed for the shortest possible duration as adjunctive therapy at the lowest dose possible, in order to provide symptomatic relief and preserve function until slower-acting DMARD treatment effects are discernible (Beers *et al.,* 2006:288; Singh *et al.,* 2016:10). Corticosteroids are especially useful in the treatment of additional extra-articular symptoms or during flares, which are common temporary exacerbations in RA patients (Bijlsma, 2012:iv9; Bykerk *et al.,* 2016:1). It is important that treatment with corticosteroids be withdrawn once DMARD therapy starts to work and the disease is under control (Bester *et al.,* 2016:224). Table 2.5 shows the recommended dosage regimens for RA treatment with corticosteroids (Altman, 2015; Rossiter *et al.,* 2016).

Table 2.5: Recommended dosage regimens for corticosteroids in rheumatoid arthritis treatment

Drug	Dosage	Adverse effects
Intra-articular injections		
Methylprednisolone acetate	Depending on joints involved Knees, ankles, shoulders: 20–80 mg Elbows, wrists: 10–40 mg Hands, sternoclavicular, acromioclavicular: 4–10 mg	With long-term use: inflammation and, rarely, infection at site of injection.
Triamcinolone acetonide	Depending on joints involved	
Triamcinolone hexacetonide	10–40 mg, depending on joints involved	
Systemic corticosteroids		
Prednisone	Long-term therapy: 7.5 mg/d every morning in conjunction with DMARDs Attempt to avoid exceeding 7.5 mg/d PO (except in patients with severe systemic manifestations).	With long-term use: weight gain, diabetes, hypertension and osteoporosis.
DMARD = disease modifying antirheumatic drugs; mg/d = milligrams per day; PO = by mouth		

2.3.6.3 Disease modifying antirheumatic drugs

This heterogeneous group of agents is called ‘disease modifying drugs’, because not only do they have anti-inflammatory actions, they are also able to reverse joint damage (Trevor *et al.,* 2010:319). Although some biologics are effective within two weeks or less, therapy with synthetic DMARDs may take six weeks to even six months before the effects become clinically evident (Furst *et al.,* 2012:643).

Disease modifying antirheumatic drug therapies are indicated for virtually every RA patient and render more effective results when used in combination with one another/a biologic/corticosteroids compared to the outcomes of monotherapy (Altman, 2015). The key to the optimal management of early RA is immediate intervention with DMARD treatment in conjunction with low dose corticosteroids (Smolen *et al.,* 2005:171). The ensuing paragraphs provide a brief description of the two DMARD groups and the drugs within these therapeutic classes used for the treatment of RA.

2.3.6.3.2 Synthetic disease modifying antirheumatic drugs

Also called ‘traditional’ or ‘conventional DMARDs’, methotrexate is recommended as first-line therapy and known as the cornerstone of treatment most commonly prescribed to RA patients (Bester *et al.,* 2016:224). Hodkinson *et al.* (2013:576) indicates that synthetic DMARDs may be appropriate for monotherapy; however, combination treatment becomes necessary in cases where therapy with methotrexate alone failed. Table 2.6 reproduces a summary of the drugs available in this therapeutic class and explains the pharmacological mechanism of action (Furst *et al.,* 2012:635; WHO, 2015).

Table 2.6: Synthetic disease modifying antirheumatic drugs

Drug	ATC classification	Pharmacological mechanism of action	Indication
Azathioprine *Available in South Africa*	L04AX01 L – Antineoplastic & immunomodulating agents L04 - Immunosuppressants L04A - Immunosuppressants L04AX - Other immunosuppressants	Suppresses, *via* its major metabolite (6-Thioguanine): • inosinic acid synthesis; • functions of B- and T-cells; • production of immunoglobulin; and • IL-2 secretion.	• RA • Psoriatic arthritis • Reactive arthritis • Polymyositis • SLE • Behçet's disease
Methotrexate *Available in South Africa*	L04AX03 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AX – Other immunosuppressants	• Inhibits AICAR transformylase and thymidilate synthetase – AICAR accumulates intracellularly. • AICAR competitively inhibits AMP deaminase – AMP accumulates. • AMP is released and extracellularly converted to adenosine, causing potent inhibition of inflammation.	• RA • Juvenile chronic arthritis • Psoriasis • Psoriatic arthritis • Ankylosing spondylitis • Polymyositis • Dermatomyositis • Wegener's granulomatosis • Giant cell arteritis • SLE • Vasculitis

Drug	ATC classification	Pharmacological mechanism of action	Indication
Mycophenolate mofetil *Available in South Africa*	L04AA06 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AA – Selective immunosuppressants	• Converted to the active form of the drug, mycophenolic acid. • Mycophenolic acid inhibits inosine monophosphate dehydrogenase – suppresses T- and B-cell proliferation.	• RA • Renal disease due to SLE • Vasculitis • Wegener's granulomatosis
Leflunomide *Available in South Africa*	L04AA13 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AA – Selective immunosuppressants	• Rapid conversion in the intestine and plasma to its active metabolite (A77-1726). • A77-1726 inhibits dehydroorotate dehydrogenase – decreases ribonucleotide synthesis and suppresses stimulated cells in the G_1 cell growth phase. • T-cell proliferation and production of B-cell autoantibodies are inhibited.	• As effective as MTX for RA
Chloroquine and hydroxychloroquine *Available in South Africa*	P01BA01 P – Antiparasitic products, insecticides and repellents P01 – Antiprotozoals P01B – Antimalarials P01BA – Aminoquinolines	• Mainly used against malaria. • Anti-inflammatory mechanism of these drugs is unclear in rheumatic diseases.	• RA • Serositis • Joint pains of SLE • Sjögren's syndrome
Cyclophosphamide *Available in South Africa*	L01AA01 L - Antineoplastic & immunomodulating agents L01 – Antineoplastic agents L01A – Alkylating agents L01AA - Nitrogen mustard analogues	• The major active metabolite (phosphoramide mustard) cross-links DNA, which prevents cell replication. • Suppression of T- and B-cell functions.	• RA (only if administered orally in doses of 2 mg/kg/d) • SLE • Vasculitis • Wegener's granulomatosis

Drug	ATC classification	Pharmacological mechanism of action	Indication
Cyclosporine *Available in South Africa*	L04AD01 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AD – Calcineurin inhibitors	• This peptide antibiotic inhibits IL-1 and IL-2 receptor production *via* regulation of gene transcription. • Secondarily inhibits macrophage-T-cell interaction and T-cell responsiveness.	• RA • SLE • Polymyositis and dermatomyositis • Wegener's granulomatosis • Juvenile chronic arthritis
Gold *Not available in South Africa*	M01CB04 – aurothioglucose M – Musculoskeletal system M01 – Anti-inflammatory & antirheumatic products M01C – Specific antirheumatic agents M01CB Gold preparations	• A number of theories have been postulated, but the mechanism of gold preparations used in patients with RA remains unclear.	Gold is no longer available in South Africa due to numerous significant toxicities and limited efficacy.
Minocycline *Available in South Africa*	J01AA08 J – Anti-infectives for systemic use J01 – Antibacterials for systemic use J01A - Tetracyclines J01AA - Tetracyclines	• Tetracycline antibiotic • Decreases the production of prostaglandins, metalloproteinases and leukotrienes (inflammatory precursors). • Increases the production of IL-10, a substance that reduces inflammation.	• Mild symptoms of RA • Infections caused by mycoplasma, chlamydiae, rickettsiae and some spirochetes • Malaria • *Helicobacter pylori* • Acne
Penicillamine *Not available in South Africa*	M01CC01 M – Musculoskeletal system M01 – Anti-inflammatory & antirheumatic products M01C – Specific antirheumatic agents M01CC - Penicillamine and similar agents	• Possibly reduces the formation of collagen (scar tissue that results from inflammation), although the exact mechanism in RA is still unknown.	Penicillamine is no longer available in South Africa due to numerous significant toxicities and limited efficacy.

Drug	ATC classification	Pharmacological mechanism of action	Indication
Sulphasalazine *Available in South Africa*	A07EC01 A – Alimentary tract & metabolism A07 – Antidiarrheal, intestinal anti-inflammatory/anti-infective agents A07E – Intestinal anti-inflammatory agents A07EC – Aminosalicylic acid and similar agents	• Metabolised to sulfapyridine and 5-aminosalicyclic acid. • IgA and IgM RF production is decreased. • Suppression of T-cell responses and B-cell proliferation. • Inhibits pro-inflammatory cytokines, e.g. IL-1, -6 and 12, and TNFα.	• RA • Juvenile chronic arthritis • Ankylosing spondylitis and its associated uveitis
ATC = Anatomical Therapeutic Chemical Classification System; SLE = systemic lupus erythematosus; AICAR = amino-imidazolecarboxamide ribonucleotide; AMP = adenosine monophosphate; Ig = immunoglobulin; IL = interleukin; RF = rheumatoid factor			

Table 2.7 illustrates the recommended daily dosage for treatment of RA with the synthetic DMARDs (Altman, 2015; Rossiter *et al.,* 2016).

Table 2.7: Recommended dosage regimens for synthetic disease modifying antirheumatic drugs used in rheumatoid arthritis

Drug	Dosage	Adverse effects
Hydroxychloroquine	Initially, 400 mg/d PO	Usually mild dermatitis Myopathy Corneal opacity (reversible) Occasionally irreversible retinal degeneration
Leflunomide	20 mg/d PO or, if adverse effects occur, reduced to 10 mg/d	Skin reactions Hepatic dysfunction Alopecia Diarrhoea
Methotrexate	Single oral dose, starting at 7.5 mg/d and gradually increased as needed to a maximum of 25 mg/d Doses > 20 mg/week best given subcutaneously (SC) to ensure bioavailability	Liver fibrosis (dose related, often reversible) Nausea Possible bone marrow suppression Stomatitis Rarely pneumonitis (potentially fatal)
Sulphasalazine*	500 mg PO in the evening, increased to 500 mg mane and 1 000 mg nocte, then increased to 1 000–1 500 mg b.i.d.	Bone marrow suppression Gastric symptoms Neutropenia Haemolysis Hepatitis
Azathioprine**	1 mg/kg/d (50–100 mg) PO or b.i.d., increased by 0.5 mg/kg/d after 6–8 weeks, then every 4 weeks to a maximum of 2.5 mg/kg/d	Liver toxicity Bone marrow suppression Possibly increased risk for cancers (e.g. lymphoma and non-melanoma skin cancers) With cyclosporine: impaired renal function, hypertension and risk of diabetes.
Cyclosporine	50 mg PO b.i.d., do not exceed 1.75 mg/kg PO b.i.d.	

mg/d = milligrams per day; b.i.d. = two times daily; t.i.d. = three times daily; q.i.d. = four times daily; PO = by mouth; mane = in the morning; nocte = in the evening

*Sulphasalazine is usually given as enteric-coated tablets. **During dosage increases for azathioprine, complete blood count (CBC), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are monitored.

2.3.6.3.3 Biologic disease modifying antirheumatic drugs

In South Africa, mainly due to the serious potential adverse effects and high costs of the medication, the initiation of biologics is normally reserved for patients with severe RA that is unresponsive to a six-month trial of standard treatment with at least three DMARDs (Hodkinson *et al.,* 2013:576; Tarr *et al.,* 2014:787). However, it should be emphasised that biologics are especially effective when treatment is introduced earlier in the development of RA, and their superiority to synthetic/conventional DMARDs has also been proven by the increasing numbers of patients achieving disease remission (CMS, 2009). Table 2.8 reproduces a summary of the drugs that are available in this therapeutic class and explains the pharmacological mechanism of action (Furst *et al.,* 2012:635; WHO, 2015).

Table 2.8: Biologic disease modifying antirheumatic drugs

Drug	ATC classification	Pharmacological mechanism of action	Indication
Abatacept *Available in South Africa*	L04AA24 L - Antineoplastic & immunomodulating agents L04 - Immunosuppressants L04A - Immunosuppressants L04AA - Selective immunosuppressants	Binds with CD80 or CD86 on the APC to prevent the interaction of CD28 on the T-cell that would cause T-cell activation. Inhibiting the binding of CD80 or CD86 to CD28 thus prevents activation of T-cells.	Monotherapy or in combination with other DMARDs in patients with moderate to severe RA
Tofacitinib *Not available in South Africa*	L04AA29 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AA – Selective immunosuppressants	JAK inhibitor JAK are the intracellular signalling pathways of cytokines that are critical to the progression of immune and inflammatory responses.	Moderate to severe RA in patients who had an inadequate response or intolerance to methotrexate
Etanercept *Available in South Africa*	L04AB01 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	Known as a recombinant fusion protein. Its two soluble TNF p75 receptor moieties link to the F_c portion of human IgG_1. Binds TNFα molecules and inhibits lymphotoxin-α.	RA, can be used as monotherapy or combined with methotrexate Juvenile chronic arthritis Psoriasis Psoriatic arthritis Ankylosing spondylitis

Drug	ATC classification	Pharmacological mechanism of action	Indication
Infliximab *Available in South Africa*	L04AB02 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	This chimeric (25% mouse, 75% human) IgG_1 monoclonal antibody binds to soluble and possibly membrane-bound TNFα. Causes down-regulation of macrophage and T-cell function.	RA, best used in combination with methotrexate Juvenile chronic arthritis Psoriasis Psoriatic arthritis Ankylosing spondylitis Crohn's disease Ulcerative colitis Wegener's granulomatosis Giant cell arthritis Sarcoidosis
Afelimomab *Not available in South Africa*	L04AB03 L - Antineoplastic & immunomodulating agents L04 - Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	Also known as Fab 2 or MAK 195F, an anti-TNFα monoclonal antibody. Administration of 195F decreases the concentration of IL6 in patients with sepsis.	Investigated for treatment in sepsis and septicaemia.
Adalimumab *Available in South Africa*	L04AB04 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	Full human IgG_1 anti-TNF monoclonal antibody. Complexes with soluble TNFα to prevent its interaction with p55 and p75 cell receptors, which lead to down-regulation of macrophage and T-cell function.	RA, used as monotherapy or in combination with methotrexate/other DMARDs Juvenile idiopathic arthritis Plaque psoriasis Psoriatic arthritis Ankylosing spondylitis Crohn's disease

Drug	ATC classification	Pharmacological mechanism of action	Indication
Certolizumab *Not available in South Africa*	L04AB05 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	Recombinant, humanised antibody Fab fragment conjugated to a polyethylene glycol with specificity for human TNFα. Neutralises membrane-bound and soluble TNFα in a dose-dependent manner.	Moderate to severe RA, can be used as monotherapy or in combination with another non-biological DMARD Reduce signs and symptoms of Crohn's disease
Golimumab *Available in South Africa*	L04AB06 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AB – TNFα inhibitors	Human monoclonal antibody with high affinity for soluble and membrane-bound TNFα. Neutralises the inflammatory effects of TNFα.	Combine with methotrexate for moderate to severe RA Psoriatic arthritis Ankylosing spondylitis
Anakinra *Not available in South Africa*	L04AC03 L - Antineoplastic & immunomodulating agents L04 - Immunosuppressants L04A – Immunosuppressants L04AC - Interleukin inhibitors	Competitive IL-1 receptor antagonist.	Neonatal-onset multisystem inflammatory disease. Adult-Onset Still's Disease (off-label use) Gout calcium pyrophosphate deposition (formerly called Pseudogout) Behcet's Disease Ankylosing spondylitis Uveitis and other auto-inflammatory syndromes

Drug	ATC classification	Pharmacological mechanism of action	Indication
Tocilizumab *Available in South Africa*	L04AC07 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AC – Interleukin inhibitors	Humanised antibody that antagonises IL-6 receptors. Interleukin-6 is a pro-inflammatory cytokine that activates T-cells.	Moderate to severe RA in patients with inadequate response to one or more TNFα antagonist
Ustekinomab *Available in South Africa*	L04AC05 L – Antineoplastic & immunomodulating agents L04 – Immunosuppressants L04A – Immunosuppressants L04AC – Interleukin inhibitors	Interleukin-12/23 monoclonal antibody.	Active psoriatic arthritis Psoriasis
Rituximab *Available in South Africa*	L01XC02 L - Antineoplastic & immunomodulating agents L01 – Antineoplastic agents L01X – Other antineoplastic agents L01XC - Monoclonal antibodies	This chimeric monoclonal antibody depletes CD20 B-cells *via* cell-mediated and complement-dependent cytotoxicity and stimulation of cell apoptosis. Depletion of B-cells reduces inflammation by decreasing the presentation of antigens to T-cells and preventing pro-inflammatory cytokine secretion.	Moderate to severe RA in combination with methotrexate in patients with inadequate response to one or more TNFα antagonist
APC = antigen presenting cell; JAK = janus kinase; IL = interleukin			

Table 2.9 illustrates the recommended daily dosage for RA treatment with biologics (Altman, 2015; Rossiter *et al.,* 2016).

Table 2.9: Recommended dosage regimens for biologics used in rheumatoid arthritis

Drug	Dosage	Adverse effects
Abatacept	500 mg IV for patients weighing < 60 kg, 750 mg for patients weighing 60–100 kg, and 1 g IV for patients weighing > 100 kg	Pulmonary toxicity Susceptibility to infection Headache Upper respiratory tract infections (URI) Sore throat Nausea
Rituximab	1 g IV at baseline and at 2 weeks	When the drug is being given: mild itching at the injection site, rashes, back pain, hypertension or hypotension and fever. After the drug is given: slightly increased risk of infection and possibly cancer, hypogammaglobulinemia and neutropenia.
Anakinra	100 mg/d SC	Reactions at injection site Immunosuppression Neutropenia
Tocilizumab	8 mg/kg IV q. 4 weeks, to a maximum 800 mg/dose	Potential risk of opportunistic infections Neutropenia Thrombocytopenia GI perforation Anaphylaxis Demyelinating neurological disorders
Adalimumab	40 mg SC once q. 1-2 weeks	Potential risk of infection (particularly TB and fungal infection) Non-melanoma skin cancers Reactivation of hepatitis B Antinuclear antibodies with or without clinical SLE
Certolizumab pegol	400 mg SC (as 2 SC injections of 200 mg) once and the repeat at week 2 and week 4, followed by 200mg SC q. 2 weeks (or 400 mg SC q. 4 weeks)	

Drug	Dosage	Adverse effects
Etanercept	25 mg SC twice/week or 50 mg SC once/week	Demyelinating neurological disorders
Golimumab	50 mg SC once q. 4 weeks	Potential risk of infection (particularly TB and fungal infection) Non-melanoma skin cancers Reactivation of hepatitis B Antinuclear antibodies with or without clinical SLE Demyelinating neurological disorders
Infliximab	3 mg/kg IV infusion in saline at baseline, at 2 weeks and at 6 weeks with subsequent injections q. 8 weeks (dosage may be increased to 10 mg/kg)	
Tofacitinib	5 mg PO b.i.d.	Risk of infection Non-melanoma skin cancers Hypercholesterolemia
IV = intravenous; q = every; SC = subcutaneous; b.i.d. = two times daily; SLE = systemic lupus erythematosus		

2.3.7 Non-pharmacological interventions

In addition to drug therapy, RA patients are often advised or prescribed to make use of non-pharmacological modalities to deal with the consequences of the disease (Vlieland, 2007:1397). A persisting level of disease activity will always remain despite treatment and interfere with a patient's daily activities, since RA is a lifelong illness (Rindfleisch & Muller, 2005:1043). Non-pharmacological interventions for the management of RA include aerobic and strengthening exercises, measurements to decrease stress, and protection of joint integrity (Stark, 2016). Education and support groups for the patients as well as their families are crucial in order to maintain patients' independence and increase compliance by encouraging participation in the planning of patient care for periods of disease exacerbation (Scott *et al.,* 2010:1101; Stark, 2016). Surgery should be reserved until pain becomes unbearable and the loss of motion and functional impairment are significantly severe (Rindfleisch & Muller, 2005:1043). The following paragraphs will provide a brief overview of some of the measures mentioned above.

2.3.7.1 Lifestyle measures

The implementation of interventions (e.g. exercise, weight loss and cessation of smoking) in order to obtain a healthy lifestyle could have a remarkable impact on the prevention and/or reduction of comorbidity development and prognosis of RA (Blom & Riel, 2007:48). Although there is still no scientific evidence that certain diets or foods may help to improve the disease; an overall nutritious diet that contains enough calories, proteins and calcium in moderation is key (NIAMS, 2016). Omega-3 fatty acids that can be found in fish oil supplements have been proven to limit or decrease

inflammation, which may help to reduce pain and morning stiffness in patients with RA (Stark, 2016). Supplements may, however, interact with certain medications, therefore fatty fish such as salmon, mackerel and herring may be the best source of fish oil for RA patients (Simon & Zieve, 2013).

It is important to draw patients' attention to their smoking habits, if any, and its negative influences on the course of RA in order to motivate the cessation of smoking (Baka *et al.,* 2009:10). Unfortunately, complete cessation of smoking after the onset of RA has no impact on the disease prognosis. In fact, the risk of developing RA may persist in otherwise healthy individuals even years after cessation of smoking, even among individuals who smoked only moderately (Fosam, 2016). Several factors that give rise to the immunological changes that result in RA development have been identified in smokers (especially genetically predisposed individuals), including chronic inflammation due to oxidative stress, a pro-inflammatory state, the production of auto-antibodies, and epigenetic effects (Chang *et al.,* 2014:22287). Cessation of smoking is still not specifically addressed in the guidelines for RA treatment. Fosam (2016) is of the opinion that it should be mandatory, since it remains a preventable and modifiable risk factor that is associated with higher morbidity and mortality rates. It is important that patients be informed and educated with regard to the effective pharmacological and also non-pharmacological options available as aids for the cessation of smoking (Schmelzle *et al.,* 2008:998). Table 2.10 provides the pharmacological therapies available to patients as an aid for smoking cessation (Jorenby, 2016).

Table 2.10: Therapy for smoking cessation

Drug	Dosage	Treatment period
Bupropion sustained-release	150 mg mane for 3 days (continuing at least 1–2 weeks before quitting), then 150 mg b.i.d.	7–12 weeks initially (may continue up to 6 months)
Nicotine gum	If smoking > 30 min after waking: 2 mg If smoking < 30 min after waking: 4 mg Schedule for both dosage strengths: 1 q 1–2 h for weeks 1–6 1 q 2–4 h for weeks 7–9 1 q 4–8 h for weeks 10–12	Up to 6 months

Drug	Dosage	Treatment period
Nicotine lozenge	If smoking > 30 min after waking: 2 mg If smoking< 30 min after waking: 4 mg Schedule for both dosage strengths: 1 q 1–2 h for weeks 1–6 1 q 2–4 h for weeks 7–9 1 q 4–8 h for weeks 10–12	Up to 6 months
Nicotine inhaler	6–16 cartridges/day for the first 6–12 weeks, then tapered down over the next 6–12 weeks	3–6 months
Nicotine nasal spray	8–40 doses/d (1 dose = 1 spray in each nostril)	14 weeks
Nicotine patch	21 mg/d for 6 weeks, then 14 mg/d for 2 weeks, then 7 mg/d for 2 weeks If smoking > 10 cigarettes/d: 21 mg as starting dose If smoking < 10 cigarettes/d: 14 mg as starting dose	10 weeks
Varenicline	0.5 mg/d PO for 3 days, then 0.5 mg b.i.d. for 4 days, then 1 mg b.i.d.	12–24 weeks*
b.i.d. = two times daily; mane = in the morning; q = every; mg/d = milligrams per day *The longer duration of treatment may increase the likelihood of long-term abstinence among patients who have stopped smoking after 12 weeks of varenicline use.		

Non-pharmacological strategies for smoking cessation include brief interventions such as advice and education, counselling (e.g. individually, *via* telephone, or group counselling), behavioural therapy and self-help materials (defined as any structured programme for smokers trying to quit, without any intensive therapist-patient contact) (Schmelzle *et al.,* 2008:996).

2.3.7.2 Physical measures

Limited functions (e.g. limited physical movement) that are commonly associated with RA can be improved with numerous rehabilitation programmes as part of a multidisciplinary approach to the management of RA (Combe, 2007:34). Exercise should be the most important intervention as it also increases the benefits for a wide variety of conditions that are most likely to occur simultaneously

with RA, for example osteoporosis, diabetes, hypertension, heart disease, depression and fatigue (March & Stenmark, 2001:S102).

Physiotherapy and a joint-specific dynamic exercise programme will help RA patients to restore, preserve or even improve their extent of motion, muscle strength and aerobic capacity that will ease the execution of certain regular daily activities (CMS, 2010; Vlieland, 2007:1397). To preclude joint laxity and muscular atrophy, patients should be motivated to maintain only a moderate level of physical activity since vigorous or intense workouts will only intensify joint inflammation and may cause weakened structures and/or traumatic injury (Ruffing & Bingham, 2016). For an optimal, comprehensive rehabilitation programme, an occupational therapist should be included in the treatment/management team to provide advice on proper ergonomics and strategies for the patients to cope with and adapt to their environment and daily lives (Blom & Riel, 2007:48).

2.3.7.3 Reduction of joint stress

In order to reduce or ultimately prevent patient dependence, doctors prescribe physical assistive devices that may help to ease pain, compensate for muscle weakness, overcome the limitations of movement and enhance safety (Vlieland, 2007:1400). It is important that RA patients achieve and maintain an ideal, healthy body weight since obesity adds stress to the musculoskeletal system which may cause further unnecessary injuries (CDC, 2017). Physical and occupational therapy strive to increase patients' knowledge in terms of more efficient use of the body and the utilisation of specially designed splints that reduce stress and tension on the joints (CMS, 2010). Walking aids such as walkers and canes are also effective measures to consider as means of stress reduction on specific joints (Ruffing & Bingham, 2016). Specially prescribed shoes for the rheumatic foot (e.g. modified rocker soles, extended steel shanks, stabilisers, wedges, and soft and semi-flexible insoles) limit painful motions of joints by means of shock absorption, the lightening of excessive pressure, and providing support for deformities (Vlieland, 2007:1400).

2.3.7.4 Surgery

Several types of surgical procedures are available to restore function and QoL, prevent the progression of RA, relieve pain, correct deformity and, in some cases, guard against further destruction (Simmen *et al.,* 2008:272). However, it should be emphasised that surgery must be limited to patients with severe joint damage, and the decision to operate should be made only after careful consideration of the patient's overall health, the condition of the involved joint or tendon, the risks and benefits of surgery, and possibly the total cost of the procedure (NIAMS, 2016). Procedures include synovectomy (arthrosynovectomy and tenosynovectomy), arthrodesis, total joint replacement (arthroplasty in the hips, knees, shoulders, elbows and hands), and soft-tissue and specialised hand surgery (Nikiphorou *et al.,* 2014:1287; Simmen *et al.,* 2008:267).

2.4 Burden of rheumatoid arthritis

Hessel (2008:94) describes 'burden of disease' as referring to the total, cumulative outcome (including cost, health and social aspects) of a defined disease or a variety of pernicious diseases in terms of the impairment caused in a community. Econex (2009) states that the measurement of a country's disease burden refers to "*the assessment of mortality, morbidity, injuries, disabilities and other risk factors specific to that country*". In 2010, RA was listed as the 42nd highest contributor of 291 conditions to global disability (measured in years lived with disability (YLDs)[7]) (Cross *et al.,* 2014).

Accurate data with regard to the anticipated burden of RA as a disease is scarce, although critical for optimal disease management as it assists healthcare providers and decision makers to strategically plan clinical and public health services (Widdifield *et al.,* 2013:e450). According to Cutolo *et al.* (2014:479), in the past, the clinical comprehension of the burden of RA placed emphasis on the destruction of joints alone; however, RA is now being acknowledged as a systemic disease that is associated with many other disease manifestations (i.e. comorbidities, psychological aspects and health-related quality-of-life (HRQoL) disabilities).

Rheumatoid arthritis has substantial influences on patients and their families in terms of decreased QoL (Boonen & Severens, 2011:S8). The disease creates a great financial burden for both the patient and society in terms of healthcare and social security utilisations, productivity loss and total societal health reductions (Uhlig *et al.,* 2014:842). Although the mortality rates among RA patients remain higher compared to those among the general population, earlier diagnosis and more aggressive treatment has helped to decrease these numbers over the past decade (Han & Han, 2016:1483). Early exposure to effective DMARD therapy improves patient outcomes in terms of decreased disability and necessity for expensive surgical interventions, leading to global disease reduction (Widdifield *et al.,* 2013:e450). Figure 2.6 summarises the different components of RA's burden as a disease (adapted from Cutolo *et al.,* 2014:480; Lajas *et al.,* 2003:64; Owens, 2014:S145).

[7] In 1992 the World Bank initiated the first Global Disease Burden intervention which incorporated time-based metrics to measure both premature mortality (i.e. years of life lost (YLL) due to early death) and morbidity (i.e. years lived with disability (YLD)) (The World Bank, 1993:213). The sum of these components lead to the origin of the term 'disability-adjusted life years' (DALY), which is used as a measure of disease burden (Lopez *et al.,* 2006:3).

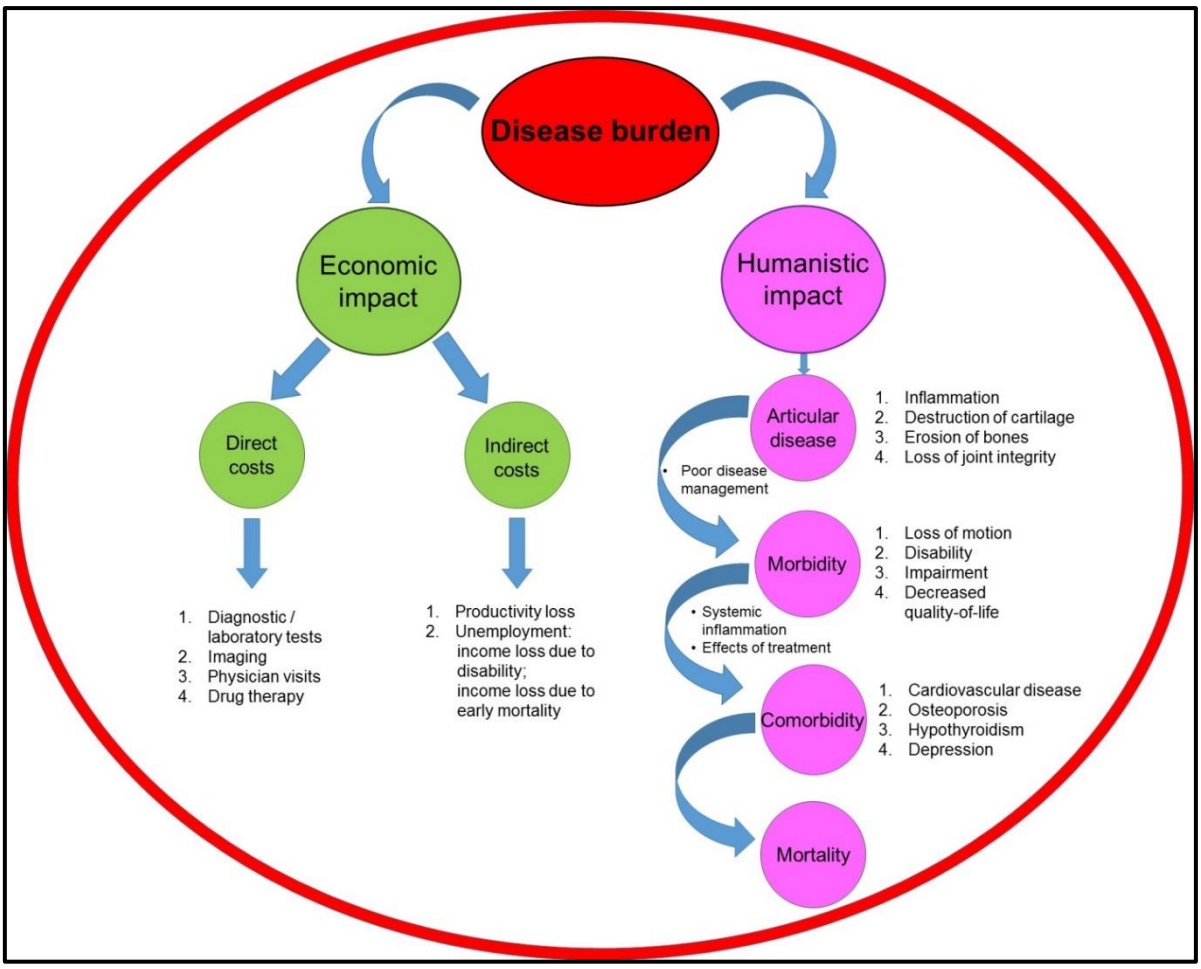


Figure 2.6: Schematic representation of rheumatoid arthritis burden of disease components

2.4.1 Disease prevalence

According to the Arthritis Foundation of South Africa (2016), RA is the most common chronic inflammatory autoimmune disease found in approximately one in a hundred people worldwide. Ruffing and Bingham (2016) too indicate that RA's global distribution is estimated at a prevalence of 1-2%, whereas Lundkvist *et al.* (2008:S49) and Luban and Li (2010:284) estimate that RA affects 0.5-1% of adults worldwide, and the WHO (2016) indicates the global prevalence of RA to vary between 0.3 and 1%. According to Lundkvist *et al.* (2008:S49), these disparities in prevalence estimation may be due to differences in the methodologies applied and in definitions of RA.

According to the CMS (2009), RA is less common in developing countries such as South Africa, Nigeria, Indonesia, Pakistan, China, the Philippines and Argentina, with a prevalence of less than or equal to 0.5%, compared to the estimated 1% of Western or developed populations. In line with the fact that Africa is the fastest urbanising continent, evidence suggests an urban-rural gradient with

regard to prevalence of RA in South Africa, with almost no cases of RA being reported in some rural areas, compared to a prevalence of 0.9% in the black urban South African population (Bester *et al.,* 2016:220; CMS, 2009). In a more recent study conducted by the South African CMS, an ongoing increased prevalence of RA has been observed from 2.09 per 1 000 beneficiaries in 2008 to 3.47 per 1 000 beneficiaries in 2015 (N = 8 809 523) (CMS, 2017d).

Rheumatoid arthritis may occur at any age, but usually has an onset from the age of 30 to 50 years (CMS, 2017c). Baser *et al.* (2013:2578) as well as Suta *et al.* (2015:220), however, indicate a peak onset between the ages of 40 and 70 years. Lundkvist *et al.* (2008:S49) estimate a prevalence of 2% among patients aged 60 years and above. Due to an increase in life expectancy and thus the proportion of older people in a population, RA is anticipated to increase even more within the next 10 years (Van Onna & Boonen, 2016). In South Africa, the estimated lifetime risk of developing RA per 100 000 population members varies according to age group: men aged 75 years and older have a nearly 0.05 times higher risk than men between the ages of 35 and 44 years; women aged 75 years and older have a nearly 0.03 times higher risk than women between the ages of 45 and 54 years (Human Sciences Research Council of South Africa, 2013:19).

The gender distribution of rheumatic diseases varies considerably, women usually being more likely to be affected by RA than men at a ratio of 2:1 to 3:1 (Kourilovitch *et al.,* 2014:26). Suta *et al.* (2015:224) indicate that the most important factor influencing gender distribution is the age of RA onset. Their study included 447 RA patients and indicated a statistically significant difference between the age of disease onset in men and women, it being approximately eight years earlier in women compared to men at the mean age of 50.56 ± 13.74 years (Suta *et al,.* 2015:221). Although the incidence of RA increases with age, according to Kvien *et al.* (2006:213) the ratio of female to male patients seems to decrease. Suta *et al.* (2015:221) identified significant differences in terms of female-male ratios among RA patients, considering various factors: women < 40 years of age were 17 times more common compared to men in the same age group, and women > 70 years were only four times more common than men; women who smoke were two times more common than men who smoke, and non-smoking women were 14 times more common than non-smoking men; women with early disease diagnosis were almost four times more common than men. These observations regarding the occurrence of RA has led to several investigational studies (e.g. Alpízar-Rodríguez *et al.,* 2016; Costenbader & Manson, 2008; Ngo *et al.,* 2014:354) that attempt to determine the possible impact of hormonal factors in disease prevalence and susceptibility, as it is known that oestrogen has stimulatory effects on the immune system and progesterone has possible anti-inflammatory effects (Alamanos & Drosos, 2005:134; Ngo *et al.,* 2014:355). Women with RA often experience a period of remission or significant improvement in symptoms during pregnancy, unfortunately usually with a relapse and flare after delivery, which further indicates possible hormonal influences on the

course of the disease in a genetically susceptible person (NIAMS, 2016). Suta *et al.* (2015:224) draws the conclusion that the hormone composition of a young man may possess protective properties against disease development.

Members of all racial and ethnic groups are affected by RA (CDC, 2017). Alamanos and Drosos (2005:134) emphasise that the observed significant geographic variations in RA prevalence might suggest some associations between the disease and ethnicity, taking into account that lifestyle factors (e.g. dietary factors) differ significantly between various ethnic groups.

2.4.2 Comorbidities

The term 'comorbidity' should be used to describe medical conditions that are present at the time or after diagnosis of an index disease, without implying that the coexisting medical conditions are an outcome of the index disease (refer to Chapter 1, section 1.2, paragraph 7). Rheumatoid arthritis is regarded as the index disease for the purposes of this study.

According to the NRAS (2012), the risk of comorbidities associated with RA is often overlooked by the public and by policy makers since the disease in general is not well understood. The consideration of comorbidities in the management of RA is imperative, because all of these conditions contribute to early mortality, have an influence on disease activity and the response to treatment, generating considerably higher additional costs for patients (Roubille *et al.,* 2015:1768). An effective reduction in medical costs results from a better understanding and prevention of these comorbid conditions which may lead to more serious consequences (Han & Han, 2016:1484). According to Han and Han (2016:1483), patients with RA are more likely to suffer from comorbidities — in terms of frequency as well as the number of comorbid conditions present — than patients without RA. Dougados *et al.* (2014:62), Grøn *et al.* (2014:870) and Rindfleisch and Muller (2005:1046) state that the increased presence of comorbidities in RA patients may occur either by chance or due to the pathogenesis of the disease, lack of thorough management of RA as a disease, or due to the medication used for treatment.

The course of RA differs from patient to patient, although several studies indicate that patients with this disease often present with an average of at least one to two comorbid conditions, a number that increases even further with age (Grøn *et al.,* 2014:870; Marques *et al.,* 2016:15; Van Onna & Boonen, 2016). Increased medical costs, disability and risk of mortality are directly proportional to the number of comorbidities a patient has (Mikuls, 2003:729; NRAS, 2012). A summary of studies on the comorbidities associated with RA is provided in Table 2.11.

Based on Table 2.11, it can be concluded that the duration of RA disease, on average (SD), ranged from 6.7 (3.5) months to 12.3 (8.3) years. The comorbidities that most commonly coexist with RA

include, *inter alia,* hypertension, dyslipidemia, depression, osteoporosis, diabetes mellitus, gastro-intestinal ulcers, asthma, chronic obstructive pulmonary disease (COPD), hypothyroidism and ischemic heart disease. Seropositive RA (i.e. RF present) is diagnosed in approximately 70% of patients. This may support previous claims that RA presents as more severe and destructive with a higher prevalence of extra-articular manifestations in patients who test positive for RF (Klareskog *et al.,* 2009:659; Kurkó *et al.,* 2013:172). An observation of the medicine utilisation in the summarised studies indicates that the majority of the patients received DMARD therapy alone or in conjunction with NSAIDs and corticosteroids; as expected, biologics on the other hand had the lowest utilisation rate in every study documented in Table 2.11.

Epidemiological data on RA in South Africa is limited, therefore the prevalence of comorbidities coexisting with RA is often overlooked by the public and by policy-makers (Ally & Visser, 2010:18).

Table 2.11: Summary of studies on rheumatoid arthritis and associated comorbidities

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Al-Bishri *et al.* (2013); Oct. 2011 – Oct. 2012	Kingdom of Saudi Arabia Al-Hada Hospital, National Guard Hospital and King Abdul-Aziz Hospital	Cross-sectional study Specially designed Performa: patient history files, reviews, examination and latest laboratory results	Patients had to fulfil the 1987 American College of Rheumatology (ACR) criteria	Socio-demographics RA medicine utilisation Prevalence and type of comorbidities	RA patients = 340 Excludes pregnant and lactating women **Mean (SD) age** 53.3 (11.3) years **Female gender** (n = 265; 77.9%) **RF positive** (n = 259; 76.1%) **Associated allergy complaints** (n = 11; 3.2%) **Disease duration (years)** 0 – 5 (n = 113; 33.2%) 6 – 10 (n = 118; 34.7%) 11 – 15 (n = 63; 18.5%) 16 – 20 (n = 25; 7.4%) > 20 (n = 21; 6.2%)	**Medicine utilisation** Prednisolone (n = 275; 80.8%) Methotrexate (n = 253; 74.4%) Sulphasalazine (n = 120; 35.3%) NSAIDs (n = 120; 35.2%) Antimalarial (n = 120; 35.2%) Biologic therapy: Rituximab (n = 57; 16.8%) Adalimumab (n = 38; 11.2%) Etanercept (n = 26; 7.6%) Infliximab (n = 20; 5.8%) DMARD regimens: 0 DMARDs (n = 47; 13.8%) 1 DMARD (n = 172; 50.6%) 2 DMARDs (n = 97; 28.5%) 3 DMARDs (n = 24; 7.1%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Al-Bishri *et al.* (2013);						**Number of comorbidities** 0 (n = 115; 33.8%) 1 (n = 69; 20.3%) 2 (n = 56; 16.5%) 3 (n = 26; 7.6%) 4 (n = 41; 12.1%) 5 (n = 11; 3.2%) 6 (n = 10; 2.9%) 7 (n = 9; 2.6%) 8 (n = 3; 0.9%)
						Prevalence of comorbidities (n = 340) Hypertension (n = 122; 36%) Diabetes mellitus (n = 105; 31%) Osteoporosis (n = 88; 26%) Dyslipidaemia (n = 66; 19.4%) Peptic ulcer disease (n = 35; 10.3%) Hypothyroidism (n = 29; 8.5%) Chronic liver disease (n = 26; 7.6) Ischemic heart disease (n = 25; 7.4%) Bronchial asthma (n = 23; 6.8%) Tuberculosis (n = 15; 4.4%) Cardiovascular accidents (n = 13; 3.3%) Interstitial lung fibrosis (n = 9; 2.7%) Malignancy (n = 9; 2.7%) Chronic renal failure (n = 8; 2.4%) Deep venous thrombosis (n = 7; 2.1%) Hyperthyroidism (n = 4; 1.2%) Inflammatory bowel disease (n = 1; 0.3%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Baser *et al.* (2013) 1 Jun. 2009 – 31 Dec. 2011	Turkey Public and private facilities under contract with the Social Security Institute	Case-control, retrospective analysis Turkish National Health Insurance Database (MEDULA) comprised of: pharmacy, in-patient, out-patient and laboratory claims	Diagnosed according to the ICD-10- clinical modification (CM) codes Requirements: 18 – 99 years and two RA diagnoses 60 days apart Subjects were grouped as incident (i.e. no RA diagnosis) and prevalent (i.e. RA diagnosis at baseline) cases	Socio-demographics Prevalence and type of comorbidity Medicine utilisation Total annual costs of incident and prevalent RA cases In-patient, out-patient and pharmacy costs comparison	RA patients = 2 613 **Incident cases (639):** **Mean age** 52.08 years **Female gender** (n = 555; 80.0%) **Prevalent cases (1 920):** **Mean age** 53.91 years **Female gender** (n = 1 604; 83.5%)	**Prevalence of comorbidities (non-RA:RA)** Respiratory – 1:3 Cardiovascular – 1:2.5 Diabetics – 1:2.9 Allergy – 2:4 **Medicine utilisation (non-RA:RA)** NSAIDs – 1:2.9 DMARDs – 1:4.7 Biologics – 1:7.2 **Total mean annual costs (non-RA:RA)** In-patient costs – 1:0.7 Out-patient costs – 1:0.9 Pharmacy costs – 1:1.5 Co-payments – 1:1 Total costs – 1:1.2 **In-patient and out-patient mean costs by service (non-RA:RA)** Physician costs – 1:1 Tests – 1:0.8 Hospital – 1:0.7 Medical devices – 1:0.9 Surgery – 1:1 Hospital pharmacy – 1:0.4 Other – 1:0.5 Total – 1:0.8

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Carmona *et al.* (2003) Nov. 1999 – Nov. 2000	Spain 34 participating rheumatology clinics	Cross-sectional, retrospective cohort analysis Clinical patient records	Patients had to fulfil the 1987 ACR criteria	Prevalence of comorbidities Disease severity	RA patients = 788 **Mean (SD) age at diagnosis** 48 (15) years **Female gender** (n = 562, 71.3%) **Female mean (SD) age** 61 (13) years **Female mean (SD) disease duration** 10 (8) years **RF positive** (n = 574; 72.8%) **DMARD therapy** (n = 205, 72%) **Remission** (n = 32; 4.1%)	**Prevalence of comorbidities** 285 (36.2%) patients presented with at least one of the following comorbidities: RA nodules (24.5%) Sjögren's syndrome (17.0%) Atlantoaxial subluxation (12.1%) Carpal tunnel syndrome (10.7%) Interstitial lung disease (3.7%) Serositis (2.5%) Eye disease (2.5%) Vasculitis (1.3%) Amyloidosis (0.6%) Felty's syndrome (0.3%) **Mean (SD) and median disease activity indexes** Disease activity score from 28 joints and 3 parameters (DAS28-3) = 3.4 (1.2) Health assessment questionnaire (HAQ) = 1.6 (0.4) Larsen score = 54.7 (26.4) Median number of painful joints = 3 Median number of swollen joints = 4

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Dougados *et al.* (2014) 2011 – 2012	Patients visiting participating rheumatologists were invited to enrol from: Argentina Austria Egypt France Germany Hungary Italy Japan Korea Morocco Netherlands Spain Taiwan UK Uruguay USA Venezuela	Cross-sectional, observational, multicentre, international study Medical records, patient interviews and questionnaires	Patients had to fulfil the 1987 ACR criteria Requirements: ≥ 18 years	Socio-demographics Disease characteristics Comorbidities	RA patients = 3 920 **Mean (SD) age** 56 (13) years **Female gender** (n = 3 203; 81.7%) **Mean (SD) disease duration** 9.6 (8.7) years **Current smokers** 13.2% **BMI (% overweight or obese)** 50.7% **Currently employed** 31.4% **Mean (SD) DAS28-ESR (mm/h)** 3.7 (1.6) **Mean (SD) HAQ** 1.0 (0.7)	**Prevalence of comorbidities (n = 3 920)** Depression (15.0%) Gastro-intestinal ulcers (10.8%) Asthma (6.6%) Myocardial infarction (5.0%) Solid malignancies (4.5%) COPD (3.5%) Hepatitis B (3.0%) Stroke (2.0%) Hepatitis C (2.0%) Basal cell carcinoma of skin (2.0%) Diverticulitis requiring surgery (0.4%) **Prevalence of risk factors for cardiovascular disease (n = 3 920)** Family history (14.0%) Hypertension (40%) Dyslipidaemia (32%) Diabetes (14%) Framingham score > 20% (43.0%) **Past and current medicine utilization** Prednisone (% currently taking) (54.3%) NSAID (% using during previous 3 months) (55.2%) Methotrexate (% ever treated) (88.6%) Any biological therapy (% ever treated) (38.9%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Eser *et al.* (2012) *Study period not indicated*	Turkey	Cross-sectional analysis	Patients had to fulfil the 1987 ACR criteria	Socio-demographics Disease activity and severity Prevalence of comorbidities Medicine utilisation	RA patients = 150 **Mean (SD) age** 53.2 (12.1) years **Female gender** (n = 126; 84%) **Mean (SD) disease duration** 147.3 (99.4) months **RF positive** (n = 132; 78.7%) **Remission** (n = 50; 33.3%)	**Mean (SD) disease activity indexes** Number of swollen joints = 0.7 (1.5) Number of tender joints = 3.0 (4.7) ESR (mm/h) = 21.9 (16.1) DAS28 = 3.4 (1.3) HAQ = 0.8 (0.8) QoL = 11.8 (9.7) Pain (VAS, 10cm) = 4.2 (2.7) **Disease activity scores** Mild DAS28 — 2.6-3.2 (n = 30; 20%) Moderate DAS28 — 3.2-5.1 (n = 51; 34%) Severe DAS28 — ≥5.1 (n = 19; 12.7%)
						Prevalence of comorbidities 50 patients (33.3%) presented with at least one of the following comorbidities: Pulmonary involvement (n = 43; 28.7%) RA nodules (n = 22; 14.7%) Sicca syndrome (n = 12; 8.0%) Peripheral neuropathy (n = 4; 2.7%) Atlantoaxial subluxation (n = 1; 0.7%)
						Medicine utilisation Methotrexate (n = 110; 73.3%) Corticosteroids (n = 82; 54.7%) Antimalarial drugs (n = 28; 18.7%) Sulphasalazine (n = 19; 12.7%) Leflunomide (n = 18; 12.0%) Etanercept (n = 12; 8.0%) Adalimumab (n = 4; 2.7%) Infliximab (n = 2; 1.3%) Azathioprine (n = 1; 0.7%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Fatima *et al.* (2013) Jan. 2007 – Dec. 2011	North Indian town, Aligarh Orthopaedics Jawaharlal Nehru Medical College	Cross-sectional study Clinical examinations and questionnaire	Patients had to fulfil the 1987 ACR criteria	Pulmonary abnormalities X-ray chest (CXR), pulmonary function tests (PFT) and high resonance computed tomography (HRCT)	RA patients = 62 **Female gender** (n = 47; 75.8%) **Smoking history** (n = 12; 19.3%)	**40.3 % (n = 25) patients had pulmonary symptoms** Exertional dyspnoea (n = 13; 21.0%) Cough with expectoration (n = 11; 17.7%) Fine respiratory rates (n = 7; 11.3%) **24.0% (n = 15) patients had abnormal CXR** Bilateral-lower zone haziness (n = 10; 16.0%) Prominent pulmonary vasculature (n = 2; 3.2%) **29.0 % (n = 18) patients had an abnormal PFT-restrictive pattern** Obstructive pattern (n = 5; 8.0%) Mixed pattern (n = 4; 6.4%) **33.8% (n = 21) patients revealed abnormal HRCT findings** Ground glass pattern in both lower lobes (n = 12; 19.3%) Sub-pleural reticulations (n = 6; 9.6%) Pleural thickening (n = 2; 3.2%) Pulmonary vascular prominence (n = 1; 1.6%)
Grøn *et al.* (2014) 2005 – Jan. 2012	**High-GDP countries:** Canada Denmark England France Finland Germany	International Quantitative Standard monitoring of patients with RA (QUEST-RA) Longitudinal, prospective study Standard protocols to evaluate RA	Patients that were seen in regular care were identified	Type and prevalence of comorbidities Fatigue (0-10cm VAS) Disease activity in 28 joints (DAS-28)	RA patients = 9 874 **Mean (SD) age** 54.9 (13.8) years **Female gender** (n = 7 484; 75.8%) **Median (SD) disease duration** 8.1 (3.7–15) years	**Number of comorbidities** 0 (25.8%) 1 (23.1%) 2 (17.9%) 3 (12.6%) 4 (8.0%) 5 (5.2%) 6 ≥ 17 (7.4%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Grøn *et al.* (2014)	Greece Ireland Italy Japan Netherlands Norway Spain Sweden United Arab Emirates USA **Low-GDP countries:** Argentina Brazil Egypt Estonia Hungary India Kenya Kosovo Latvia Lithuania Morocco Poland Romania Russia Serbia South Korea Taiwan Turkey	(SPERA)*, consisting of self-report questionnaires and clinician assessments		Physical disability (HAQ; 0 to 3 = worse)	**RF positive** (n = 7 227; 73.2%) **Erosive disease** (n = 5 331; 54.0%) **Caucasian race** (n = 6 299; 63.8%)	**Distribution of comorbidities according to country GDP status (low-GDP:high-GDP)** Hypertension – 1:0.9 Osteoporosis at scan – 1:0.9 Hyperlipidaemia – 1:1.3 Osteoarthritis – 1:1 Obesity (BMI>30 kg/m²) – 1:1.2 Chronic back pain – 1:0.9 Thyroid disease – 1:1.2 Diabetes mellitus – 1:1.3 Cataracts – 1:1.3 Infection requiring hospitalisation – 1:1.4 Asthma – 1:2.1 Cancer – 1:3.2 Musculoskeletal trauma – 1:1.7 Other heart disease – 1:1.5 Psychiatric disease – 1:1.7 Herpes zoster/Shingles – 1:2.1 Low energy fractures – 1:1.3 Coronary artery disease – 1:1 Chronic bronchitis – 1:1.1 Angina – 1:0.9 Fibromyalgia – 1:1.3 Peripheral vascular disease – 1:1.5 Heart attack – 1:2.3 Psoriasis – 1:4 Impaired renal function – 1:1 Stroke – 2.2 Inflammatory bowel disease – 1:1.1 Alcoholism – 1.4 Parkinson's disease – 1:0.8 AIDS – 1:0

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Grøn *et al.* (2014)						**Mean (SD) disease activity indexes according to country GDP status(low-GDP:high-GDP)** Mean fatigue score – 1:0.8 Patients with high level of fatigue (>6.6) – 1:0.9 Mean DAS-28 score – 1:0.8 Patients with high level of DAS28 (>5.1) – 1:0.4 Mean HAQ score – 1:0.8 Patients with high level of HAQ (2 to 3) – 1:0.6
Han and Han (2016) 1 Jan. 2007 – 31 Dec. 2012	Nebraska	Observational, cross-sectional study Emergency Department (ED) discharge, hospital in-patient discharge and death certificate data	Diagnosed according to the ICD-9-CM codes (714) for ED discharge and hospital discharge records The ICD-10-CM diagnosis codes (M05, M06, M08) were used for death certificate data	Number of comorbidities Primary causes of ED visits, hospitalisations and deaths Length of hospital stay and hospital charges	All-cause ED visit patients = 2 590 679 All-cause hospitalisation patients = 1 182 831 All-cause deaths = 91 387	**Difference in mean number of comorbidities in patients that result in the following (non-RA:RA):** ED visits – 1:2.6 Hospitalisations – 1:1.6 Death – 1:1.5 **Top 10 leading causes of ED visits among RA patients (n = 4 921; 0.2%)** RA flare (11.7%) Chest pain / other cardiovascular symptoms (10.4%) Injury (6.7%) Fractures (3.6%) Abdominal pain (3.2%) Pneumonia (2.5%) Muscle and joint sprains (2.1%) COPD (2.0%) Digestive system symptoms (1.9%) Acute respiratory infections (1.8%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Han and Han (2016)						**Top 10 leading causes of hospitalisation among RA patients (n = 16 592; 1.4%)** Joint replacement or arthroplasty (6.3%) Pneumonia (6.1%) Fractures (4.4%) Myocardial infarction and other ischemic heart disease (3.8%) COPD (3.4%) Cardiac dysrhythmias or conduction disorders (2.8%) Heart failure (2.7%) Septicaemia (2.7%) RA flare and cellulitis (2.5%) Abscess of skin and subcutaneous tissue (2.5%)
						Top 10 leading causes of deaths among RA patients (n = 491; 0.5%) RA (21.6%) Myocardial infarction and other ischemic heart disorders (9.6%) COPD (9.4%) Dementia (4.5%) Cerebrovascular disease (4.1%) Malignant neoplasms of bronchus and lung (3.7%) Hypertensive disease (3.5%) Diabetes mellitus (2.4%) Acute respiratory distress syndrome (2.2%) Cardiac dysrhythmias or conduction disorders (1.8%)
						Length of hospital stay 5.8% increase (in days) among RA patients with one number of comorbidity increase **Hospital charges** 5.6% increase among RA patients with one number of comorbidity increase

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results		
Inbanathan *et al.* (2016) Jan. 2013 – Jan. 2015	India Krishnarajendra Hospital, Princess Krishnajammanni Tuberculosis and Chest Disease Hospital attached to Mysore Medical College	Observational, cross-sectional study Pre-tested questionnaires	Patients had to fulfil the ACR and EULAR 2010 criteria	Socio-demographics Comorbidities	RA patients = 50 **Mean (SD) age** 42.4 (11.15) years **Female gender** (n = 33; 66%) **RF positive** (n = 33; 66%) **Comorbidity prevalence** (n = 18; 36%)		**With comorbidity**	**Without comorbidity**
						Mean (SD) age	51.2 (12.5) years	33.6 (9.8) years
						Mean (SD) hemoglobulin values	9.11 (2.14) g/dl	11.38 (2.59) g/dl
						RF factor	n = 18 (36.0%)	n = 15 (30.0%)
						Comorbidities Cardiac involvement (n = 6; 12.0%) Pulmonary involvement (n = 4; 8.0%) Lymphadenopathy (n = 4; 8.0%) Vasculitis (n = 3; 6.0%) Rheumatoid nodule (n = 1; 2%)		

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Innala *et al.* (2016) Dec. 1995 – Nov. 2012	Northern Sweden	Prospective, observational study Patient records from the Swedish Rheumatology Quality Register and validated questionnaires	Patients had to be diagnosed with early RA (symptomatic < 12 months) that fulfilled the American Rheumatism Association classification criteria	Prevalence of comorbidities at onset of disease Investigation of development of new comorbidities at five-year follow up	RA patients at baseline = 950 RA patients at five-year follow-up = 726 **Mean (SD) age** 55.6 (14.4) years **Female gender** (n = 649; 68.3%) **Mean (SD) disease duration at baseline** 6.7 (3.5) months **RF positive** (n = 715; 75.3%) **Smoking** (n = 625; 65.8%)	**Prevalence of comorbidity (baseline:new comorbidity during five years)** Prevalence of comorbidity – 1:0.6 Hypertension – 1:0.4 Asthma/COPD – 1:0.1 Diabetes mellitus – 1:0.3 Hypothyroidism – 0:2 Thyroid disease[8] - 1:0.2 Osteoporosis – 1:2.1 Hyperparathyroidism – 1:0.7 Malignancy – 1:1.1 Myocardial infarction – 1:0.7 Stroke/transient ischemic attack – 1:1 **Number of new comorbidity development during five years of disease (N = 726)** 1 (n = 202; 27.8%) 2 (n = 66; 9.1%) 3 (n = 25; 3.4%) 4 (n = 5; 0.7%) **Medicine utilisation** DMARDs (97.8%) Methotrexate (86.9%) NSAIDs (84.0%) Corticosteroids (71.0%) COX-2 inhibitors (26.5%) Biologics (16.5%)

[8] Defined as hypothyroidism, hyperthyroid disease and goiter.

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Kalappan *et al.* (2016) *Study period not indicated*	India In-patients and out-patients of a tertiary care hospital	Observational, cross-sectional study Patient records and a baseline examination	Patients had to fulfil the 1987 ACR criteria Exclusion criteria: age at onset ≤ 16 years; disease duration < 6 weeks; seronegative spondyloarthritis and overlap syndromes	Patient's perception of pain (*via* VAS) Disease severity (*via* DAS-28) Prevalence of comorbidities	RA patients = 100 **Mean (SD) age** 52.6 (14.45) years **Female gender** 84% **RF positive** 72% **Mean (SD) disease duration** 5.9 (5.68) years **Early morning stiffness** 2.0 (0.93) hours **Tender joints** 10.8 (5.9) **Swollen joints** 5.1 (4.3) **Mean (SD) VAS** 45.80 (18.6) mm **Mean (SD) DAS-28** 5.44 (1.44) **Mean (SD) ESR** 46.24 (28.11) mm/hr	**Distribution of disease severity according to mean (SD) age** Mild – 58.5 (15.7) years Moderate – 52.8 (15.2) years Severe – 52.2 (14.4) years **Distribution ratios of disease severity according to sex (mild:moderate:severe)** Female – 1:3:10 Male – 0:6:9 **Distribution ratios of disease severity according to comorbidity (mild:moderate:severe)** Haematological - 0:1:5 Pulmonary – 1:2:4 Neurological – 1:2:1 None – 1:6:17 **Prevalence of comorbidities** Interstitial lung disease (11.0%) Rheumatoid nodule (10.0%) Anaemia (5.0%) Obstructive airway disease (4.0%) Peripheral neuropathy (4.0%) Pleural effusion (2.0%) Carpal tunnel syndrome (2.0%) Vasculitis (1.0%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Machado-Alba *et al.* (2015) Dec. 2009 – Aug. 2013	Colombian cities Bogotá, Cali, Manizales, Medellin and Pereira Service Providing Institution in the application of medication (IPS-Especializada de Audifarma S.A.)	Observational cohort analysis Health system of Colombia (SGSSS) and Health Assurance Company (EPS) data analysis	Diagnosed according to the ICD-10 codes: RA unspecified (M069); arthritis unspecified (M159); seropositive RA NOS (M059); juvenile arthritis unspecified (M080); seronegative RA (M060); juvenile RA (M080); other seropositive RA (M058); other specified RA (M068)	Socio-demographics DAS-28 Pharmacological treatment received Type and prevalence of comorbidities	RA patients = 1 364 **Mean (SD) age** 53.2 (13.9) years **Female gender** (n = 1111; 81.9%) **Mean (SD) age of disease onset** 41.3 (14) years **Mean (SD) disease duration** 116 (91.9) months **RF positive** (n = 781; 57.3%) **Juvenile RA** (n = 25; 1.8%) **Smoking** (n = 135; 12.9%) **Alcohol consumption** (n = 22; 2.2%) **Remission** (216; 20.2%)	**DAS-28** Mild (n= 425; 39.7%) Moderate (n = 370; 34.6%) Severe (n = 59; 5.5%) **Prevalence of comorbidities** Osteoporosis (n = 440; 32.3%) Hypertension (n = 438; 32.1%) Dyslipidaemia (n = 327; 24.0%) Other autoimmune diseases (n = 139; 10.2%) Diabetes mellitus (n = 93; 6.8%) COPD (n = 56; 4.1%) Congestive heart failure (n = 23; 1.7%) **Medicine utilisation** Methotrexate (n = 1 343; 98.5%) Prednisolone (n = 1 246; 91.3%) Leflunomide (n = 979; 71.8%) Chloroquine (n = 657; 48.2%) Sulfasalazine (n = 515; 37.7%) Deflazacort (n = 288; 21.1%) Etanercept (n = 133; 9.8%) Hydroxychloroquine (n = 113; 8.3%) Abatacept (n = 79; 5.8%) Methylprednisolone (n = 70; 5.1%) Adalimumab (n = 68; 4.9%) Infliximab (n = 58; 4.3%)

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Norton *et al.* (2013) 1986 – Jun. 2009	Nine regions in the United Kingdom	Observational, prospective cohort study Patient medical files and the General Practice Research Database	Diagnosed according to the ICD-10 codes	Socio-demographics Prevalence at diagnosis and cumulative incidence of comorbidities Impact of comorbidities on outcome	RA patients at baseline = 1 460 **Mean (SD) age** 55.34 (14.61) years **Female gender** (n = 969; 66.4%) **RF positive** (n = 1 056; 73.1%) **Employed** (n = 645; 46.3%) **Past/current smoker** (n = 199; 21.9%) **Mean (SD) BMI** 25.5 (4.5) **Erosions** (n = 366; 25.6%) **Swollen joints, median (IQR)** 15 (19) **Tender joints, median (IQR)** 10 (12) **Mean (SD) HAQ** 1.2 (1.0) **Mean (SD) VAS pain** 45.9 (27.8) **Mean (SD) DAS** 4.2 (1.6)	**Baseline demographics by number of comorbidities (one:>one)** Low education – 1:0.6 Low social class – 1:0.6 Employed – 1:0.4 Past/current smoker – 1:0.4 Mean BMI – 1:1 Erosions – 1:0.4 Swollen joints – 1:0.8 Tender joints 1:0.8 Mean HAQ – 1:1 Mean VAS pain – 1:1 Mean DAS – 1:1 DMARD start < three months – 1:0.9 Methotrexate use ever – 1:0.9 Steroid use in first year – 1:1.2

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Norton *et al.* (2013)						**Prevalence of comorbidities (baseline prevalence:15-year cumulative incidence)** Total comorbidities – 1:3 Solid tumours – 1:10 Haematological cancers – 1:30 Thyroid disease – 1:3 Diabetes – 1:3 Psychiatric disorder – 1:4 Dementia – 0:1 Parkinson's disease – 0:2 Eye disease – 1:100 Ischemic heart disease – 1:5 Congestive heart failure – 1:14 Peripheral vascular disease – 1:15 Hypertension – 1:5 Stroke – 1:34 Thrombo-embolic disease – 1:41 Deep vein thrombosis – 1:12 Respiratory disease – 1:3 Asthma – 1:3 COPD – 1:2 Gastrointestinal disease – 1:4 Peptic ulcer disease – 1:4 Mild liver disease – 0:0.1 Psoriasis – 1:2 Osteoarthritis and spinal degeneration – 1:4 Chronic renal damage – 1:12

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Osiri and Sattayasomboon (2013) 1 Oct. 2008 – 30 Sept. 2009	Bangkok, Thailand Out-patient, King Chula-longkorn Memorial Hospital	Observational, cross-sectional study Hospital database	Diagnosed according to ICD-10-Thai modification (TM) codes (M05, M06) Requirements: ≥ 18 years; prescribed one ≥ synthetic/biologic DMARD	Prevalence and type of comorbid conditions Contents of out-patient medication prescriptions Out-patient direct medical costs of RA and non-RA-related treatments	RA patients = 684 **Mean (SD) age** 55.2 (12.9) years **Female gender** (n = 617; 90.2%) **Mean (SD) duration of DMARDs used** 6.3 (6.1) years	**Prevalence of comorbidities** Hypertension (n = 222; 51.2%) Dyslipidaemia (n = 150; 34.6%) Eye conditions[9] (n = 150; 34.6%) Degenerative joint diseases and non-articular rheumatism (n = 112; 25.8%) Osteoporosis (n = 86; 19.8%) Diabetes mellitus (n = 57; 13.1%) Ear, nose and throat conditions[10] (n = 42; 9.7%) Coronary heart disease (n = 39; 9.0%) Skin conditions[11] (n = 27; 6.2%) Chronic pulmonary disease (n = 25; 5.8) Menopausal symptoms and benign gynaecological tumours[12] (n = 19;4.4%)
						Medicine utilisation 1 DMARD (n = 158; 23.1%) 2 DMARDs (n = 315; 46.1%) 3 DMARDs (n = 176; 25.7%) > 3 DMARDs (n = 18; 2.6%) Biologics ± DMARDs (n = 17; 2.5%) NSAIDs (n = 485; 70.3%) Prednisolone (n = 301; 44.0%) Analgesics (n = 195; 28.5%) Folic acid (n = 631; 92.3%) Calcium (n = 623; 91.1%) Vitamin D (n = 344; 50.3%)

[9] Including keratoconjunctivitis sicca, cataracts and glaucomas.
[10] Including allergic rhinitis, sinusitis and otitis media.
[11] Including allergic contact dermatitis, xerosis and drug eruptions.
[12] Inluding myoma uteri, endometriotic cysts and endometrial polyps.

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Continued Osiri and Sattayasomboon (2013)						**Mean annual direct medical costs in RA patients (without comorbidity:with comorbidity)** Costs of RA-related medications – 1:1.1 Costs of non-RA-related medications – 1:6.8 RA-related costs – 1:1.3 Costs of non-RA-related visits – 1:14.9 Total direct medical costs – 1:2

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Petri *et al.* (2010) 1 Jul. 2006 – 30 Jun. 2007	United States In-patient, out-patient and prescription claims	Retrospective cohort study Thomson's Market Scan Commercial Claims and Encounters Research Database and the Medicare Supplemental	Diagnosed according to ICD-9 codes (714.0*, 714.1*, 714.2*, 714.3*) Requirements: ≥ 16 years; persons with at least 2 claims for RA that were non-diagnostic (i.e. not blood, laboratory or radiological claims); active insurance status	All comorbidities with an ICD-9 diagnostic code were identified Relative risks associated with RA	RA patients = 62 681 **Mean age** 59.0 years **Female gender** (n = 45 454; 73.8%)	**6 897 different ICD-9 diagnostic codes were recorded, of which 2 220 occurred in 20 or more RA patients. Most prevalent comorbidities in RA patients (n = 62 681)[13]:** Hypertension (NOS) (n = 12 773; 20.4%) Benign hypertension (n = 12 482; 19.9%) Chest pain (NOS) (n = 8 742; 13.9%) Hyperlipidaemia (NEC/NOS) (n = 8 690; 13.9%) Diabetes mellitus II without complication (n = 7 504; 12.0%) Malaise & fatigue (NEC) (n = 6 046; 9.6%) Urinary tract infection (NOS) (n = 5 965; 9.5%) Abdominal pain at unspecified site (n = 5 712; 9.1%) Cough (n = 5 649; 9.0%) Hypothyroidism (NOS) (n = 5 524; 8.8%) Shortness of breath (n = 5 516; 8.8%) Acute bronchitis (n = 5 400; 8.6%) Pure hypercholesterolemia (n = 5 046; 8.1%) Acute sinusitis (NOS) (n = 4 833; 7.7%) Anaemia (NOS) (n = 4 632; 7.4%) Osteoporosis (NOS) (n = 4 529; 7.2%) Coronary atherosclerosis in native vessel (n = 4 325; 6.9%) Oesophageal reflux (n = 4 288; 6.8%) Actinic keratosis (n = 4 249; 6.8%) Bone & cartilage disease (NOS) (n = 4 113; 6.6%) Acute upper respiratory infection (NOS) (n = 4 112; 6.6%) Chronic airway obstruct (NEC) (n = 4 041; 6.4%) Senile nuclear cataract (n = 3 914; 6.2%) Respiratory abnormality (NEC) (n = 3 605; 5.8%) Headache (n = 3 246; 5.2%) Coronary atherosclerosis in unspecified vessel (n = 3 002; 4.8%)

[13] Excludes arthritis/RA-related codes ICD 710-729 and 996.4.

Authors and study inception period	Country/study setting	Study design and data source	Diagnosis	Measurements	Study sample (N)	Results
Radner *et al.* (2011) Jun. 2007 – Jul. 2008	Austria, Vienna Out-patient clinic	Longitudinal, observational study Care of RA database and questionnaires	Patients had to fulfil the 1987 ACR criteria Requirements: the most recent visit < 6 months before study onset; two completely documented visits during study period	Comorbidities Functional disabilities	RA patients = 380 **Mean (SD) age** 60.7 (13.2) years **Female gender** (n = 306; 80.5%) **RF positive** (n = 222; 58.4%) **Mean (SD) disease duration** 11.7 (10.1) years	**Prevalence of comorbidity** Chronic pulmonary diseases (20.5%) Diabetes (20.5%) Peripheral vascular diseases (17%) Myocardial infarction (15.2%) Cerebrovascular disease (13.4%) Solid non-metastatic tumours (10.7%) Peptic ulcer disease (9.8%) Mild liver disease (8.9%)
						Medicine utilisation No DMARDs (8.2%) DMARDs (61.3%) Biologics (30.5%)
						Mean (SD) functional disability indexes Simplified DAS – 10.06 (9.47) Clinical DAS – 9.08 (8.59) Pain (VAS, mm) – 31.66 (23.29) HAQ – 0.94 (0.82)

*SPERA = Standard Protocol to Evaluate Rheumatoid Arthritis (Pincus *et al*., 1999)

ACR = American College of Rheumatology; RF = rheumatoid factor; DMARD = disease modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs; VAS = visual analogue scale; DAS-28 = disease activity score in 28 joints; HAQ = health assessment questionnaire; ESR = erythrocyte sedimentation rate; BMI = body mass index; QoL = quality-of-life; AIDS = acquired immune deficiency syndrome; ICD-9 = International Statistical Classification of Diseases and Related Health Problems 9th Revision diagnosis-code; ICD-10 = International Statistical Classification of Diseases and Related Health Problems 10th Revision diagnosis-code; COPD = chronic obstructive pulmonary disease; EULAR = European League against Rheumatism; NOS = not otherwise specified; NEC = not elsewhere classified; GDP = gross domestic product

2.4.3 Economic impact

Boonen and Severens (2011:S3) explain that it is important to clarify both "whose perspective" and "which impact" are being considered when discussing the economic impact of a disease. According to Rat and Boissier (2004:518), the economic burden that results from RA is substantial. Rheumatoid arthritis has an overall significant impact on various stakeholders: evidently the patient is at the centre, although their family and friends can also be affected by the disease; healthcare systems; and society as a whole (Boonen & Severens, 2011:S3). Klimeš *et al.* (2014:75) emphasise the crucial importance of cost studies in aiding comprehension of the full burden of a disease such as RA; such studies can simultaneously serve as stepping stones in the cost-effectiveness modelling of RA. In order to determine what impact comorbidities have on the total direct treatment cost of RA, it is important to first determine the total treatment cost of RA alone. The subsequent paragraphs contain somewhat more extensive information from the literature on RA treatment costs.

2.4.3.1 Total treatment cost of rheumatoid arthritis

The total treatment cost of RA can be described as the sum of all direct, indirect and intangible costs paid or incurred in order to acquire a specific health outcome. Direct medical costs associated with RA are directly attributable to healthcare utilisation, such as the cost of products (e.g. prescribed medication and diagnostic/laboratory tests) and services (e.g. physician visits, biological and imaging assessments, hospital care, physical therapy and surgery) used in the prevention, treatment and rehabilitation of the illness (Kirch, 2008:267; Owens, 2014:S145). On the other hand, direct non-medical costs result from the outcome of the disease or treatment and refer to out-of-pocket expenses that are not reimbursed on a regular basis (e.g. transportation, daily care requirements, assistive devices and modifications around a patient's home) (Lambert, 2001:961; Owens, 2014:S145; Walter & Zehetmayr, 2006:5). For RA patients, the major cause of indirect costs is loss of productivity or unemployment as a consequence of disability or premature mortality (Lajas *et al.,* 2003:64). Intangible costs are the most difficult to measure and are associated with substantial QoL reductions due to pain, disability, fatigue, depression, diminished self-esteem and well-being, and other psychological disturbances (Kawatkar *et al.,* 2012:1649).

Baser *et al.* (2013:2578) estimate that, annually in Europe, 250 000 hospitalisations and 9 million physician visits are associated with RA, resulting in a total annual economic impact of approximately €46 million (translating to R550 million)[14]. The total annual societal cost (i.e. the sum of all direct, indirect and intangible costs) of RA in the United States was estimated to be $39 million (translating

[14] Calculated on grounds of the average currency rate between 2006 and 2016 (US Forex Inc., 2016); €1:R11.9461.

to R248 million)[15], computed on grounds of data from administrative claims databases that cover privately insured and Medicare and Medicaid beneficiaries (Birnbaum *et al.,* 2010:89).

Lundkvist *et al.* (2008:S49) indicate that in South Africa, RA prevalence and cost data is limited and was not available for their study. Tarr *et al.* (2014:791) also state that long-term studies in South Africa are needed to measure and evaluate the cost of treatment against the economic burdens of poorly controlled RA. Kawatkar *et al.* (2012:1650) conducted a study to determine the annual costs that result from RA, using the data from a nationally representative sample of the United States population obtained from the 2008 *Medical Expenditure Panel Survey Household Component.* Their results indicate that RA patients had a 1.5- to 3-fold increase in average healthcare expenditures compared to the non-RA control cohorts. Over the past decade, the economic burden and cost estimations for RA have significantly evolved, primarily due to the commencing era of biologic therapy (Fautrel *et al.,* 2011:609). This may also be a result of discrepancies in the sample characteristics (e.g. disease characteristics and duration, size and representativeness), the healthcare systems and the methodology applied in determining these costs (Owens, 2014:S146). For this reason, Michaud *et al.* (2003:2750) state that the total cost of RA will have to be determined again.

The direct expenses associated with chronic conditions often receive more attention than the indirect costs, although Lundkvist *et al.* (2008:S52) state that indirect costs are known to be the most important cost driver in RA. Direct costs of RA have been fairly low in the past, but Chaudhari (2008:38) indicates that the recent increased utilisation of expensive biologics has resulted in a dramatic increase in the costs associated with RA and a shift in the management of this disease. Michaud *et al.* (2003:2750) emphasise the possibility of reducing the hospitalisation costs incurred by RA patients with more effective biologic therapy. Studies concerning the cost of a disease or illness are of more value towards indicating where the majority of costs are incurred (i.e. in helping determine the structure of costs) than in aiding decision-making with regard to resource allocation (Lundkvist *et al.,* 2008:S52). A study in the United States using retrospective analysis of data from health insurance claims in the Human Capital Management Services Research Reference Database included 340 740 individuals and assessed the impact of RA from employers' perspective over a period of 9 years (2001 through 2010) (Kleinman *et al*., 2013:240). According to Kleinman and colleagues, the total annual health insurance claims of employees with RA amounted to $5 212 (R39 746.71)[16] more than that of those employees without RA (at a ratio of 2.5:1). Similarly, Han and Han (2016:1483) state that the mean annual costs of RA patients is two to three times more

[15] Calculated on grounds of the average currency rate in 2005 (US Forex Inc., 2016); $1:R6.360857.
[16] Calculated on grounds of the average currency rate between 2001 and 2010 (US Forex Inc., 2016); $1:R7.6260.

compared to that of the general population. The following paragraphs will outline, respectively, the indirect and direct treatment costs incurred as a result of RA.

2.4.3.2 Direct treatment cost of rheumatoid arthritis

Patients who are diagnosed with RA have direct medical costs that are two to three times more than that of patients (of the same age and gender) who are not diagnosed with the disease (Baser *et al.*, 2013:2578; Lambert, 2001:961). The complexity of RA results in increased healthcare utilisation and medical costs. In a study of Wang *et al.* (2016:A239), RA patients had 0.3 times more in-patient follow-up visits, almost two times more out-patient hospital visits, and 8 times more out-patient physician visits and pharmacy visits compared to non-RA patients. Klimeš *et al.* (2014:75) explain that the costs of RA treatment are usually directly proportional to health assessment questionnaire (HAQ) scores, which they confirmed with a retrospective cross-sectional study in the Czech Republic including 261 RA patients. Their results indicate that the average annual direct medical costs increased almost two-fold from €5 315 (R68 126.61)[17] for those patients with a HAQ score of < 0.6, to €8 968 (R114 950.03)[17] for those patients with a HAQ score of 2.1.

Gleason *et al.* (2013:542) performed a descriptive analysis of integrated medical and pharmacy administrative claims data from 2008 to 2010 in order to compare multiple sclerosis (MS), RA, psoriasis and inflammatory bowel disease (IBD) costs among privately insured United States patients under 65 years of age. The total healthcare cost associated with RA per member per year was found to be the highest (R830.18)[18] across the entire population (N = 979 735) registered in 2010; RA costs were almost two times higher than MS and psoriasis costs, and 1.1 times higher than IBD costs.

Husher *et al.* (2015:738) analysed data from the National Database of the German Collaborative Arthritis Centres to estimate the changes in the total cost incurred by RA patients between 2002 and 2011. The results indicate a considerable increase of approximately R31 600[19] in direct costs for patients between the ages of 18 and 64 years, and a R20 400[19] increase for patients ≥ 65 years. However, in-patient expenditures and indirect costs (i.e. the costs associated with sick leave and work disability) decreased significantly. Husher *et al.* (2015:738) describe the 3- to 6-fold growth in direct costs as a result of constant daily increases in the use of biologic agents in rheumatology. Tarr *et al.* (2014:791) describe the cost of biologics for RA disease management as a huge problem in South Africa, with prices ranging from R110 000 to R160 000 per patient annually. The results of Roux's (2010:171) study show an average total cost of R9 586.25 ± R5 956.56 in 2008 per biological

[17] Calculated on grounds of the average currency rate for 2013 (US Forex Inc., 2016); €1:R12.8178.
[18] Calculated on grounds of the average currency rate between 2008 and 2010 (US Forex Inc., 2016); $1:R7.9963.
[19] Calculated on grounds of the average currency rate between 2002 and 2011 (US Forex Inc., 2016); €1:R9.5957.

immunomodulating medicine item (e.g. adalimumab, etanercept, infliximab, interferon beta-1a, interferon beta-1b, and rituximab). On average, the aforementioned cost per biologic is 77 times higher than the average cost per medicine item reported at R124 in the private healthcare sector of South Africa in 2008 (Bester & Badenhorst, 2008).

According to Hodkinson *et al.* (2013:585), RA patients' cost of therapy is relatively low if they are treated with non-biological or traditional DMARDs, this being in contrast to the treatment cost escalations due to biologicals. Klimeš *et al.* (2014:80) compared the costs of patients treated with and without biologics in the Czech Republic, and found the total treatment cost of RA with biologics to be nearly six times higher (R28 904 *vs.* R162 440)[17] than the costs of non-biologic therapy. In Roux's study (2010:227), during phase two of RA treatment with onset of biologic therapy, the average cost per medicine item increased with 1000% from R128.45 ± 155.93 to R1 477.88 ± 3 134.39, as calculated on grounds of medicine claims data for 2005 to 2008.

Biologics are often given as injections or infusions that usually require trained staff for special handling and administration (Gleason *et al.,* 2013:542). An analysis of claims from a United States PBM database from 2007 to 2012 showed that RA treatment with subcutaneously administered biologics (etanercept and adalimumab) had greater effectiveness (36% *vs.* 23%; $p<0.001$) and almost 1.3 times lower annual costs than intravenously administered biologics (abatacept and infliximab), leading to an overall annual cost saving of $16 000 (R124 009.60)[20] per patient effectively treated (Allen, 2016).

Although biologic treatment is expensive, the inhibition of joint damage and the slowing of disease progression improve disease control, which might potentially decrease future costs incurred due to increased healthcare utilisation and the development of comorbidities (Ohinmaa *et al.,* 2014:1319).

2.4.3.3 Indirect treatment cost of rheumatoid arthritis

The indirect costs incurred by RA patients are typically three to four times higher than those incurred by non-RA patients (Baser *et al.*, 2013:2578). Work-related disability and sick leave associated with RA create major global economic burdens, and it remains a difficult task to assign accurate figures to these losses (Zhang & Anis, 2011:S25). Within five years of RA onset, patients affected by the disease typically experience substantial irreversible work disability, with associated factors that include reduced work performance, absenteeism, the inability to retain employment, and early retirement (Lundkvist *et al.,* 2008:S52). These indirect costs have been estimated to be three times more than direct medical costs (Cardarelli, 2012:S316). Sick leave among early RA patients can be as high as 118 days per patient in the first year, and 46 days annually on average for established

[20] Calculated on grounds of the average currency rate between 2007 and 2012 (US Forex Inc., 2016); $1:R7.7506.

RA patients; these numbers are significantly higher than the population average of 11 days per individual per year (Boonen & Severens, 2011:S6).

Boonen and Severens (2011:S7) combined and reviewed the results of 26 cost-of-illness studies to determine the annual costs of RA patients, including the costs incurred due to lowered paid productivity. They found that the indirect costs vary from less than 20% to as high as 50% greater than the direct costs. Aggregate earning losses in the United States are estimated to be approximately $12.3 million (R96 million)[21] on average per year from 2008 to 2011, with a total average earning loss of $13 886 (R108 464)[21] per year per patient attributed to RA (Helmick & Watkins-Castillo, 2014).

The variance in indirect costs incurred as a consequence of RA-related work loss and disability may be due to differences in the methodology applied in the measurement of costs (Filipovic *et al.,* 2011:1087). For the purposes of this study, the researcher will focus on the impact that comorbidities have on the total direct medicine treatment cost of RA. This will be discussed in the subsequent paragraphs.

2.4.3.4 The impact of comorbidities on the total direct treatment cost of rheumatoid arthritis

According to Rat and Boissier (2004:523), increases in the cost of RA treatment are not solely based on the treatment of the disease itself. Comorbidities and costs beyond joint damage may have significant influences on the management of the disease (Owens, 2014:S147). The NRAS (2012) states that a considerable proportion of increases in the average and aggregate healthcare expenditures of RA patients is due to increasing cases of chronic comorbid conditions. Unfortunately, in many cases, prescribed RA medication may exacerbate these comorbidity profiles or influence the regimens for RA treatment and disease management (Al-Bishri *et al.,* 2013:16).

Comorbidities are associated with increased healthcare utilisation that includes multidisciplinary health professional services associated with a considerably higher quality of care (NRAS, 2012). Han and Han (2016:1490) found an increase of 5.6% in hospital charges per group of RA patients with one or more comorbidity.

Depression commonly occurs in patients with chronic illnesses such as RA, leading to higher healthcare utilisation among the patients and lowering their adherence to therapy as depression is generally not adequately addressed in current treatment regimens of RA (Margaretten *et al.,* 2011:618). Patients with depression tend to complain more about pain and visit physicians and

[21] Calculated on grounds of the average currency rate between 2008 and 2011 (US Forex Inc., 2016); $1:R7.8110.

general practitioners on a more regular basis to place requests for analgesia medication (Imran *et al.,* 2015:394). It is also known that depression is one of the conditions that has a significant impact on work disability, one of the most costly outcomes of RA (Sokka *et al.,* 2013:243).

Rheumatoid arthritis patients have an increased relative risk (1.5-2.0) of developing CVD (i.e. dyslipidaemia, hypertension and ischaemic heart disease), which is one of the main acute causes of excess mortality among these patients (Turesson, 2016). Joyce *et al.* (2009:750) performed a retrospective analysis of healthcare claims data to examine resource utilisation and the direct healthcare costs associated with depression and CVD as comorbid conditions among 10 298 RA patients. The results of the study indicate that all patients with comorbidities incurred higher healthcare costs compared to patients with RA alone. For example, annual healthcare costs[22] for patients with RA plus CVD came to R116 645, which was followed by the costs for patients with RA plus CVD and depression at R111 434, then RA plus depression at R100 812[22], and finally RA alone at R94 042. Long-term use of biologics (specifically TNFα inhibitors) and DMARDs (specifically methotrexate, leflunomide and sulphasalazine) has shown to decrease the risk of CVD, in contrast to the increased risk associated with NSAID and corticosteroid use (Turesson, 2016).

Osiri and Sattayasomboon (2013:611) compared average annual total direct medical costs of RA patients with comorbidities to those of RA patients without comorbidities between 2008 to 2009; the costs of the patients with comorbidities were nearly twice as high (R37 146 *vs.* R18 447)[23] as the costs of the patients without comorbidities. Comorbid conditions were prevalent in 63.5% of the patients, hypertension being the most common comorbidity (affecting 51.2% of the patients). The majority of patients were receiving DMARD therapy, either alone or in combination with other DMARDs, while biologic utilisation was the lowest at 2.5%. Osiri and Sattayasomboon (2013:610) observed that the presence or absence of comorbidities had no significant impact on the type of DMARD prescribed, only a longer duration of DMARD treatment was identified in patients with comorbid conditions.

Baser *et al.* (2013:2582) noted that the 5% of patients in their study with a comorbidity index score of zero to one had, due to the prescription of biologic therapy, nearly 4.5 times higher average annual direct medical costs (R34 702)[24], than those patients receiving standard therapy (i.e. DMARDs or NSAIDs) (R7 763)[24]. Another 12% of patients had a comorbidity index score of more than two and presented with average annual direct costs that were almost 3.3 times higher for biological treatment compared to standard therapy. Several studies (Meissner *et al.,* 2014; Rosenblatt *et al.,* 2013:A222;

[22] Calculated on grounds of the average currency rate for 2008 (US Forex Inc., 2016); $1:R8.2464.
[23] Calculated on grounds of the average currency rate between 1 Oct. 2008 and 30 Sep. 2009 (US Forex Inc., 2016); $1:R9.0205.
[24] Calculated on grounds of the average currency rate between 1 Jun. 2010 and 31 Dec. 2010 (US Forex Inc., 2016); €1:R9.4095.

Wang *et al.,* 2012:A239) indicate that patients who switch from first-line to second-line biologic therapy (due to adverse effects or ineffective outcomes) incur approximately 1.2 to 1.6 times higher total healthcare costs than those who did not switch. As previously stated, comorbid conditions have a significant impact on the management of RA, thus affecting the choice of treatment (Al-Bishri *et al.,* 2013:12). In order for physicians to make an informed decision with regard to treatment strategies for RA patients, further research is needed to form a better understanding of which specific comorbidity influences the response to a given type of treatment (Ranganath *et al.,* 2013:1816).

2.5 South African private healthcare sector

The healthcare system in South Africa is divided into the public and private health sectors (Ramjee *et al.,* 2013:94). In 2014, the total healthcare expenditure in South Africa represented 8.8% of GDP which was slightly below the global average of 9.9% (The World Bank, 2016). An estimated 84.0% of the population receives healthcare from the public health sector and the remaining 16.0% from the private health sector (Department of Health (DoH), 2017:15). Inequity that exists between the two sectors is based upon differences in financial and human resources (Ramjee *et al.,* 2013:94). However, current estimations indicate an equal shortfall of employees in both sectors since only 0.7 physicians are available per 1 000 members of the population, and for the 64 SARAA registered rheumatologists, this ratio is 1:820 000 members of the population (Bester *et al.,* 2016:220).

The South African National DoH reported private healthcare expenditure at R198.4 billion, accounting for 4.4% of the GDP in 2016/2017 (DoH, 2017:42). Contributions to medical schemes remain as the primary mechanism to finance beneficiaries, estimated at R164.3 billion in 2016/2017, followed by patient co-payments at R27.3 billion; other sources include medical insurance and private employer contributions (DoH, 2017:42; Econex, 2013). By September 2015 there were 87 medical schemes, all managed as non-profit entities and serving an estimation of 8 776 279 beneficiaries (CMS, 2017e; South African Government, 2016). The Medical Schemes Act (131 of 1998) of South Africa initiated a statutory body — the CMS — that is accountable to the national Minister of Health and responsible for regulatory supervision in terms of private healthcare financing *via* medical schemes (CMS, 2017e; Ramjee *et al.,* 2013:94). The funds that are needed to maintain the CMS as a public agency are raised through levies charged to medical schemes (CMS, 2012:10). Medical schemes are classified as “open-membership schemes” and “restricted-membership schemes”. According to the CMS (2016), 60 of the current 83 accredited medical schemes are restricted and the remaining 23 are open to the general public. In order to qualify for membership to a restricted medical scheme, an individual has to work in a certain industry sector, have specific academic qualifications or belong to a professional association or certain trade union (SA Medical Aids, 2016). Any individual can become a member of an open medical scheme, provided that the person is 18 years or older, not a member of any other medical scheme, and capable of paying the monthly contributions (SA Medical Aids, 2016). Benefit Management Units, such as the PBM

companies, support the CMS to ensure that medical schemes comply with Act 131 of 1998 and that beneficiaries have access to affordable and appropriate quality healthcare. According to the CMS (2015a), Benefit Management Units do this by means of:

- approval granted after taking into account any changes in policy, such as patient contributions for certain benefits;
- the evaluation and approval of benefits and benefit options offered by a medical scheme;
- verification of the medical scheme's compliance with the rules of the Act; e.g. management and supervision of marketing material;
- the management and reviewing of medical scheme registrations; and
- administering of the amalgamation and liquidation process.

In South Africa, private health insurance is voluntary and represents as much as 41.8% of the total healthcare expenditures, which is equal to 3.7% of the South African GDP (OECD, 2016). In the subsequent paragraphs, the treatment of RA according to legislation in the private health sector of South Africa will be discussed.

2.5.1 Treatment guidelines for rheumatoid arthritis in the private health sector of South Africa

As mentioned previously, 26 chronic/non-communicable diseases, among other RA, and HIV/AIDS are included in the PMB regulations as CDL conditions in South Africa (see Annexure A) (CMS, 2017c). Prescribed minimum benefits need to be approved first, which is dependent on protocols, formularies and the use of designated service providers (CMS, 2014). A series of interventions within the private health sector were launched with the development of a National Drug Policy in 1996 in an attempt to reduce medicine prices in South Africa. These interventions include generic substitution, the SEP mechanism and a dispensing fee (Gray, 2009:15). The SEP mechanism was the first regulation to be implemented in August 2004. 'Single exit price' can be defined as *"the ex-manufacturer price determined by the manufacturer or importer of a medicine or scheduled substance in terms of these regulations combined with the logistics fee and value added tax (VAT) and is the price of the lowest unit of the medicine or scheduled substance within a pack multiplied by the number of units in the pack"* (South Africa, 2012).

The SEP represents the purchase price for wholesalers; a *maximum SEP adjustment* of 4.8% was gazetted in 2016 (South Africa, 2016a). Pharmaceutical manufacturers or importers usually negotiate a distribution fee for products with the logistics service provider, this fee generally varying between 10% and 15% of the final price (Bagalee & Suleman, 2015). Although a proposed maximum

logistics fee was to be implemented from the start of 2013, it has been delayed due to arguments between the government and various stakeholders (Bangalee & Suleman, 2015). The maximum logistics fee was calculated according to the following guidelines (South Africa, 2012):

- ex-manufacturer price ≤ R100 (excluding VAT), the logistics fee is capped at 8% plus R3;
- ex-manufacturer price R100–R500 (excluding VAT), the logistics fee is capped at 6% plus R4;
- ex-manufacturer price R500–R1 000 (excluding VAT), the logistics fee is capped at 4% plus R5; and
- ex-manufacturer price ≥ R1 000 (excluding VAT), the logistics fee is capped at R54.

Bangalee and Suleman (2015) analysed data from the South African Medicine Price Registry as at 20 December 2013; concluding that the greatest benefit of the application of a logistics fee cap, in lowering the SEP, would be observed for medicines where no generic equivalents are available.

Value added tax is a type of indirect tax levied at the standard rate of 14% on the consumption of any goods and services, except zero-rated or exempt products and services (South African Revenue Service (SARS), 2016). All medicines are subject to 14% VAT — calculated on grounds of the sum of the manufacturer's price and logistics fee — regardless of their therapeutic value; even prescription drugs with high therapeutic value are taxed the same as over-the-counter supplements, which is one of the main factors causing high medicine prices (Hassim *et al.,* 2007:442).

Table 2.12 (adapted from the Database of Medicine Prices) (South African Medicine Price Registry, 2016) lists DMARDs and biologics that are used for RA treatment and depicts the medicine cost components of the single exit price for the individual products.

Table 2.12: Medicine cost components of the single exit price for disease modifying antirheumatic drugs and biologic products used for rheumatoid arthritis treatment

DMARDs									
Medicine's proprietary name	**Active ingredients**	**Original* or generic****	**Pack size**	**Manufac-turer price (R)**	**Logistics fee (R)**	**VAT (R)**	**SEP (R)**	**Unit price (R)**	**Logistics fee / SEP (%)†**
Azamun® 50 mg tablets	Azathioprine	Generic	100	570.76	46.28	86.39	703.42	7.03	6.58
Azathioprine 50® 50 mg tablets	Azathioprine	Generic	100	434.11	35.20	65.70	535.01	5.34	6.58
Azapress® 50 mg tablets	Azathioprine	Generic	100	559.80	83.96	90.13	733.89	7.34	11.44
Zaprine 50® 50 mg tablets	Azathioprine	Generic	100	559.79	83.96	90.11	733.86	7.33	11.44
Imuran® 50 mg tablets	Azathioprine	Generic	100	1 258.60	222.10	207.30	1 688.00	16.88	13.16
Nivaquine® 200 mg tablets	Chloroquine	Original	100	333.28	15.81	48.87	397.96	3.98	3.97
Mirquin® 68 mg 1 mg/5 ml syrup	Chloroquine sulphate	Generic	100 ml	24.27	3.45	3.88	31.60	0.31	10.92
Plasmoquine® 200 mg capsules	Chloroquine	Original	20	35.61	5.09	5.70	46.40	2.32	10.97

Medicine's proprietary name	Active ingredients	Original* or generic**	Pack size	Manufac-turer price (R)	Logistics fee (R)	VAT (R)	SEP (R)	Unit price (R)	Logistics fee / SEP (%)†
Sandimmun® 100 mg capsules	Ciclosporin	Original	50	2 995.46	228.59	451.37	3 765.41	73.51	6.07
Sandimmun® 100 mg 1 mg/1 ml syrup	Ciclosporin	Original	50 ml	3 117.56	237.89	469.76	3 825.21	76.50	6.22
Sandimmun® 25 mg capsules	Ciclosporin	Original	50	760.72	58.04	114.63	933.39	18.67	6.22
Avara® 10 mg tablets	Leflunomide	Original	30	825.16	39.15	121.00	985.31	32.84	3.97
Avara® 20 mg tablets	Leflunomide	Original	30	843.29	40.01	123.66	1 006.96	33.57	3.97
P&U Methotrexate CSV® 500 mg/20 ml injection	Methotrexate	Original	20 ml	335.78	17.65	49.48	402.91	20.15	4.38
P&U Methotrexate CSV® 50 mg/2 ml injection	Methotrexate	Original	2 ml	167.90	8.84	24.74	201.48	20.15	4.39
Emthexate Rtu 50® 1 mg/2 ml solution	Methotrexate	Generic	2 ml	17.62	1.23	2.64	21.49	10.74	5.72

Medicine's proprietary name	Active ingredients	Original* or generic**	Pack size	Manufac-turer price (R)	Logistics fee (R)	VAT (R)	SEP (R)	Unit price (R)	Logistics fee / SEP (%)†
Emthexate Rtu 500® 1 mg/20 ml solution	Methotrexate	Generic	20 ml	176.18	12.33	26.39	214.91	10.75	5.74
Emthexate Rtu 1 000® 1 mg/40 ml solution	Methotrexate	Generic	40 ml	371.43	30.03	56.20	457.67	11.44	6.56
Abitrexate® 500 mg solution	Methotrexate	Generic	1 ml	104.47	8.47	15.81	128.75	0.26	6.58
Abitrexate® 1 G/10 ml solution	Methotrexate	Generic	1 ml	407.24	33.01	61.63	501.88	0.50	6.58
Abitrexate® 5 000 mg/50 ml	Methotrexate	Generic	50 ml	2 257.66	183.05	341.70	2 782.42	55.65	6.58
Abitrexate® 2.5 mg tablets	Methotrexate	Generic	100	104.13	8.44	15.76	128.33	1.28	6.58
Methotrexate-Lederle® 2.5 mg tablets	Methotrexate	Original	100	142.08	12.43	21.63	176.14	1.76	7.06
Salazopyrin® 500 mg EN tablets	Sulphasalazine	Original	100	294.28	19.12	43.88	357.28	3.57	5.35
Salazopyrin® 500 mg tablets	Sulphasalazine	Original	100	294.28	19.12	43.88	357.28	3.57	5.35

Biologics									
Medicine's proprietary name	**Active ingredients**	**Original* or generic****	**Pack size**	**Manufac-turer price (R)**	**Logistics fee (R)**	**VAT (R)**	**SEP (R)**	**Unit price (R)**	**Logistics fee / SEP (%)†**
Orencia® 250 mg 1 mg/10 ml solution for infusion	Abatacept	Original	10 ml	1 845.00	55.35	266.05	2 166.40	216.64	2.55
Humira® 40 mg 1 mg/0.8 ml solution for injection	Adalimumab	Original	0.8 ml x 2	7 558.93	400.61	1114.33	9 073.88	5 671.17	4.41
Enbrel® 25 mg powder for injection	Etanercept	Original	1	3 557.39	263.25	534.89	4 355.53	1 088.88	6.04
Enbrel® 25 mg prefilled syringe	Etanercept	Original	0.5 ml x 4	3 557.39	263.25	534.89	4 355.53	2 177.77	6.04
Enbrel® 50 mg prefilled syringe	Etanercept	Original	1 ml x 2	3 557.39	263.25	534.89	4 355.53	2 177.77	6.04
Enbrel® 50 mg prefilled syringe	Etanercept	Original	1 ml x 4	7 114.78	526.50	1 069.78	8 711.06	2 177.77	6.04
Simponi® 1 mg/0.5 ml solution for injection	Golimumab	Original	0.5 ml	7 145.89	941.83	1 132.28	9 220.00	18 440.00	10.22

Medicine's proprietary name	Active ingredients	Original* or generic**	Pack size	Manufac-turer price (R)	Logistics fee (R)	VAT (R)	SEP (R)	Unit price (R)	Logistics fee / SEP (%)†
Revellex® 100 mg 1 mg/10 ml injection	Infliximab	Original	10 ml	4 007.78	400.78	617.20	5 025.76	502.58	7.97
Mabthera® 100 mg 1 mg/10 ml solution for infusion	Rituximab	Original	10 ml x 2	5 460.73	441.77	826.35	6 728.85	336.44	6.57
Mabthera® 500 mg 1 mg/10 ml solution for infusion	Rituximab	Original	50 ml	13 651.82	1 104.52	2 065.89	16 822.22	336.44	6.57
Actemra® 80 mg 1 mg/4 ml IV infusion	Tocilizumab	Original	4 ml	886.84	20.71	127.06	1 034.60	258.66	2.00
Actemra® 200 mg 1 mg/10 ml IV infusion	Tocilizumab	Original	10 ml	2 132.73	136.14	317.64	2 586.51	258.66	5.26
Actemra® 400 mg 1 mg/20 ml IV infusion	Tocilizumab	Original	20 ml	4 265.48	272.26	635.28	5 173.02	258.66	5.26

Medicine's proprietary name	Active ingredients	Original* or generic**	Pack size	Manufac-turer price (R)	Logistics fee (R)	VAT (R)	SEP (R)	Unit price (R)	Logistics fee / SEP (%)†
Stelara® 45 mg 1 mg/0.5 ml prefilled syringe	Ustekinumab	Original	0.5 ml	22 088.71	2 911.29	3 500.00	28 500.00	57 000.00	10.22

SEP = single exit price; VAT = value added tax; mg = milligram; ml = millilitre

*Original without an available generic equivalent; **Generic equivalent; †Logistics fee as a percentage of the SEP

Deduced from the information in Table 2.12, it seems that the logistics fee as a percentage of the SEP is relatively low for the listed RA medications, keeping in mind that the average logistics fee ranges from 10% to 15% (Bangalee & Suleman, 2015). Only seven (Stelara® 10.22%, Simponi® 10.22%, Mirquin® 10.92%, Plasmoquine® 10.97%, Azapress® 11.44%, Zaprine® 11.44% and Imuran® 13.16%) of the 39 products have a logistics fee that falls in this average price range. The highest percentage logistics fees are generated by some of the generic products with azathioprine (a DMARD) as active ingredient (i.e. Azapress® 11.44%, Zaprine® 11.44% and Imuran® 13.16%).

According to Gray (2009:15), the implementation of generic substitution for various medicines has been successful in lowering medicine costs; however, to determine and enforce a reasonable dispensing fee has become a more difficult hurdle to overcome. Therefore, SEPs were introduced as a means to control the dispensing fee. 'Dispensing fee' can be defined as "the maximum fee, exclusive of VAT, that may be charged to dispense a medicine" (South Africa, 2014). In striving towards a transparent pricing system, the Medicines and Related Substances Control Amendment Act (90 of 1997) states that an appropriate dispensing fee shall be introduced as contemplated in section 22G(2)(b) of the Act, and will be charged by pharmacists or any persons licensed in terms of section 22C(1)(a) (South Africa, 1997:26). On recommendation of the Pricing Committee, the regulations, as reflected in the Medicines and Related Substances Act (101 of 1965), were amended in July 2016 and now state that:

- *where the SEP of a medicine or scheduled substance is less than R94.32, the dispensing fee shall not exceed R8.05 plus 46% of the SEP;*

- *where the SEP of a medicine or scheduled substance is greater than or equal to R94.32, but less than R251.58, the dispensing fee shall not exceed R20.55 plus 33% of the SEP;*

- *where the SEP of a medicine or scheduled substance is greater than or equal to R251.58, but less than R880.56, the dispensing fee shall not exceed R69.00 plus 15% of the SEP;*

- *where the SEP of a medicine or scheduled substance is greater than or equal to R880.56, the dispensing fee shall not exceed R165.00 plus 5% of the SEP* (South Africa, 2016b:80).

Prescriptions for specialty medicine for RA treatment (i.e. biologics) dramatically improve patients' health outcomes, but the costs are known to be relatively expensive, which impacts access to treatment and affordability (South Africa, 2013). Unfortunately, the high costs of these drugs have been a major deterrent for medical schemes in South Africa to fund biologic usage (NGO Pulse, 2006). Pharmaceutical companies place emphasis on the fact that these genetically engineered drugs require complex manufacturing processes, making it difficult to decrease the cost of biologics (NGO Pulse, 2009). According to the Johns Hopkins Bloomberg School of Public Health (2016), it is

expected that biologics will only constitute 20% of the pharmaceutical market by 2017 as the generic versions (biosimilars currently under development) could potentially increase cost-savings to health systems as well as patients, a few of the biologics' patent rights being due to expire soon. The biologic therapy patent expiration dates in the United States include, among others, 2017 for adalimumab, 2018 for infliximab and rituximab, and 2026 for etanercept (Strand & Brasington, 2016). The extended regulatory approval processes in South Africa will, however, cause a delay in this potentially immediate solution (Miot *et al.,* 2016:885). In April 2016, the United States Food and Drug Administration (FDA) approved the only TNFα inhibitor biosimilar for infliximab (Remicade®) that is indicated for RA treatment among other diseases, i.e. Inflectra® (Johns Hopkins Bloomberg School of Public Health, 2016). The latter will be sold following the patent expiration of infliximab in the United States (Johns Hopkins Bloomberg School of Public Health, 2016).

A medical scheme is obliged to fully cover an alternative drug when treatment of a patient with formulary medicines fails or causes serious adverse effects (CMS, 2017e). Co-payment levies and annual price restrictions on biologics by various medical schemes result in unaffordable treatment costs for most beneficiaries suffering from RA (NGO Pulse, 2009). A formulary contains regulated lists of medicines that are used in the treatment of specific medical conditions and are covered by medical schemes without any co-payment (CMS, 2017e). Medical schemes use the national health reference price list (NHRPL) — established by the CMS in 2004 and published in 2006 by the DoH — as a guideline to determine their own level of reimbursement (DoH, 2016). According to the CMS (2015b), co-payments are levied on pharmaceutical items, special investigations and non-adherence to specific medical scheme rules, i.e. mainly benefits that fall outside of a patient's PMB package. Medical aid cover insurers require patients to make their part of the payment before the health insurer pays their portion; co-payments will, however, differ from one medical scheme to another (SA Medical Aid, 2011). The NHRPL is compiled on grounds of suggestions regarding the actual healthcare costs from all disciplines of health service; used by practitioners and medical schemes as a guideline to calculate tariff structures and design benefit structures that minimise possible co-payments for the beneficiaries (Selfmed Medical Scheme, 2016). Neither practitioners nor medical schemes are bound to the NHRPL; the reference price is only valid for 30 days, may vary per option and includes VAT (MediKredit, 2016; Selfmed Medical Scheme, 2016).

2.6 Chapter summary

In this chapter, various studies were reviewed in order to comprehend both the full burden of RA as a disease, the legislation in South Africa with regard to PMBs and the calculation of medicine prices (including RA therapy) in the private healthcare sector. Determining the different cost components of RA treatment contributes to a better understanding of the impact that comorbidities have on the aggregate direct medicine cost associated with RA.

The following chapter contains the results and a discussion of how the objectives stated for the empirical phase of this investigation were met.

CHAPTER 3 RESULTS AND DISCUSSION

3.1 Introduction

Chapter 3 consists of the results and discussions of this study's empirical investigation. The results from the first two objectives are presented in the form of manuscripts, and that of the third objective, in paragraph form. The manuscripts were each written according to the author guidelines specified by the respective journals (Annexures E and F).

Manuscript one, based on the first empirical objective, is entitled "Chronic disease list conditions in patients with rheumatoid arthritis in the private healthcare sector of South Africa". This manuscript was submitted and published in the *Rheumatology International* journal (refer to Annexure E). The specific guidelines of the *Rheumatology International* journal as was given at http://www.springer.com/medicine/internal/journal/296 on the 18th of October 2017, is included in Annexure F. These results were also presented as a poster presentation at the European Drug Utilisation Research Group (EuroDURG) Conference 2017, in Glasgow (Scotland) November 15-17, 2017 (refer to Annexure I for the letter of acceptance for the poster presentation).

Manuscript two (second empirical objective), entitled "Antirheumatic prescribing patterns and direct medicine costs in the South African private health sector", was submitted to the *Value in Health Regional Issues* journal (refer to Annexure G). The specific guidelines of the *Value in Health Regional Issues* journal as was given at https://www.ispor.org/publications/VIHRI/submission_instruction.asp on the 18th October 2017, is included in Annexure H.

Objective three, i.e. to determine the impact of comorbidities on the total direct medicine treatment cost of RA patients per year, is presented in section 3.4.

3.2 Manuscript 1

Title

Chronic disease list conditions in patients with rheumatoid arthritis in the private healthcare sector of South Africa

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Running title

Cohort Studies on Comorbidities

Conflict of Interest

Author Olivier has received a master's bursary from the North-West University (grant number 23465174). Authors Burger, Joubert, Lubbe, Naudé and Cockeran declare that they have no conflict of interest.

Acknowledgements

The authors would like to thank the Pharmaceutical Benefit Management Company for providing the data in order to conduct the study.

Disclaimer about previous similar publications

Some of the results of the study were presented as a poster presentation at the European Drug Utilisation Research Group (EuroDURG) Conference 2017, held on the 15th – 17th November 2017, at the Technology & Innovation Centre, University of Strathclyde, Glasgow, UK. The poster was entitled "Prevalence of rheumatoid arthritis and associated chronic disease list conditions in the private health sector of South Africa".

Abstract

Introduction: Little is known about the burden of rheumatoid arthritis (RA) in South Africa. The aim of this study was to establish the prevalence of RA and coexisting chronic disease list (CDL) conditions in the private health sector of South Africa.

Method: A retrospective, cross-sectional analysis was performed on medicine claims data for 4352 patients from 1 January 2014 to 31 December 2014, obtained from a Pharmaceutical Benefit Management (PBM) company. The population was divided into those with RA only and those with RA and CDL conditions using the standard International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes (e.g. M05; M06; and M08).

Results: Overall, 69.3% (3016) presented with coexisting CDL conditions. Patients had a mean age of 60.32 ± 14.29 years (95% CI: 59.90-60.75), and 74.8% were female. Patients with RA and other CDL conditions were older than those patients with RA only ($p < 0.001$; Cohen's $d = 0.674$). Gender had no influence on the presence of CDL conditions in RA patients ($p = 0.456$). Men had relatively higher odds for hyperlipidemia (OR, 1.83; CI 1.33-2.51; $p < 0.001$) and lower odds for asthma (OR, 0.83; CI 0.48-1.42; $p = 0.490$) than women did. In combination with hyperlipidemia, the odds for asthma were reversed and strongly increased (OR, 6.74; CI 2.07-21.93; $p = 0.002$). The odds for men having concomitant hyperlipidemia, hypertension, type 2 diabetes mellitus and hypothyroidism were insignificant and low (OR, 0.40; CI 0.16-1.02; $p = 0.055$); however, in the absence of hypothyroidism, the odds increased to 3.26 (CI 2.25-4.71; $p < 0.001$).

Conclusion: Hypothyroidism was an important discriminating factor for comorbidity in men with RA. This study may contribute to the body of evidence about the burden of RA and coexisting chronic conditions in South Africa.

Keywords: South Africa, rheumatoid arthritis, prevalence, medicine claims data, comorbidity, chronic disease list

Introduction

Rheumatoid arthritis (RA) is a debilitating autoimmune disease that causes progressive and chronic joint inflammation, resulting in the development of miscellaneous multisystem comorbidities [1-3]. The presence of comorbidities in RA patients may occur either by chance or due to the pathogenesis of the disease, lack of sufficient management of these comorbidities or related to the medication used for treatment [4, 5]. Several studies indicate that RA patients present with an average of at least one to two comorbidities [6-9].

Comorbidities that most commonly coexist with RA include, *inter alia*, hypertension, dyslipidemia, depression, osteoporosis, diabetes mellitus, hypothyroidism, and ischemic heart disease [8-11]. These conditions are all included in the chronic disease list (CDL) of South Africa [12]. The CDL of South Africa consists of 26 chronic/non-communicable diseases and HIV/AIDS for which the patient's medical scheme, by law, not only has to cover medication, but also the physicians' consultations, as well as the tests related to the condition [13]. These CDL conditions are stipulated under prescribed minimum benefits (PMB) as part of 270 medical conditions (defined in the Diagnosis and Treatment Pairs list), as well as any emergency condition [14]. The South African Medical Schemes Act (131 of 1998) includes PMBs as one of the medical schemes' features to ensure that all members are continuously provided with certain minimum health services, irrespective of their selected benefit option [14].

The prevalence of multiple CDL conditions in patients diagnosed with RA in South Africa is not known. Consequently, the aim of this study was to determine the prevalence of CDL conditions within South African private healthcare patients diagnosed with RA.

Method

Study design, data source and study population

This retrospective, cross-sectional study analyzed medicine claims data for a total of 838,618 patients (446,382 female, 392,235 male) patients to identify patients with RA based on the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis-codes M05; M06; and M08, in conjunction with a claim for medicine paid from a patient's PMBs. The medicine claims data (1 January 2014 to 31 December 2014) were obtained from a South African Pharmaceutical Benefit Management (PBM) company's database.

The number and type of CDL conditions per patient for the cohort of 4352 rheumatoid arthritis patients were then determined. Patients were divided into two disease groups based on patient diagnosis: patients without CDL conditions; and patients with one or more CDL conditions.

Statistical analysis

The Statistical Analysis System®, SAS 9.4® software was used to analyze the data [15]. The study population was characterized using descriptive statistics, including frequencies (n) interpreted as percentage (%) values, arithmetic means, standard deviations (SD) and 95% confidence intervals (Cl), medians, minimums (min) and maximums (max). Data following non-normal distribution are presented as medians (min; max).

An independent two-sample *t*-test was used to compare mean values and assessed the age difference between men and women. A *p*-value of 0.05 or less was considered statistically significant at a two-sided α-level. Cohen's *d*-value was considered for practical significance; the magnitude of the *d*-values was interpreted as: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect [16].

The strength of association between the number of CDL conditions and patients' age were evaluated by the beta coefficient exponentiation (Exp(β)) interpreted as an OR, where 1 = no effect and 0 = practically significant [17]. Chi-square distribution models were used to determine the association between patients' gender and the number of CDL conditions present. Cramer's *V* was used to evaluate the strength of any significant association, where 0.1 = small effect, 0.3 = medium effect and 0.5 or higher = large effect [17].

Logistic regression analysis was performed to assess the association between the specific CDL condition and patients' gender expressed as odds ratios (ORs) and associated 95% Wald confidence intervals (95% CI). For the univariate model, the independent variable was gender [(female (0), male (1)], with each PMB CDL condition as the dependent variable [with present (1), absent (0)]. An increase in multiple chronic conditions is denoted as a function of ageing; therefore, we included age as covariate for an adjusted model [18, 19]. The effect sizes of the ORs were interpreted as >2 = moderate effect; and, >3.64 as practically significant [20].

Results

Patient demographics

The general characteristics of the study population are displayed in Table 1. Rheumatoid arthritis was present in 4352 (0.5%) of patients (N = 838,618) (median age 61.31 [3.38; 98.51]). Of the 4352 RA patients, 3016 (69.3%) presented with at least one other CDL condition.

There was no difference in mean age within the overall population between men and women ($p = 0.539$; Cohen's $d = 0.022$). Patients with CDL conditions (64.15 [9.76; 96.43]), however, were meaningfully older than those patients without CDL conditions (53.84 [3.38; 98.51]) ($p < 0.001$, Cohen's $d = 0.674$). Within-group analysis showed that there was no difference in the mean age of men and women without CDL conditions ($p = 0.271$; Cohen's $d = 0.068$) or those with ($p = 0.653$; Cohen's $d = 0.019$) (Table 1).

Cross-tabulation showed that there was no association between patients' gender presence of CDL conditions ($p = 0.456$; Cramer's $V = 0.011$).

Number of CDL conditions per patient

Table 2 depicts the number of CDL conditions per patient according to gender. The median (min; max) number of coexisting CDL conditions per patient was 1 (0; 8), and there were no differences between men and women ($p = 0.941$; Cohen's $d = 0.003$). There was also no difference in terms of the number of coexisting CDL conditions between men and women per group of patients with one or more CDL condition ($p = 0.954$; Cohen's $d < 0.001$).

Table 3 displays the mean number of CDL conditions according to different age groups. Analysis showed that patients' age had a significant effect on the number of CDL conditions present per patient ($p < 0.001$; Exp(β) = 1.013). The size of the effect was highest among patients 52 years and younger, who presented with fewer coexisting CDL conditions (mean number of CDL conditions per patient 1.70; 95% CI 1.62-1.78) compared to patients 61 to 70 years (mean number of CDL conditions per patient 2.49; 95% CI 2.39-2.58) and patients older than 70 years (mean number of CDL conditions per patient 2.72; 95% CI 2.62-2.82).

Prevalence of CDL conditions

The prevalence of coexisting CDL conditions according to patients' gender for the subgroup of patients with one or more CDL condition is shown in Table 4. Hypertension was the most prevalent CDL condition, recorded in 47.5% of RA patients. Other cardiovascular CDL conditions include hyperlipidemia that was documented in 25.9%, cardiac failure in 3.8% and dysrhythmias in 2.2% of the patients. Endocrine conditions such as hypothyroidism were found in 19.7% and 11.4% of patients were diagnosed with type 2 diabetes mellitus. Pulmonary disease such as asthma was recorded in 7.8% of patients. Neurological disorders include epilepsy and bipolar mood disorder that were documented in 2.1% and 1.9% of the patients, respectively.

The univariate and age-adjusted ORs for the presence of CDL conditions among females compared with males are shown in Table 5. Men had higher odds of having hyperlipidemia than women did (OR, 1.83; CI 1.33-2.51; $p < 0.001$). Although it was not deemed practically significant as a single coexisting CDL condition, hyperlipidemia conferred significant effects on the odds of men having several other CDL conditions. For example, the insignificant odds of men having asthma (OR, 0.83; CI 0.48-1.42; $p = 0.490$) were reversed and strongly increased in the co-presence of hyperlipidemia (OR, 6.74; CI 2.07-21.93; $p = 0.002$), and statistically as well as practically significant. However, it should be noted that this combination of the two conditions was present in only 13 of 4352 patients from our study population (male:female ratio = 2.6). Furthermore, the higher odds of men having type 2 diabetes mellitus (OR, 2.71; CI 1.43-5.13; $p = 0.002$) were statistically significant with a moderate effect, increased to be practically significant in combination with hyperlipidemia (OR, 4.31; CI 2.17-8.56; $p < 0.001$). The odds of men having co-prevalent hypertension and type 2 diabetes mellitus (OR, 1.58; CI 1.03-2.41; $p = 0.037$), strongly increased in combination with hyperlipidemia (OR, 3.26; CI 2.25-4.71; $p < 0.001$) and deemed practically significant. Hypertension coexisting with RA alone had no significant effect on the odds and were near unity (OR, 0.96; CI 0.80-1.15; $p = 0.650$); however, in the co-presence of dysrhythmia (OR, 3.30; CI 1.40-7.78; $p = 0.007$), the odds of men having both conditions increased to be statistically and practically significant.

Age adjustment had no significant effect on the odds of having coexisting CDL conditions. The male population had a significant 'advantage' over females having prevalent hypothyroidism with 5.3 times lower odds than women (in age-adjusted analysis). This advantage had a significant influence on the odds of men having other CDL conditions that were otherwise deemed practically significant in combination with hyperlipidemia. For instance, the age-adjusted odds of having co-present cardiovascular disease risk factors (combination of hyperlipidemia, hypertension and type 2 diabetes mellitus) and hypothyroidism were 2.5 times lower in men than women. Furthermore, the age-adjusted odds of men having hypertension that were near unity, decreased in combination with hypothyroidism to be 11.1 times lower in men than women.

Discussion

Rheumatoid arthritis' global prevalence varies between 0.3 and 1% [21-23]. Developed countries report a prevalence of 0.5-1% and developing countries ≤0.5% [10, 23]. According to Ally and Visser [24], this lower prevalence in developing countries such as South Africa may be due to insufficient data available. This cross-sectional study found the prevalence of RA to be 0.5% on the medicines claims database, which is similar to the rate reported for developing countries [10, 23, 25]. South Africa's RA prevalence, although not very high, could be under-reported since our health information systems are rudimentary [26].

Within our study population, the ratio of female:male was 3:1. This is in accordance to the literature reporting on the gender distribution of RA [8, 27]. Various factors may account for the gender distribution within rheumatic conditions, which include hormonal influences in a genetically susceptible person, the age of disease onset and smoking status [28]. These covariates were not available in our data, and therefore could not be adjusted for. Although RA may occur at any age, the peak onset of disease is between 40 and 70 years, with an increased prevalence of 2% from the age of 60 years and above [3, 28, 29]. This was somewhat similar to the findings of our study, where both men and women were approximately 60 years of age.

Chronic disease list conditions were prevalent in 68.7% of the study population, which is in line with other literature findings [8, 10], with no relationship between gender and the prevalence of comorbidity. The increased risk of developing coexisting conditions in RA patients is either associated with its treatment or the disease activity itself, since excessive, longstanding inflammation will evidently affect other organs and areas of the body apart from the joints itself [30, 31]. The RA patients from our study who presented with coexisting CDL conditions were significantly older than the patients with RA only, with an age difference of 10 years. Multiple chronic conditions are described as the "rule rather than the exception" among older people [32]. Increasing life expectancies and the ageing of the population are the combined effects of an increase in multiple chronic conditions [20]. This was also reflected in our study population where older patients, from 60 years and above, had nearly 1.5 times more CDL conditions compared to patients who were almost 10 years younger.

It has been suggested that cardiovascular morbidity and mortality are doubled in RA patients [33]. This may be explained by the effect of chronic inflammation and/or the modulation of traditional cardiovascular risk factors (e.g. hypertension, dyslipidemia, diabetes) most commonly encountered in patients with RA [31, 34]. This corroborates our findings in that hypertension, hyperlipidemia and type 2 diabetes mellitus were the most prevalent CDL conditions associated with RA in our study. Hypertension was the single most prevalent CDL condition, encountered by three times more women than men — a result that is similar to that found by Norton et al. in RA patients from the United Kingdom [35]. In addition, women from our study population also showed a higher likeliness for hyperlipidemia, hypothyroidism and type 2 diabetes mellitus compared to their male counterparts, which accords with the estimates of a South African National Health and Nutrition Examination Survey [36].

Our results furthermore showed that being male accorded a protective effect against prevalent cardiovascular disease risk factors in the co-presence of hypothyroidism. In the absence of hypothyroidism, however, this advantage was reversed, and the odds strongly increased. This corresponds with the findings from another South African study [37]. From our study population, the co-presence of hyperlipidemia seemed to have a significant effect on the odds for men

having other cardiovascular disease risk factors. According to Boyer et al. [38], the results of their analysis indicated that the prevalence of hypercholesterolemia did not differ between populations with or without RA. However, RA patients had lower levels of high-density lipoproteins (HDL) and an increased prevalence of type 2 diabetes mellitus, which might indicate an association with RA and contribute to the two-fold increase of cardiovascular disease seen in RA patients. Finally we also observed a significant increase in the odds of men having asthma in combination with hyperlipidemia. However, it should be noted that only 13 out of 4352 patients presented with this combination of conditions. Literature refers to hypercholesterolemia as a potential independent risk factor for asthma, although no difference between men and women was documented [39].

This study has some limitations that should be taken into account when interpreting the findings. Firstly, our data represent only a portion of patients registered by medical schemes as beneficiaries in the private health sector of South Africa; the results may, therefore, not be generalizable to all South African RA patients. Secondly, information such as patients' genetic make-up, presence of RA biomarkers, disease duration, smoking status, alcohol consumption, place of birth and residence, birth weight and diet was not available on the database and therefore could not be adjusted for in prevalence estimations. Thirdly, because of the design of the study, our analysis lacked a control group. It was therefore not possible to establish the cause and effect relationship between the presence of rheumatoid arthritis and the other CDL conditions in patients.

Conclusion

Our results, which indicate the prevalence of RA and coexisting CDL conditions in the private healthcare sector of South Africa, correspond with the reported statistics of developing countries. The findings of our study revealed strong similarities with regard to evidence from literature and the overall South African population. In conclusion, our data may provide valuable insight that may contribute to resolving the under-recognized effect of coexisting conditions present in RA patients, emphasizing the need for future research in terms of effective management strategies of comorbidities that can reduce the burden of illness in RA patients. Future studies should focus on the inclusion of comparator groups to establish cause and effect relationships.

Compliance with ethical standards

Conflict of interest Nericke Olivier, Johanita Burger, Rianda Joubert, Martie Lubbe, Adele Naudé, and Marike Cockeran declare no conflict of interest with regard to the research, authorship and/or publication of this manuscript.

Ethical approval The study protocol was reviewed and approved by the Health Research Ethics Committee of the North-West University (Potchefstroom campus), Potchefstroom, South Africa, on the July 19, 2016 (Ethics number: NWU-00179-14-A1-02). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal participants This study was a retrospective analysis of administrative claims data and does not contain any human participants or animals.

Informed consent Since the PBMs database contain only retrospective depersonalized claims data, the need for informed consent from each individual patient, medical scheme, prescriber and service provider was waived by the Health Research Ethics Committee.

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Table 1 Patient demographics

	Total	Female	Male	*p*-value	Cohen's *d*
Total number of patients on database for 2014, N (%)	838,618	446,382 (53.2%)	392,235 (46.8%)		
Number of RA patients, n (%)	4352 (0.5%)	3257 (74.8%)	1095 (25.2%)		
Age (years), mean ± SD (95% CI)	60.32 ± 14.29 (59.90-60.75)	60.40 ± 14.27 (59.91-60.89)	60.09 ±14.38 (59.24-60.95)	0.539	0.022
Age (years), median (min; max)	61.31 (3.38; 98.51)	61.53 (3.79; 98.51)	60.92 (3.38; 96.43)		
Number of patients without CDL conditions, n (%)	1336 (30.7%)	990 (74.1%)	346 (25.9%)	*< 0.001*	
Age (years), mean ± SD (95% CI)	52.96 ± 15.76 (52.11-53.80)	53.24 ± 15.70 (52.26-54.22)	52.16 ± 15.91 (50.47-53.84)	0.271	0.068
Age (years), median (min; max)	53.84 (3.38; 98.51)	54.03 (3.79; 98.51)	53.23 (3.38; 94.27)		
Number of patients with CDL conditions, n (%)	3016 (69.3%)	2267 (75.2%)	749 (24.8%)	*< 0.001*	
Age (years), mean ± SD (95% CI)	63.59 ± 12.26 (63.15-64.02)	63.53 ± 12.35 (63.02-64.04)	63.76 ± 11.96 (62.90-64.62)	0.653	0.019
Age (years), median (min; max)	64.15 (9.76; 96.43)	64.21 (9.76; 94.66)	63.92 (20.33; 96.43)		

RA: rheumatoid arthritis

CDL: chronic disease list

Significant *p*-values in italics

Table 2 Frequency of CDL conditions according to gender

	Total	Female	Male	*p*-value	Effect size
Mean ± SD (95% CI) number of CDL conditions in RA patients	1.29 ± 1.18 (1.25-1.32)	1.29 ± 1.18 (1.24-1.33)	1.29 ± 1.18 (1.22-1.36)	0.941	0.003*
Number of CDL conditions per patient, median (min; max)	1 (0; 8)	1 (0; 8)	1 (0; 6)		
Number of CDL conditions per patient, n (%)				0.954	<0.001*
1	1366 (31.4%)	1041 (76.2%)	325 (23.8%)		
2	976 (22.4%)	732 (75.0%)	244 (25.0%)		
3	467 (10.7%)	338 (72.4%)	129 (27.6%)		
4	165 (3.8%)	120 (72.7%)	45 (27.3%)		
5	35 (0.8%)	30 (85.7%)	5 (14.3%)		
≥ 6	7 (0.2%)	6 (85.7%)	1 (14.3%)		

RA: rheumatoid arthritis

CDL: chronic disease list

*Cohen's *d*-value

Table 3 Frequency of CDL conditions according to age

	Age group 1	Age group 2	Age group 3	Age group 4	*p*-value (Effect size)
Age (years)	> 0 ≤ 52	> 52 ≤ 61	> 61 ≤ 70	> 70	
n (%)	1086 (25%)	1086 (25%)	1088 (25%)	1086 (25%)	*< 0.001* (1.013)**
Mean number of CDL conditions (95% Wald CI)	1.70 (1.62-1.78)	2.24 (2.16-2.34)	2.49 (2.39-2.58)	2.72 (2.62-2.82)	*<0.001**

*Cohen's *d*-value = 0.2 (Group 1 *vs.* Group 2)

*Cohen's *d*-value = 0.3 (Group 1 *vs.* Group 3)

*Cohen's *d*-value = 0.3 (Group 1 *vs.* Group 4)

*Cohen's *d*-value = 0.1 (Group 2 *vs.* Group 3)

*Cohen's *d*-value = 0.1 (Group 2 *vs.* Group 4)

*Cohen's *d*-value = 0.1 (Group 3 *vs.* Group 4)

**Exp(*B*)

Significant *p*-values in italics

CDL: chronic disease list

Table 4 Prevalence of CDL conditions

	Total	Female	Male	*p*-value	Cramer's *V*
Hypertension, n (%)	2069 (47.5%)	1547 (74.8%)	522 (25.2%)	0.921	0.002
Hyperlipidemia, n (%)	1126 (25.9%)	754 (67.0%)	372 (33.0%)	*< 0.001*	0.107
Hypothyroidism, n (%)	858 (19.7%)	795 (92.7%)	63 (7.3%)	*< 0.001*	0.204
Type 2 diabetes mellitus, n (%)	498 (11.4%)	308 (61.9%)	190 (38.1%)	*< 0.001*	0.108
Asthma, n (%)	339 (7.8%)	268 (79.1%)	71 (20.9%)	0.062	0.029
Cardiac failure, n (%)	164 (3.8%)	122 (74.4%)	42 (25.6%)	0.893	0.002
Glaucoma, n (%)	109 (2.5%)	81 (74.3%)	28 (25.7%)	0.898	0.002
Dysrhythmias, n (%)	96 (2.2%)	58 (60.4%)	38 (39.6%)	*0.001*	0.050
Epilepsy, n (%)	93 (2.1%)	70 (75.3%)	23 (24.7%)	0.923	0.002
Bipolar mood disorder, n (%)	81 (1.9%)	69 (85.2%)	12 (14.8%)	*0.030*	0.033

CDL: chronic disease list
Significant *p*-values in italics

Table 5 Odds ratios with 95% Wald confidence intervals (95% CI) for CDL condition combinations

CDL condition combinations	n	Model 1 OR [95% Wald CI]	*p*-value	Model 2 aOR [95% Wald CI]	*p*-value
Hyperlipidemia	64M, 107F	1.83 [1.33-2.51]	*< 0.001*	1.84 [1.34-2.52]	*< 0.001*
Hyperlipidemia / Asthma	9M, 4F	6.74 [2.07-21.93]	*0.002*	6.76 [2.08-22.00]	*0.002*
Hyperlipidemia / Type 2 diabetes mellitus	20M, 14F	4.31 [2.17-8.56]	*< 0.001*	4.32 [2.18-8.59]	*< 0.001*
Hyperlipidemia / Hypertension / Type 2 diabetes mellitus	60M, 57F	3.26 [2.25-4.71]	*< 0.001*	3.30 [2.28-4.78]	*< 0.001*
Hyperlipidemia / Hypertension / Asthma	14M, 19F	2.21 [1.10-4.42]	*0.025*	2.24 [1.12-4.48]	*0.023*
Hyperlipidemia / Hypertension	111M, 183F	1.90 [1.48-2.43]	*< 0.001*	1.93 [1.51-2.48]	*< 0.001*
Hyperlipidemia / Hypertension / Dysrhythmias	4M, 7F	1.70 [0.50-5.83]	0.397	1.73 [0.51-5.94]	0.389
Hyperlipidemia / Cardiac failure	5M, 11F	1.35 [0.47-3.91]	0.575	1.38 [0.47-4.00]	0.556
Hyperlipidemia / Hypertension / Glaucoma	3M, 9F	0.99 [0.27-3.67]	0.990	1.00 [0.27-3.72]	0.995
Hyperlipidemia / Hypothyroidism	7M, 51F	0.41 [0.18-0.89]	*0.025*	0.41 [0.18-0.90]	*0.026*
Hyperlipidemia / Hypertension / Hypothyroidism / Type 2 diabetes mellitus	5M, 37F	0.40 [0.16-1.02]	0.055	0.40 [0.16-1.03]	0.056
Hyperlipidemia / Hypertension / Hypothyroidism	5M, 88F	0.17 [0.07-0.41]	*< 0.001*	0.17 [0.07-0.41]	*< 0.001*
Hypertension	186M, 573F	0.96 [0.80-1.15]	0.650	0.96 [0.80-1.15]	0.678
Hypertension / Dysrhythmias	11M, 10F	3.30 [1.40-7.78]	*0.007*	3.36 [1.42-7.96]	*0.006*
Hypertension / Type 2 diabetes mellitus	33M, 63F	1.58 [1.03-2.41]	*0.037*	1.58 [1.03-2.43]	*0.035*
Hypertension / Glaucoma	3M, 17F	0.52 [0.15-1.79]	0.302	0.53 [0.16-1.82]	0.312
Hypertension / Epilepsy	1M, 10F	0.30 [0.04-2.32]	0.247	0.30 [0.04-2.34]	0.249
Hypertension / Asthma	3M, 49F	0.18 [0.06-0.58]	*0.004*	0.18 [0.06-0.58]	*0.004*
Hypertension / Asthma / Hypothyroidism	1M, 20F	0.15 [0.02-1.10]	0.060	0.15 [0.02-1.11]	0.063
Hypertension / Hypothyroidism	6M, 183F	0.09 [0.04-0.21]	*< 0.001*	0.09 [0.04-0.21]	*< 0.001*
Type 2 diabetes mellitus	18M, 20F	2.71 [1.43-5.13]	*0.002*	2.68 [1.41-5.10]	*0.003*
Type 2 diabetes mellitus / Hypothyroidism	3M, 8F	1.12 [0.30-4.21]	0.872	1.10 [0.30-4.17]	0.885
Cardiac failure	4M, 17F	0.70 [0.24-2.08]	0.520	0.71 [0.24-2.11]	0.536
Cardiac failure / Hypothyroidism	1M, 17F	0.17 [0.02-1.31]	0.090	0.18 [0.02-1.32]	0.092
Hypothyroidism	13M, 191F	0.19 [0.11-0.34]	*< 0.001*	0.19 [0.11-0.34]	*< 0.001*
Hypothyroidism / Asthma	1M, 10F	0.30 [0.04-2.32]	0.247	0.30 [0.04-2.32]	0.246
Epilepsy	7M, 11F	1.90 [0.73-4.91]	0.186	1.86 [0.71-4.82]	0.204
Glaucoma	6M, 14F	1.28 [0.49-3.33]	0.618	1.30 [0.50-3.40]	0.595
Asthma	17M, 61F	0.83 [0.48-1.42]	0.490	0.82 [0.48-1.41]	0.475
Bipolar mood disorder	2M, 23F	0.26 [0.06-1.09]	0.066	0.25 [0.06-1.06]	0.060

CDL: chronic disease list; M: Male; F: Female;; OR: Odds ratio; aOR: Age adjusted odds ratio

Data are odds ratios (OR) (95% Wald confidence interval (CI)). Conditions with frequencies (n) < 10 were excluded from the analyses. For the univariate model, the dependent variable was gender (female (0); male (1)), with the type of CDL condition as the independent variable (present (1); absent (0)). Model 1 = Univariate (crude) model; Model 2 = Age adjusted model; significant *p*-values in italics

3.3 Manuscript 2

Title: Antirheumatic prescribing patterns and direct medicine costs in the South African private health sector

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Funding Sources: These findings are the result of work supported by the North-West University (NWU master's bursary), Potchefstroom, SA. The views expressed in this paper are those of the authors.

Keywords: rheumatoid arthritis, cost drivers, direct medicine cost, medicine utilization

Running Title: Treatment and Cost of Rheumatoid Arthritis

Abstract

Objective: This study aimed to evaluate antirheumatic medicine prescribing patterns and to estimate the total annual direct medicine cost of rheumatoid arthritis (RA) in the private health sector of South Africa.

Method: A retrospective, cross-sectional drug utilization study was performed on medicine claims data from 1 January 2014 to 31 December 2014 for a total of 4,352 RA patients, obtained from a Pharmaceutical Benefit Management (PBM) company. The population was divided into those patients with RA only and those with RA and other chronic disease list (CDL) conditions. Antirheumatic treatment was categorized into phase one treatment (non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids only) and phase two treatment (NSAIDs, corticosteroids, disease modifying antirheumatic drugs (DMARDs) and biologics). Cost-driving products, the 90% drug utilization (DU90%) segment, mean and median medicine item costs were calculated.

Results: The annual direct medicine cost of RA management summed to ZAR59,264,203.68. The mean (median) cost per medicine item was ZAR660.49 ± 3,605.00 (ZAR129.70). DMARDs represented 47.6% (n = 42,699) and biologics 2.4% (n = 2,150) of the 89,728 medicine items claimed. The DU90% of phase one treatment products accounted for 92.8% of the total medicine cost, with celecoxib as the main cost driver for phase one treatment due to high volumes and mean cost. The DU90% segment of phase two treatment accounted for 34.7% of the total medicine cost, with adalimumab as the main cost driver due to its high mean cost.

Conclusion: The direct medicine treatment cost of RA in the South African private health sector is driven by the high volume of DMARDs and the high mean costs of biologics.

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory, auto-immune disease, found in approximately one out of a hundred people worldwide [1]. The South African Rheumatism and Arthritis Association (SARAA) documented the prevalence of RA as being the highest (n = 1,582; 64%) among ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis diagnosis (N = 2,481) in the private health sector of South Africa during 2015 [2].

Rheumatoid arthritis patients have mean annual medical costs that are two to three times more than those of their peers without the disease [3, 4, 5]. It has been estimated that the total annual economic burden of RA ranges between €41.6 billion in the United States of America and €45.3 billion in Europe [6]. Data and literature on RA medicine costs in South Africa are limited, necessitating studies that measure and evaluate the cost of treatment against the economic burden of RA in the South African population [6, 7]. In the private healthcare sector of South Africa, the cost per patient per annum for RA was estimated at ZAR5,366 (€380), accounting for 2.6% of the total amount spent on chronic disease list (CDL) conditions during 2015 [8].

The CDL of South Africa is a list of 26 chronic/non-communicable diseases, including RA, which qualify as "prescribed minimum benefits" (PMBs), meaning all medical schemes, by law, have to cover the medication, physicians' consultations and tests related to these conditions [6, 8]. The South African Medical Schemes Act (131 of 1998) included PMBs as one of the features of medical schemes to ensure that all members are continuously provided with affordable, predetermined health service standards, irrespective of their benefit option [9]. In the past decade, total PMB medicine expenditure increased by 15.5%, highlighting CDL conditions as important cost drivers in the South African private healthcare sector [8]. The South African National Department of Health (DoH) reported annual private health care expenditure at ZAR198.4 billion, accounting for 4.4% of the GDP in 2016/2017 [10]. Medicine cost drivers may contribute to the total medicine cost either via a high volume of items claimed or via a high mean cost per item.

Several strategies such as mandatory generic substitution and treatment algorithms, developed in terms of regulations stipulated by the South African Council for Medical Schemes, have been implemented in the country to ensure cost-effective and/or affordable healthcare [8, 11, 12]. According to the South African treatment algorithm for RA, treatment should be initiated using non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and non-drug measures such as rest and range-of-motion exercises [13]. Disease

modifying antirheumatic drug (DMARD) therapy (e.g. methotrexate/sulphasalazine) is initiated when a RA patient is diagnosed with active erosive disease [13]. If the patient shows an inadequate response to the aforementioned treatment strategy, other DMARD therapies (e.g. leflunomide/azathioprine) should be considered [13]. This treatment algorithm lacks an indication for biologic therapy initiation; however, according to SARAA, biologic therapy should be considered for RA patients after at least six months of DMARD therapy has failed [7].

The direct medicine costs of RA have been fairly low in the past [6]. The increased utilization of expensive biologics has, however, resulted in a dramatic shift in the costs and management of the disease [14]. For example, according to Husher *et al.* [15], the direct medicine costs of RA patients (aged 18 to 64 years) more than doubled from €2,522 to €6,089 between 2001 and 2011 because of the growing trend in prescribing biologics. A recent socioeconomic survey across Europe showed a 7.5-fold increase in total mean annual direct medical costs when treatment with biologics/biosimilars is compared to treatment with conventional synthetic DMARDs [16]. An earlier study conducted on South African prescription claims data for 2005 to 2008 showed the average cost per medicine item to have increased with 1000% from ZAR128.45 ± 155.93 (€13.48 ± 16.36) to ZAR1,477.88 ± 3,134.39 (€155.07 ± 328.88) when treatment with biologics was initiated [17].

Rheumatoid arthritis patients commonly present with an average of at least one to two comorbidities [18, 19]. An increase in the number of comorbidities is directly proportional to an increase in medical costs [20]. Osiri and Sattayasomboon [21] documented the total annual direct medical costs of patients with RA and comorbidities between 2008 and 2009 as 1.12 times higher than the costs of patients without any comorbidity. They concluded, however, that it was not the comorbidities posing a major economic burden, but rather RA itself.

The increasing medical costs of RA result in a substantial economic burden, with a significant impact on patients, their families and society [22, 23]. Therefore, the aim of this study was to evaluate the antirheumatic prescribing patterns and to estimate the total annual direct medicine cost of RA in the private health sector of South Africa.

Methodology

Study design

We performed a retrospective, cross-sectional drug utilization study on medicine claims data from 1 January 2014 to 31 December 2014, this data having been obtained from the medicine claims database of a Pharmaceutical Benefit Management (PBM) company.

Study sample

A total of 838,618 patients (446,382 female, 392,235 male) were registered on the PBM company's database for the year 2014. The study population included 4,352 patients with an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis-code for RA (i.e. M05, M06 and M08) in conjunction with a claim for antirheumatic medicine paid from the patient's PMBs during the study period.

Evaluation of prescribing patterns

Patients were divided into two disease groups, i.e. those patients with RA only and those with RA and one or more coexisting CDL condition. The patients within each disease group were then stratified according to treatment phase. Treatment phase was based on the South African therapeutic algorithm for RA, categorized into phase one treatment, consisting of NSAIDs and corticosteroids only, and phase two treatment, consisting of NSAIDs, corticosteroids, plus DMARDs or biologics [13]. Antirheumatic medicine was identified according to active substances using the MIMS Desk Reference (MDR) and National Pharmaceutical Product Interface (NAPPI)-codes [13, 24]. Medicine items were further classified according to product type, e.g. originals without a generic equivalent available in the South African healthcare market, originals with an available generic equivalent, and generic equivalents. The 90% drug utilization (DU90%) segments (i.e. the number of medicines that account for 90% of medicine prescriptions) for both phase one and phase two treatment were determined.

Direct medicine cost analysis

The cost analysis was based on claims for RA medicines only and presented as mean ± standard deviation (SD) (median) cost per medicine item for both disease groups, stratified by treatment phase. We determined the cost-driving products for both phase one and phase two treatment. Total cost comprised of the sum of the medical scheme's contribution, the patient's contribution, single exit price (SEP), professional fee and value added tax (VAT). All costs are shown in 2014 South African Rand value (ZAR1.00 = €14.40) [25].

Statistical analysis

Data were analyzed using Statistical Analysis System®, SAS 9.4® software [26]. Descriptive statistics (frequency, percentage, mean, standard deviation, 95% confidence intervals, median and interquartile range) were used to characterize the study population, prescribing patterns and cost data. An independent two-sample *t*-test was performed to compare means. A *p*-value of 0.05 or less at a two-sided α-level was considered statistically significant. Cohen's *d*-value was considered for practical significance; the magnitude of the *d*-values was interpreted as follows: 0.2 = small effect, 0.5 = medium effect and 0.8 = large effect [27]. Chi-square distribution models were used to determine the association between categorical variables. Cramér's *V* was used to evaluate the strength of any significant association, where 0.1 = small effect, 0.3 = medium effect and 0.5 or higher = large effect [28].

Results

Patients' characteristics

Table 1 shows the demographic characteristics of the study population, consisting of 4,352 (N = 838,618) patients. Of these, 3,016 (69.3%) patients presented with at least one coexisting CDL condition. The gender ratio of female:male was 3:1 for the study population as a whole and also within both disease groups. The majority of patients (87.2%) received phase two treatment, and were meaningfully younger than patients on phase one treatment at 59.24 ± 14.10 years vs. 67.74 ± 13.40 years ($p < 0.001$; Cohen's $d = 0.6$). Patients with RA only on phase one treatment were also older than those on phase two treatment at 60.08 ± 18.33 vs. 52.29 ± 15.34 years ($p < 0.001$; Cohen's $d = 0.4$), similar to patients with coexisting CDL conditions at 69.71 ± 11.00 vs. 62.53 ± 12.15 years ($p < 0.001$; Cohen's $d = 0.6$).

Prescribing patterns

Table 2 presents the antirheumatic medicine items claimed during the study period according to product type. Both disease groups claimed significantly more medicine items as part of phase two treatment than items used as part of phase one treatment ($p < 0.001$; Cramér's $V = 0.1$). Patients on phase one and phase two treatment received mainly originals with an available generic equivalent and generic equivalents. The usage of originals without an available generic equivalent were much lower in patients on phase one treatment compared to those patients on phase two treatment ($p < 0.001$; Cramér's $V = 0.1$). Within disease group analyses showed no difference in the ratio of medicine items claimed according to product type ($p = 0.055$; Cramér's $V < 0.1$).

The drugs representing the DU90% segment for phase one treatment are celecoxib (26.6%), meloxicam (24.4%), prednisone (20.5%), diclofenac (7.7%), etoricoxib (7.3%), piroxicam (2.9%) and diclofenac/misoprostol (2.2%) (Table 4). The DU90% segment for phase two treatment consists of methotrexate (26.5%), prednisone (14.7%), sulphasalazine (10.2%), chloroquine (9.8%), meloxicam (8.9%), celecoxib (7.2%), diclofenac (3.8%), leflunomide (3.2%), etoricoxib (3.0%), naproxen/esomeprazole (1.3%), betamethasone (1.2%) and methylprednisolone (1.2%) (Table 5). In total, DMARDs represented the highest volume of items at 47.6% (n = 42,699) and biologics the lowest at 2.4% (n = 2,150) of the 89,728 medicine items claimed during 2014 (Table 5).

Costs of RA

Table 3 presents a detailed description of the direct annual cost per medicine item, stratified by disease group and treatment phase. The total annual direct medicine cost of RA summed to ZAR59,264,203.68 for the entire population, the cost of items for phase two treatment constituting 98.0% of this total cost. For the study population as a whole, the mean (median) cost per item was ZAR660.49 ±3,605.00 (ZAR129.70). Within disease group analyses showed no difference in the mean cost per item for patients with coexisting CDL conditions and for those with RA only, at ZAR623.27 ± 3,494.73 (ZAR130.33) vs. ZAR746.36 ± 3,846.09 (ZAR127.21) (Cohen's $d < 0.1$). Among patients with RA only, the mean (median) cost per item was ZAR248.04 ± 232.86 (ZAR211.78) for phase one treatment, compared to ZAR762.07 ± 3,904.99 (ZAR125.87) for phase two treatment (Cohen's $d = 0.1$). Patients with RA and coexisting CDL conditions had

mean (median) costs per item of ZAR232.21 ± 237.01 (ZAR195.16) for phase one treatment and ZAR651.69 ± 3,617.28 (ZAR126.01) for phase two treatment (Cohen's *d* = 0.1).

Table 4 depicts the cost per medicine item for phase one treatment products. Drugs representing the DU90% segment accounted for 92.8% (n = ZAR1,104,974.46) of the total annual medicine cost of phase one treatment. Celecoxib was the main cost driver with the highest volume (n = 1,350) and mean (median) cost at ZAR460.34 ± 184.96 (ZAR446.28) per item, representing 52.2% (n = ZAR621,461.74) of the total annual medicine item cost of phase one treatment during 2014 (Table 4). For phase two treatment, the DU90% segment accounted for only 34.7% (n = ZAR20,133,594.49) of the total annual medicine cost (Table 5). Although adalimumab was not included in the DU90% segment, it was the main cost-driver with a relatively high mean (median) cost of ZAR16,746.34 ± 984.28 (ZAR17,053.00) per item, representing 25.6% (n = 14,870,746.48) of the total annual medicine item cost of phase two treatment during 2014 (Table 5).

Discussion

Our study provides a description of the prescribing patterns and direct medicine costs for RA patients in the private health sector of South Africa. There were a number of key findings in our study. Firstly, we determined that the study population mainly consisted of elderly patients. Secondly, the most commonly used medicine item was methotrexate, followed by prednisone and meloxicam. Furthermore, the biologics infliximab and ustekinumab had the lowest utilization rate within our study population. Thirdly, only 42.7% of the antirheumatic medicine items claimed during 2014 were generic equivalents. Finally, we found that RA patients' total annual direct medicine cost accounted for 1.5% of the total annual medicine expenditure on the PBM company's database for 2014 (N = ZAR4,031,952,734.26), 1.4% of this 1.5% represented by drugs used as part of phase two treatment.

The gender distribution in our study population, i.e. a female to male ratio of 3:1, is in accordance with various other studies' findings [29, 30, 31]. The mean age of our patients was approximately 60 years, which is in line with literature that reports an increased prevalence of RA at 2.0% from the age of 60 years and above [32]. According to Van Onna and Boonen [33], less intensive treatment regimens are initiated when treating elderly RA patients. Köller *et al.* [34] further explain that older people are less likely to receive DMARD therapy due to the uncertainty and concern around DMARD efficacy and safety in the elderly. This was also observed in our study where patients who received phase two treatment (NSAIDs, corticosteroids,

DMARDs and biologics) were, on average, 8 to 9 years younger than the patients who received phase one treatment (NSAIDs and corticosteroids), irrespective of disease group.

Observation of the medicine utilization in our study indicates that prescribing patterns generally complied with the guidelines stipulated in the South African therapeutic algorithm for RA, i.e. methotrexate is recommended as first-line therapy for RA patients, with NSAIDs and corticosteroids as adjunctive therapy [13]. The South African treatment algorithm for RA lacks an indication of biologic therapy initiation [12], which may explain the low utilization rate in our study. According to Tarr et al. [7], possible adverse effects also prevent the use of biologics as first-line therapy. Biologics, however, are referred to as prominent cost drivers [8], which was also the case in our study as this group of medicine had the highest mean medicine item costs. For example, in our study these specialty medicines were responsible for 62.0% of the total medicine expenditure, which is relatively low compared to other studies [21, 35, 36] that show specialty medicines accounting for 80% of the total annual drug costs. The mean cost per item of the least expensive biologic (tocilizumab) was five times higher than that of the most expensive DMARD (leflunomide) prescribed in the study population. This corroborates the findings of Hodkinson *et al.* [37] that RA patients' cost of therapy is relatively low if they are treated with DMARDs, in contrast to the medicine cost escalations due to biologics. When treatment without biologics is compared financially to treatment with biologics, six- to seven-fold cost increases from the former to the latter have been documented [17, 18, 35]. Our results were relatively lower at a 2.6-fold cost increase, which might be due to the low biologic utilization rate.

The mean cost per medicine item prescribed for our study population was 4.4 times higher than the average medicine item cost of ZAR148.00 in the private health sector of South Africa in 2014 [8]. Our study population claimed 12.9% less generic equivalents than the reported generic utilization rate of 55.6% in the South African private health sector [8]. Although generic equivalent substitution may be an option in attempts to reduce medicine costs, generic equivalents for biologics were not yet available at the time of the study. Thus, prescribers may have had no other choice as to prescribe originals without an available generic equivalent to the RA patients in our study. Gray [38] states that an increase in generic equivalent utilization may also be fortified by the promotion of generic equivalent substitution.

Possible limitations of this study are that the data represent only a portion of patients registered by medical schemes as beneficiaries in the private health sector of South Africa. However, the PBM company database used for this study contains longitudinal patient medicine claims for 1.7 million medical scheme beneficiaries

and is connected to all the pharmacies in South Africa as well as 98% of dispensing doctors [8]. We therefore believe that our study population can be seen as an accurate estimate of the total database which represents current trends in the private health sector of South Africa, considering that it is mandatory to specify accurate ICD-10 codes for the reimbursement of medical claims relating to CDL conditions. Covariates such as age of disease onset, disease duration and smoking status were not available in our data, and therefore could not be adjusted for. The impact on patients' treatment costs of switching from phase one to phase two treatment is recommended as a topic for future studies, as this fell outside the scope of our study.

In conclusion, as was expected, biologics and DMARDs were drivers of RA medication costs. Attention to both volume and price of medication is required when intervening in an attempt to reduce medicine expenditure [38]. An increase in generic equivalent substitution, where possible and strict adherence to the South African RA therapeutic algorithm may result in cost savings. Determining the cost of and utilization patterns in RA treatment on grounds of real-time claims data provided valuable information relating to the high costs of RA management in the private health sector of South Africa, which is important for consideration in formulary decision-making [39]. Consequently, optimization of standard care protocols for RA patients and the provision of appropriate biologic therapy can possibly be addressed, stated as current and future challenges in South Africa [7].

Nericke Olivier, Johanita Burger, Martie Lubbe, Rianda Joubert and Adele Naudé have no conflicts to declare.

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Table 1. Demographic characteristics of the study population, stratified by disease group and treatment phase

	Total	Phase one treatment	Phase two treatment	*p*-value	Effect size
Overall study population:					
RA patients					
Number of patients, n (%)	4,352	556 (12.8)	3,796 (87.2)		
Women, n (%)	3,257 (74.8)	416 (12.8)	2,841 (87.2)		
Age (years), mean ± SD (95% CI)	60.32 ± 14.29 (59.90-60.75)	67.74 ± 13.40 (66.62-68.85)	59.24 ± 14.10 (58.79-59.69)	< 0.001	0.6*
Patients with RA only					
Number of patients, n (%)	1,336 (30.7)	114 (8.5)	1,222 (91.5)		
Women, n (%)	990 (74.1)	69 (7.0)	921 (93.0)		
Age (years), mean ± SD (95% CI)	52.96 ± 15.76 (52.11-53.80)	60.18 ± 18.33 (56.68-63.48)	52.29 ± 15.34 (51.43-53.16)	< 0.001	0.4*
Patients with RA and coexisting CDL conditions					
Number of patients, n (%)	3,016 (69.3)	442 (14.7)	2,574 (85.3)		
Women, n (%)	2,267 (75.2)	347 (15.3)	1,920 (84.7)		
Age (years), mean ± SD (95% CI)	63.59 ± 12.26 (63.15-64.02)	69.71 ± 11.00 (68.68-70.74)	62.53 ± 12.15 (62.06-63.00)	< 0.001	0.6*

RA: rheumatoid arthritis

CDL: chronic disease list

Phase one treatment: RA patients treated with NSAIDs and corticosteroids only

Phase two treatment: RA patients treated with NSAIDs, corticosteroids, DMARDs and biologics

*Cohen's *d*-value

Table 2. Antirheumatic medicine items claimed during the study period, stratified by disease group and treatment phase

	Total	Phase one treatment	Phase two treatment	*p*-value	Effect size
Overall study population:					
RA patients					
Antirheumatic medicine by generic status					
Total, n (%)	89,728	5,070 (5.7)	84,658 (94.3)		
Originals with an available generic equivalent, n (%)	28,861 (32.2)	2,178 (43.0)	26,683 (31.5)		
Originals without an available generic equivalent, n (%)	22,518 (25.1)	147 (2.9)	22,371 (26.4)	$p < 0.001$	0.1*
Generic equivalents, n (%)	38,349 (42.7)	2,745 (54.1)	35,604 (42.1)		
Patients with RA only					
Antirheumatic medicine by generic status†					
Total, n (%)[#]	27,129 (30.2)	829 (3.1)	26,300 (96.9)		
Originals with an available generic equivalent, n (%)	8,573 (31.6)	391 (4.6)	8,182 (95.4)		
Originals without an available generic equivalent, n (%)	6,884 (25.4)	18 (0.3)	6,866 (99.7)		
Generic equivalents, n (%)	11,672 (43.0)	420 (3.6)	11,252 (96.4)		
Patients with RA and coexisting CDL conditions					
Antirheumatic medicine by generic status†					
Total, n (%)[#]	62,599 (69.8)	4,241 (6.8)	58,358 (93.2)		
Originals with an available generic equivalent, n (%)	20,288 (32.4)	1,787 (8.8)	18,501 (91.2)		
Originals without an available generic equivalent, n (%)	15,634 (25.0)	129 (0.8)	15,505 (99.2)		
Generic equivalents, n (%)	26,677 (42.6)	2,325 (8.7)	24,352 (91.3)		

RA: rheumatoid arthritis

CDL: chronic disease list

Phase one treatment: RA patients treated with NSAIDs and corticosteroids only

Phase two treatment: RA patients treated with NSAIDs, corticosteroids, DMARDs and biologics

*Cramer's *V*

†Statistics for disease group by generic status: $p = 0.055$; Cramer's $V < 0.1$

[#]Statistics for disease group by treatment phase: $p < 0.001$; Cramer's $V = 0.1$

Table 3. Direct annual medicine item costs for rheumatoid arthritis patients, stratified by disease group and treatment phase

	Total	Phase one treatment	Phase two treatment
Overall study population:			
RA patients			
Total annual medicine cost (R)	59,264,203.68 (n = 89,728)	1,190,424.46 (n = 5,070)	58,073,779.22 (n = 84,658)
Mean cost (R) per item ± SD (95% CI)	660.49 ± 3,605.00 (636.90-684.08)	234.80 ± 236.39 (228.29-241.31)	685.98 ± 3,709.38 (660.99-710.97)
Median cost (R) per item (IQR)	129.70 (65.16-389.06)	195.54 (56.31-392.88)	125.87 (65.16-389.06)
Patients with RA only			
Total annual medicine cost (R)	20,247,936.92 (n = 27,129)	205,624.48 (n = 829)	20,042,312.45 (n = 26,300)
Mean cost (R) per item ± SD (95% CI)	746.36 ± 3,846.09 (700.59-792.13)	248.04 ± 232.86 (232.16-263.91)	762.07 ± 3,904.99 (714.87-809.26)
Median cost (R) per item (IQR)	127.21 (67.50-389.07)	211.78 (29.78-441.04)	125.87 (68.10-387.67)
Patients with RA and coexisting CDL conditions			
Total annual medicine cost (R)	39,016,266.76 (n = 62,599)	984,799.98 (n = 4,241)	38,031,466.77 (n = 58,358)
Mean cost (R) per item ± SD (95% CI)	623.27 ± 3,494.73 (595.90-650.65)	232.21 ± 237.01 (225.07-239.34)	651.69 ± 3,617.28 (622.34-681.04)
Median cost (R) per item (IQR)	130.33 (63.66-388.87)	195.16 (61.18-364.85)	126.01 (63.77-390.31)

n: number of items

RA: rheumatoid arthritis

CDL: chronic disease list

IQR: interquartile range

Phase one treatment: RA patients treated with NSAIDs and corticosteroids only

Phase two treatment: RA patients treated with NSAIDs, corticosteroids, DMARDs and biologics

Table 4. Cost per medicine item for phase one treamtment products

Active ingredient	Number of items (n)	Mean cost (R) per item ± SD (95% CI)	Median cost (R) per item (IQR)	Total annual medicine item cost (R)
Celecoxib	1,350	460.34 ± 184.96 (450.47-470.22)	446.28 (344.33-508.42)	621,461.74
Meloxicam	1,236	160.39 ± 57.57 (157.18-163.61)	167.67 (117.99-197.77)	198,245.53
Etoricoxib	370	405.55 ± 160.37 (389.15-421.94)	443.03 (304.72-485.51)	150,052.81
Diclofenac	392	153.77 ± 138.04 (140.06-167.47)	107.82 (34.38-232.44)	60,276.03
Diclofenac / misoprostol	113	323.90 ± 108.43 (303.69-344.11)	273.69 (260.35-424.99)	36,600.19
Betamethasone	91	345.65 ± 815.13 (175.89-515.40)	144.37 (91.28-253.94)	31,453.75
Prednisone	1,039	26.26 ± 62.50 (22.45-30.06)	8.19 (7.93-16.20)	27,281.77
Naproxen / esomeprazole	89	232.74 ± 124.41 (206.53-258.95)	210.01 (105.02-309.87)	20,713.99
Indomethacin	69	160.66 ± 238.52 (103.36-217.96)	61.65 (15.29-127.84)	11,085.71
Piroxicam	146	75.73 ± 45.60 (68.27-83.19)	66.13 (54.86-74.40)	11,056.39
Ibuprofen	28	268.94 ± 234.36 (178.06-359.81)	321.65 (16.54-450.82)	7,530.22
Methylprednisolone	94	75.91 ±51.64 (65.33-86.49)	48.56 (41.49-89.40)	7,135.68
Naproxen	34	124.84 ± 126.42 (80.72-168.95)	64.27 (58.93-141.38)	4,244.40
Ketoprofen	12	194.97 ± 4.93 (191.84-198.10)	197.70 (192.25-197.70)	2,339.67
Dexamethasone	6	151.55 ± 83.73 (63.68-239.42)	191.37 (70.04-202.92)	909.29
Lornoxicam	1	37.30	37.30	37.30

Phase one treatment: RA patients treated with NSAIDs and corticosteroids only

Table 5. Cost per medicine item for phase two treatment products

Active ingredient	Number of items (n)	Mean cost (R) per item ± SD (95% CI)	Median cost (R) per item (IQR)	Total annual medicine item cost (R)
Adalimumab	888	16,746.34 ± 984.28 (16,681.51-16,811.16)	17,053.00 (17,046.16-17,055.28)	14,870,746.48
Etanercept	499	16,780.37 ± 2,811.50 (16,533.09-17,027.65)	17,451.76 (17,444.92-17,454.04)	8,373,404.17
Sulphasalazine	8,630	693.95 ± 246.68 (688.74-699.15)	785.72 (430.74-829.58)	5,988,777.94
Rituximab	71	83,277.05 ± 45,468.74 (72,514.78-94,039.33)	67,324.83 (57,214.73-134,607.46)	5,912,670.79
Tocilizumab	534	8,843.20 ± 5,807.16 (8,349.53-9,336.86)	8,412.10 (4,963.44-9,904.10)	4,722,266.67
Leflunomide	2,676	1,683.39 ± 383.02 (1,668.88-1,697.91)	1,185.05 (1,718.94-1,819.54)	4,504,763.39
Celecoxib	6,075	461.88 ± 189.18 (457.12-466.64)	453.24 (403.29-495.12)	2,805,904.94
Methotrexate	22,422	93.14 ± 63.71 (92.31-93.98)	88.51 (65.88-111.66)	2,088,451.34
Abatacept	134	13,785.79 ± 4,607.09 (12,998.58-14,573.00)	13,025.76 (13,021.20-13,030.30)	1,847,296.06
Meloxicam	7,528	158.24 ± 59.55 (156.89-159.59)	166.98 (98.07-199.51)	1,191,229.89
Chloroquine	8,270	128.91 ± 39.84 (128.05-129.77)	142.85 (97.81-144.28)	1,066,088.33
Etoricoxib	2,541	405.69 ± 128.32 (400.70-410.68)	447.99 (349.36-481.10)	1,030,851.51
Infliximab	20	27,471.08 ± 8,353.51 (23,561.52-31,380.65)	30,184.20 (30,184.20-30,186.48)	549,421.67
Diclofenac	3,254	152.53 ± 155.31 (147.19-157.86)	86.66 (27.77-238.14)	496,317.33
Ustekinumab	4	114,029.64	114,029.64	456,118.56
Azathioprine	673	637.03 ± 292.53 (614.89-659.17)	639.98 (406.76-797.60)	428,719.85
Naproxen / esomeprazole	1,083	287.91 ± 122.12 (280.63-295.19)	230.16 (210.01-406.75)	311,802.97
Prednisone	12,467	24.40 ± 74.44 (23.09-25.70)	8.19 (7.75-16.04)	304,164.64
Diclofenac / misoprostol	660	341.30 ± 121.75 (332.00-350.61)	289.78 (241.52-452.18)	225,258.97
Betamethasone	1,043	173.01 ± 151.77 (163.79-182.24)	145.08 (61.95-258.39)	180,454.52
Methylprednisolone	998	165.12 ± 144.97 (156.11-174.12)	114.06 (76.95-215.14)	164,787.69
Cyclosporine	28	4,215.78 ± 1,476.07 (3,643.42-4,788.14)	4,006.48 (3,521.88-5,670.79)	118,041.96
Naproxen	640	150.83 ± 119.27 (141.58-160.09)	105.50 (68.16-199.03)	96,533.14

Active ingredient	Number of items (n)	Mean cost (R) per item ± SD (95% CI)	Median cost (R) per item (IQR)	Total annual medicine item cost (R)
Lornoxicam	292	203.71 ± 158.95 (185.40-222.02)	135.81 (84.76-268.44)	59,482.72
Ibuprofen / paracetamol / codeine	614	77.77 ± 36.30 (74.89-80.65)	87.31 (42.61-97.85)	47,750.64
Ibuprofen / paracetamol / codeine[2]	350	108.38 ± 57.86 (102.30-114.46)	97.85 (71.58-135.30)	37,932.47
Ibuprofen / paracetamol	365	101.47 ± 55.11 (95.80-107.14)	83.48 (64.83-133.25)	37,035.87
Ibuprofen / paracetamol / codeine[3]	388	89.25 ± 34.50 (85.81-92.69)	100.44 (48.76-107.07)	34,628.45
Indomethacin	345	81.61 ± 99.98 (71.02-92.20)	42.75 (15.60-101.86)	28,155.66
Ibuprofen	332	78.77 ± 109.10 (66.99-90.54)	37.42 (18.48-73.29)	26,150.28
Piroxicam	359	66.47 ± 37.44 (62.59-70.36)	60.08 (52.50-68.44)	23,863.96
Paracetamol / orphenadrine	213	57.95 ± 28.91 (54.04-61.85)	60.43 (31.36-68.04	12,343.17
Dexamethasone	68	179.86 ± 115.43 (151.92-207.80)	133.17 (91.96-275.66)	12,230.73
Ketoprofen	51	198.47 ± 27.27 (190.80-206.14)	203.84 (179.47-224.27)	10,121.93
Paracetamol / mephenesin	76	68.78 ±53.83 (56.47-81.08)	53.42 (47.94-62.55)	5,226.99
Ketorolac	50	68.11 ± 39.96 (56.76-79.47)	64.50 (40.15-84.96)	3,405.71
Ibuprofen / codeine	11	66.33 ± 25.65 (49.10-83.57)	55.53 (50.46-92.53)	729.67
Fludrocortisone	3	141.13 ± 6.61 (124.70-157.56)	137.58 (137.04-148.76)	423.39
Ibuprofen / paracetamol[1]	3	74.93 ± 35.92 (-14.31-164.17)	92.91 (33.56-98.31)	224.78

[1]200 mg Ibuprofen / 250 mg paracetamol

[2]200 mg Ibuprofen / 250 mg paracetamol / 10 mg codeine

[3]200 mg Ibuprofen / 350 mg paracetamol / 10 mg codeine

Phase two treatment: RA patients treated with NSAIDs, corticosteroids, DMARDs and biologics

3.4 Impact of comorbidities on the total direct medicine treatment cost of rheumatoid arthritis patients per year

The total annual direct antirheumatic medicine cost related to the most prevalent coexisting CDL conditions in RA patients is depicted in Table 3.1. All costs are based on claims for RA medicines only and are presented as the total annual treatment cost, mean cost per item ± SD and median cost per item with the IQR.

Table 3.1 Total annual direct antirheumatic medicine cost per item relating to the most prevalent coexisting chronic disease list conditions

CDL conditions	Number of antirheumatic medicine items (n)	Total annual treatment cost (R)	Mean cost (R) per item ± SD (95% CI)	Median cost (R) per item (IQR)
Hypertension	16 762	9 124 831.15	544.38 ± 2 983.08 (499.21-589.54)	119.66 (58.65-287.50)
Hypothyroidism	4 340	4 181 827.14	963.55 ± 5 440.29 (801.65-1 125.45)	143.35 (78.19-441.04)
Hyperlipidaemia	3 380	2 547 620.64	753.73 ± 3 567.55 (633.42-874.05)	125.53 (57.14-412.30)
Asthma	1 655	1 932 587.34	1 167.73 ± 3 606.12 (993.86-1 341.59)	142.85 (71.78-439.44)
Bipolar mood disorder	533	469 905.84	881.62 ± 2 946.10 (630.94-1 132.31)	147.54 (97.74-505.57)
Glaucoma	359	282 984.78	788.26 ± 3 045.67 (472.14-1 104.38)	101.77 (57.72-275.92)
Type 2 diabetes mellitus	827	270 058.41	326.55 ± 1 563.35 (219.85-433.26)	117.28 (52.69-172.04)
Cardiac failure	511	124 385.66	243.42 ± 331.81 (214.58-272.25)	95.23 (23.21-408.82)
Epilepsy	327	96 709.07	295.75 ± 368.65 (255.64-335.85)	144.28 (65.87-470.93)
Dysrhythmias	166	56 702.18	341.58 ± 482.56 (267.63-415.53)	89.33 (71.45-441.04)

CDL = chronic disease list; IQR = interquartile range

The total annual direct antirheumatic medicine cost for RA patients with hypertension summed to R9 124 831.15, accounting for 15.4% of the total annual direct medicine cost (N = R59 264 203.68) generated by the study population during 2014. Analysis showed no difference in the mean cost per item among patients with RA only (R746.36 ± 3 846.09) and among those with RA plus hypertension (Cohen's *d* = 0.05). Since the mean (median) cost per medicine item of RA patients with hypertension was relatively low at R544.38 ± 2 983.08 (R119.66), it can be deduced that the high volume of items claimed (n = 16 762), were the main cost driving factor of the direct annual medicine treatment cost in these patients. Previous retrospective healthcare claims analysis performed by Joyce *et al.* (2009) indicated that the annual mean healthcare costs were higher for patients with RA plus CVD than for patients with RA only and for patients with RA plus depression. Osiri and Sattayasomboon (2013:608) documented total direct medical costs from 2008 to 2009 that were two times higher among RA patients with comorbidities than among patients with RA only, hypertension being the most common comorbidity affecting 51.2% (n = 434) of the patients with comorbidities.

Table 3.1 also shows that the mean (median) cost per RA medicine item was the highest among RA patients presenting with asthma, at R1 167.73 ± 3 567.55 (R142.85). However, there was also no difference in the mean cost per antirheumatic medicine item among patients with RA only and among those with RA plus asthma (Cohen's *d* = 0.11). A small volume of items was claimed (n = 1 655) by RA patients with asthma during 2014, therefore the high mean (median) cost per item seem to be the main cost driving factor in these patients' total annual direct antirheumatic medicine cost. According to the literature, little is known about the association between an increase in the healthcare costs of asthma patients and chronic conditions such as RA (Kauppi *et al.*, 2015).

In conclusion, CDL conditions showed no practical significant impact on the total direct antirheumatic medicine cost of RA patients from the study population.

3.5 Chapter summary

Chapter three fulfilled the objectives of the empirical phase of this study by means of the results and discussion. The following chapter concludes the content of this dissertation with the final conclusions based on the objectives, by highlighting the limitations and strengths of the study, and by offering recommendations for future research.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Introduction

The purpose of this final chapter is to review how the objectives of this study, outlined in Chapter 1, were met and to encapsulate the results that were reported in Chapter 3. Finally, it identifies the limitations and highlights the strengths of the study, whilst offering recommendations for future studies.

The aim of this study was to determine the prevalence of RA and associated comorbidities, as well as to investigate antirheumatic medicine prescribing patterns and the impact of comorbidities on the total annual direct medicine cost for patients diagnosed with RA in the private healthcare sector of South Africa.

4.2 Conclusions derived from the literature study

The literature study objectives were to:

- Conceptualise RA in order to form a better understanding of the pathogenesis of the disease.
- Describe the prevalence of RA and associated comorbidities (i.e. type and description), nationally as well as internationally.
- Determine the impact of comorbidities on the total medicine treatment cost (i.e. direct and indirect) of RA.

The conclusions that were drawn after meeting the above objectives are discussed in the following paragraphs.

4.2.1 Conceptualisation of rheumatoid arthritis to form a better understanding of the pathogenesis of the disease

It was established that RA is autoimmune in nature and characterised as an inflammatory disease that may result in the development of comorbidities or systemic complications due to the effect of chronic inflammation (Aletaha *et al.,* 2010:2570; Choy, 2012:v3; Cojocaru *et al.,* 2010:287; Widmaier *et al.,* 2011:661). Arthritis can be mainly classified as inflammatory and non-inflammatory arthritis (Refer to section 2.1.6 and Figure 2.2). Inflammatory arthritis, such as RA, is characterised by marked morning stiffness that lasts longer than 30 minutes and pain that improves with gentle movement of the joints. Non-inflammatory arthritis, such as OA, is characterised by mild morning stiffness that lasts less than 30 minutes and pain that worsens on joint movement (Handa, 2003:191).

Autoimmunity is defined as an abnormal immune response that causes the production of antibodies that act against the body's own healthy cells/tissues (Dictionary for the Health Sciences, 2011:591). The precise aetiology of RA is yet unknown; however, certain genetic, environmental and various other factors have been identified as possible precursors of disease development, e.g. presence of the shared epitope, gender, alcohol consumption, smoking and birth weight (refer to sections 2.1.3.1, 2.1.3.2 and 2.1.3.3). Activation of pro-inflammatory cytokines, T- and B-cells is involved in the multifaceted pathogenesis of RA and is followed by characteristic chronic inflammation (Choy, 2012:v3; Rindfleisch & Muller, 2005:1038). In response, the innate immune system causes antigen presentation via B-cells, macrophages and dendritic cells, and the production of auto-antibodies (e.g. RF, ACPA) and cytokines (e.g. CD8+ T-cells, NK-cells, TNFα, IL-6, IL-1) (Beers *et al.,* 2006:283; Choy, 2012:v4; Wells *et al.,* 2015:26; Widmaier *et al.,* 2011:635). The joint spaces are filled with these inflammatory cells that mediate cartilage destruction, bone resorption via osteoclasts and inhibit cartilage reparation, leading to detrimental end results such as the loss of joint space, ultimately causing irreversible deformity and inability to use the affected joints (Beers *et al.,* 2006:283; McInnes & Schett, 2011:2214; Wells *et al.,* 2015:26).

Rheumatoid arthritis has a typical clinical presentation of bilateral, symmetrical involvement of more than one joint for at least six weeks, most commonly affecting the hands and feet, followed by the onset of prodromal symptoms such as fever or malaise (Beers *et al.,* 2006:284; Wells *et al.,* 2015:26). The ensuing paragraphs outline some of the comorbidities most typically present in RA patients.

4.2.2 Prevalence of rheumatoid arthritis and associated comorbidities (i.e. type and description), nationally as well as internationally

Rheumatoid arthritis is regarded as one of the most common chronic inflammatory arthritis diseases (Arthritis Foundation of South Africa, 2016). Some controversy in terms of reported prevalence exists, which may be ascribed to the difference in methodologies applied or definition of the disease (Lundkvist *et al.*, 2008:S49). The global prevalence of RA is reported at 0.3% to 1%; Western or developed countries report prevalence at 0.5% to 1% and developing countries such as South Africa have a low estimate equal to or less than 0.5% (Choy, 2012:v3; Osiri & Sattayasomboon, 2013:608; WHO, 2016). Although recent prevalence studies on RA in South Africa were difficult to find due to a paucity of information, the CMS documented 3.47 per 1000 beneficiaries from the private healthcare sector of South Africa as having been diagnosed with RA during 2015 (CMS, 2017d). The disease may manifest from any age, but a peak onset has been observed between 40 to 70 years (Baser *et al.,* 2013:2578; Suta *et al.,* 2015:220). An increased prevalence of 2% has been observed among patients 60 years and older (Baser *et al.,* 2013:2578; Lundkvist *et al.,* 2008:S49). Women are usually two to three times more likely than men to be affected by RA (Kourilovitch *et al.,*

2014:26). However, the inequality in the gender ratio seems to decrease with an increase in age (Kvien *et al.,* 2006:213). Other factors such as age, smoking status, disease onset and hormones may also influence the gender distribution of RA (refer to section 2.3).

Various terms are used to refer to comorbidity, for example 'coexisting diseases', 'multiple pathology', 'multi-morbidity', 'co-occurring diseases', 'concomitant diseases' and 'disease clustering' (Meghani *et al.,* 2013:2). For the purposes of this study, 'comorbidity' describes medical conditions that are present at the time of, or after, diagnosis of an index disease, without implying that the medical conditions are an outcome of the index disease (Ording & Sørensen, 2013:200). Rheumatoid arthritis was regarded as the index disease in the present study. The term 'index disease' refers to the main condition under study that has a relatively large impact on the development, course and outcome of the comorbidities present (Meghani *et al.,* 2013:3; Ording & Sørensen, 2013:200). The pathogenesis of RA itself, the effect of medication used for treating RA or mere coincidence may be the cause of comorbidity development (Osiri & Sattayasomboon, 2013:608). According to literature, RA patients usually present with one or more comorbidity (Grøn *et al.,* 2014:870; Marques *et al.,* 2016; Van Onna & Boonen, 2016). The following conditions are among those that most commonly coexist with RA (Al-Bishri *et al.,* 2013; Michaud & Wolfe, 2007; Osiri & Sattayasomboon, 2013; Petri *et al.,* 2010):

- CVD (e.g. hypertension, dyslipidaemia, myocardial infarction and ischemic heart disease);
- diabetes mellitus;
- depression;
- osteoporosis; and
- interstitial lung disease.

Several international studies have been conducted on the prevalence of comorbidities in RA patients. A summary of these studies were presented in Table 2.11. The following paragraph presents the conclusions drawn from this summary.

In each study population, comorbidities were documented among 30% to 60% of every group of patients with RA. Seropositive RA (i.e. when RF is present) was diagnosed in approximately 70% of the overall group of patients with RA. This may support previous claims that RA presents as more severe and destructive with a higher prevalence of comorbidities in patients who test positive for RF (Klareskog *et al.,* 2009:659; Kurkó *et al.,* 2013:172). The medicine utilisation patterns indicate that the majority of the patients in the reviewed studies received DMARD therapy either alone or in

conjunction with NSAIDs and corticosteroids; as expected, biologics had the lowest utilisation rate in every study documented in Table 2.11.

4.2.3 The impact of comorbidities on the total medicine treatment cost (i.e. direct and indirect) of rheumatoid arthritis

Literature describes the economic impact of RA as substantial, with direct medical costs (i.e. the costs of medication, laboratory tests and physician visits) being two to three times higher and indirect medical costs (i.e. the costs of work disability or loss of productivity) three to four times higher than the medical costs of patients without the disease (Baser *et al.*, 2013:2578; Rat & Boissier, 2004:518). For the purposes of this study, only the direct medicine treatment costs of RA were analysed. Although indirect costs have been estimated to be the largest contributing factor to the total economic burden of RA, biologic therapy increases direct medicine costs to the point of it being relatively expensive (Bester *et al.,* 2015:4; Chaudhari 2008:38; Lundkvist *et al.*, 2008:S52). The components that contribute to the burden of RA as a disease were shown in Figure 2.6. 'Burden of disease' comprises of both economic factors (direct and indirect costs) and humanistic factors (disease onset, morbidity, comorbidity development and mortality) (Cutolo *et al.,* 2014:480; Lajas *et al.,* 2003:64; Owens, 2014:S145).

Furthermore, the presence of comorbidities in RA patients contributes to a considerable proportion of the increases in the average and aggregate healthcare expenditure of these patients (NRAS, 2012). Rheumatoid arthritis patients with comorbidities may have direct medical costs that are two times higher than the costs of RA patients without any comorbidities (Osiri & Sattayasomboon, 2013:611). Depression is an example of a common comorbidity in RA patients that has significant effects on indirect treatment costs due to loss of work productivity (Sokka *et al.,* 2013:243). It was also reported that RA patients with depression and CVD have direct healthcare costs that are 1.2 times higher than the costs of patients with RA only (Joyce, 2009:750). In addition, biologic therapy utilisation in RA patients with comorbidities causes direct treatment costs to increase 3.3- to 4.5-fold (Baser *et al.,* 2013:2582). Apart from the high medicine costs per biologic item, several studies also indicate an increase in the direct healthcare costs of RA patients with comorbidities to be the result of changes in the treatment regimen, for example switching from first-line to second-line biologic therapy (Meissner *et al.,* 2014; Rosenblatt *et al.,* 2013:A222; Wang *et al.,* 2012:A35). Aggregate healthcare costs in these RA patients are directly proportional to an increase in the number of comorbidities present (Mikuls, 2003:729).

4.3 Conclusions derived from the empirical study

The objectives of the empirical study were to:

- Establish the prevalence of RA as well as comorbidities associated with RA from the medicine claims database.

- Evaluate antirheumatic medicine prescribing patterns in RA patients and estimate the total annual direct medicine cost of RA.

- Determine the impact of comorbidities on the total direct medicine treatment cost of RA patients per year.

The conclusions derived from the empirical investigation are discussed in the following paragraphs.

4.3.1 Prevalence of rheumatoid arthritis and associated comorbidities, as indicated by the medical claims database

The empirical objective to establish the prevalence of RA and associated comorbidities was achieved and reported in manuscript 1, entitled: **"Chronic disease list conditions in patients with rheumatoid arthritis in the private healthcare sector of South Africa"**. This manuscript was submitted and published in the *Rheumatology International* journal (refer to Annexure E). The aforementioned objective was met by means of a retrospective, cross-sectional medicine claims data analysis.

The study population included 4352 RA patients, representing 0.5% of the total number of beneficiaries on the medical claims database in 2014 (N = 838 618). This number is in accordance with the reported global prevalence of RA that varies between 0.3% and 1% (WHO, 2016). According to the SARAA, the prevalence of RA was the highest in the private healthcare sector of South Africa in 2015 compared to the prevalence of ankylosing spondylitis, juvenile idiopathic arthritis and psoriatic arthritis (Van Duuren, 2017). It was concluded that three times more women (n = 3257) was diagnosed with RA compared to men (n = 1095) on the database for 2014. This is similar to the literature findings on the gender distribution of RA (Alamanos & Drosos, 2005:133; Al-Bishri *et al.,* 2013:12). Various factors may account for the gender distribution within rheumatic conditions (refer to section 2.3), including hormonal influences in a genetically susceptible person, the age of disease onset and smoking status (Suta *et al.,* 2015:223). In the present study, information on these covariates was not available and therefore they could not be adjusted for. Overall, patients had a mean age of 60 years. Literature reports a peak onset of disease between 40 and 70 years, and an increased prevalence at the age of 60 years and older (Baser *et al.,* 2013:2578; Lundkvist *et al.,* 2008:S49; Suta *et al.,* 2015:220).

The majority of RA patients (69.3%) presented with at least one coexisting CDL condition. The mean number of coexisting CDL conditions was the highest among older RA patients. Patients with RA

plus coexisting CDL conditions were approximately 10 years older than the patients with RA only. Literature suggests that aging and increasing life expectancies contribute to the increased burden of comorbidity development (Meghani *et al.,* 2013:5; Parekh *et al.,* 2011:461). Hypertension was the single most prevalent coexisting CDL condition (47.5%), followed by hyperlipidaemia (25.9%), hypothyroidism (19.7%), type 2 diabetes mellitus (11.4%), asthma (7.8%), cardiac failure (3.8%), glaucoma (2.5%), dysrhythmias (2.2%), epilepsy (2.1%) and bipolar mood disorder (1.9%). According to the literature, RA patients have a 1.5- to 2.0-fold increased risk of developing CVD (i.e. dyslipidaemia, hypertension, ischaemic heart disease) (Turesson, 2016). The odds of men having co-present CVD risk factors (e.g. a combination of hyperlipidaemia, hypertension and type 2 diabetes mellitus) were practically significant, but, decreased 2.5-fold in patients who were also diagnosed with hypothyroidism. Furthermore, it was concluded that hypothyroidism was an important discriminating factor for comorbidity in men with RA. These findings are in line with those of a recent study that indicate a possible association between thyroid disease and metabolic syndrome traits, such as the abovementioned combination of hyperlipidaemia, hypertension and type 2 diabetes mellitus (Burger *et al.,* 2017:92).

In its summary of the relevant findings, this section has met the first objective of the empirical investigation, which pertained to the prevalence of RA and coexisting CDL conditions.

4.3.2 Antirheumatic medicine prescribing patterns and the total annual direct medicine cost of rheumatoid arthritis

The empirical objective of evaluating antirheumatic medicine prescribing patterns and estimating the total annual direct medicine cost of RA in the private healthcare sector of South Africa was achieved and reported on in manuscript two, entitled: **"Antirheumatic prescribing patterns and direct medicine costs in the South African private health sector"**. This manuscript was submitted to *Value in Health Regional Issue* (refer to Annexure F). The study was based on a retrospective, cross-sectional drug utilisation review of medicine claims data.

Overall, the population consisted of elderly patients with a mean age of 60 years. Within disease group analysis showed that the patients who received phase one treatment (i.e. NSAIDs and corticosteroids only) were approximately 10 years older than the patients on phase two treatment (i.e. NSAIDs, corticosteroids, and DMARDs or biologics); Cohen's *d*-values approached medium levels and were therefore not practically significant. Literature findings suggest that less intensive treatment regimens, such as NSAIDs and corticosteroids, are reserved for older populations due to concerns regarding the safety and efficacy of DMARD and biologic therapy in the elderly (Köller *et al*., 2009:1575; Van Onna & Boonen, 2016). The majority of the study population (87.2%) received phase two treatment during 2014. The use of originals without available generic equivalents were

much higher among patients on phase two treatment compared to patients on phase one treatment. According to Gray (2009:17), an increase in generic equivalent utilisation may be fortified by the promotion of generic equivalent substitution. The low utilisation rate of generic equivalents among RA patients receiving phase two treatment might be an indication of poor promotion of generic equivalent substitution to the prescribers, pharmacists/dispensers and/or the patients.

The most commonly prescribed medicine items (i.e. the DU90% segment) for patients on phase one treatment were, in descending order, celecoxib, meloxicam, prednisone, diclofenac, etoricoxib, piroxicam and diclofenac/misoprostol. For phase two treatment it was methotrexate, prednisone, sulphasalazine, chloroquine, meloxicam, celecoxib, diclofenac, leflunomide, etoricoxib, naproxen/esomeprazole, betamethasone and methylprednisolone. Medicine claim patterns were compared to the South African therapeutic algorithm for RA, showing adherence to the guidelines. The course of therapy, including the initiation of biologic treatment in some patients, was outside the scope of this study. Future studies may, however, focus on the course of therapy (refer to the Recommendations).

The total annual direct medicine cost of RA treatment accounted for 1.5% (N = R59 264 203.68) of the total medicine expenditure on the medicine claims database for 2014. Phase two treatment constituted 98.0% of this cost. This is in line with other studies showing that specialty medicines (e.g. biologics) may account for 50% to 80% of total annual drug costs (Gleason *et al.,* 2013:542; Klimeš *et al.,* 2014:79; Osiri & Sattayasomboon, 2013:611; Silverman, 2006:25). It was concluded that DMARDs and biologics were overall the main drivers of antirheumatic medication treatment costs during 2014, with DMARDs representing the highest volume of items claimed. Biologics had the lowest utilisation rate, but represented the highest direct medicine cost component at 62.0% (n = R36 731 924.40) of the total medicine expenditure among RA patients. This was similar to the findings in Osiri and Sataysomboon's (2013:611) study, where biologics accounted for 2.5% and DMARDs for 75.0% of the medicine used.

In conclusion, this section established antirheumatic medicine prescribing patterns and the total annual direct treatment cost of RA in the private healthcare sector of South Africa in 2014 on grounds of data obtained from the PBM Company's database. This study adds to the limited literature on the economic burden suffered by RA patients in the private healthcare sector of South Africa.

4.3.3 The impact of comorbidities on the total direct medicine treatment cost of rheumatoid arthritis patients per year

The total annual direct medicine treatment cost of RA patients with coexisting CDL conditions was nearly twice the total annual direct medicine treatment cost of patients with RA only; however, the number of RA patients with coexisting CDL conditions was 2.3 times higher than the number of

patients with RA only. Cohen's *d*-value indicated no practical significance in the mean cost per item among patients with coexisting CDL conditions and those with RA only.

The most prevalent coexisiting CDL conditions in RA patients accounted for 32.2% of the total annual direct medicine treatment cost, which is comparable to 37.5% from a previous study that also measured the cost of comorbidities in RA patients (Osiri & Sattayasomboon, 2013:611). Literature indicates that CVD has the most significant impact on the total annual healthcare costs of RA patients (Joyce *et al.,* 2009; NRAS, 2012). Hypertension was the most prevalent coexisting CVD in RA patients and the highest contributor, among the other coexisting CDL conditions, to the total annual direct medicine treatment cost. Cohen's *d*-values calculated for the difference in mean costs per item between patients with RA only and patients with RA plus one of the most prevalent coexisting diseases, respectively, approached small levels, indicating no practical significant difference.

In conclusion, similar to a previous study (Osiri & Sattayasomboon, 2013:611), RA itself may be regarded as the major contributing factor to the economic burden of RA patients. Chronic disease list conditions showed no practical significant impact on the total annual direct antirheumatic medicine treatment cost of RA patients from the study population.

4.4 Strengths and limitations of the study

Limiting factors that are applicable to either the literature review or the empirical investigation of the present study are listed below:

- Since data from only one PBM company were used, only medical scheme beneficiaries administered by the specific PBM company were represented in the study. This data represents approximately 11% of the private healthcare sector in South Africa (CMS, 2017e).

- Generalisation of the results to the South African population as a whole was not possible, since the public health sector's data is not available on the database.

- Information such as patients' genetic make-up, presence of RA biomarkers, disease duration, smoking status, alcohol consumption, place of birth and residence, birth weight and diet is not available on the database and therefore could not be adjusted for in prevalence estimations.

- The analysis of data was limited to only the direct medicine cost of antirheumatic treatment, as this is the only information available on the database. The total economic burden, including direct non-medical and indirect costs, could therefore not be determined.

In spite of its limitations, this study contributes to a better understanding of RA which may assist in resolving the under-recognised effect of comorbidities on RA patients. Other strengths of the study are listed below:

- The database employed for analysis comprise of a large number of South African medical scheme beneficiaries from the private health sector (refer to section 1.6.2.2).
- The PBM company ensured the validity and reliability of the data, therefore the assumption was made that the data is correct. The data was, however, checked for outliers and duplications (refer to Chapter 1, section 1.8).
- The study population can be seen as an accurate representation of the total database, considering that it is mandatory to specify accurate ICD-10 codes when claiming reimbursement for CDL conditions (refer to Table 2.3).

4.5 Recommendations

This study highlighted the prevalence of RA and comorbidities, outlined RA medicine prescribing patterns, established the direct medicine cost of antirheumatic treatment and determined the impact of coexisting conditions on the total annual direct antirheumatic medicine cost. As such, it serves as a first step towards determining the economic burden of RA in the private healthcare sector of South Africa. The following recommendations are made for future research:

- The prevalence of RA in the public healthcare sector should be determined in order to comprehend the full burden of RA as it relates to the entire South African population.
- Longitudinal studies should be conducted to determine whether comorbidities are the cause or effect of RA.
- The impact of coexisting conditions (i.e. the medicine utilisation and –cost per patient for the specific coexisting conditions in RA) on the total direct treatment cost for RA patients should be determined.
- Longitudinal studies should be conducted to investigate the course of RA therapy and to investigate the prescribers and/or the patients' perception in terms of generic substitution.

4.6 Chapter summary

This final chapter summarised and concluded the specific objectives as stated for the literature review and empirical investigation. In addition, the strengths and limitations of the study were identified and discussed, and recommendations for future research were made.

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ANNEXURE A: CHRONIC DISEASE LIST OF SOUTH AFRICA

The CMS (2017a) in South Africa indicate the 26 chronic conditions and HIV/AIDS that are covered in a section of the PMBs and are listed below.

Addison's disease
Asthma
Bipolar mood disorder
Bronchiectasis
Cardiomyopathy
Chronic renal failure
Chronic obstructive pulmonary disease
Congestive heart failure
Coronary artery disease
Crohn's disease
Diabetes insipidus
Type 1 diabetes mellitus
Type 2 diabetes mellitus
Dysrhythmia
Epilepsy
Glaucoma
Haemophilia
HIV/AIDS
Hyperlipidaemia
Hypertension
Hypothyroidism
Multiple sclerosis
Parkinson's disease
Rheumatoid arthritis
Schizophrenia
Systemic lupus erythematosus
Ulcerative colitis

ANNEXURE B: REVISED CRITERIA OF THE AMERICAN COLLEGE OF RHEUMATOLOGY 1987

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.
2. Arthritis of three or more joint areas	At least three joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left proximal interphalangeal joints, metacarpophalangeal joints, wrist, elbow, knee, ankle and metatarsophalangeal joints.
3. Arthritis of hand joints	At least one area swollen (as defined above) in a wrist, metacarpophalangeal joints or proximal interphalangeal joint.
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in number two) on both sides of the body (bilateral involvement of proximal interphalangeal joints, metacarpophalangeal joints or metatarsophalangeal joints is acceptable without absolute symmetry).
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxta-articular regions, observed by a physician.
6. Serum RF	Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in < 5% of normal control subjects.
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (OA changes alone do not qualify).

OA = osteoarthritis; RF = rheumatoid factor

For classification purposes, a patient shall be said to have RA if he/she has satisfied at least four of these seven criteria. Criteria one through four must have been present for at least six weeks. Patients with two clinical diagnoses are not excluded. Designation as classic, definite or probable RA is not to be made.

Depicted from Arnett *et al*. (1988:319).

ANNEXURE C: THE 2010 AMERICAN COLLEGE FOR RHEUMATOLOGY/EUROPEAN LEGUE AGAINST RHEUMATISM CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

	Score
Target population: test patients who 1. have at least one joint with definite clinical synovitis (swelling)[1] 2. with the synovitis not better explained by another disease[2] Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)[3]	
A. Joint involvement[4]	
one large joint[5]	0
two - 10 large joints	1
one - three small joints (with or without involvement of large joints)[6]	2
four - 10 small joints (with or without involvement of large joints)	3
< 10 joints (at least one small joint)[7]	5
B. Serology (at least one test result is needed for classification)[8]	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least one test result is needed for classification)[9]	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< six weeks	0
≥ six weeks	0

RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

[1] The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfilment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

[2]Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[3]Although patients with a score of < 6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

[4]Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[5]'Large joints' refers to shoulders, elbows, hips, knees, and ankles.

[6]'Small joints' refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

[7]In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular).

[8]Negative refers to IU values that are ≤ to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ three times the ULN for the laboratory and assay; high-positive refers to IU values that are > three times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.

[9]Normal/abnormal is determined by local laboratory standards.

Depicted from Aletaha *et al.* (2010:2574).

ANNEXURE D: CERTIFICATE OF ETHICAL APPROVAL

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2016-07-19

ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by **Health Research Ethics Committee (HREC)** on **13/07/2016**, the North-West University Institutional Research Ethics Regulatory Committee (NWU-IRERC) hereby **approves** your study as indicated below. This implies that the NWU-IRERC grants its permission that provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Medicine prescribing patterns in a section of the private health sector utilising data from a Pharmaceutical Benefit Management company in South Africa

Sub-study title: Burden of rheumatoid arthritis in the private healthcare sector of South Africa: analysis of medicine claims data

Study Leader/Supervisor: Dr JR Burger
Student: N Olivier

Ethics number:

N	W	U	-	0	0	1	7	9	-	1	4	-	A	1
Institution				Study Number						Year			Status	

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Sub-study

Commencement date: 2016-07-13 **Risk:** Minimal

Continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation up to a maximum period of three years.

Special conditions of the approval (if applicable):

- Translation of the informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The study leader (principle investigator) must report in the prescribed format to the NWU-IRERC via HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, and upon completion of the study*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *Annually a number of studies may be randomly selected for an external audit.*
- *The approval applies strictly to the proposal as stipulated in the application form. Would any changes to the proposal be deemed necessary during the course of the study, the study leader must apply for approval of these amendments at the HREC, prior to implementation. Would there be deviated from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-IRERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the HREC or that information has been false or misrepresented,*
    - *the required amendments, annual (or otherwise stipulated) report and reporting of adverse events or incidents was not done in a timely manner and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

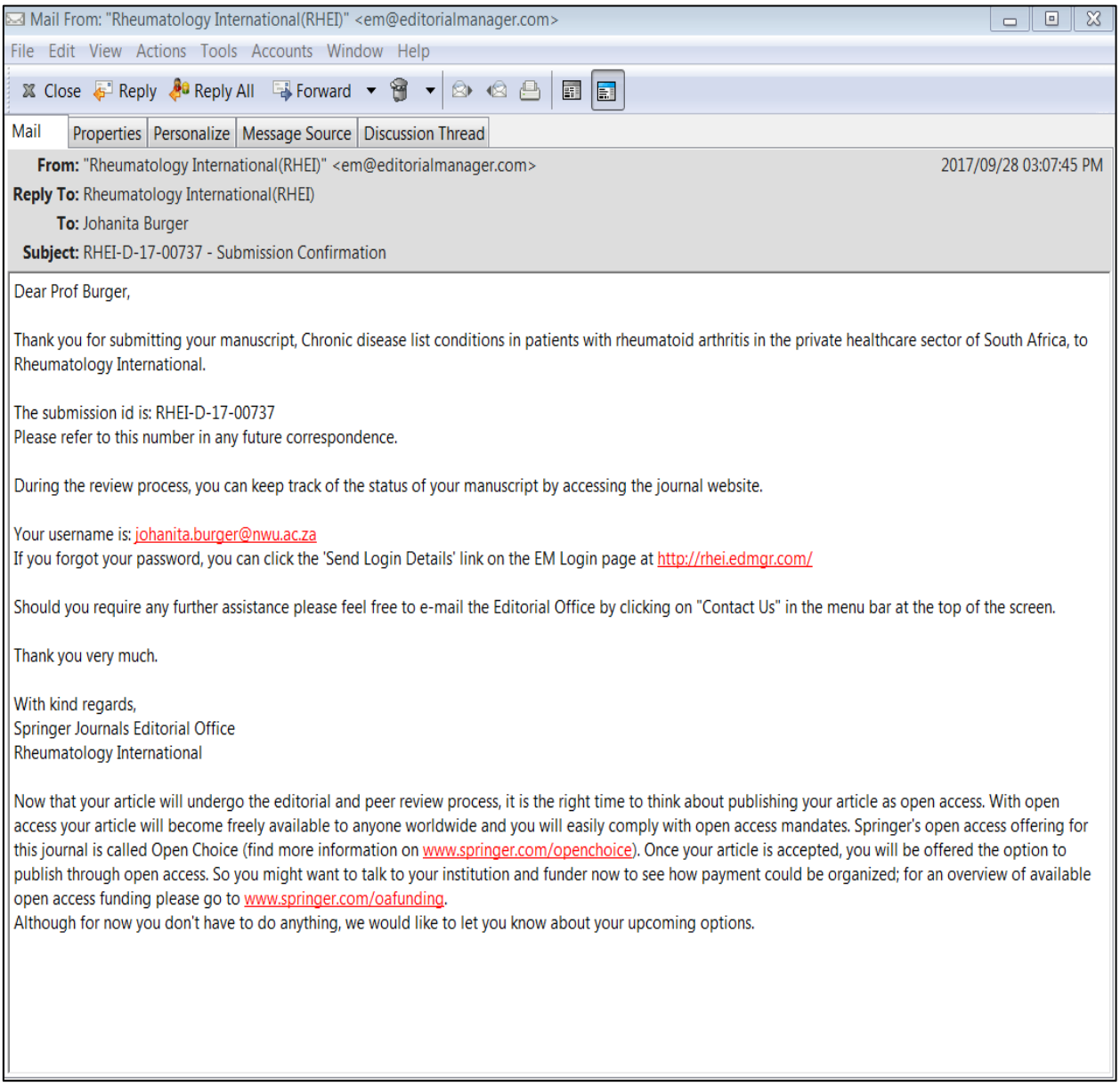
The IRERC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the IRERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Prof LA Du Plessis
Digitally signed by Prof LA Du Plessis
Date: 2016.07.19 16:19:36 +02'00'

Prof Linda du Plessis
Chair NWU Institutional Research Ethics Regulatory Committee (IRERC)

ANNEXURE E: PROOF OF MANUSCRIPT 1 SUBMISSION



Mail From: "Rheumatology International(RHEI)" <em@editorialmanager.com>

File Edit View Actions Tools Accounts Window Help

Close Reply Reply All Forward

Mail Properties Personalize Message Source Discussion Thread

From: "Rheumatology International(RHEI)" <em@editorialmanager.com> 2017/09/28 03:07:45 PM

Reply To: Rheumatology International(RHEI)

To: Johanita Burger

Subject: RHEI-D-17-00737 - Submission Confirmation

Dear Prof Burger,

Thank you for submitting your manuscript, Chronic disease list conditions in patients with rheumatoid arthritis in the private healthcare sector of South Africa, to Rheumatology International.

The submission id is: RHEI-D-17-00737
Please refer to this number in any future correspondence.

During the review process, you can keep track of the status of your manuscript by accessing the journal website.

Your username is: johanita.burger@nwu.ac.za
If you forgot your password, you can click the 'Send Login Details' link on the EM Login page at http://rhei.edmgr.com/

Should you require any further assistance please feel free to e-mail the Editorial Office by clicking on "Contact Us" in the menu bar at the top of the screen.

Thank you very much.

With kind regards,
Springer Journals Editorial Office
Rheumatology International

Now that your article will undergo the editorial and peer review process, it is the right time to think about publishing your article as open access. With open access your article will become freely available to anyone worldwide and you will easily comply with open access mandates. Springer's open access offering for this journal is called Open Choice (find more information on www.springer.com/openchoice). Once your article is accepted, you will be offered the option to publish through open access. So you might want to talk to your institution and funder now to see how payment could be organized; for an overview of available open access funding please go to www.springer.com/oafunding.
Although for now you don't have to do anything, we would like to let you know about your upcoming options.

ANNEXURE F: INSTRUCTIONS FOR AUTHORS FOR THE *RHEUMATOLOGY INTERNATIONAL* JOURNAL

Editorial procedure

Double-blind peer review

This journal follows a double-blind reviewing procedure by experts in the field. Editors are ultimately responsible for weighing reviewer critics and revision or publication decisions that may not abide by reviewer recommendations.

Authors are requested to submit:

- A blinded manuscript without any author names and affiliations. This blinded version should start directly in the introduction. The abstract or the title should be included only in revised versions to highlight changes. Self-identifying text and references that could unblind the authors can be masked by highlighting the text with black pen or by changing the text by XXX.
- A separate title page, containing title, all author names, affiliations, and the contact information of the corresponding author. Any acknowledgements, disclosures, or funding information should also be included on this page.

Types of papers

- Original articles: Word limit 4000 words, 50 references, no more than 6 figures or tables
- Review articles: Word limit 5000 words, 100 references, no more than 6 figures or tables
- Consensus articles: word limit 4000 words, 100 references, no more than 6 figures or tables
- Short Communication: word limit 2000 words, 25 references, no more than 4 figures or tables
- Protocols: word limit 2000 words, 25 references, no more than 4 figures or tables.
- Letters to editor: up to 600 words, 10 references, no more than a figure or table.
- Case Based Reviews: word limit 2500 words, 50 references, no more than 6 figures

Please note:

Rheumatology International no longer accepts Case Reports, neither as Letter to the Editor or as Short Communications. Instead authors are invited to submit a Case Based Review. Case Based Reviews are case reports of extreme clinical interest incorporating a mini literature review in an area of new knowledge; the author should state the search strategy, the flow-chart, and the excluded studies when performing the literature review.

Manuscript submission

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

Permissions

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

Online submission

Please follow the hyperlink “Submit online” on the right and upload all of your manuscript files following the instructions given on the screen.

Title page

The title page should include:

- The name(s) of the author(s)
- A concise and informative title
- The affiliation(s) and address(es) of the author(s)
- The e-mail address, and telephone number(s) of the corresponding author
- If available, the 16-digit ORCID of the author(s)

Abstract

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

Keywords

Please provide 4 to 6 keywords which can be used for indexing purposes.

The keywords should preferably be taken from the Medical Subject Headings (MeSH) thesaurus of the National Library of Medicine of the U.S., which reflect the essence of the submission.

Additional note on abstract

Abstracts of studies must follow the structure: Introduction / Objective – Methods – Results – Conclusion. In addition they must coherent and provide main results in numbers, not just p-values or interpretations. We encourage following guidelines for reporting abstracts (such as those listed in the EQUATOR network library)

Text formatting

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.
- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX.

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

Templates

Templates are available for download below and in the “For authors and editors” section on the journals homepage in order to facilitate the submission process.

Scientific style

Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

We at Rheumatology International heartily encourage the authors to make sure that their manuscripts report the studies in the most appropriate form as recommended by the corresponding reporting guideline.

References

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

- Journal article

Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. doi: 10.1007/s00421-008-0955-8

Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. doi:10.1007/s001090000086

- Book

South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

- Dissertation

Trent JW (1975) Experimental acute renal failure. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations

If you are unsure, please use the full journal title.

For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.

Authors preparing their manuscript in LaTeX can use the bibtex file spbasic.bst which is included in Springer's LaTeX macro package.

Important note on citation

Referring to publicized scientific facts and ideas requires proper citations. Citing widely visible items from ethical sources is strongly advisable. Authors should refrain from referring to retracted items and 'predatory' media. Multiple examples of references to a single fact and abundant (auto) citations to one's own publications should be avoided.

Tables

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.

- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Artwork and illustrations guidelines

Electronic figure submission

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line art

- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

Halftone art

- Definition: Photographs, drawings, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

Combination art

- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

Color art

- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

Figure lettering

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.
- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

Figure numbering

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).

- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,
- "A1, A2, A3, etc." Figures in online appendices (Electronic Supplementary Material) should, however, be numbered separately.

Figure captions

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

Figure placement and size

- Figures should be submitted separately from the text, if possible.
- When preparing your figures, size figures to fit in the column width.
- For most journals the figures should be 39 mm, 84 mm, 129 mm, or 174 mm wide and not higher than 234 mm.
- For books and book-sized journals, the figures should be 80 mm or 122 mm wide and not higher than 198 mm.

Permissions

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may

have occurred to receive these permissions. In such cases, material from other sources should be used.

Accessibility

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)
- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)
- Any figure lettering has a contrast ratio of at least 4.5:1

Please note:

- Pie charts are not acceptable in the journal.
- Bar graphs are only acceptable in the case too many levels of a variable need to be depicted. Use tables with n (%) instead.
- Use graphics only with data that would be too complicated to present in a table.

Electronic Supplementary Material

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as electronic supplementary material, authors should read the journal’s Research data policy. We encourage research data to be archived in data repositories wherever possible.

Submission

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

Audio, video and animations

- Aspect ratio: 16:9 or 4:3
- Maximum file size: 25 GB
- Minimum video duration: 1 sec
- Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

Text and presentations

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

Spreadsheets

Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

Specialized formats

Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

Collecting multiple files

It is possible to collect multiple files in a .zip or .gz file.

Numbering

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
- Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

Captions

For each supplementary material, please supply a concise caption describing the content of the file.

Processing of supplementary files

Electronic supplementary material will be published as received from the author without any conversion, editing, or reformatting.

Accessibility

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that:

- The manuscript contains a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

English language editing

For editors and reviewers to accurately assess the work presented in your manuscript you need to ensure the English language is of sufficient quality to be understood. If you need help with writing in English you should consider:

- Asking a colleague who is a native English speaker to review your manuscript for clarity.
- Visiting the English language tutorial which covers the common mistakes when writing in English.
- Using a professional language editing service where editors will improve the English to ensure that your meaning is clear and identify problems that require your review. Two such services are provided by our affiliates Nature Research Editing Service and American Journal Experts.

Please note that the use of a language editing service is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted.

If your manuscript is accepted it will be checked by our copyeditors for spelling and formal style before publication.

Ethical responsibilities of authors

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation can be achieved by following the rules of good scientific practice, which include:

- The manuscript has not been submitted to more than one journal for simultaneous consideration.
- The manuscript has not been published previously (partly or in full), unless the new work concerns an expansion of previous work (please provide transparency on the re-use of material to avoid the hint of text-recycling ("self-plagiarism")).
- A single study is not split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (e.g. "salami-publishing").
- No data have been fabricated or manipulated (including images) to support your conclusions
- No data, text, or theories by others are presented as if they were the author's own ("plagiarism"). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks are used for verbatim copying of material, and permissions are secured for material that is copyrighted.

Important note: the journal may use software to screen for plagiarism.

- Consent to submit has been received explicitly from all co-authors, as well as from the responsible authorities - tacitly or explicitly - at the institute/organization where the work has been carried out, **before** the work is submitted.
- Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.
- Authors are strongly advised to ensure the correct author group, corresponding author, and order of authors at submission. Changes of authorship or in the order of authors are **not** accepted **after** acceptance of a manuscript.

- Adding and/or deleting authors **at revision stage** may be justifiably warranted. A letter must accompany the revised manuscript to explain the role of the added and/or deleted author(s). Further documentation may be required to support your request.

- Requests for addition or removal of authors as a result of authorship disputes after acceptance are honored after formal notification by the institute or independent body and/or when there is agreement between all authors.

- Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential proprietary data is excluded.

If there is a suspicion of misconduct, the journal will carry out an investigation following the COPE guidelines. If, after investigation, the allegation seems to raise valid concerns, the accused author will be contacted and given an opportunity to address the issue. If misconduct has been established beyond reasonable doubt, this may result in the Editor-in-Chief's implementation of the following measures, including, but not limited to:

- If the article is still under consideration, it may be rejected and returned to the author.

- If the article has already been published online, depending on the nature and severity of the infraction, either an erratum will be placed with the article or in severe cases complete retraction of the article will occur. The reason must be given in the published erratum or retraction note. Please note that retraction means that the paper is **maintained on the platform**, watermarked "retracted" and explanation for the retraction is provided in a note linked to the watermarked article.

- The author's institution may be informed.

Compliance with ethical standards

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest

- Research involving Human Participants and/or Animals
- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

Disclosure of potential conflicts of interest

Authors must disclose all relationships or interests that could influence or bias the work. Although an author may not feel there are conflicts, disclosure of relationships and interests affords a more transparent process, leading to an accurate and objective assessment of the work. Awareness of real or perceived conflicts of interests is a perspective to which the readers are entitled and is not meant to imply that a financial relationship with an organization that sponsored the research or compensation for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

- Research grants from funding agencies (please give the research funder and the grant number)
- Honoraria for speaking at symposia
- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest

- Intellectual property rights (e.g. patents, copyrights and royalties from such rights)
- Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors.

The corresponding author will include a summary statement **on the title page that is separate from their manuscript,** that reflects what is recorded in the potential conflict of interest disclosure form(s).

See below examples of disclosures:

Funding: This study was funded by X (grant number X).

Conflict of interest: Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: Author A, Author B, and Author C declare that they have no conflict of interest.

Research involving human participants and/or animals

1. Statement of human rights

When reporting studies that involve human participants, authors should include a statement that the studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

The following statements should be included in the text before the References section:

Ethical approval: “All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

For retrospective studies, please add the following sentence:

“For this type of study formal consent is not required.”

2. Statement on the welfare of animals

The welfare of animals used for research must be respected. When reporting experiments on animals, authors should indicate whether the international, national, and/or institutional guidelines for the care and use of animals have been followed, and that the studies have been approved by a research ethics committee at the institution or practice at which the studies were conducted (where such a committee exists).

For studies with animals, the following statement should be included in the text before the References section:

Ethical approval: “All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.”

If applicable (where such a committee exists): “All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.”

If articles do not contain studies with human participants or animals by any of the authors, please select one of the following statements:

“This article does not contain any studies with human participants performed by any of the authors.”

“This article does not contain any studies with animals performed by any of the authors.”

“This article does not contain any studies with human participants or animals performed by any of the authors.”

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to

what they have said during a study or an interview, as well as to any photograph that was taken. Hence it is important that all participants gave their informed consent in writing prior to inclusion in the study. Identifying details (names, dates of birth, identity numbers and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scientific purposes and the participant (or parent or guardian if the participant is incapable) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort scientific meaning.

The following statement should be included:

Informed consent: “Informed consent was obtained from all individual participants included in the study.”

If identifying information about participants is available in the article, the following statement should be included:

“Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.”

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After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article.

Online first

The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI. After release of the printed version, the paper can also be cited by issue and page numbers.

ANNEXURE G: PROOF OF MANUSCRIPT 2 SUBMISSION

-------- Original message --------
From: Value in Health Regional Issues <onbehalfof+vihrieditor+ispor.org@manuscriptcentral.com>
Date: 2017/10/24 17:22 (GMT+02:00)
To: Johanita Burger <Johanita.Burger@nwu.ac.za>
Subject: Value in Health Regional Issues - Manuscript ID VIHRI-CEEWAA-2017-0084

24-Oct-2017

Manuscript Number: VIHRI-CEEWAA-2017-0084
Manuscript Title: Antirheumatic prescribing patterns and direct medicine costs in the South African private health sector

Dear Prof. Burger:

Thank you for submitting your above-referenced manuscript to Value in Health Regional Issues.

Your paper will undergo an internal review by our Editors. Papers that are outside of the journal's scope or deemed unsuitable for a formal peer review will be returned to authors promptly (usually within 1-2 weeks). For papers that are sent to external peer reviewers, authors typically can expect to receive a first decision within 6-8 weeks of submission.

If you have any questions about your manuscript, please mention the above Manuscript ID in all future correspondence or when calling the Editorial Office. Alternately, you can log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/vihregionalissues to check the status of your paper or to update your user information as appropriate.

Thank you for again for submitting your manuscript to Value in Health Regional Issues.

Sincerely,

Lyn Beamesderfer
Editorial Office
Value in Health Regional Issues

ANNEXURE H: INSTRUCTIONS FOR AUTHORS FOR THE *VALUE IN HEALTH REGIONAL ISSUES* JOURNAL

Manuscript languages

Value in Health Regional Issues (ViHRI) articles may be published in a language of the region. Acceptable languages for a specific issue are determined by the ViHRI Editorial Board. Acceptable languages for the following issues are below:

- Manuscripts submitted to the Value in Health Regional Issues for Asia 2012 and 2013 issues should be in English.
- Manuscripts submitted to the Value in Health Regional Issues for Latin America may be in English, Spanish or Portuguese.
- Manuscripts submitted to the Value in Health Regional Issues for Central & Eastern Europe, Western Asia and Africa 2013 issue should be in English.

Submission contents

Each submission should contain separate documents as follows:

Cover letter

The cover letter should include: 1) title of the manuscript; 2) name of the document file(s) containing the manuscript and the software (and version) used; 3) name and all contact information for the corresponding author and a statement as to whether the data, models, or methodology used in the research are proprietary; 4) names of all sponsors of the research and a statement of all direct or indirect financial relationships the authors have with the sponsors; and 5) if applicable, a statement that the publication of study results was not contingent on the sponsor's approval or censorship of the manuscript.

Title page

The title page should contain the following: 1) title; 2) full names (first and surname) of all authors including academic degrees and affiliation(s); 3) name, mailing and email addresses, telephone and fax numbers of corresponding author (with whom all correspondence will take place unless other arrangements are made); 4) all sources of financial or other support for the manuscript (if no funding was received, this should be noted on the title page); 5) at least four key words for indexing purposes; and 6) a running title of not more than 45 characters including spaces.

Manuscripts

Manuscripts must be written in English (unless otherwise indicated; see "Manuscript Languages" above for more information), typed in either Microsoft Word (Version 5.0 or later) or WordPerfect (version 5.1 or later). Manuscripts should be in 8.5x11-inch page format, double-spaced with 1-inch margins on all sides and size 10 font (Arial or Times New Roman fonts are preferred). Minimal formatting should be used, i.e., no justification, italics, bold, indenting, etc. There should be no hard returns at the end of lines. Double-spacing after each element is requested (e.g., headings, titles, paragraphs, legends). The 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' should be consulted for specific style issues not addressed here (www.acponline.org, Ann Intern Med 1997;126:36-47). The word count should be less than 4500.

Highlights

Value in Health Regional Issues publishes papers that add to the literature in a substantive way to inform health care decision making. Therefore, during the submission process, authors are asked to identify several "Highlights" that illustrate the paper's contribution to the field. Highlights should not summarize the article, but rather should highlight the novel insights related to value in health care delivery that the paper provides.

1. What is already known about the topic?

2. What does the paper add to existing knowledge?

3. What insights does the paper provide for informing health care-related decision making? (optional)

Abstract

An abstract of 250 words or less is required, summarizing the work reported in the manuscript. Original research manuscripts should use a structured format for the abstract, i.e., Objectives, Methods, Results, Conclusions.

Text

The body of the manuscript should be divided into sections that facilitate reading and comprehension of the material. This should normally include sections with the major headings: Introduction, Methods, Results, Conclusions, Acknowledgments (if needed), and References. There should be no footnotes. Figures (inclusive of figure legends) and Tables must each be submitted as separate documents.

References

References should be listed in a separate section and numbered consecutively with Arabic numerals in the order in which they are cited in the text. Citing unpublished or non-peer-reviewed work such as abstracts and presented papers is discouraged. Personal communications may be indicated in the text as long as written acknowledgment from the authors of the communications accompanies the manuscript. Reference style should follow that of Index Medicus. Spell out single-word journals and abbreviate all others according to the style of Index Medicus. If there are more than four authors, use only the names of the first three, followed by et al.

The three most common types of references are illustrated below for example.

- **Journal article:** Surname and initials of author(s), title of article, name of journal, year, volume number, first and last page.

Arocho R, McMillan CA. Discriminant and criterion evaluation of the U.S.-Spanish version of the SF-36 Health Survey in a Cuban-American population with benign hyperplasia. Med Care 1998;36:766-72.

- **Book:** Surname and initials of author(s)/editor(s), title and subtitle, volume, edition (other than first), city, publisher, year.

Johnston J. Econometric Methods (3rd ed.). New York: McGraw-Hill, 1984.

- **Chapter in book:** Surname and initials of author(s), title of chapter, author(s)/editor(s) of book, title of book, volume, edition (other than first), city, publisher, year.

Luce BR, Manning WG, Siegel JE, et al. Estimating costs in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, et al., eds., Cost-effectiveness in Health and Medicine. New York: Oxford University Press, 1996.

Tables

Tables should be clearly labeled, neatly typed, and easy to understand without reference to the text. Each should be double-spaced and submitted as separate files, independent of the main manuscript file. Statistical estimates should indicate parameter estimates and, as appropriate, t ratios or standard error, statistical significance, sample size, and other relevant information. All abbreviations must be explained below each table. Each table should be numbered and have a self-explanatory title.

Figures

Figures should each be submitted as a separate image file, not embedded in the manuscript document or in a slide presentation. Cite figures consecutively, as they appear in the text, with Arabic numbers (Figure 1, Figure 2, Figure 3A, etc.). If, together with your accepted article, you submit usable color figures then the Journal will ensure, at no additional charge that these figures will appear in color on the Web (e.g., ScienceDirect and other sites) regardless of whether or not these illustrations are reproduced in color in the printed version. There will be a charge for color reproduction in print; you will receive information regarding the costs from Elsevier after receipt of your accepted article. Please indicate your preference for color in print or on the Web only. Each figure must be assigned a brief title (as few words as possible, and reserving abbreviations for the legend) as well as a legend. The corresponding legend should be typed double-spaced on a separate page. All symbols, arrows, and abbreviations must be explained in the legend. Please submit files with a resolution of at least 300 DPI. Line artwork should contain a resolution of least 1000 DPI. Elsevier recommends submitting figures in the following formats: TIFF, JPG, EPS, and PDF. Please be sure to delete any identifying patient information such as name, social security number, etc. Photographs in which a person's face is recognizable must be accompanied by a letter of release from that person explicitly granting permission for publication in the Journal. For any previously published material, written permission for both print and electronic reprint rights must be obtained from the copyright holder. For further explanation and examples of artwork preparation, see Elsevier's Author Artwork Instructions at www.elsevier.com/artwork.

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You may submit appendices that describe either methods or results in more detail if these are needed for clarity of understanding by either peer reviewers or readers. If appropriate, materials suitable for Web publication but not print publication (eg, audio or video files, see below) can also be submitted. If you do so, indicate the particular reasons for the appendix and whether you are submitting it for possible Web publication or simply for peer review purposes. Value in Health Regional Issues accepts audio and video files as ancillaries to the main article. Audio files should be in .mp3 format; the recommended upper limit for the size of a single file is 10 Mb. Video files should be submitted in .mpg or .mp4 format, the recommended upper limit for the size of a single file is 10Mb. Any alternative format supplied may be subject to conversion (if technically possible) prior to online publication.

Survey instrument (if applicable)

For papers analyzing preferences, Value in Health Regional Issues requires the submission of a copy of the survey instrument used to generate the preference data. This is to help in the review process and the survey instrument need not appear in a final publication. If the authors wish the questionnaire to be published with the paper, it should be submitted through ScholarOne Manuscripts as part of the paper. If they do not wish it to be published, it should be submitted through ScholarOne Manuscripts as Supporting Information and then will be sent to the reviewers as a reviewer's appendix.

Submission instructions

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(a) Indicate the study topic and method;

(b) Indicate the disease or disorder studied; and

(c) Upload the following documents:

(i) Cover Page

(ii) Title Page

(iii) Manuscript

(iv) Tables & Figures (use separate document for each table/figure)

(v) Survey Instrument (if applicable)

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For questions on the Central & Eastern Europe, Western Asia and Africa issue, email vihriceewaa@ispor.org

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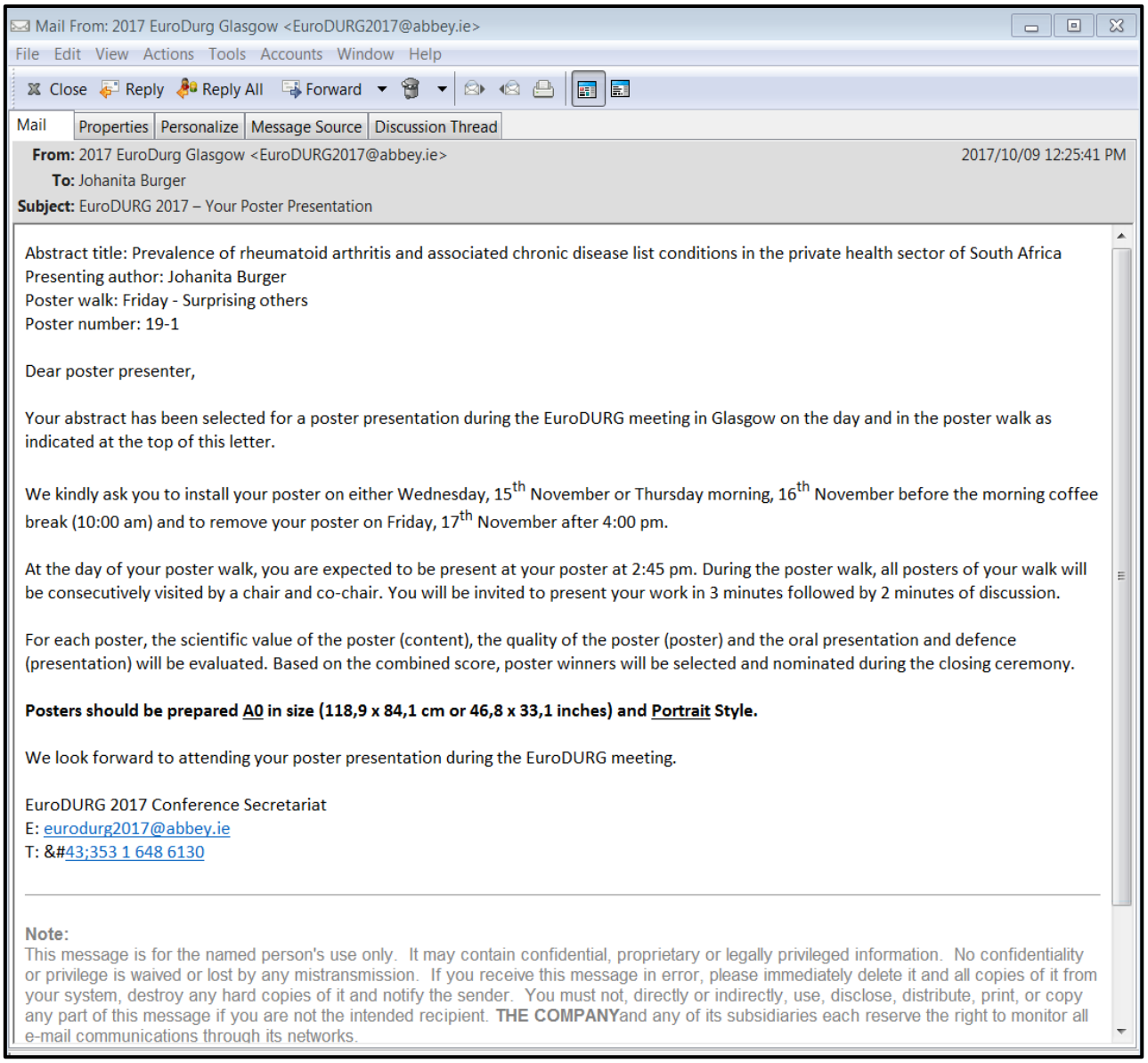
ANNEXURE I: EURODURG 2017 LETTER OF ACCEPTANCE FOR THE POSTER PRESENTATION



Mail From: 2017 EuroDurg Glasgow <EuroDURG2017@abbey.ie>

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From: 2017 EuroDurg Glasgow <EuroDURG2017@abbey.ie> 2017/10/09 12:25:41 PM
To: Johanita Burger
Subject: EuroDURG 2017 – Your Poster Presentation

Abstract title: Prevalence of rheumatoid arthritis and associated chronic disease list conditions in the private health sector of South Africa
Presenting author: Johanita Burger
Poster walk: Friday - Surprising others
Poster number: 19-1

Dear poster presenter,

Your abstract has been selected for a poster presentation during the EuroDURG meeting in Glasgow on the day and in the poster walk as indicated at the top of this letter.

We kindly ask you to install your poster on either Wednesday, 15th November or Thursday morning, 16th November before the morning coffee break (10:00 am) and to remove your poster on Friday, 17th November after 4:00 pm.

At the day of your poster walk, you are expected to be present at your poster at 2:45 pm. During the poster walk, all posters of your walk will be consecutively visited by a chair and co-chair. You will be invited to present your work in 3 minutes followed by 2 minutes of discussion.

For each poster, the scientific value of the poster (content), the quality of the poster (poster) and the oral presentation and defence (presentation) will be evaluated. Based on the combined score, poster winners will be selected and nominated during the closing ceremony.

Posters should be prepared A0 in size (118,9 x 84,1 cm or 46,8 x 33,1 inches) and Portrait Style.

We look forward to attending your poster presentation during the EuroDURG meeting.

EuroDURG 2017 Conference Secretariat
E: eurodurg2017@abbey.ie
T: +353 1 648 6130

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ANNEXURE J: EURODURG 2017 POSTER

Prevalence of rheumatoid arthritis and associated chronic disease list conditions in the private health sector of South Africa

Nericke Olivier[1], Johanita Burger[1], Rianda Joubert[1], Martie Lubbe[1], Adele Naudé[1], Marike Cockeran[2]

[1] Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom Campus, Potchefstroom

[2] Statistics, Statistical and Mathematical Sciences, North-West University, Potchefstroom Campus, Potchefstroom

Introduction and aim

Rheumatoid arthritis (RA) is a debilitating autoimmune disease that causes progressive and chronic joint inflammation, resulting in the development of miscellaneous multisystem coexisting conditions.[1] Epidemiological data with regard to RA in South Africa are limited.[2] The prevalence of coexisting conditions in RA is often overlooked by the public and policy-makers,[3] even though RA patients commonly present with an average of one to two coexisting conditions.[4]

To this end, the aim was to establish the prevalence of RA and coexisting chronic disease list (CDL) conditions in the private health sector of South Africa.

Methods

Study design & Data source:

- Retrospective, cross-sectional design
- Medicine claims data from 1 Jan. 2014 to 31 Dec. 2014; N = 838 618 patients.

Study population:

- Patients with RA, identified using ICD-10 codes (e.g. M05; M06; and M08).

Data analysis:

- RA patients were divided into those with RA only (disease group 1) and those with RA and CDL conditions[5] (disease group 2).

Statistical analysis:

- Descriptive statistics included frequencies (n), arithmetic means, medians, standard deviations (SD) and 95% confidence intervals (CI).
- Independent two-sample *t*-tests were used to compare means.
- *P*-values ≤.05 was considered statistically significant. Cohen's *d*-value was used for effect size; interpreted as small (0.2), medium (0.5) and large (0.8).
- Strength of association between the number of CDL conditions and age were evaluated by the beta coefficient exponentiation (Exp(β)) interpreted as an odds ratio, where 1 = no effect and 0 = practically significant.
- Association between gender and number of CDL conditions were assessed using chi-square distribution models. Cramer's *V* was used as effect size, interpreted as small (0.1), medium (0.3) or large (0.5).
- Association between specific CDL conditions and gender were assessed using logistic regression analysis, expressed as ORs and associated 95% Wald confidence intervals (95% CI). For the univariate model, the independent variable was gender [(female (0), male (1)], with each CDL condition as the dependent variable [with present (1), absent (0)]. An increase in multiple chronic conditions is denoted as a function of ageing; therefore, age was included as covariate for an adjusted model. ORs were interpreted as effect sizes, with OR>2 = moderate effect, and >3.64 as practically significant.

Results

Table 1: Patient demographics

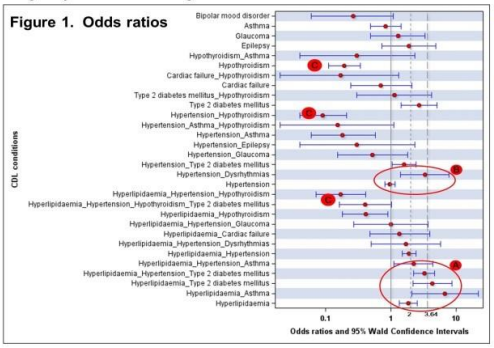
	Total	Female	Male	*p*-value	Cohen's *d*
Number of RA patients, n (%)	4352 (0.5)	3257 (74.8)	1095 (25.2)		
Age (years), mean ± SD (95% CI)	60.32 ± 14.29 (59.90-60.75)	60.40 ± 14.27 (59.91-60.89)	60.09 ±14.38 (59.24-60.95)	0.539	0.022
Disease group 1, n (%)	1336 (30.7)	990 (74.1)	346 (25.9)	< 0.001	
Age (years), mean ± SD (95% CI)	52.96 ± 15.76 (52.11-53.80)	53.24 ± 15.70 (52.26-54.22)	52.16 ± 15.91 (50.47-53.84)	0.271	0.068
Disease group 2, n (%)	3016 (69.3)	2267 (75.2)	749 (24.8)	< 0.001	
Age (years), mean ± SD (95% CI)	63.59 ± 12.26 (63.15-64.02)	63.53 ± 12.35 (63.02-64.04)	63.76 ± 11.96 (62.90-64.62)	0.653	0.019

RA: rheumatoid arthritis; CDL: chronic disease list

- Patients with RA represented 0.5% of the total database for 2014 (N = 838 618)
- Majority (74.8%) were female
- No difference in mean age between men and women (*d* =0.02)
- Patients with CDL conditions were significantly older (*p* <.0001; Cohen's *d* =0.7) (**Table 1**).

- A total of 3796 patients (87.2%) received second-line therapy, of whom 67.8% had other CDL conditions.
- There was no association between gender and whether patients had RA only or RA and other CDL conditions (*p* =0.456; Cramer's *V* =0.011).
- Women had a mean of 1.29 ± 1.18 (95% CI, 1.24-1.33) CDL conditions compared to men (1.29 ± 1.18 (95% CI, 1.22-1.36) (*p* =0.941; Cohen's *d* = 0.003).
- Age had a significant effect on the number of CDL conditions present per patient (p <0.001; Exp(β) =1.013). The size of the effect was highest among patients 52 years and younger, who presented with fewer coexisting CDL conditions (mean number of CDL conditions per patient 1.70; 95% CI 1.62-1.78) compared to patients 61 to 70 years (mean number of CDL conditions per patient 2.49; 95% CI 2.39-2.58) and patients older than 70 years (mean number of CDL conditions per patient 2.72; 95% CI 2.62-2.82).
- The most prevalent CDL conditions present included hypertension (47.5%), hyperlipidemia (25.9%), cardiac failure (3.8%), dysrhythmias (2.2%), hypothyroidism (19.7%), type 2 diabetes mellitus (11.4%), epilepsy (2.1%), asthma (7.8%), and chronic obstructive pulmonary disease (0.9%)
- **Figure 1** shows the univariate ORs for the presence of CDL conditions among females compared with males. Age adjustment had no significant effect on the odds.

Figure 1. Odds ratios



- Figure 1 show that men had higher odds of having hyperlipidemia than women (OR, 1.83; CI 1.33-2.51; *p* < 0.001).
- Although it was not deemed practically significant as a single coexisting CDL condition, hyperlipidemia conferred significant effects on the odds of men having several other CDL conditions, e.g.
  - Asthma (OR, 6.74; CI 2.07-21.93; *p* =0.002),
  - Type 2 diabetes mellitus (OR, 4.31; CI 2.17-8.56; *p* <0.001),
  - Co-prevalent hypertension and type 2 diabetes mellitus (OR, 3.26; CI 2.25-4.71; *p* <0.001).

- Hypertension coexisting with RA alone had no significant effect on the odds and were near unity (OR, 0.96; CI 0.80-1.15; *p* = 0.650); however, in the co-presence of dysrhythmia (OR, 3.30; CI 1.40-7.78; *p* =0.007), the odds of men having both conditions increased to be statistically and practically significant.
- Males had 5.3 times lower odds for prevalent hypothyroidism. This 'advantage' had a significant influence on the odds of men having other CDL conditions that were otherwise deemed practically significant in combination with hyperlipidemia, e.g. odds of having co-present cardiovascular disease risk factors (combination of hyperlipidemia, hypertension and type 2 diabetes mellitus) and hypothyroidism were 2.5 times lower in men than women.

Conclusions

- Our results correspond with the reported statistics of developing countries. The findings of this cross-sectional study revealed strong similarities with regard to evidence from literature and the overall South African population.
- The study may contribute in resolving the under-recognized effect of coexisting conditions present in RA patients, which may provide valuable insight in terms of effective management strategies of these coexisting conditions that can help to reduce the burden of disease in RA patients.

References

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4. Gren, K.L., Ørnbjerg, L.M., Hetland, M.L. *et al.* 2014. The association of fatigue, comorbidity burden, disease activity, disability and gross domestic product in patients with rheumatoid arthritis. Results from 34 countries participating in the Quest-RA program. *Clinical and experimental rheumatology*, 32(6):869-877.
5. Council for Medical Schemes (2017) Which chronic diseases are covered? https://www.medicalschemes.com/medical_schemes_pmb/chronic_disease_list.htm. Accessed 15 May 2017

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ANNEXURE K: LANGUAGE EDITOR'S LETTER

Anneke Potgieter Language Editing & Translation Services

Cell: 076 379 8806

Email: annekeppot@gmail.com

30 October 2017

To whom it may concern

Re: Language editing of dissertation titled "Burden of rheumatoid arthritis in the private health sector: medicine cost and comorbidities"

I hereby declare that I language edited the above-mentioned dissertation by Ms Nericke Olivier (student number 23465174) in October 2017.

Please feel free to contact me should you have any queries.

Kind regards

Anneke Potgieter

Language practitioner

PhD in General Linguistics, Stellenbosch University

ANNEXURE L: TECHNICAL EDITOR'S LETTER

CERTIFICATE OF TECHNICAL EDITING

I, Engela Oosthuizen, declare that the dissertation titled

Burden of rheumatoid arthritis in the private health sector: medicine cost and comorbidities

by

N Olivier

orcid.org/0000-0002-5743-6572

has been checked and corrected technically, which includes figures, tables and the layout of the text as well as the aspects of the contents.

E Oosthuizen

November, 2017