FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH AFRICA)

BY

M. MOCKE-RICHTER

Thesis submitted in fulfilment of the requirements for the degree Philosophiae Doctor in Pharmacology

in the

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF THE FREE STATE
BLOEMFONTEIN

June 2019

PROMOTER: PROF. A. WALUBO
DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF THE FREE STATE

PROMOTER DECLARATION

I, Professor A. Walubo, the promoter of this thesis entitled: Factors influencing the utilization of Biological Medicines in the Free State (South Africa), hereby declare that the doctoral research thesis of this project was done by Martlie Mocke-Richter at the Department of Pharmacology, University of the Free State.

I hereby approve submission of this thesis and also affirm that it has not been submitted previously to this or any other institution or the assessors, either as a whole or partially, for admission to a degree or any other qualification.

24/6/2019

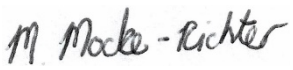
Prof. A. Walubo **Date**

STUDENT DECLARATION

I, Martlie Mocke-Richter, hereby declare that the doctoral research thesis that I herewith submit for the degree Philosophiae Doctor in Pharmacology at the University of the Free State is my independent work and that I have not previously submitted it for a qualification at another institution of higher education. Where help was sought, it has been acknowledged.

I, Martlie Mocke-Richter, hereby declare that I am aware that copyright of this doctoral thesis is vested in the University of the Free State.

I, Martlie Mocke-Richter, hereby declare that all royalties as regards to intellectual property that was developed during the course of and/or in connection with the study at the University of the Free State will accrue to the university.



24.06.2019

....

Ms M. Mocke-Richter **Date**

DEDICATION

I would like to dedicate this thesis to both my parents, Wouter and Sanita Mocke, who have been my consistent inspiration, source of wisdom and support. Words could never describe my appreciation and love towards you. Thank you for providing me with the best education, for your motivation, and for always believing in me, because without you this would not have been possible.

"At the end of the day, the most overwhelming key to a child's success is the positive involvement of parents" – Jane D. Hull

ACKNOWLEDGEMENTS

To God, all the praise, honour and gratitude, because He gave me the ability, the opportunity, the interest and perseverance to complete this study. I bring Him all the glory and honour. Philippian's 4:13: "For I can do everything through Christ, who gives me the strength."

I would like to express my sincere gratitude towards everyone that assisted and guided me throughout the study:

- My promoter, Prof. A. Walubo, Head, Department of Pharmacology, Faculty of Health Sciences, University of the Free State. For his support, valuable advice, contributions, patience and beliefs that I can complete this study. Thank you for spending so many hours assisting me. I have learnt so much from you not only in an academic way, but also life lessons.
- My dear husband, Chris Richter, thank you for your loyal support, encouragement and understanding, during the duration of this study.
- A heartfelt thank you to my dear parents, Wouter and Sanita Mocke, for your never-ending support, loyalty and inspiration.
- My brother Pieter Mocke, thank you for your loyal support and encouragement.
- Dr Luna Bergh (D.Litt. et Phil.), University of the Free State for language editing of the thesis, support and also for her excellent advice with conference presentations.
- Cornel van Rooyen, Bio-statistician, Faculty of Health Sciences, University of the Free State, for his expert advice and analysing of data.
- Ms Elmarie Robberts, for the typing, editing and her meticulous attention to technical detail with this thesis.
- The respondents who participated in this study, for your input. Without your time and cooperation, this project would not have been possible.
- Ms A. Bisschoff for language editing and translation of the abstract.
- To my friends and colleagues specially, Zanelle Bekker and Hanneke van Emmenis for their support and encouragement.
- Free State Department of Health for their support.
- Dr J. Bezuidenhout, Head: Division Health Sciences Education, Faculty of Health Sciences, University of the Free State, for his support during the study.
- The National Research Fund, for financial support.
- The University of the Free State, for their financial support.

LIST OF ABBREVIATIONS

BLys	:	B-Lymphocyte Stimulator
BM	:	Biological Medicines
CD	:	Cluster of differentiation
cf.	:	Confer
CLL	:	Chronic lymphocytic leukaemia
CME	:	Continuing Medical Education
CPD	:	Continuing Professional Development
CTLA	:	Cytotoxic T-lymphocyte Antigen
EGER	:	Endothelial Growth Factor Receptor, Glycoprotein Iib/Iiia Receptor Found On The Human Platelets
IL	:	Interleukin
LCL	:	Large-cell Lymphoma
MME	:	Microtubule Disrupting Agent-Conjugated to Anti – CD30 Antibody
MS	:	Multiple Sclerosis
NHL	:	Non-Hodgkin's Lymphoma
PD1	:	Programmed Cell Death Protein 1
PDGFR	:	Platelet-derived growth factor receptor
PNH	:	Paroxysmal Nocturnal Haemoglobinuria
RA	:	Rheumatoid Arthritis
RANKL	:	Receptor Activator of Nuclear Factor Kappa-B Lignand
RSV	:	Respiratory Syncytia Virus
SAS	:	Statistical Analysis Software
SD	:	Standard deviation
SLAMF7	:	Signaling lymphocytic activation molecule family member 7
SLE	:	Systemic lupus erythematosus
TNF	:	Tumour Necrosis Factor
TNF-α	:	Tumour Necrosis Factor alpha
UCT	:	University of Cape Town
UFS	:	University of the Free State
UP	:	University of Pretoria
US	:	University of Stellenbosch
UKZN	:	University of KwaZulu-Natal
VEGF	:	Vascular Endothelial Growth Factor
VEGFR2	:	Vascular Endothelial Growth Factor Receptor 2
WITS	:	University of the Witwatersrand

TABLE OF CONTENTS

CHAPTER 2:

PART 3 - AN APPROACH FOR DEVELOPING A FRAMEWORK FOR THE USE OF BIOLOGICAL MEDICINES

CHAPTER 3:

STUDY PROTOCOL

CHAPTER 4:

PART 1: PERCEPTION AND KNOWLEDGE OF BIOLOGICAL MEDICINES BY NEWLY QUALIFIED DOCTORS (< 2 YEARS OF PRACTICE)

CHAPTER 4:
PART 2: FACTORS INFLUENCING THE USE OF BIOLOGICAL MEDICINES IN THE FREE STATE: PRESCIRBERS' OPINIONS

CHAPTER 4:
PART 3: FACTORS INFLUENCING THE USE OF BIOLOGICAL MEDICINES IN THE FREE STATE: PATIENTS' OPINIONS

APPENDICES:

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Keywords: Biological Medicines, Monoclonal antibodies, Delphi method

Biological Medicines are substances derived from animal or other biological origin, and are used to treat, diagnose or prevent mainly inflammatory diseases and cancer. The use thereof has grown worldwide and is aimed at improving the quality of life of patients. However, in South Africa access to Biological Medicines remains limited. Unfortunately, the use of Biological Medicines has presented challenges with regard to the requirements for appropriate therapeutic responses and their side-effects. In order to obtain an appropriate therapeutic response, patients have to be selected and continuously monitored during therapy.

The two-fold aim of the study was to identify the factors influencing the utilization of Biological Medicines in South Africa, and to develop a framework for the use of Biological Medicines in South Africa. Therefore, the objective of the study was to determine perception, knowledge of and training in Biological Medicines by clinicians who have been practising for two years or less since graduating and to identify the factors that might influence the prescribing of Biological Medicines by some doctors in the Free State. It was also important to evaluate patient knowledge and experience with Biological Medicines and identify the factors (age, gender, race, disease, patient perception, and adverse effects) that might influence patient compliance with Biological Medicines in some institutions in South Africa. The above mentioned helped to develop a framework for the use of Biological Medicines in South Africa.

A cross-sectional study design was used. The literature review was used as the foundation to compile the questionnaires. The study consists of three different questionnaires, one for the newly qualified doctors, one for the specialists who prescribed Biological Medicines as well as the one for the patients who used Biological Medicines. The Delphi survey consisted of the data generated through the previous phases of the study, which consisted of literature cited, as well as three different questionnaires. For the purpose of this study, the Delphi method was used as a tool for achieving consensus, where experts validated some of the statements and criteria that were used to draft a framework.

As it was, out of the 79 newly qualified doctors in the Mangaung district (Bloemfontein) in the Free State, 79,7% (n = 63) completed the questionnaire. There were 17 specialists that prescribed Biological Medicines in the Free State, and 70,6% (n = 12) of them completed the questionnaire. Biological Medicines do not have more adverse effects than pharmaceutical agents. As it was, out of the 38 patients that used Biological Medicines and were identified by the clinicians, 81,6% completed the questionnaire. In the Delphi questionnaire study, there were 15 panel members that responded out of 20 who received the invitation.

In conclusion, there was general lack of knowledge on Biological Medicines among newly qualified doctors; therefore, there was a need to educate these young doctors, and to offer support in the form of a framework on the use of Biological Medicines to ensure that current patients benefit. The clinicians have limited knowledge of the pharmacology of Biological Medicines and therefore there is still much to be learned about the adverse effects of Biological Medicines. Furthermore, there is a need to educate the prescribers, and to offer support in the form of a framework on the use of Biological Medicines to ensure that current patients benefit and also to improve the procurement process to obtain Biological Medicines. Biological Medicines are improving the quality of life of patients. Seen from above, Biological Medicines had a positive impact on patient lives; therefore, there was a need to make them more available to patients who need them.

The framework containing the findings of the research will be brought to the attention of the Biological Medicine Committee of South Africa, the Medicine Control Council, as well as the National Department of Health. It will furthermore be recommended that the framework that was developed may be adapted by the Health care professionals who prescribed Biological Medicines. The research findings were submitted to academic journals with a view to publication, as well as presented at conferences.

PUBLICATIONS AND CONFERENCE/CONGRESS PRESENTATIONS

1. Mocke-Richter*, M., Walubo, A. & Van Rooyen, C. Perception and knowledge of Biological Medicines by Newly, Qualified Doctors, less than 2 years of experience. This was presented as a poster presentation at the 18th World Congress of Basic and Clinical Pharmacology. 1 to 6 July 2018, Kyoto, Japan. (Appendix I)

2. Mocke-Richter, M. & Walubo, A. Knowledge and attitudes on use of Biological Medicines by South-African Health professionals. This was presented as a podium presentation by M. Mocke-Richter at the First Conference of Biomedical, Natural Science and Therapeutics, 7 -10 October 2018, Spier Wine Estate, Stellenbosch. (Appendix J)

3. Mocke-Richter, M. & Walubo, A. Knowledge and Attitudes concerning use of Biological Medicines by South-African Health Professionals. This was presented by Mocke-Richter, M, as a podium presentation by the 33rd Annual Conference of South-African Association of Hospital and Institutional pharmacist, 7-9 March 2019, Champaign Resort, Drakensberg. (Appendix K)

4. Mocke-Richter, M. & Walubo, A. Perception and Knowledge on Biological Medicines by Newly Qualified Doctors in the Free State (South-Africa). This article was submitted to Advance in Therapy journal. We are waiting for feedback (Appendix L)

FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH AFRICA)

CHAPTER 1

GENERAL INTRODUCTION

Biological Medicines are substances (serum, antibodies, cytokines, etc.) derived from animal, human and recombinant human products or other biological sources, and used to treat, diagnose or prevent disease. Over the past ten years, Biological Medicines have become more available for clinical use (Aubin *et al.,* 2013). Their clinical effectiveness of has been extremely significant and this success has driven the development of increasing numbers of Biological Medicines (Lee & Kavanaugh 2005) for a wide variety of illnesses or disorders. Monoclonal antibodies and cytokines are used for the treatment of immune diseases, tumours and inflammatory conditions such as cancer and rheumatoid arthritis (Aubin *et al.,* 2013).

Unfortunately, the use of Biological Medicines has presented challenges (Heinen-Kammerer *et al.,* 2007; Banacloche & Weinberg 2007). Clinical response to drugs varies usually between patients and depends on disease characteristics including presence of autoantibodies, disease activity and severity. Characteristics of the patient-such as gender, age, body mass index, other drugs in use, or smoking-also play a role in the variability between patients (Daïen & Morel 2014). Cytokine levels, immune cell phenotypes and genetic background could also influence response (Daïen & Morel 2014). Because Biological Medicines are target specific and mimic the physiological actions of the respective endogenous compounds, they require appropriate patient selection, which involves preliminary and continuous testing for monitoring response and safety during therapy (Heinen-Kammerer *et al.,* 2007; Banacloche & Weinberg 2006).

Continuous testing and monitoring for response is essential, because the appropriate duration of treatment for some Biological Medicines is still undetermined (Scherer *et al.,* 2010). The clinical response to Biological Medicines varies between patients (Daïen & Morel 2014). On the other hand, the side-effects of some Biological Medicines are still not well documented. Whereas some of the side-effects are immunologic in nature, and some are related to the actions of the respective Biological Medicines, they are more complex than initially thought. The side-effect profile of Biological Medicines does not fit into the current

pharmaceutical-based paradigm (Lee & Kavanaugh 2005). For instance, the occurrence and severity of some of the side-effects may differ according to the underlying disease or patient (Aubin *et al.,* 2013). Therefore, appropriate use of Biological Medicines requires cautious selection of suitable patients and identification of risk groups in order to reduce the incidence of adverse events among patients (Weber 2004). Even then, patient selection is also complicated by the fact that some of the diagnostic tests are still limited and not well standardized on large populations (Scherer *et al.,* 2010). Lastly, the use of Biological Medicines is costly and this is not only in respect of the drug but also of all the requirements for its appropriate use, creating another hurdle for the prescription thereof (Heinen-Kammerer *et al.,* 2007; Pichler 2006; Rodney 2014).

Immune cell phenotypes, cytokine levels and genetic background influence biological therapy response (Daïen & Morel 2014). Therapeutic response and toxicity to Biological Medicines may vary in different populations or individual patients (Rodney 2014). This implies that appropriate use of any Biological Medicines requires adequate knowledge - not only of its pharmacology, but also of the factors that determine appropriate response and safety, i.e., patient population demographics, diagnosis or disease disorder, and the prior use of Biological Medicines (Pichler 2006; Rodney 2014). It is therefore of utmost importance for a clinician to take such factors into consideration before Biological Medicines can be utilised to the patient's advantage (Salvana & Salata 2009). Pharmacokinetic and drug concentration is influenced by characteristics of the patient such as gender, age, liver and renal functions, smoking status and body mass index (Daïen & Morel 2014).

It is envisaged that such knowledge would empower clinicians to search for major determinants of response and toxicity in their local populations of patients. Unfortunately, this information is still not generally available in standard textbooks or literature (Lee & Kavanuagh 2005). Therefore, the two-fold aim of the study was to identify the factors influencing the utilization of Biological Medicines in South Africa, and to develop a framework for the use of Biological Medicines in South Africa.

CHAPTER 2

LITERATURE REVIEW: PART 1 - AN OVERVIEW OF THE PHARMACOLOGY OF BIOLOGICAL MEDICINES

The aim of Chapter 2, Part 1, is to provide an overview of the pharmacology of Biological Medicines.

2.1 PHARMACOLOGY OF BIOLOGICAL MEDICINES

Biological Medicines are substances (serum, antibodies, cytokines, etc.) derived from animal products or other biological sources and used to treat, diagnose or prevent disease or disorders. They are large complex molecules, structurally similar to autologous proteins (cf. Figure 2.1) that are currently produced using molecular genetics techniques and purified from engineered cells. Unlike pharmaceutical medicines, Biological Medicines are not metabolized, but are digested and processed in a similar way to the endogenous proteins (Pichler 2006).

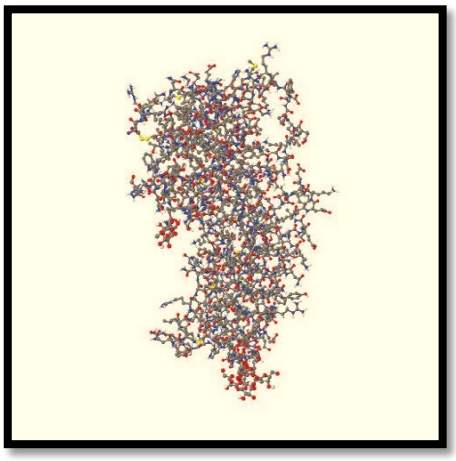


Figure 2.1: Example of a Protein structure from RCSB Protein data bank (Identifier #AU1)

2.2 EXAMPLES OF BIOLOGICAL MEDICINES

Monoclonal antibodies used for treatment of breast cancer (e.g. HER2/neu receptor monoclonal antibody for HER2 positive breast cancer), rheumatoid arthritis and psoriasis (e.g. tumour necrosis factor-alpha blockers - receptor antagonists and antibodies), and inflammatory bowel disease.

Cytokines and growth factors used for treatment of multiple sclerosis (e.g. interferons), diabetic foot ulcers (e.g. topical platelet-derived growth factor), and chemotherapy-induced neutropenia (e.g. granulocyte colony stimulating factor) or erythropoietins for anaemia.

Botulinum neurotoxins; focal upper-limb spasticity and focal dystonias such as cervical dystonia and blepharospasmand chronic migraine (e.g. Onabotulinumtoxin A).

2.2.1 Monoclonal antibodies

In 1975, monoclonal antibody technology became a practical application due to the development of immortalized antibody-secreting hybrid cells (Kohler & Milstein 1975). The first monoclonal antibody, muromonab, was approved by the Food and Drug Administration (FDA) in 1986.

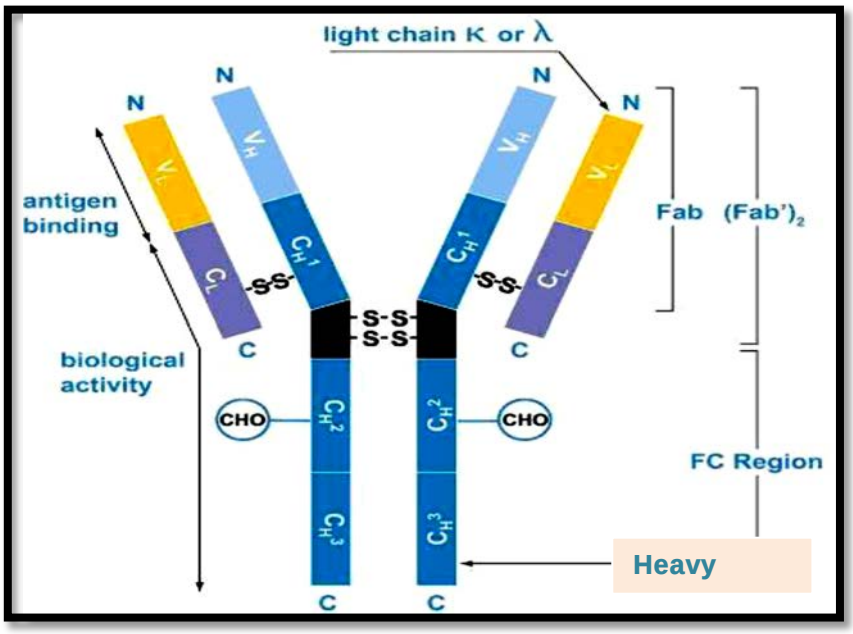


Figure 2.2: Schematic presentation of an immunoglobulin molecule
(Available from: https://www.microbiologybook.org/mayer/IgStruct2000.htm)

Each immunoglobulin molecule is composed of two light and two heavy chains, respectively, which are connected by four disulphide(s-s) bridges. The light chain consists of two subclasses, namely κ or ʎ. Antibody-mediated immunity involves a class of immunoglobulins called antibodies. An antibody molecule is Y-shaped with two identical antigen-binding sites or Fab at the end of the Y. The Fc-region does not have antigen-binding functions and is responsible for its biological activity (Harris *et al.,* 1992).

The first monoclonal antibody was generated from mouse cells by a process called hybridomatechnology. Unfortunately, mouse antibodies are regarded as foreign by the human immune system, hence a side effect may be provoked in order to attempt getting rid of these antibodies (Protein Design Laboratory BioPharmaInc 2015). Over time, molecular and cellular strategies have been applied to replace some parts of the mouse antibody protein with more human components (Rodney 2013). This approach has led to the development of chimeric monoclonal antibodies, which consist of a mixture of mouse and human components (Protein Design Laboratory BioPharmaInc 2015). To date, there are a few monoclonal antibodies that are completely human (Protein Design Laboratory BioPharmaInc 2015).

Monoclonal IgG is derived from expansions of a particular clone of IgG-producing cells that present monospecific antibodies. These monospecific antibodies derived from a single, immortal cell clone are monoclonal antibodies (Rodney 2013).

Humanized therapeutic monoclonal antibodies mostly derived from a human source replaced all mouse amino acids, except for the hypervariable complementarily determining regions, which are murine (Imai & Takaoka 2006).

Recombinant monoclonal antibody technology is a field that enables the improvement of antibody properties by genetic engineering (Donzeau & Knappik 2007). Human recombinant cells produce most humanized, chimeric and human antibodies, using fermentation technologies, as well as the recombinant mouse myeloma cells designed to manufacture human IgG (Rodney 2013). A general answer for applications in which an antibody is only used to block the signalling molecule, is the use of antibody fragments that do not have the Fc domain (Holilinger & Hudson 2015).

2.2.1.1 *Different types of monoclonal antibodies*

Monoclonal antibodies can be divided into different types that are used for the treatment of cancer.

2.2.1.2 *Naked monoclonal antibodies*

Naked monoclonal antibodies are the monoclonal antibodies that are used most, and have no drug or radioactive material attached to them. Naked monoclonal antibodies attach to specific antigens on cancer cells, but several work by binding to antigens on other non-

cancerous cells, or free-floating proteins (Adams & Weinar 2005). They work this in different ways, for example:

Alemtuzumab is an antibody, which combats the CD52 antigen, which is found on cells called lymphycytes. Once the antibody is attached it attracts the immune cells to destroy these cells.

Trastuzumab is an antibody, which neutralises HER2 protein. A large quantity of HER2 proteins are present on tumour cells in several cancers. If HER2 protein is activated, the tumour cell grows, Trastuzumab prevents these proteins from becoming active.

Bevacizumab targets a protein with the name VEGF. Bevacizumab blocks VEGF that have an influence on tumour cells to develop more blood vessels to feed tumour cell growth (Rodney 2013).

2.2.1.3 *Conjugated monoclonal antibodies*

Monoclonal antibodies joined to radioactive particle, chemotherapy drugs, or cancer killing agents, are called conjugated monoclonal antibodies (Adams & Weinar 2005).

An example of a radiolabelled monoclonal antibody is Ibritumomab tiuxetan that is an antibody counteracting the CD20 antigen that is focused on B-cells (Rodney 2013).

An example of chemolabelled monoclonal antibodies is Brentuximab vedotin. Chemolabeled monoclonal antibodies have chemotherapy or other drugs attached to the antibody (Rodney 2013).

Anti-tumour activity can be demonstrated by immunotoxins consisting of recombinant antibody fragments conjugated to catalytic toxins, and radioimmunoconjugates directed against CD20 show substantial anti-tumour activity (Adams & Weinar 2005).

2.2.1.4 *Bispecific monoclonal antibodies*

Bispecific antibodies are a class of antibody-like proteins and engineered antibodies that combine two different specific antigen-binding elements into a single construct (Gunasekaran *et al.,* 2010).

Table 2.1 and 2.2 refer to currently available Biological Medicines worldwide; South Africa has limited access to some of the drugs.

Table 2.1: Biological Medicines targeting lymphocyte surface markers (Jameson *et al.*, 2018; Rodney 2013; Salvana & Salata 2009)

CHEMICAL NAME	TARGET	ANTIBODY TYPE	INDICATION
Alefacept	CD2	CD2-bp-Fc Fusion	Psoriasis
Alemtuzumab	CD52	Humanized unconjugated	B-cell chronic lymphocytic leukaemia, transplant, multiple sclerosis
Atezolizumab	CD274	Humanized	Metastatic urothelial carcinoma
Basiliximab	CD25	Chimeric IgG1	Allograft rejection
Belatacept	CD80/CD86	CD80/8-r-Fcfusion	Kidney transplant (to prevent rejection)
Blinotumumab	CD19 & CD3	Mouse	Acute lymphoblastic leukaemia
Brentuximab vedotin	CD30	Chimeric IgG1	Hodgkin's lymphoma, systemic anaplastic large cell lymphoma
		MME-Conjugated	Hodgkin's lymphoma, systemic anaplastic large cell lymphoma
Britumomab-tiuxetan	CD20	Mouse IgG1	Non-Hodgkin's lymphoma
Daclizumab	CD25	Humanized IgG1	Allograft rejection
Daratumumab	CD38	Human	Multiple myeloma
Efalizumab	CD11a	Humanized IgG1	Chronic moderate to severe plaque psoriasis
Fanolesomab	CD15	Mouse IgM	Imaging of patients with equivocal signs and symptoms of appendicitis
Gemtuzumab-ozogamicin	CD33	Humanized IgG4 conjugate	Acute myeloid leukaemia
I-tositumomab	CD20	Non-Hodgkin's	Mouse IgG2a
Muromonab-CD3	CD3	Mouse IgG2	Allograft rejection
Obinutuzumab	CD20	Humanized	Follicular lymphoma, Chronic lymphycytic leukemia
Ofatumumab	CD20	Human IgG1	Chronic lymphoctytic leukemia
Rituximab	CD20	Chimeric IgG1	Non-Hodgkin's lymphoma

BLys - B-lymphocyte stimulator, CD - lymphocyte surface marker, CTLA cytotoxic T-lymphocyte antigen, EGFR – endothelial growth factor receptor, glycoprotein IIb/IIIa receptor found on the human platelets, IL- interleukin, LCL – Large-cell lymphoma, MME- microtubule disrupting agent-conjugated to anti – CD30 antibody, MS – multiple sclerosis, NHL – non-Hodgkin's lymphoma, PD1- Programmed cell death protein 1, PNH, paroxysmal nocturnal hemoglobinuria, RA – rheumatoid arthritis, RANKL- receptor activator of nuclear factor kappa-B lignand, RSV- respiratory syncytia virus, SLAMF7- Signaling lymphocytic activation molecule family member 7, SLE-systemic lupus erythematosus, TNF-α – tumour necrosis factor alpha, VEGF vascular endothelial growth factor, VEGFR2- vascular endothelial growth factor receptor 2

Table 2.2: Biological Medicines targeting other structures (Jameson *et al.*, 2018; Rodney 2013; Salvana & Salata 2009)

CHEMICAL NAME	TARGET	ANTIBODY TYPE	INDICATION
Abagovomab	CA-125	Mouse	Ovarian cancer
Abatacept	CTLA-4-r	CTLA-Fc fusion	Second line treatment for active rheumatoid arthritis

CHEMICAL NAME	TARGET	ANTIBODY TYPE	INDICATION
Adalimumab	TNF	Human IgG1	Used for Rheumatoid arthritis, Ulcerative colitis
Abciximab	IIIa receptor Glycoprotein IIB /	Chimeric Fab	Coronary angioplasty Antiplatelet
Belimumab	B-cell stimulator BLys	Human IgG1	SLE
Bevacizumab	VEGF	Humanized IgG1	Metastatic carcinoma of the colon or rectum, metastatic cervical cancer
Canakinumab	1L-1ββ	HumanbIgG1	Cryopyin-associated periodic syndromes
Certolizumab	TNF-α	Humanized Fab PEG	Rheumatoid arthritis, Crohn's disease
Cetuximab	Extracellular domain of EGFR	Chimeric IgG	Metastatic colorectal carcinoma
Denosumab	Human RANKL	Humanized IgG2	Postmenopausal osteoporosis, chemotherapy, and bone metastasis-related bone loss
Dinutuximab	Chimeric	Ganglioside GD2	Paediatric patients with high-risk neuroblastoma
Eculizumab	Complement protein C5	Humanized IgG2	Paroxysmal nocturnal hemoglobinuria and atypical haemolytic uremic syndrome
Elotuzumab	SLAMF7	Humanized	Multiple myeloma
Etanercept	TNF	TNFr-Fc fusion	Active rheumatoid arthritis
Golimumab	TNF-α	HumanbIgG1	Rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
Infliximab	TNF-α	Chimeric IgG1	Crohn's disease
Ipilimumab	CTLA-4	Human IgG1	Metastatic melanoma
Idarucizumab	Dabigaatran	Humanized	Reversal of anticoagulant effects of dabigatran
Natalizumab	α4-subunit ofintegrins	Humanized IgG4	Multiple sclerosis
Necitumumab	EGFR	Human	Metastatic squamous non-small cell lung cancer
Nivolumab	PD-1	Humanized	Hodgkin lymphoma, Metastatic non-small cell lung cancer, Metastatic melanoma
Omalizumab	Human IgE	Humanized IgG1	Moderate to severe persistent asthma
Olarutumab	PDGFR-α	Humanized	Soft Tissue Sarcoma
Panitumumab	EGFR	Human IgG2	Colorectal cancer
Palivizumab	F-Protein	Humanized IgG1	Respiratory syncytia virus
Pembrolizumab	PDCD1	Humanized	Metastatic melanoma, metastatic non-small cell lung cancer
Pertuzumab	Breast cancer	Humanized IgG1	HER2-dimer II
Ranibizumab	VEGF-A binding	Humanized IgG1	Age-related macular site degeneration
Ramucirumab	VEGFR2	Humanized	Metastatic colorectal cancer, metastatic non-small cell lung cancer
Siltuximab	IL-6	Chimeric	Multicentric Castleman's disease
Tocilizumab	II-6R	Humanized IgG1	Rheumatoid arthritis, systemic juvenile idiopathic arthritis
Trastuzumab	HER2/neu	Humanized IgG1	Breast cancer
Ustekinumab	II-12 and II-23	Humanb IgG1	Plaque psoriasis

CHEMICAL NAME	TARGET	ANTIBODY TYPE	INDICATION
BLys - B-lymphocyte stimulator, CTLA cytotoxic T-lymphocyte antigen, EGFR – endothelial growth factor receptor, glycoprotein IIb/IIIa receptor found on the human platelets, IL-interleukin, LCL – Large-cell lymphoma, MME- microtubule disrupting agent-conjugated to anti – CD30 antibody, MS – multiple sclerosis, NHL – non-Hodgkin's lymphoma, PDGFR- Platelet-derived growth factor receptor, PD1- Programmed cell death protein 1, PNH, paroxysmal nocturnal hemoglobinuria, RA – rheumatoid arthritis, RANKL- receptor activator of nuclear factor kappa-B lignand, RSV- respiratory syncytia virus, SLAMF7- SLAM family member 7, SLE-systemic lupus erythematosus, TNF-α – tumour necrosis factor alpha, VEGF vascular endothelial growth factor, VEGFR2- vascular endothelial growth factor receptor 2			

2.2.1.5 *Cytokines*

Cytokines are extracellular proteins or peptides that act as mediators in cell communication (Wink 2011). Cytokines facilitate their biological effects indirectly by influencing accessory proteins or a number of immune and other cells (Chawla-Sarkar *et al.,* 2003). The intracellular signalling of cytokines, as well as the outcome of their molecular and cellular interactions, can lead to immune suppression or induction, and are used for therapeutic interventions for infections, cancer and multiple sclerosis. Therefore, cytokines modulate disease symptoms by regulating immune functions and effector cells (Rodney 2013).

Growth factors consist of cytokines and protein hormones, and are regulating a range of biological processes, such as stimulating proliferation, differentiation and maturation of responsive cells (Rodney 2013).

Tumour necrosis factor (TNF), a soluble cytokine, is mainly produced as a Type 2 transmembrane protein arranged in stable homotrimers (Tang *et al.,* 1996), involved in systemic inflammation, and is a cytokine that is involved in the acute phase reaction (Rodney 2013).

Cytokines are mainly secreted from leukocytes, and their main functions can be classified into the following categories (Gad 2007):

- Autocrine: Cytokine acts on the cells that conceal it;
- Paracrine: Cytokine action is limited to the abrupt vicinities of cytokine secretion; and
- Endocrine: Cytokine diffuses to isolated regions of the body to affect different tissues.

Cytokines can be divided into recombinant interferons and interleukins (Rodney 2013) as indicated in Table 2.3.

Table 2.3: List of cytokines, growth factors and interferons and their indication for use (Rodney 2013)

CHEMICAL NAME	INDICATION FOR USE
Aldesleukin	Metastatic renal cell carcinoma
Anakinra	Rheumatoid arthritis (IL-2R)
Denileukin diftitox	T-cell lymphoma
Erythropoietin (EPO)	Promote erythrocyte formation and release from marrow
Granulocyte Colony-stimulating Factor (G-CSF)	Stimulates function and formation of neutrophils
Interferon alfa-2a	Leukemia, hairy cell leukemia, malignant osteoporosis, malignant osteoporosis, chronic hepatitis C
Interferon alfa-2b	Hairy cell leukemia, malignant melanoma, non-Hodgkin's lymphoma, condylomata acuminate, AIDS-related Kaposi sarcoma, chronic hepatitis B and C
Interferon alfacon-1	Chronic hepatitis C
Interferon beta – 1a	Multiple sclerosis
Interferon beta – 1b	Multiple sclerosis
Interferon gamma -1b	Granulomatus, malig osteoporosis
Oprelvekin	Thrombocytopenia
Peginterferonalfa- 2a	Chronic hepatitis B and C, cirrhosis, Chronic hepatitis C and HIV coinfection
Peginterferon alfa-2b	Melanoma
Peginterferon alfa-2b	Chronic hepatitis C

2.2.1.6 *Interferons*

Interferons have pleiotropic biological effects and were among the first human protein drugs to be effective in the treatment of cancer (Chawla-Sarkar *et al.,* 2003). There are three main types of interferons, namely interferon alpha (IFN-α), interferon-beta (IFN-β) and interferon-gamma (IFN-γ) (Arnuad 2002). Interferons may mediate anti-tumour effects by directly affecting the proliferation or cellular differentiation of tumour cells, or indirectly by modulating immunomodulatory and anti-angiogenic responses (Chawla-Sarkar *et al.,* 2003). IFN-α and IFN-β are, as a group, referred to as type I interferons or acid stable interferons (Walsh 2003). IFN-γ differs from the others, as it binds to another receptor and induces a different variety of biological effects. Furthermore, IFN-γ can also be referred to as type 2 interferon (Walsh 2003).

2.2.1.7 *Interleukins*

Interleukins are soluble molecules, which promote their biological effect by binding to specific receptors on the surface of target cells (Walsh 2003). These molecules are involved in pro-inflammatory and anti-inflammatory processes, and mediate cells in the immune system. They also mediate lymphocyte proliferation and activation functions (Rodney

2013). Most of the interleukins exhibit paracrine activity, while others display autocrine activity and endocrine effects, respectively (Walsh 2003).

Table 2.4: List of interleukins and their cell source (Oldham & Dilman 2009)

NAME	CELL SOURCE	MAIN FUNCTION
IL-1	Monocytes, macrophages, dendrite cells	Inflammation, early hematopoietic stem cell stimulation
IL-2	T-helper lymphocytes	T-cell expansion and proliferation
IL-3	Active T-cells, granulocytes	Mast cell proliferation, hematopoietic B - and T-cell proliferation
IL-4	T-helper lymphocytes type 2, mast cell,	B- and T-cell activation and proliferation may induce allergy macrophages and immunoglobulin E
IL-5	T-helper lymphocytes type 2, mast cell, macrophages	Eosinophil differentiation and proliferation, B-cell, immunoglobulin A production
IL-6	T-helper lymphocytes type 2, mast cell, macrophages, astrocytes, endothelium	Proliferation of plasma cells and bone marrow, induce acute T-cell inflammation and reactions
IL-7	Thymas stromal cells and bone marrow	B- and T-cell differentiation, co-stimulate with IL - 2
IL-8	Macrophages, lymphocytes, epithelial and endothelial cells	Chemotactic for neutrophilis, B- and T-cells
IL-9	T-helper lymphocytes type 2, mast cells	Proliferation of potentiate immunoglobulin E and mask cells and to some extent immunoglobulin M and immunoglobulin G
IL-10	T-helper lymphocytes type 2, mast cells, macrophages, B-monocytes	Stimulate T-helper lymphocytes type 2, but inhibit cytokine release of T-helper lymphocytes type 1, activate B-cells, elicit macrophages cytokine release
IL-11	Bone marrow	Hematopoietic stem cell proliferation and differentiation through megakaryocyte to platelet cells
IL-12	Dendritic, B- and T-cells, macrophages	Synergistic with IL-2, induce NK cell to release TNF-α and IFN-γ
IL-13	Activated T-helper lymphocytes type 2 mast cells	Stimulate differentiation and growth of cells to release immunoglobulin G and release of IL-1 and IL-6
IL-14	T-cell and malignant B-cells	Control growth of activated immunoglobulin secretion and B-cell proliferation
IL-15	Monocytes, viral infected	Induce NK cells
IL-16	CD8+T-cells, eosinophilis, ephithelial cells, lymphocytes	Chemotatic for $CD4^{+}$T and other cells
IL-17	T-helper type 17 cell	Osteoclast cells, angiogenesis, inflammatory
IL-18	Macrophages	Induce production of IFN-γ in T-helper lymphocytes, and NK cells
IL-19	Monocytes and nonimmune inflamed cells	Signal transducer and activator of transcription 1 and STAT3
IL-20	Monocytes and nonimmune inflamed cells	Keratinocyte differentiation and proliferation
IL-21	Activated T-helper lymphocytes and NK-cells	Activate and proliferate $CD8^{+}$ T-cell, B-cell isotype switching and NK functions

NAME	CELL SOURCE	MAIN FUNCTION
IL-22	Activated T- and NI-cells, T-helper	Signal transducer and activator of transcription 1 and 3, induced acute phase proteins in hepatoma cells and serum amyloid A 17 lymphocytes
IL-24	Monocytes, T helper lymphocytes, Melanocytes	Tumour suppression, psoriasis and wound healing
IL-26	Monocytes, memory T-cells	Induce cell secretion of IL-8 and IL-10 by CD54 and epithelial cells
IL-27	Macrophages	T- and B-lymphocyte activity
IL-28	Dendritic and other cells with infection	Defence against viral infection
IL-29	Dendritic cells with infection	Enhance host defence against microbes in epithelial and hepatocytes
IL-30	Macrophages	Interacts with IL-27
IL-31	T-helper type 2 lymphocytes	Skin inflammation
IL-32	Lung carcinoma A549 cell	Induce macrophages and monocyte to secrete tumour necrosis factor and IL-8 and CXCL2 chemokine
IL-33	Endothelial and other cells	Induce T helper lymphocytes to produce cytokine, mast cell
IL-34	Giant bone tumours	Osteoclast bone genesis, adherence
IL-35	Regulatory T-cells	Suppress T helper lymphocytes

CHAPTER 2

LITERATURE REVIEW: PART 2 - AN OVERVIEW ON THE FACTORS THAT INFLUENCE THE USE OF BIOLOGICAL MEDICINES

2.3 INTRODUCTION

The aim of Part 2 is to provide an overview on the factors that influence the use of Biological Medicines.

2.3.1 The side-effects of Biological Medicines

The side-effects of Biological Medicines require special knowledge as they differ from the side-effects of chemical drugs (xenobiotics) (Aubin *et al.,* 2013). Adverse effects caused by chemical drugs are heterogeneous, and can be classified into five sub-groups (Naisbitt *et al.,* 2000). Regarding Type A, the reactions correspond to the pharmacological activity of the drug and are predictable (Naisbitt *et al.,* 2000). With Type B, reactions are not predictable, are immune-mediated, and include hypersensitivity reactions (Aberer *et al.,* 2003). A Type C reaction is a chemical reaction and is short-term, and Type D reactions are long-term toxicities. A Type E reaction occurs after drug withdrawal (Naisbitt *et al.,* 2000).

Biological Medicine's adverse drug reactions are classified by their pathomechanism (Scherer *et al.,* 2010) and can be divided into five types (Pichler 2006).

Type α adverse effects are related to the cytokine released syndrome, or to the systematic application of cytokines in high doses (Vasquez *et al.,* 1995), and these side-effects can include headache, fever, asthenia, arthragia, myalgia, nausea, vomiting and diarrhoea (Aubin *et al.,* 2013).

Type β adverse drug reactions include both immediate and delayed hypersensitivity reactions (Barbaud *et al.,* 2011) related to the immunogenicity of the Biological Medicines (Descotes & Gourand 2008). The hypersensitivity reaction can be divided into three forms of allergies: anaphylaxis immediate injection side reaction, T-cell induction, and drug induced autoimmunity (Descotes & Gourand 2008).

Type Y adverse drug reactions are related to immune deviation from therapeutic protein, and are the most important group of side-effects, but they cannot be explained by typical

hypersensitivity reactions or high cytokine levels (Pichler 2006). They are immune or cytokine imbalance syndromes and these side-effects can be further divided into impaired functions, and can unmask or cause an immune or cytokine imbalance leading to autoimmune, auto-inflammatory or allergic reaction (Scherer *et al.,* 2010).

Type δ adverse drug reactions refer to cross-reactions and are related to expression of the similar binding antigen molecules on different tissue cells (Perez-Soler & Saltz 2005). An example is the occurrence of folliculitis and acneiform exanthems during the treatment of antagonists of the epidermal growth factor receptor (EGFR) (Scherer *et al.,* 2010). EGFR is also expressed by a range of carcinomas and moderately associated with tumour progression (Perez-Soler & Saltz 2005). The manifestation of this side-effect correlates, in terms of severity and size, with the response of the tumour (Scherer *et al.,* 2010).

Type ε adverse drug reaction is associated with new and unpredicted physiological functions of Biological Medicines (Aubin *et al.,* 2013). The *in vivo* use of Biological Medicines in patients may reveal these unpredicted physiological functions (Aubin *et al.,* 2013).

Biological Medicines are not small chemical compounds like chemical drugs, but are large complex protein produced molecules, with a biological effect (Pichler 2006). Biological Medicines' side-effects differ from xenobiotics in terms of chemistry, mode of action, metabolism and immunogenicity (Pichler 2006).

Adverse effects induced by chemical drugs are linked to their pharmacological effect, whereas adverse effects of Biological Medicines are linked to their biological activity (Lee & Kavanaugh 2005), are relevant to the molecular target and can be explained by inhibition as well as activation or other working mechanisms (Scherer *et al.,* 2010).

Table 2.5: Chemical name and adverse drug reactions (Jameson *et al*., 2018; Rodney 2013; Scherer 2009; Lee & Kavanaugh 2005)

CHEMICAL NAME	ADVERSE DRUG REACTIONS
Abatacept	Urticaria, infusion reactions, anaphylaxis, neutralizing antibodies, infections, autoimmune disorders
Abcixmab	Bleeding, thrombocytopenia, hypersensitivity reactions
Adalimumab	Developing serious infections
Alefacept	Infusion reactions, infections, fever, electrolyte changes, hypertension
Alemtuzumab	Infusion reactions, fever, infection, auto-immunity
Anakinra	Injection site reaction, neutralizing antibodies, infections
Atezolizumab	Urinary tract infection, pyrexia, fatigue, hepatitis, pneumonitis, dermatitis/rash, colitis, adrenal insufficiency, diabetes, pancreatitis.

CHEMICAL NAME	ADVERSE DRUG REACTIONS
Basiliximab	Lymphopenia, mild injection site reaction, very rare: angioedema, urticara, anaphylaxis, pre-existent antibodies
Belatacept	Increased risk for developing post-transplant lymphoproliferative disorder, infections
Belimumab	No comprehensive information
Bevacizumab	Proteinuria, hypertension, bleeding, arterial thromboembolism, reversible posterior leukencephalopathy syndrome, nephtotic syndrome, chronic cardiac insufficiency
Blinatumomab	Pyrexia, headache, nausea, peripheral oedema, febrile neutropenia, nausea, hypokalemia
Brentuximab vedotin	Progressive multifocal leukoencephalopathy and/or death may occur, as a result of JC virus infection
Canakinumab	Injection site reaction, infections
Certolizumab-pegol	Infections, sepsis
Cetuximab	Leukopenia, anaemia, oedema, rash, fever, anaphylaxis, infusion reactions
Daclizumab	Tachycardia, polyuria, oedema, hypersensitivity reactions
Daratumumab	Thrombocytopenia, anaemia, neutropenia, lymphopenia, infusion reactions
Denosumab	No comprehensive information
Dinutuximab	Back pain, headache, arthralgia, nausea, fatigue, pain
Eculizumab	Infection (especially meningococci) rarely: infusion reactions, fever, antibody production
Efalizumab	Lymphocytosis thrombocytopenia, oedema, infusion reaction, rarely: urticaria (1-8%), progressive multifocal leukencephalopathy
Elotuzumab	Acute renal failure, pulmonary embolism, anaemia, pneumonia, respiratory tract infection, pyrexia
Etanercept	Injection site reaction, autoantibodies, anti-etanercept antibodies, lupus erythematosus-like diseases, infections psoriasis (especially palmoplantar, pustular), Stevens-Johnson syndrome, toxic epidermal necrolysis, macrophage activation syndrome, vasculitis, interstitial pulmonary disease, lymphoma
Gemtuzumab ozogamicin	Infusion reactions, anaphylaxis, hepatotoxicity, veno-occlusive disease, tumour lysis syndrome, infections
Golimumab	Infections demyelinating disease, severe systemic hypersensitivity reations, autoimmune phenomena, injection site reaction
Ibritumomab-tiuxetan	Erythema multiforme, Stevens-Johnson syndrome, bullous dermatitis, toxic epidermal necrolysis, exfoliative dermatitis, anaphylaxis, infusion
Idarucizumab	Delirium, pneumonia, pyrexia, constipation, hypokalemia
Infliximab	Immune phenomena: enterocolitis (possible involvement of other sections of Gastro intestinal tract, hypophysitis, hepatitis, exanthema with lymphocytic infiltration of the deep dermis and perivascularly with massive pruritus (>50%)
Ipilimumab	Infection, infusion reaction (3.8%), hypersensitivity reaction, autoantibody production (6%), lupus erythematosus, serum sickness (2.8%), vasculitis, exanthema.
IFN-α	Pancytopenia, flu-like symptoms, fever, injection site reaction
IFN-β	Pancytopenia, flu-like symptoms, fever, injection site reaction
IFN-y	Fever, rash, injection site reaction
Muromonab-CD3	Hypersensitivity reactions, cytokine release syndrome (first dose syndrome), acute tubular necrosis, infusion reactions, cytopenias

CHEMICAL NAME	ADVERSE DRUG REACTIONS
Natalizumab	Infections (among others progressive multifocal leukencephalopathy, anaphylaxis, urticaria, infusion reactions
Necitumumab	Venous and arterial thromboembolic, infusion reactions, dermatologic toxicities, hypomagnesemia
Nivolumab	Hypothyroidism, thyroiditis, fatigue, upper respiratory tract infection, rash, pruritus, infusion related reactions, musculoskeletal pain
Obinutuzumab	Neutropenia, anemia, musculoskeletal disorder, infusion-related reactions, thrombocytopenia, cough
Ofatumumab	Upper respiratory tract infection, neutropenia, pneumonia, pyrexia
Olarutumab	Inflammation of mucous membranes in the digestive tract, fatigue, musculoskeletal pain, infusion-related reactions, neutropenia, hyperglycemia, hypokalemia, hypophosphatemia
Omalizumab	Infections, anaphylaxis (in part delayed), serum sickness, fever, lymphadenopathy, systemic hypereosinophilic syndrome, Churg-Strauss syndrome, injection site reaction
Palivizumab	Diarrhoea, injection site reaction, fever, anaphylaxis, urticaria, hypersensitivity reactions, anaemia, liver test abnormalities
Panitumumab	Toxicity on skin, eye and mucous membranes, gastrointestinal toxicity, infusion reactions including anaphylaxis, angioedema (in part delayed)
Pembrolizumab	Dyspnoea, fatigue, decreased appetite, pneumonia, pulmonary embolism, colitis, hypophysitis, thyroid disorders
Pertuzumab	No comprehensive
Ramucirumab	Neutropenia, diarrhoea, fatigue, epistaxis
Ranibizumab	Hypersensitivity, erythema, urticaria, pruritus, ant-ranibizumab
Rilonacept	Injection site reaction, infections, anti-rilonacept antibodies
Rituximab	Infusion reactions (even fatal, especially at the first dose), tumour lysis syndrome, anaphylaxis, infections, cytopenias, paraneoplastic emphigus, lichenoid or vesiculobullousdermatitis, progressive multifocal leukencephalopathy, Hepatitis B
Siltuximab	Hyperuricemia, pruritus, increased weight, upper respiratory tract infection
Trastuzumab	Infection, cardiotoxicity, pulmonary toxicity, hepatotoxicity, infusion reactions (25%), anaphylaxis, urticaria, angioedema
Tocilizumab	Severe bacterial infection, angioedema, infusion reactions
Tositumomab	Flu-like symptoms, prolonged, partially severe cytopenias, malignancies, injection site reaction, hypersensitivity reactions, anaphylaxis
Ustekinumab	No comprehensive information

2.3.2 Limited knowledge, toxicology and therapeutic response of Biological Medicines

According to Lee and Kavanuagh (2005), clinicians need to develop a better understanding of the spectrum and types of reactions of Biological Medicines, as well as the underlining mechanisms primary to such reactions. The main complexity is that response of Biological Medicines depends on at least three diverse parameters, namely disease pathophysiology, disease state and drug concentration (Daïen & Morel 2014). The in vivo activity of these medicines should be explained better to develop more predictive assays for clinical efficacy and provide information useful in the rational selection of these medicines (Oldham &

Dilman 2009). This will aid in their support to use these medicines optimally. Currently, diagnostic possibilities are still limited and not standardized on large collectives (Scherer *et al.,* 2010). A reason for this might be the pharmacokinetic and drug concentration, which is influenced by characteristics such as the patient's gender, age, liver and renal functions, smoking status, and body mass index (Daïen & Morel 2014).

The form of experience regarding pharmacological information and social influences on decision making plays a very important role in the prescribing of new medicines (Prosser *et al.,* 2003). Therefore, it is important for clinicians to have a clear understanding of the toxicology of Biological Medicines, especially the pharmacokinetic and pharmacodynamic data, as this will help them to choose the best regimen for the patient (Rodney 2013). The pharmacokinetic data of most Biological Medicines come directly from the plasma drug concentration (Wisniacki *et al.,* 2013).

The pharmacodynamics of Biological Medicines refer to the time-course of effect response (Wisniacki *et al.* 2013). The therapeutic response of Biological Medicines experienced by individual patients may be influenced by the pharmacodynamics (genetic factors, physiological, pathological, tolerance and receptor interactions) and the pharmacokinetics (distribution, elimination, extent, & rate of absorption) (Rodney 2013).

It is therefore of utmost importance for a clinician to take all of the above into consideration before Biological Medicines can be utilised to the patient's advantage (Salvana & Salata 2009).

2.3.3 Pharmacoeconomics of Biological Medicines

The increasing use of Biological Medicines have left questions with regard to the cost of these medicines (Heinen-Kammerer *et al.,* 2007). Biological Medicines have demonstrated to be an effective form of treatment for rheumatoid arthritis, but because of the high cost, they are not considered first-line treatment (Joensuu *et al.,* 2015).

Pricing of Biological Medicines is complex, and depends on several factors such as cost, public perspective, competitor strategies and political pressures (Rodney 2013). The administration of Biological Medicines requires high standards of sterility and purity and well-trained personnel, and this adds additional cost to the treatment (Rodney 2013).

A report by Broomberg, CEO of Discovery Health (2015), stated that Biological Medicines offer life-saving hope to many patients, but the cost implication is threatening, leaving medical aid schemes with very high expenses, and individual patients not capable of affording them.

The value of Biological Medicines can be measured by different methods of analyses, for example, cost consequences, cost minimization, cost-effectiveness, cost utility and cost benefit analyses (Rodney 2013).

Quality adjusted life year (QALY) combines the quality and the length of life into a single measurement. Therefore, cost per QALY refers to the cost-effectiveness of the quality adjusted life years, which can be used as a measurement of the efficiency of Biological Medicines (Drummond *et al.,* 2009). According to Heinen-Kammerer (2007), a study that was performed in Germany showed that entanercept was cost-effective within the German healthcare system, held greater benefits for patients, but also led to higher treatment cost.

Costs of Biological Medicines are related to the national economy, health policy and price level, thus the incremental cost-effectiveness ratio cannot be generalized when analysing results from different countries (Joensuu *et al.,* 2015).

2.4 CONCLUSION

From the above discussion, it can be concluded that Biological Medicines have many advantages, but that there are different factors that influence the use of these medicines in different countries, such as therapeutic response, side-effects, cost, genetic factors, demography, and limited knowledge of clinicians about these medicines.

There is a number of publications that characterize the pharmacokinetics and pharmacodynamics of monoclonal antibodies in Asian versus non-Asian populations, and the biological effects of cytokine on Chinese and non-Chinese patients (Rogge *et al.,* 2014), but no similar studies have been done in South Africa.

The aim of this study is to investigate (search for) factors that influence the utilization of Biological Medicines in a sample of South African patients and develop a framework for the use of Biological Medicines.

CHAPTER 2

LITERATURE REVIEW: PART 3 - AN APPROACH FOR DEVELOPING A FRAMEWORK FOR THE USE OF BIOLOGICAL MEDICINES

The aim of Part 3 is to provide an overview of the approach to develop a framework for the use of Biological Medicines in South Africa. There are variations in the Delphi method, for example, argument delphi, classical delphi, decision delphi, disaggregated policy delphi, EFTE delphi, mini delphi, online delphi, and technological delphi (Strasser 2016:120). For the purpose of this study, the classical delphi was used, due to the fact that it focus on facts, elicits opinions and gain consensus, with independent panellists and anonymous responses (Strasser 2016:121). It is a fast and cost- effective way to gather experts' opinions and defeats difficulties. In the Delphi process, experts from various backgrounds can participate equally in the process, while they consider their opinions carefully and respond at their own time.

2.5 INTRODUCTION

The Delphi method as described by Linstone and Turoff (2002:3) can be characterised as a method for structuring a group; according to De Villiers, De Villiers and Kent (2005:639), it is a method for the collection of an expert point of view on a specific topic. It is, furthermore, a method that allows a large range of expert opinions from different backgrounds to take part in the communication process (Critcher & Glastone 1998:433). The Delphi method was named after an oracle on an island of Delphi in Greece (Clayton 1997:337), which had a system of informants considered to be one of the most trustworthy resources in predicting the future (Kennedy 2004:505). Linstone and Turoff (2002:3) refer to the Delphi method as a group of experts who are geographically apart and reply to specific questions through e-mail. It is adaptable and flexible; this makes it the appropriate method of finalising a framework by a panel of experts using the technique of consensus (Powell 2003:376). The Delphi method is a cost-effective and quick method of gathering expert opinions. Previous difficulties with a face-to-face discussion were overcome with the Delphi method, and experts from different backgrounds participate equally in the process (Critcher & Gladstone 1998:432; Murry & Hammons 1995:426).

According to Jones and Hunter (1995:376), the Delphi method can be used for the development of health-related education programmes. The utilisation of the Delphi method is not new in health care research (Loo 2002:762).

2.6 DELPHI METHOD

According to De Villiers *et al.,* (2005:61), a critical step in the Delphi method is the development of the questionnaire that is based on a series of questions to the panellist for rating and evaluation. The preparation phase of the questionnaire is essential in ensuring a successful process; part of this process would include a carefully constructed Delphi questionnaire that enables clear statements as well as remarks by the panel (Clarke-Farr 2005:225). The Delphi method gave the panel the opportunity to re-evaluate their opinions regarding the framework and receive feedback from their fellow experts (Ali 2005:731).

Two important aspects of the Delphi method are the utilisation of a number of questionnaire Rounds and anonymous answering of questions (McKenna 1994:1222). The Delphi method consist of a minimum of two Rounds (Tangaratinam & Redman 2005:122). According to Critcher and Glastone (1998:433), the number of Rounds in the Delphi Method may range from two to five. Only two or three Rounds are used in most studies (Thangaratinam & Redman 2005:121).

The panel members' responses after each Round are analysed and each panel member receives feedback in the next Round (Goodman 1987:730).

The first Round of the Delphi process consists of a structured questionnaire based on the literature and is used as a template (Hsu & Sanford 2012:346).

In Round 2, the Delphi panel members receive the second questionnaire and are asked to reconsider items summarized on the answers provided in the first Round. The researcher also provides the panel members with their earlier responses (Hsu & Sanford 2012:346).

The relationship between the Delphi group size and reliability has been illustrated by an increase in reliability of the group feedback after increasing the size of the group (Dalkey 1969:12). It was established that there was a huge increase in the reliability of the Delphi method when the group size increased from 1 to 11 members, but after that, reliability did

not increase remarkably (Dalkey 1969:12). According to Thangaratinam and Redman (2005:120), representation is judged by the characteristics of the expert panel rather than its number. Fixed and specific criteria must be used to select the Delphi panel experts (Murry & Hummons 1995:428). Critchner and Gladstone (1998:435) emphasise that the selection of the appropriate panel of experts is crucial.

Clarke-Farr (2005:226-228) provides an overview of essential aspects of the Delphi method and summarises the following advantages and disadvantages as listed by the Michigan State University (1994:1-3).

Advantages of the Delphi method:

- *"It allows participants to remain anonymous;*
- *It is inexpensive;*
- *It is free of social pressure, personality influence and individual dominance;*
- *A reliable judgement or forecast of results is likely;*
- *It allows sharing of information and reasoning among participants;*
- *It is conducive to independent thinking and gradual formulation;*
- *It consists of a well-selected respondent panel;*
- *It can provide a broad analytical perspective on potential growth impacts; and*
- *It can be used to reach consensus among groups hostile to one another*."

Disadvantages of the Delphi method:

- "*The judgements are those of a selected group of people and may not be representative;*
- *There may be a tendency to eliminate extreme positions and force a middle-of-the-road consensus;*
- *It is more time-consuming than the group process method;*
- *It should not be viewed as a total solution to forecasting;*
- *It requires skill in written communication; and*
- *It requires adequate time and participant commitment (about 30-45 days)".*

2.7 CONCLUSION

The Delphi method is a method for the collection of an expert point of view on a specific topic. It is a critical step in the development of a questionnaire that is based on a series of questions to the panellist for rating and evaluation. It gives the panel the opportunity to re-evaluate their opinions regarding the framework and receive feedback from their peers. As no framework for the use of Biological Medicines in South Africa was available, the Delphi method was seen as the best option for the final Round of this study to compile a framework for the use of Biological Medicines in South Africa.

CHAPTER 3

STUDY PROTOCOL

3.1 OBSERVATIONS FROM REVIEW

i. Biological Medicines are therapeutic substances derived from biological sources that have improved the quality of life of patients with chronic diseases such as rheumatoid arthritis and cancer.
ii. Biological Medicines are large, complex proteins with peculiar pharmacokinetics, pharmacodynamics and toxic profiles.
iii. There are different types of Biological Medicines that include monoclonal antibodies (naked, conjugated and bispecific), cytokines, interferons, and interleukins.
iv. Biological Medicines are subject to genetic variation in their targets and this may differ in different populations, leading to variations in therapeutics and toxicity experienced by different populations or patients.
v. Consequently, it has been observed that the following factors may influence use and access of Biological Medicines in a specific population or patient.
    - Patient demographic;
    - Prevalence of side-effects or other genetic factors;
    - Knowledge of pharmacology by advocate groups, doctors or patients;
    - Availability of scientific information to prescribers; and
    - Pharmaco-economics, cost, cold chain and supply chain.

It is not known how these factors influence the use of Biological Medicines in South Africa and there is no policy or framework to guide the use of Biological Medicines.

3.2 AIM OF THE STUDY

The two-fold aim of the study was to identify the factors influencing the utilization of Biological Medicines in the Free State (South Africa) and

- To develop a framework for the use of Biological Medicines in South Africa.

3.3 THE OBJECTIVES OF THE STUDY

To achieve the aims of the study, the following objectives were pursued:

i. To evaluate perceptions and knowledge of Biological Medicines by young doctors (who have been practising for two years or less since graduating).
ii. To identify the factors that might influence the prescribing of Biological Medicines by Specialists in the Free State.
iii. To identify the factors that might influence patients' compliance with Biological Medicines in the Free State.
iv. To develop a framework for the use of Biological Medicines in South Africa via the Delphi method.

3.4 EXPECTED OUTCOMES OF THE STUDY

- Knowledge of the most common factors that influence the prescribing and utilisation of Biological Medicines in South Africa.
- A Framework for the use of Biological Medicines in South Africa.

CHAPTER 4

PART 1: PERCEPTION AND KNOWLEDGE OF BIOLOGICAL MEDICINES BY NEWLY QUALIFIED DOCTORS (< 2 YEARS OF PRACTICE)

4.1 INTRODUCTION

This chapter consists of the results of the newly qualified doctors' survey. The information sought included the doctors' particular experience in the use of Biological Medicines' available source of medical information source on Biological Medicines; their role in patients' care/management using Biological Medicines; their perception of Biological Medicines with regard to efficacy, toxicity or other; any problems with obtaining Biological Medicines; undergraduate training on Biological Medicines; and procurement processes.

4.2 METHODS

A prospective survey was conducted on the newly qualified doctors (i.e. doctors with less than two years of practice). The selection criteria delineated the study population to doctors who were practising in the Mangaung district (Bloemfontein) in the Free State for a six-month period from 1 April 2017 – 30 September 2017. The doctors were identified at their point of work. They received an information leaflet about the study (cf. Appendix A1) and consent form (cf. Appendix A2) before they completed the questionnaire (cf. Appendix A3). Voluntary counselling was done before participation in this study.

4.3 INFORMATION SOUGHT

The questionnaire is divided into different categories. The category concerned first is the prescribers' particulars, in terms of the gender, age, years of work experience, and where they studied.

Section B of the questionnaire refers to the use of Biological Medicines; specifically, the doctor's knowledge about Biological Medicines; whether patients demand to use Biological Medicines; at what stage of the disease they prescribe Biological Medicines; the determining factor indicating when a patient should be given Biological Medicines; and the names of Biological Medicines as well as the condition for which it can be prescribed.

Section C refers to the available medical information source on Biological Medicines; whether the doctors were taught about Biological Medicines at any time during their medical training; whether they think Biological Medicines were adequately covered in the standard medical textbooks they used or lectures they attended; how relevant it was to their current requirements to prescribe these drugs; where they get information that enable them to prescribe and care for patients using Biological Medicines; and the steps that must be followed when a doctor decides to prescribe Biological Medicines for a patient.

Section D describes patient care and management; how doctors approach these aspects; how requirements or criteria for prescribing Biological Medicines differ from prescribing pharmaceutical agents; how the care of patients on Biological Medicines differ from those on pharmaceutical agents; on average, when the doctors start administering Biological Medicines to the patients.

Section E covers the doctors' perception; more specifically, the reason why Biological Medicines are difficult to use; the perception that Biological Medicines' use is limited; when the doctor will not prescribe Biological Medicines; whether Biological Medicines have more adverse effects than pharmaceutical agents; and the factors that play a role in the efficacy and safety of Biological Medicines.

Section F refers to the procurement process, specifically the processes whether satisfactory and suggestions of how it should be improved.

4.4 INCLUSION CRITERIA

Clinicians with less than two years' experience since graduation.

4.5 EXCLUSION CRITERIA

Clinicians with more than two years' experience since graduation.

4.6 ETHICAL CONSIDERATIONS

Ethical approval was granted by the University of the Free State (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee (cf. Appendix A6 & A7).

4.7 PILOT STUDY

A pilot study was done by testing the questionnaire on three individuals (two newly qualified doctors, as well as a biostatistician). This was done in order to test whether the availability of information will be sufficient for further evaluation, and to determine how much time would be needed to complete the questionnaire. A few questions on the questionnaire were restricted to ensure that all participants have the same interpretation of the questions. The responses of those individuals were not included in the final questionnaire survey.

4.8 STATISTICAL ANALYSES

The data was captured in Excel, and imported into SAS (Statistical Analysis Software). The analysis was done using SAS 9.4. Descriptive statistics, namely means, medians, standard deviations, percentages and frequencies were calculated for continuous data.

4.9 RESULTS

4.9.1 Prescribing particulars

As it was, out of the 79 doctors in the Mangaung district (Bloemfontein) in the Free State, 79,7% (n = 63) completed the questionnaire. The study population consisted of 60,3% females and 39,7% males (cf. Appendix B, Table B1). The mean age of the doctors was 26.01 (SD, 2.4) (cf. Appendix B, Table B2). Regarding the doctors' work experience, 73% had worked one year, while 20,6% had 1.5 to 2 years' work experience (cf. Appendix B, Table B3). Figure 4.1 displays the different institutions where the doctors completed their studies.

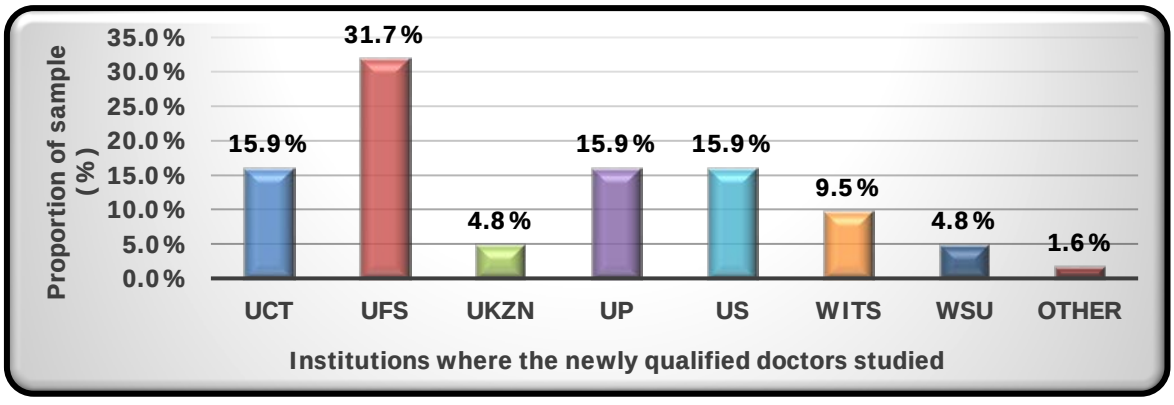


Figure 4.1: The institutions of study of newly qualified doctors
UCT = University of Cape Town; UFS = University of the Free State; UKZN = University of KwaZulu-Natal; UP = University of Pretoria; WITS = University of Witwatersrand

A majority of 31,7% studied at the University of the Free State (UFS), and then 15,9% at the University of Cape Town (UCT) as well as the University of Pretoria (UP) and University of Stellenbosch (US).

4.9.2 Use of Biological Medicines

Fifty-four percent (n = 63) of the doctors did not know what Biological Medicines are (cf. Appendix B, Table B4). Figure 4.2 illustrates that of the 46% (n = 63) doctors that indicated they know what Biological Medicines are, a majority of 57,7% (n = 29) indicated that Biological Medicines are used for the treatment of rheumatoid arthritis and cancer.

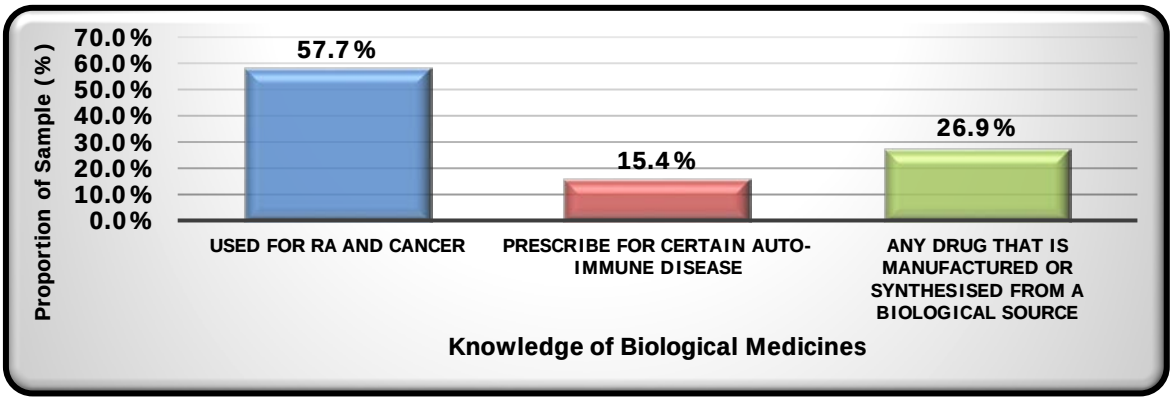


Figure 4.2: Knowledge of the newly qualified doctors about Biological Medicines
RA = Rheumatoid Arthritis

A majority of 74,6% (cf. Appendix B, Table B5) indicated that they did not prescribe Biological Medicines at their institutions, while 55,8% (n = 43) of them indicated that they want to prescribe Biological Medicines at their institutions (cf. Appendix B, Table B6). An overwhelming majority of 95,2% of patients did not demand that Biological Medicines be used (cf. Appendix B, Table B7). Figure 4.3 illustrates that 49,2% of the doctors indicated they were not allowed to prescribe Biological Medicines, while 42,9% indicated that it was only prescribed in severe cases.

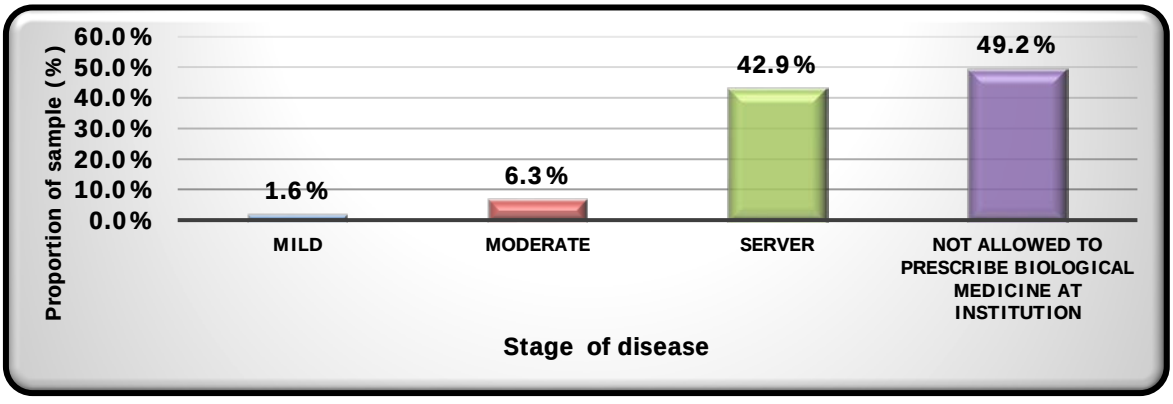


Figure 4.3: The different stages of a disease when Biological Medicines are prescribed

Figure 4.4 shows that 37,7% (n = 53) indicated that the regular determining factor when a patient should be given Biological Medicines is when a patient is not responding to other treatment (pharmaceutical agents). Thirty-four percent (n = 53) indicated that they were uncertain because they had not yet the opportunity to prescribe Biological Medicines.

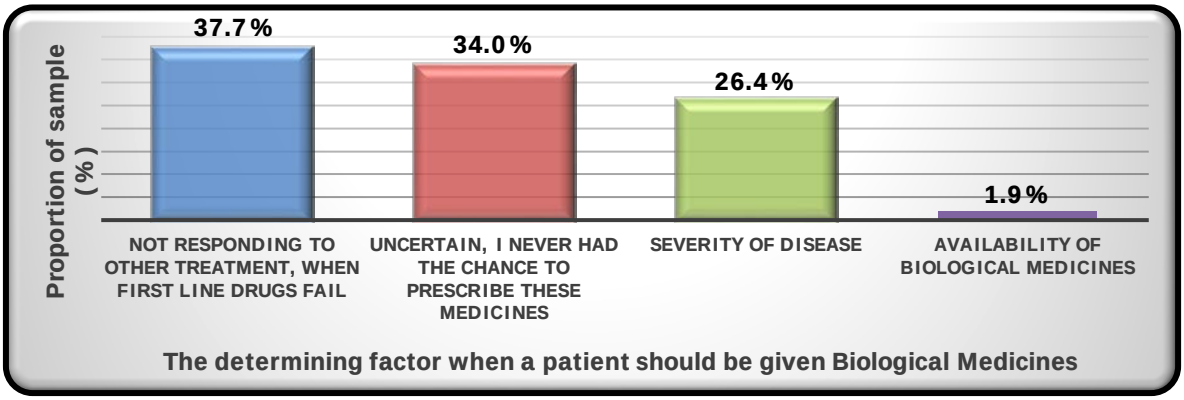


Figure 4.4: The determining factor when a patient should be given Biological Medicines

Table 4.1 lists the Biological Medicines that the doctors knew can be prescribed, and for what condition. Altogether 47,6% indicated that Infliximab can be prescribed and 44,4% of the participants pointed out that it can be prescribed for Rheumatoid arthritis.

Table 4.1: Biological Medicines and condition

BIOLOGICAL MEDICINES	N=63	PERCENTAGE	CONDITION	N=63	PERCENTAGE
Infliximab	30	47,60%	Rheumatoid arthritis	28	44,40%
Rituximab	15	23,80%	Rheumatoid arthritis	14	22,20%
Adalimumab	2	3,20%	Rheumatoid arthritis	2	3,20%
Interferon	3	4,80%	Cancer	3	4,80%
Trastuzumab	2	3,20%	Breast cancer	1	1,60%

4.9.3 Information resource

Eighty-two and a half percent (n = 63) of the doctors indicated that they were taught about Biological Medicines at some time during their medical training (cf. Appendix B, Table B8), while 77,1 % (n = 61) indicated that Biological Medicines were not adequately covered in the standard medical textbooks they used (cf. Appendix B, Table B9). Sixty-four and a half percent (n = 62) indicated that their current knowledge about prescribing Biological Medicines was insufficient (cf. Appendix B, Table B10). Figure 4.5 illustrates that most doctors (58,7%) obtained information on Biological Medicines from the Internet, while 83,0% (n = 53) indicated that Biological Medicines were not readily available to all clinicians (cf. Appendix A-11).

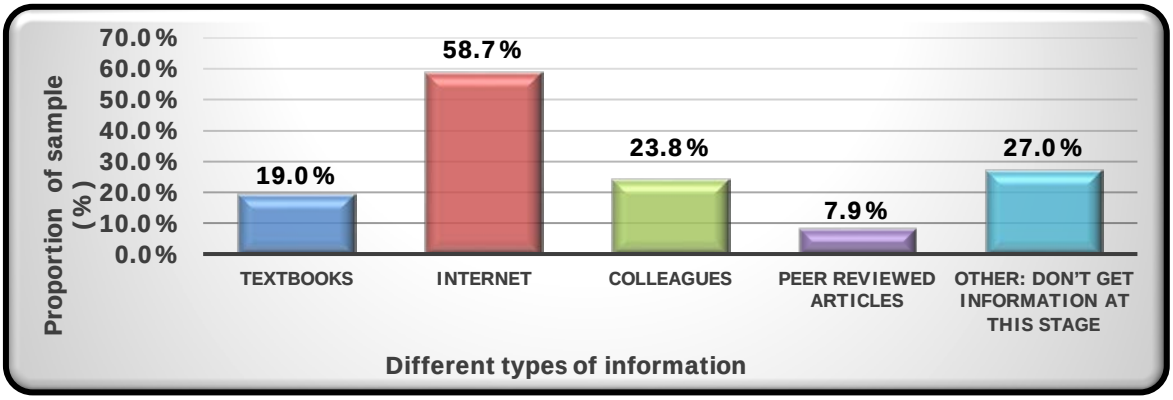


Figure 4.5: Different types of information resources available

Figure 4.6 illustrates that 54,7% (n = 33) of participants suggested that there should be more lectures and seminars on Biological Medicines, while some of them 45,3% (n = 28) suggested that there should be more specific guidelines for the use of Biological Medicines in textbooks.

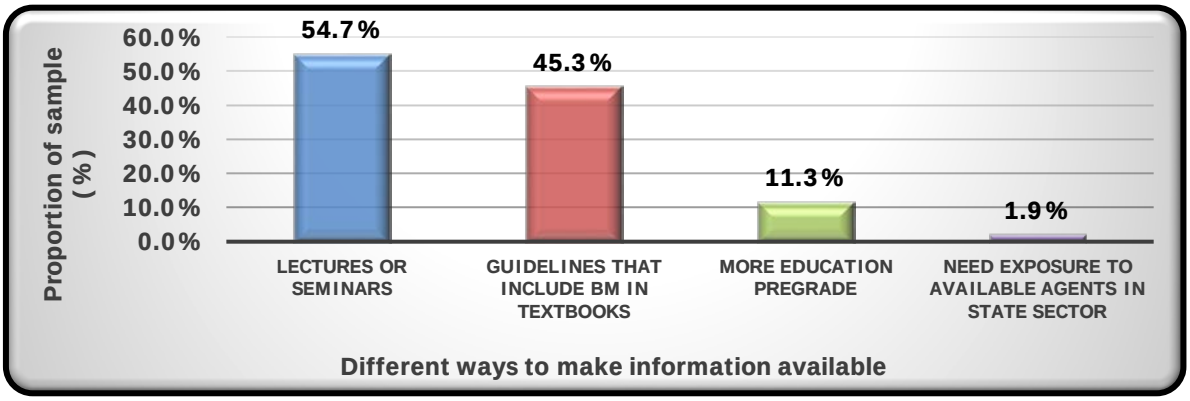


Figure 4.6: Suggestions to make information more readily available
BM = Biological Medicines

Ninety-four comma eight percent (n = 55) (cf. Appendix B, Table B12.1) of them indicated they were not allowed to prescribe Biological Medicines at their institution and would refer the patient to someone senior or to a specialist.

4.9.4 Patient care and management

The results of patient care and management follow: Figure 4.7 shows how the approaches, requirements or criteria to prescribe Biological Medicines differ from prescribing of pharmaceutical agents; 41,3% of the respondents indicated that they were unsure, while 33,3% answered that they were not allowed to prescribe Biological Medicines at their institutions.

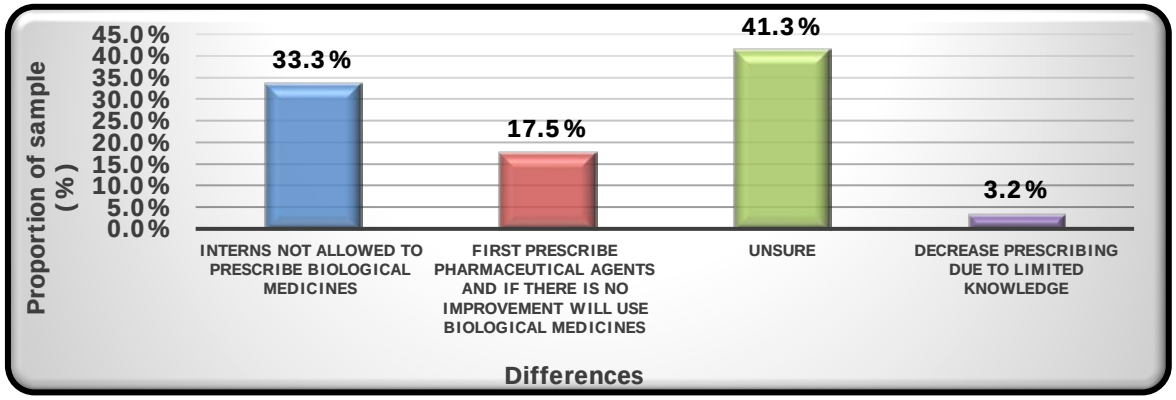


Figure 4.7: How the approaches, requirements, or criteria to prescribe Biological Medicines differ from the prescribing of pharmaceutical agents

Figure 4.8 illustrates that 39,7% indicated that they were unsure regarding the differences in care of patients on Biological Medicines and those that use pharmaceutical agents, while 34,9% indicated that frequent follow-ups, close monitoring and good screening are required.

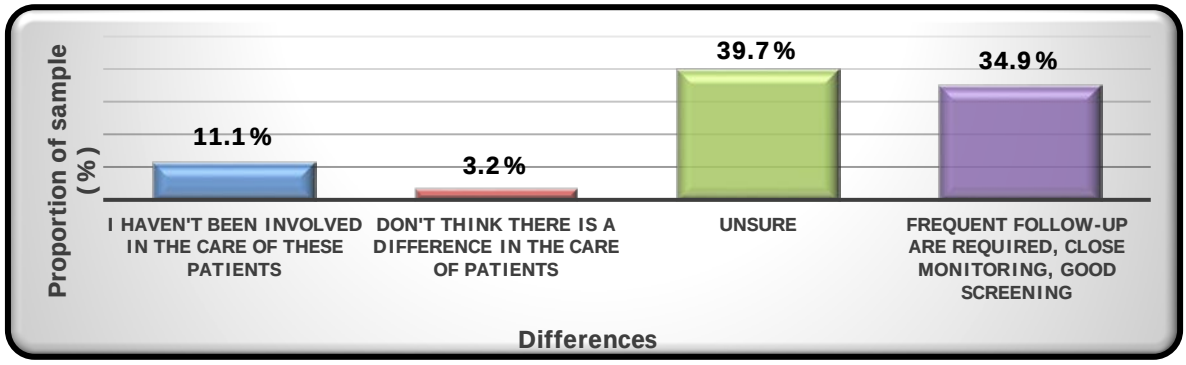


Figure 4.8: How the care of patients on Biological Medicines differs from that of patients on pharmaceutical medicines

In Figure 4.9 we can see that 69,5% (n = 59) of the respondents indicated that they were not allowed to prescribe Biological Medicines, while 15,3% (n = 59) indicated that Biological Medicines should be prescribed in time to be effective, and 11,9% (n = 59) indicated the Biological Medicines were given too late.

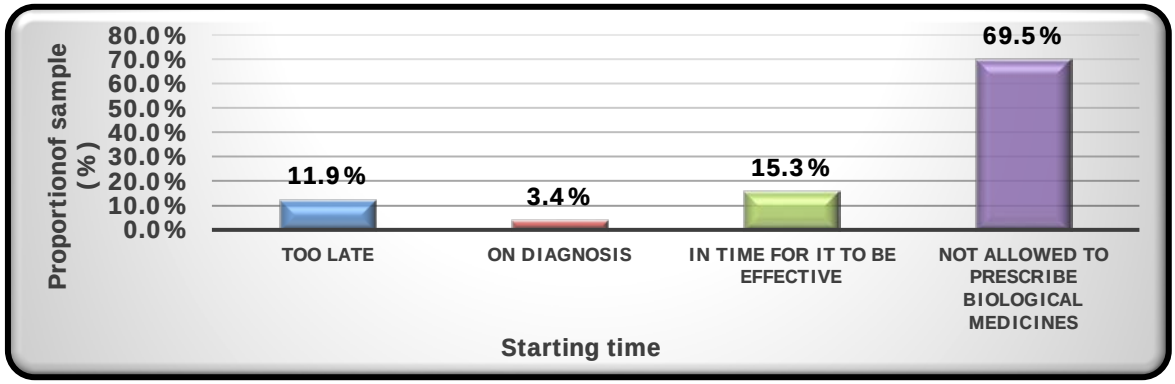


Figure 4.9: When they start giving patients Biological Medicines

4.9.5 Doctors' knowledge

Direct questioning tested the newly qualified doctors' knowledge and they were allowed to choose more than one option. Table 4.2 captures some of the reasons why Biological Medicines are difficult to use: 76,2% (n = 63) of the respondents indicated they had limited knowledge of the pharmacology of Biological Medicines, whereas 66,7% mentioned that Biological Medicines were expensive to use.

Table 4.2: Reasons why Biological Medicines are difficult to use

DESCRIPTION	QUANTITY	PERCENTAGE
They are time-consuming in that patient selection may involve special tests	9	14,3%
They are administered parenteral, hence require close monitoring	15	23,8%
Adverse reactions are more common in that patients need more review than in the case of pharmaceutical agents	15	23,8%
I have limited knowledge of the pharmacology of biological agents	48	76,2%
They are expensive	42	66,7%
Other (specify)	0	0,0%

Table 4.3 shows why the use of Biological Medicines is limited: 55,6% (n = 63) of the respondents indicated that the availability of knowledge and information about Biological Medicines was limited and 46,0% (n = 63) indicated that the availability or affordability of specialized tests for monitoring efficacy was difficult and expensive.

Table 4.3: Use of Biological Medicines is limited

DESCRIPTION	QUANTITY	PERCENTAGE
Attitudes and perceptions towards Biological Medicines: I consider genetically derived products as unsafe, hence may not recommend them to patients	4	6,3%
Beliefs: especially religions that do not allow the use of human derivatives	10	15,9%

DESCRIPTION	QUANTITY	PERCENTAGE
Availability/affordability of specialized tests for monitoring efficacy is difficult and expensive	29	46,0%
Procurement process to obtain Biological Medicines is difficult	21	33,3%
Lack of monitoring safety: adequate knowledge to enable detection of side-effects, clinical exam and lab tests	10	15,9%
Availability of knowledge/information about Biological Medicines is limited	35	55,6%
Prescribing practice: use of guidelines or individual's ethos can limit the use of Biological Medicines	12	19,0%

Table 4.4 shows that 50,8% (n = 63) of the doctors will not prescribe Biological Medicines when there is coexisting disease such as TB or the presence of serious infections or organ failure. Sixty-four comma nine percent (n = 57) of the doctors indicated that Biological Medicines had no more adverse effects than pharmaceutical agents (cf. Appendix B, Table B13).

Table 4.4: When will you NOT prescribe Biological Medicines?

DESCRIPTION	QUANTITY	PERCENTAGE
Coexisting disease: TB or presence of serious infections or organ failure	32	50,8%
Previous treatment, especially with Biological Medicines, is associated with poor response to another biological medication	19	30,2%
Presence of drug antibodies: render Biological Medicines ineffective	14	22,2%

The table below reveals that 74,6% of the doctors indicated that there was still much to be learned about the adverse effects of biological agents, while 58,7% indicated that Biological Medicines should be prescribed by specialists only.

Table 4.5: Newly qualified doctors in agreement with the statement/s below

DESCRIPTION	QUANTITY	PERCENTAGE
Biological Medicines are more effective than pharmaceutical agents	26	41,3%
There is still much to be learned about the adverse effects of biological agents	47	74,6%
Biological Medicines should be prescribed by specialists only	37	58,7%
My patients on Biological Medicines have reported more adverse side-effects than those on pharmaceutical medicines	0	0,0%
I consider prescribing Biological Medicines as a last resort when pharmaceutical medicines have failed	20	31,7%

Table 4.6 lists the factors that play a role in the efficacy and safety of Biological Medicines: 50,8% (n = 63) stated that plasma concentrations of Biological Medicines were useful to know in patients with poor response.

Table 4.6: The factors that play a role in the efficacy and safety of Biological Medicines

DESCRIPTION	QUANTITY	PERCENTAGE
Plasma concentrations of Biological Medicines: are useful to know in patients with poor response	32	50,8%
Presence of neutralizing antibodies: likely in patients who lose response after showing good response.	29	46,0%
Genetics: some SNP polymorphism associated with better response to TNFa inhibitors in RA	17	27,0%
Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNFa	7	11,1%

4.9.6 Procurement

The procurement process has a huge impact on the availability of Biological Medicines. Sixty comma eight percent (cf. Appendix B, Table B14) of the doctors indicated that they had not yet prescribed these drugs, so they were uncertain what channels they must use to obtain Biological Medicines for their patients, while 39,2% (cf. Appendix B, Table B14) indicated that they had to get consent from a specialist to prescribe Biological Medicines.

On the question whether the process is satisfactory, a large majority of 93,2% (cf. Appendix B, Table B15.1) of doctors indicated they have not had exposure to the process, while 3,4% (cf. Appendix B, Table B15.2) responded negatively, because the process took very long.

4.10 SUMMARY

- Some of the doctors knew what Biological Medicines are, while a few knew that Biological Medicines are used mainly for rheumatoid arthritis and cancer.
- Generally, the younger Doctors did not prescribe Biological Medicines, because they were not allowed to, but they wanted to start prescribing Biological Medicines. They were working in the public sector at primary, secondary and tertiary level.
- They thought Biological Medicines are used when other medication has failed.
- Infliximab and Rituximab can be prescribed for Rheumatoid arthritis were cited by the Doctors.
- Doctors were told about Biological Medicines during their undergraduate training.
- Biological Medicines were not adequately covered in standard medical textbooks.
- The Doctors' current knowledge of Biological Medicines were not substantial enough for the prescribing of Biological Medicines.
- The Doctors obtained information on Biological Medicines from the Internet or colleagues.

- There was a need for more training, seminars and guidelines.
- The young Doctors found Biological Medicines difficult to use, because they had inadequate knowledge:
    - To prescribe Biological Medicines,
    - To take care of patients on Biological Medicines.
- Biological medicines were expensive and there was a lack of information resources.

CHAPTER 4

PART 2: FACTORS INFLUENCING THE USE OF BIOLOGICAL MEDICINES IN THE FREE STATE: PRESCRIBERS' OPINIONS

4.11 INTRODUCTION

This section describes the results of the survey among the prescribers who prescribe Biological Medicines; in the Free State. This information sought included: Doctors' particulars, experience in the use of Biological Medicines, available medical information source on Biological Medicines; their role in patients' care/management using Biological Medicines; their experience of Biological Medicines with regard to efficacy, toxicity or other; any problems with obtaining Biological Medicines; undergraduate training on Biological Medicines and procurement processes.

4.12 METHODS

A prospective survey was conducted. The study population consisted of the specialists that prescribe Biological Medicines in the Free State. Selection criteria were as follows: all the specialists that prescribe Biological Medicines in the Free State. The study period was from 1 April 2017 – 30 September 2017.

The prescribers were identified at their point of work. They work in the public sector, at tertiary level as well as the private sector. They received an information leaflet about the study (cf. Appendix A1) and consent form (cf. Appendix A2) before they completed the questionnaire (cf. Appendix A4).

The therapeutic response of Biological Medicines experienced by individual patients may be influenced by the pharmacodynamics (genetic factors, physiological, pathological, tolerance and receptor interactions) and the pharmacokinetics (distribution, elimination, extent and rate of absorption; Rodney 2013). It is, therefore, of utmost importance for a clinician to take all of this into consideration before Biological Medicines can be utilized to the patient's advantage (Salvana & Salata 2009).

4.13 INFORMATION SOUGHT

The questionnaire (cf. Appendix A4) completed by the specialists is divided into different categories. The prescribers' particulars are requested in Section A, and concern their gender, age, years of work experience, whether they have a Master's degree or hold a fellowship, and their field of specialization.

Section B of the questionnaire consists of the following questions: When was the first time you started prescribing Biological Medicines, and for which condition? In the past two years, have you prescribed more Biological Medicines? Do patients sometimes demand to use Biological Medicines? At what stage of a disease do you prescribe Biological Medicines? What is the determining factor indicating when a patient should be given Biological Medicines? List the Biological Medicines you prescribe, and associated conditions.

Section C consists of different questions regarding information resources. Were they taught about Biological Medicines at any time during their medical training? Do they think Biological Medicines were adequately covered in the standard medical textbooks they used or lectures they attended? How relevant was it to their current requirement to prescribe these drugs? Where do they currently get information that enables them to prescribe and care for patients using Biological Medicines? Do they think information on Biological Medicines are readily available to all clinicians? In what ways can this information be made more readily available? What steps must be followed when prescribing Biological Medicines for a patient?

Section D has questions regarding patient care and management. How do the prescribers approach Biological Medicines? Do requirements or criteria to prescribe Biological Medicines differ from prescribing of pharmaceutical agents? How does the care of patients on Biological Medicines differ from those on pharmaceutical agents? What are the common problems the prescribers encounter in patients on Biological Medicines? When is the most suitable time to prescribers Biological Medicines? On average, when do the prescriber start giving Biological Medicines to the patients? For what reason?

Section E consists of questions regarding the clinician's perception. The prescriber was allowed to give more than one answer to a specific question. Why are Biological Medicines difficult to use? Why is Biological Medicines' use limited? When will the doctor not prescribe Biological Medicines? Do Biological Medicines have more adverse effects than pharmaceutical agents do? What factors play a role in the efficacy and safety of Biological Medicines?

Section F focus on the procurement process. Does the company (supplier or sponsor) play a role in the use of Biological Medicines, and if so, what role? What channel does the prescriber use to obtain Biological Medicines for their patients? Is the process satisfactory, and if not, how should it be improved?

4.14 INCLUSION CRITERIA

All doctors who prescribe Biological Medicines in the Free State at any time during the study period to patients.

4.15 EXCLUSION CRITERIA

Doctors who do not prescribe Biological Medicines to patients in the Free State.
Request by study participant.

4.16 PILOT STUDY

Pre-testing of the study questionnaire was done with three doctors who prescribed Biological Medicines. The objective of the pre-test was to identify difficulties and ambiguities in questions, record the time it took to complete the questionnaire to identify whether the time is reasonable and access whether the content of information received was sufficient for further evaluation. There were three grammar mistakes on the questionnaire which were corrected.

4.17 ETHICAL CONSIDERATIONS

Ethical approval was granted by the University of the Free State (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee (cf. Appendix A6 & A7). None of the medical practices was identified.

4.18 STATISTICAL ANALYSES

The data were captured in Excel, and imported into SAS (Statistical Analysis Software). The analysis was done using SAS 9.4. Descriptive statistics, namely means, medians, standard deviations, percentages and frequencies were calculated for continuous data. In some questions, the prescribers were allowed to write or choose more than one answer.

4.19 RESULTS

4.19.1 Prescribing particulars

There were 17 specialists that prescribed Biological Medicines in the Free State, and 70,6% (n = 12) of them completed the questionnaire. The study population consisted of 58,3% females and 41,7% males (cf. Appendix C, Table C1). The mean age of the specialists was 45,9 years (SD, 11.8) (cf. Appendix C, Table C2). The average number of years of work experience of the prescribers was 21,5 years (SD, 12,04) (cf. Appendix C, Table C3). Seventy-five percent of them did their Master's and 25% did their Master's and fellowship (cf. Appendix C, Table C4). Out of the 17 specialists 58,3% specialized in Clinical-Radiation Oncology (cf. Appendix C, Table C5).

4.19.2 Use of Biological Medicines

Sixty percent (n = 10) of the specialists started prescribing Biological Medicines for the first time 5 to 8 years ago (cf. Appendix C, Table C6). Fifty percent of the specialists prescribed it for non-Hodgkin's lymphoma, while 16,7% prescribed it for Melanoma (cf. Appendix C, Table C7). In the past two years 81,8% (n = 11) of the specialists prescribed Biological Medicines more often than before (cf. Appendix C, Table C8). According to the specialists 83,3% of the patients did not demand to use Biological Medicines (cf. Appendix C, Table C9). Seventy-five percent of the specialists indicated that Biological Medicines were prescribed at any stage of the disease (cf. Appendix C, Table C10).

From Figure 4.10 below, it follows that guidelines represent the determining factor when a patient should be given Biological Medicines.

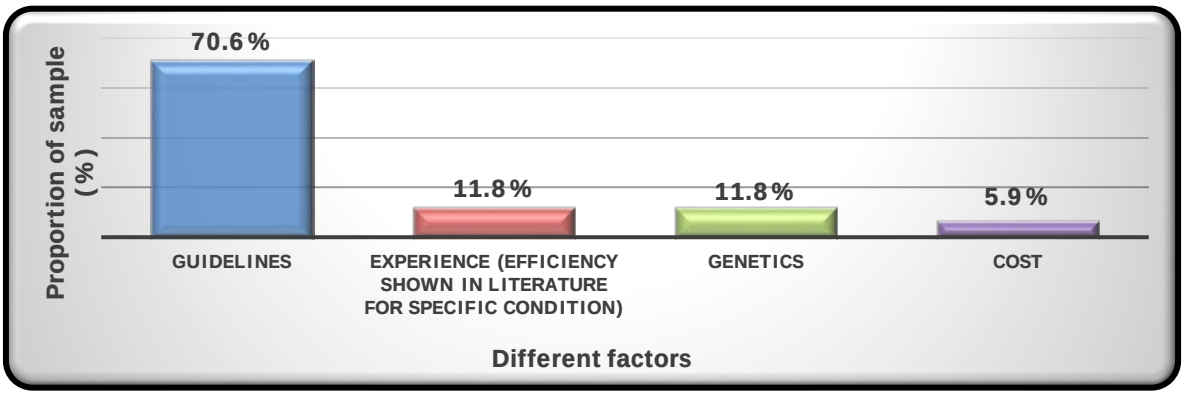


Figure 4.10: Determining factors indicating when a patient should be given Biological Medicines

Table 4.7 below shows that 75% (n = 12) of the specialists prescribed Rituximab, and it was mostly for non-Hodgkin's lymphoma, diffuse large B-cell, follicular, idiopathic thrombocytopenic purpura, and autoimmune haemolytic anaemia. Trastuzumab was prescribed by 50% (n = 12) of the specialists and is indicated for breast cancer.

Table 4.7: List of Biological Medicines prescribed and associated conditions

BIOLOGICAL MEDICINES	N = 12	PERCENTAGE	CONDITION	N = 12	PERCENTAGE
Etanercept	1	8,3%	Psoriasis	1	8,3%
			Rheumatoid Arthritis, Ankylosing Spondylitis	1	8,3%
Ustekinumab	1	8,3%	Psoriasis	1	8,3%
Interferon	1	8,3%	Melanoma	1	8,3%
Interleukin	1	8,3%	Melanoma	1	8,3%
Filgrastim	2	16,7%	Cancer Neutropenia	2	16,7%
Trastuzumab	6	50,0%	Breast Cancer	6	50,0%
Bevacizumab	2	16,7%	Colon Cancer	2	16,7%
Cetuximub	4	33,3%	Colon Cancer, Metastatic Head and Neck	4	33,3%
Rituximab	9	75%	Non-Hodgkin's Lymphoma, Diffuse Large B-cell and Follicular, Itp, Autoimmune Haemolytic Anaemia	8	75%
			Rheumatoid Arthritis	1	8,3%
Imatinib	1	8,3%	Gastrointestinal Stromal Tumour	1	8,3%
Infliximab	2	16,7%	Rheumatoid Arthritis, Ankylosing Spondylitis, Ulcerative Colitis	2	16,7%
Tociluzimab	1	8,3%	Rheumatoid Arthritis	1	8,3%
Abatacept	1	8,3%	Rheumatoid Arthritis	1	8,3%
Golimimab	1	8,3%	Rheumatoid Arthritis, Ankylosing Spondylitis	1	8,3%
Adalumimab	2	16,7%	Rheumatoid Arthritis, Ankylosing Spondylitis	2	16,7%
Alemtuzumab	1	8,3%	T-cell Lymphoma	1	8,3%

Itp = Idiopathic thrombocytopenic purpura

4.19.3 Information resource

It is noted that 83,3% (n = 12) of the specialists who prescribe Biological Medicines indicated they were taught about these Medicines during their medical training (cf. Appendix C, Table C11), while 54,5% (n = 12) indicated that Biological Medicines were not

adequately covered in the standard medical textbooks they used (cf. Appendix C, Table C12). Also 77,8% (n = 12) indicated that their current knowledge about prescribing Biological Medicines were sufficient (cf. Appendix C, Table C13).

Figure 4.11 below shows information sources for the specialists. They were allowed to give more than one answer to a specific question. An overwhelming majority of 91,7% (n = 12) of them obtained most of their information via peer-reviewed articles, and 58,3% also used the Internet for information.

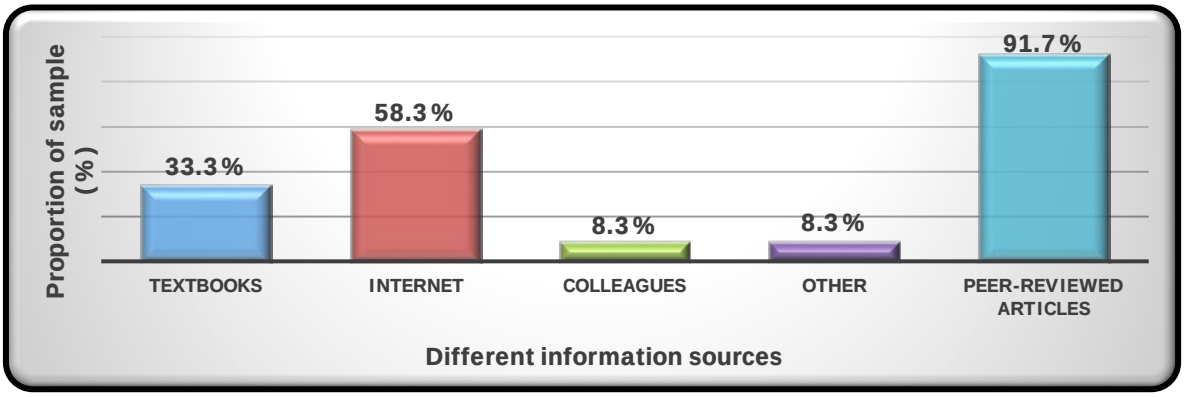


Figure 4.11: Information sources on prescribing Biological Medicines and caring for patients using Biological Medicines

Seventy-five percent (n = 12) of the doctors indicated that Biological Medicines were readily available to all clinicians (cf. Appendix C, Table C14). Furthermore, the specialists that indicated that Biological Medicines were not readily available to all clinicians suggested that there should be more education on this field in lectures (cf. Appendix C, Table C15).

Table 4.8 emphasizes the importance of the different steps that must be taken into consideration when Biological Medicines are prescribed by specialists. Sixty-six comma seven percent (n = 12) of the specialists indicated that it is important to first check the based-on guidelines that are indicated for the specific condition; that the patient met the criteria, administration to specified protocol; determine dose and scheduling premedication. Fifty-eight comma three percent (n = 12) of the respondents also indicated that it is important to exclude tuberculosis and other contra-indications.

Table 4.8: Steps to follow in deciding to prescribe Biological Medicines for a patient

DESCRIPTION	QUANTITY	PERCENTAGE
Exclude tuberculosis and other contra-indications	7	58,3%
Based-on guidelines must be indicated for the specific condition, criteria met in patient, administration to specified protocol, determine dose and scheduling premedication	8	66,7%
Apply (motivation) to medical aid or complete H101 form Department of Health	5	41,7%
Consent form from patient, religious beliefs	3	25,0%
Motivation to South Africa rheumatology association	2	16,7%
Financial implications have to be managed	2	16,7%

4.19.4 Patient care and management

Figure 4.12 below reveals how the different approaches, requirements and criteria to prescribe Biological Medicines differ from prescribing of pharmaceutical agents. Hours of motivation and paperwork are needed; for example, they must also make sure that the informed consent is signed prior to administration; this was mentioned by 33,3% (n = 12) of the specialists.

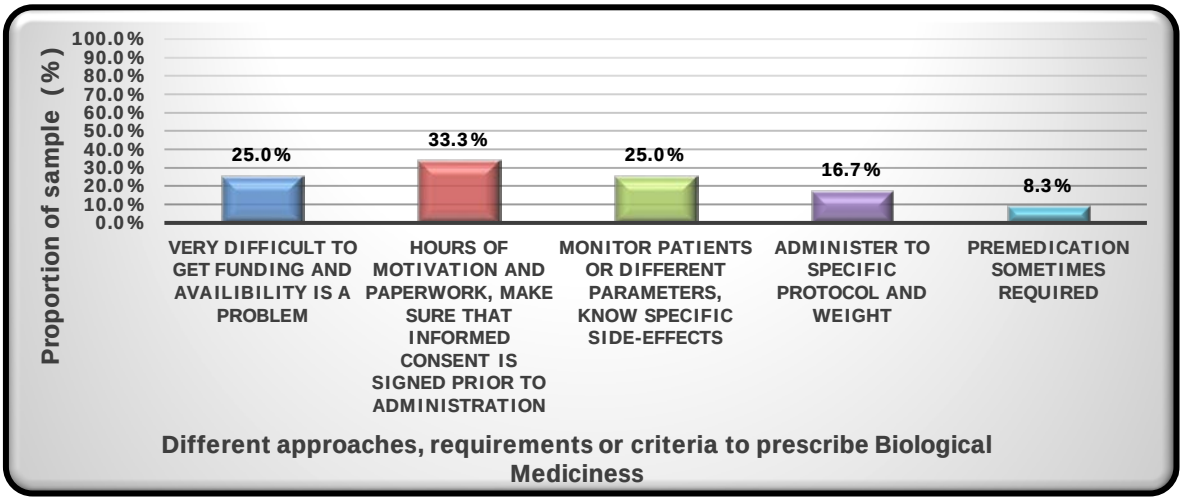


Figure 4.12: Approaches, requirements, or criteria to prescribe Biological Medicines differ from prescribing of pharmaceutical agents

Refer to Appendix C, Table C16, where 75% (n = 12) of the specialists indicated that the care of patients on Biological Medicines differ from those on pharmaceutical medicines. For example, close monitoring during administration is needed, because the side-effect profile of each patient differs, and allergic reactions are more common. Forty-one comma seven percent (n = 12) also indicated that endocrine effects must be checked; monitoring for viral replication is important; and evaluation for adverse events and complications is needed.

In Figure 4.13 below, 58,3% (n = 12) of the specialists indicated that limited access due to funding and availability was the most common problem for patients on Biological Medicines. Fifty percent of the respondents indicated that plasma concentration of Biological Medicines is useful to know for patients with poor response.

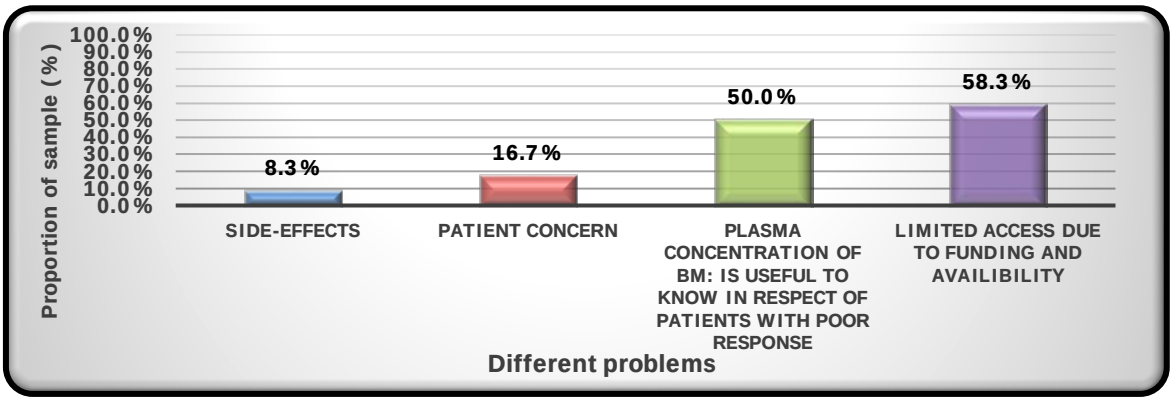


Figure 4.13: Common problems encountered in patients on Biological Medicines
BM = Biological Medicines

As seen from Figure 4.14 below, the most suitable time to prescribe Biological Medicines is either after failure of medicine normally used, or as indicated by guidelines.

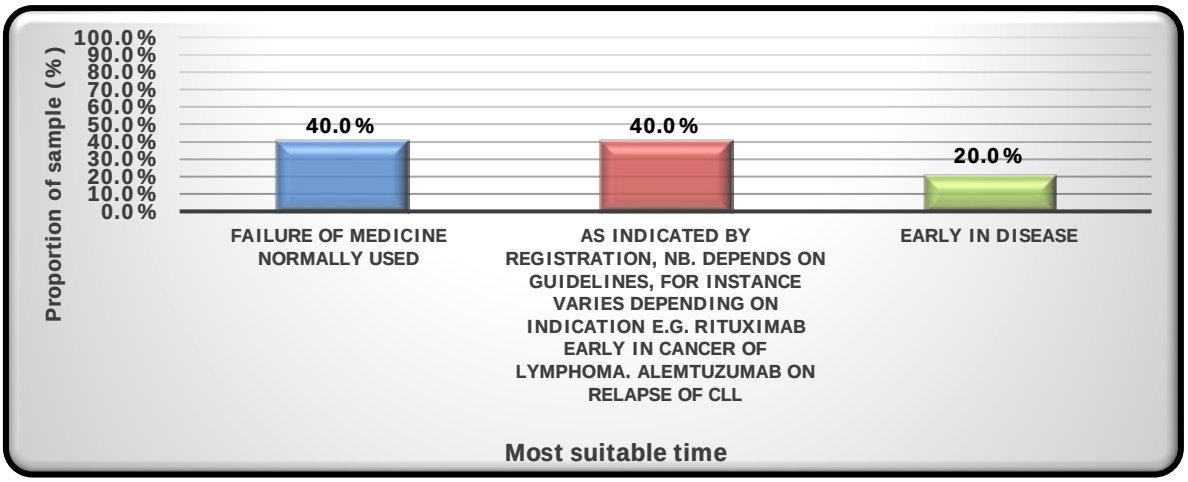


Figure 4.14: The most suitable time to prescribe Biological Medicines
E.g. = example; CLL = chronic lymphocytic leukaemia

Figure 4.15 shows that 54,5% (n = 11) start giving Biological Medicines to patients promptly, while 27,3% (n = 11) indicated that patients started getting Biological Medicines too late.

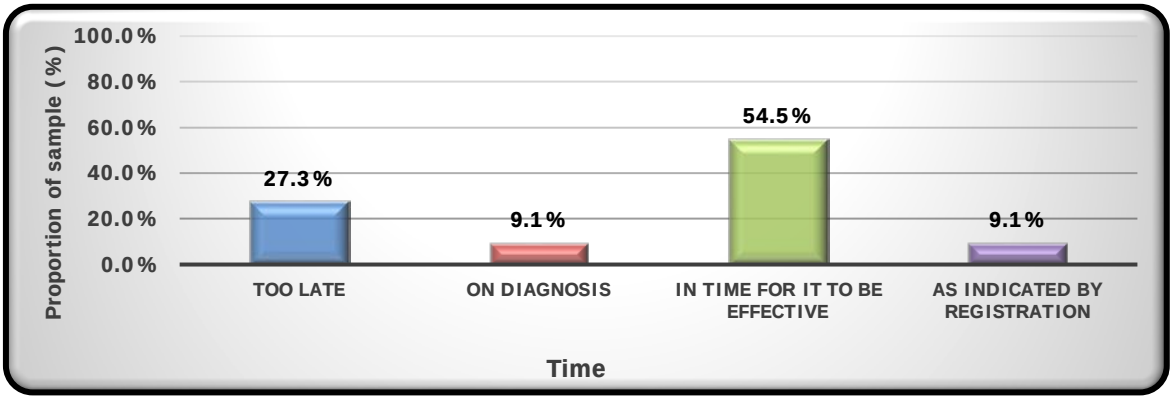


Figure 4.15: Time of giving the patient Biological Medicines

4.19.5 Specialist perception

Table 4.9 shows, a large majority of 91,7 % (n = 12) of the specialists indicated that they had limited knowledge of the pharmacology of biological agents.

Table 4.9: Biological Medicines are difficult to use

DESCRIPTION	QUANTITY	PERCENTAGE
Time-consuming in that patient selection may involve special tests	1	8,3%
They are administered parentally, hence require close monitoring	2	16,7%
Adverse reactions are more common in that patients need more review than in the case of pharmaceutical agents	2	16,7%
I have limited knowledge of the pharmacology of biological agents	11	91,7%
They are expensive	2	16,7%
Too much paper work	2	16,7%

Table 4.10 shows why the use of Biological Medicines is limited: 75,0% (n = 12) of the specialists indicated that it is difficult because of challenges with the procurement process to obtain Biological Medicines.

Table 4.10: Reasons why use of Biological Medicines is limited

DESCRIPTION	QUANTITY	PERCENTAGE
Attitudes and perceptions towards Biological Medicines: I consider genetically derived products as unsafe, hence may not recommend them to patients	0	0%
Beliefs: especially religions that do not allow use of human derivatives	1	8,3%
Availability/affordability of specialized tests for monitoring efficacy are difficult and expensive	1	8,3%
Procurement process to obtain Biological Medicines is difficult	9	75,0%
Lack of monitoring safety: adequate knowledge to enable detection of side-effects, clinical exam and lab tests	0	0%
Availability of knowledge/information about Biological Medicines is limited	0	0%

DESCRIPTION	QUANTITY	PERCENTAGE
Prescribing practice: use of guidelines or individual's ethos can limit the use of Biological Medicines	2	16,7%

Table 4.11 shows circumstances when the specialists will not prescribe Biological Medicines; 100% (n = 12) of the respondents mentioned that when there was coexisting disease such as TB or the presence of serious infections or organ failure, they would not prescribe Biological Medicines. Hundred percent (n = 12) of the specialists indicated that Biological Medicines did not have more adverse effects than pharmaceutical agents (cf. Appendix C, Table C18).

Table 4.11: Situations when specialists will not prescribe Biological Medicines

DESCRIPTION	QUANTITY	PERCENTAGE
Coexisting disease: TB or presence of serious infections or organ failure	12	100,0%
Previous treatment, especially with Biological Medicines, is associated with poor response to another biological medication	0	0%
Presence of drug antibodies: render Biological Medicines ineffective	3	25,0%

Table 4.12 below reveals that 83,3% (n = 12) of the specialists indicated that Biological Medicines should be prescribed by specialists only.

Table 4.12: Areas and levels of agreement by specialists

DESCRIPTION	QUANTITY	PERCENTAGE
Biological Medicines are more effective than pharmaceutical agents	4	33,3%
There is still much to be learned about the adverse effects of biological agents	5	41,7%
Biological Medicines should be prescribed by specialists only	10	83,3%
My patients on Biological Medicines have reported more adverse side-effects than those on pharmaceutical medicines.	0	0%
I consider prescribing Biological Medicines as a last resort when pharmaceutical medicines have failed	1	8,3%

Table 4.13 captures the factors that play a role in the efficacy and safety of Biological Medicines: 33,3% (n = 12) of the respondents stated that plasma concentrations of Biological Medicines were useful to know in patients with poor response.

Table 4.13: Factors that play a role in the efficacy and safety of Biological Medicines

DESCRIPTION	QUANTITY	PERCENTAGE
Plasma concentrations of Biological Medicines: are useful to know in patients with poor response	4	33,3%
Presence of neutralizing antibodies: likely in patients who lose response after showing good response	3	25,0%

DESCRIPTION	QUANTITY	PERCENTAGE
Genetics: some SNP polymorphism associated with better response to TNF alpha inhibitors in rheumatoid arthritis	2	16,7%
Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNF alpha	2	16,7%
I don't know	2	16,7%

TNF = Tumour necrosis factor

4.19.6 Procurement

The procurement process has a major impact on the availability of Biological Medicines. Sixty-six comma seven percent (cf. Appendix C, Table C19) of the specialist prescribers indicated that the company plays a role in the use of Biological Medicines. Sixty-two and a half percent (Appendix C, Table C20) of the respondents that indicated the company played a role in the use of Biological Medicines indicated that such a role was limited.

There are different channels that the prescribers use to prescribe Biological Medicines; it depends on whether the prescriber works in the public or the private sector. Fifty-eight comma three percent (cf. Appendix C, Table C21) indicated that Biological Medicines were dispensed by the pharmacy, sent and ordered from the company; depends on supplier, but if stock was available, the current institution works well. Refer to Appendix C, Table C22, where it is shown that 75% (n = 12) of the prescribers indicated that the process is satisfactory, while of the 25% (cf. Appendix C, Table C23) indicated that the process was not satisfactory; 33,3% suggested that the administrative burden should be reduced, while 66,7% suggested that financing from National Department of Health should improve.

4.20 SUMMARY

- Few specialists prescribed Biological Medicines.
- Few patients used Biological Medicines.
- Most of the specialist's had 5 – 8 years' experience in prescribing of Biological Medicines.
- The use of Biological Medicines by Specialists has increased.
- Biological Medicines were used appropriately for the target diseases.
- Most common Biological Medicines used:
    - Rituximab prescribed for Non-Hodgkin's Lymphoma, Diffuse Large B-cell and Follicular, Idiopathic thrombocytopenic purpura, autoimmune Haemolytic Anaemia, arthritis;

  - Trastuzumab prescribed for breast cancer;
  - Adalumimab prescribed for Rheumatoid Arthritis and Ankylosing Spondylitis;
  - Bevacizumab prescribed for Colon Cancer;
  - Infliximab prescribed for Rheumatoid Arthritis, Ankylosing Spondylitis, Ulcerative Colitis;
- Guidelines were needed to use Biological Medicines: Specialized training including pharmacology of Biological Medicines.
- Use of Biological Medicines was limited because of need for special motivation as well as increased cost.
- Biological Medicines were commonly used after other medication have failed; even then, specialists had limited knowledge of Biological Medicines.
- Biological Medicines used at the correct time were effective.
- Procurement process limited their use.

CHAPTER 4

PART 3: FACTORS INFLUENCING THE USE OF BIOLOGICAL MEDICINES IN THE FREE STATE: PATIENTS' OPINIONS

4.21 INTRODUCTION

This part presents of the results of the patient survey that evaluated the patient knowledge of, and experience with Biological Medicines and identify the factors that might influence patient compliance with Biological Medicines in some institutions in South Africa. The information sought included: patient particulars (age, weight, gender, occupation and level of education); type of Biological Medicines (name, dosage, period of use, smoking and adverse effect); other drugs in concurrent use; patients' knowledge of their disease; perception of the effects of the Biological Medicines on their diseases; adverse effects; and inconveniences (cf. Appendix A5).

4.22 METHODS

In this study, retrospective and prospective surveys was conducted. The study population consisted of patients who use Biological Medicines in the private sector as well as the public sector (in the Free State) in South Africa, who were exposed to (use) Biological Medicines at any one time during the study period from 1 April 2017 – 30 September 2017. The patients were identified via the clinicians. They received an information leaflet about the study (cf. Appendix A1) and consent form (cf. Appendix A2) before they completed the questionnaire (cf. Appendix A5). The patients were appropriately counselled and gave voluntary consent. Prospective data was collected via direct interviews with patients (cf. Appendix A5).

Ethical approval was granted by the University of the Free State (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee (cf. Appendix A6 & A7).

4.23 INFORMATION RESOURCE

The questionnaire for patients consists of the following sections. Section A contains the patient demographics: gender, height, weight, smoking status, and whether their religion allows them to use human derivatives.

Section B consists of the following questions. Does the patient know the diagnosis leading to the Biological Medicines they use? When were they first diagnosed with the disease? Name the Biological Medicines they used, duration of use, route of administration, and other chronic diseases. Does the patient use any other medicines apart from the Biological Medicines? What side-effects do the patient experience while taking Biological Medicines and what is the worst side-effect they experience?

Section C contains the information regarding the patient knowledge and experience, the disease or disorder they are suffering from. Can they explain the disease to someone else? Do they know what Biological Medicines are? From who do they receive information/ explanation regarding Biological Medicines? Are Biological Medicines improving their condition? Do they go for frequent clinical check-ups?

4.24 INCLUSION CRITERIA

All patients that received Biological Medicines at any one time from 1 April 2017 – 30 September 2017, in the Free State (South Africa); the patients were identified either by clinicians who prescribe Biological Medicines or at the institutions. All the patients were older than 18 years.

4.25 EXCLUSION CRITERIA

- Patients who cannot give consent
- Patients who are unable to express their feelings on the effects of medicines (too ill) or for whatever reason
- Patients who cannot understand English
- Children (<18 years of age).

4.26 PRE-TESTING OF STUDY QUESTIONNAIRE

Pre-testing of patients' questionnaire and interview guide were done by means of a pilot study. This was done to ensure the validity, reliability, and trustworthiness of the study. The panel for the pilot study consisted of four patients who received Biological Medicines, they were not included in the main study.

4.27 ETHICAL CONSIDERATIONS

Confidentiality was maintained at all times. Ethical approval was granted by the University of the Free State (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee (cf. Appendix A6 & A7). Patients gave their consent before they were interviewed or completed the questionnaire.

4.28 STATISTICAL ANALYSES

The data were captured in Excel, and imported into SAS (Statistical Analysis Software). The analyses were done using SAS version 9.4. Descriptive statistics, namely means, medians, standard deviations, percentages and frequencies were calculated for continuous data. In some questions, the patients were allowed to write or give more than one answer to a specific question.

4.29 RESULTS

The results of the patient questionnaire follow (cf. Appendix A5).

4.29.1 An overview of the patient's demographics

Out of the 38 patients that used Biological Medicines and were identified by the clinicians, 81,6% completed the questionnaire. One of the patient's reason why they did not complete the questionnaire was that their religion did not allow them to use it. The other four indicated that they were in too much pain to complete the questionnaire. Seventy-one percent of the patients consulted doctors in the private sector, while 29% (n = 31) consulted doctors in the public sector (Appendix D, Table D1). The patient study population consisted of 77,4% (n = 31) females (Appendix D, Table D2). Eighty comma six percent (n = 31) of the patients indicated that they did not smoke (cf. Appendix D, Table D3). The mean height of the patients was 1,69 meters (SD, 0.8) (cf. Appendix D, Table D4) and the mean weight was 82,3 kilograms (SD, 19.1) (cf. Appendix D, Table D5). The religion of patients that completed the questionnaire allowed them to use human derivatives (cf. Appendix D, Table D6).

4.29.2 A report of the medical history of the patients

Ninety-three and a half percent (n = 31) of the patients knew their diagnosis leading to the Biological Medicines they used (cf. Appendix D, Table D7). As it were, the first patient was diagnosed with the disease leading to the use of Biological Medicines in 1958 (cf. Appendix D, Table D8). The mean use of Biological Medicines was 32 months (SD, 29.9) (cf. Appendix D, Table D9). Eighty-seven comma one percent of the Biological Medicines were administrated intravenously (cf. Appendix D, Table D10). Table 4.14 specifies the other chronic conditions that patients who use Biological Medicines suffered from: 25,8% (n = 31) of them had hypertension, while 25,8% (n = 31) indicated that they did not have any (other) chronic disease.

Table 4.14: Comorbidities of the patient that used Biological Medicines (n = 31)

DESCRIPTION	QUANTITY	PERCENTAGE
Hypothyroidism	5	16,1%
Hypertension	8	25,8%
Gastroesophageal reflux	1	3,2%
Palpitations - Heart problems	3	9,7%
Multinodular thyroid, Hashimato disease	4	12,9%
Raynaud phenomenon	1	3,2%
Dermalogical Psoriasis	2	6,5%
Arterial fibrillation	3	9,7%
Diabetes	1	3,2%
None	8	25,8%
Depression	2	6,5%
HIV positive	2	6,5%
Asthma	2	6,5%

Ninety comma three percent (n = 31) of the patients used other medicines apart from the Biological Medicines (cf. Appendix D, Table D11). As seen in Table 4.15 below 57,1% (n = 28) of the patients used pain medication with their Biological Medicines and 32,1% (n = 28) of them used antimetabolites.

Table 4.15: Concurrent medications prescribed with Biological Medicines (n = 31)

DESCRIPTION	QUANTITY	PERCENTAGE
Pain	16	57,1%
Antimetabolites	9	32,1%
Rheumatoid arthritis	1	3,6%
Corticosteroid	7	25,0%
Hypertension treatment	9	32,1%
Hypothyroidism	7	25,0%
Gastric and duodenal ulcers	11	39,3%
Antidepressant	8	28,6%
Cholesterol	3	10,7%

DESCRIPTION	QUANTITY	PERCENTAGE
Hormone replacement	4	14,3%
Arthritis, ankyspondylitis, chronic back pain	2	7,1%
Anti-diabetes	2	7,1%
Folic acid	7	25,0%
Antihistamine	3	10,7%
Heart	3	10,7%
Anti-epileptic/anticonvulsant	3	10,7%
Cancer treatment (chemotherapy)	6	21,4%
Vomiting and nausea	4	14,3%
Sedation/anxiolysis	1	3,6%
Gout	4	14,3%
Constipation	1	3,6%
ARV drugs	1	3,6%
Diuretic	1	3,6%
Asthma	1	3,6%

Fifty-one comma seven percent (n = 29) of the patients indicated that they experienced side-effects with the use of Biological Medicines (cf. Appendix D, Table D12). Table 4.16 lists the different side-effects the patients experienced; 53,3% of them experienced headache when taking Biological Medicines, while 33,3% of them experienced nausea as a side-effect of the Biological Medicines.

Table 4.16: The following side-effects were experienced by the patients (n = 15)

DESCRIPTION	QUANTITY	PERCENTAGE
Abdominal Pain	1	6,7%
Infection	1	6,7%
Fever	1	6,7%
Nausea	5	33,3%
Chills	3	20,0%
Back Pain	1	6,7%
Headache	8	53,3%
Pharyngitis	1	6,7%
Constipation	2	13,3%
Night sweat	1	6,7%
Depression	1	6,7%
Allergic reaction	1	6,7%
Diarrhoea	2	13,3%
Urinary tract infection	1	6,7%
Tiredness, feeling weak	1	6,7%

Table 4.17 below shows that 33,3% of the respondents experienced tiredness as the worst side-effect while 22,0% experienced headaches.

Table 4.17: The worst side-effect experienced while being treated with drug x (Biological Medicines)

DESCRIPTION	QUANTITY	PERCENTAGE
Tiredness	5	33,3%
None	1	6,7%
Worsening of recurrent Zoster (Entanercept)	1	6,7%
Dizzy	1	6,7%
Headaches	3	20,0%
Nausea	1	6,7%
Heart Fibrilation	1	6,7%
Itchy	1	6,7%
Diarrhoea	1	6,7%
Halucination	1	6,7%
Pimples all over face and body (Ritiximab)	1	6,7%
Sinusitis (Aduliximab)	1	6,7%
Rituximab with prednisone - very tired, cramps, influenced hearing, eyes & concentration	1	6,7%
Body pain	1	6,7%
Infliximab (infection) and Abatacept (mouth ulcers)	1	6,7%
Urinary tract infection	1	6,7%
Tiredness, feeling weak	1	6,7%

4.29.3 Patient knowledge and experience

Figure 4.16 below shows that 54,8% (n = 31) was suffering from rheumatoid arthritis, while 25,8% was suffering from lymphoma cancer.

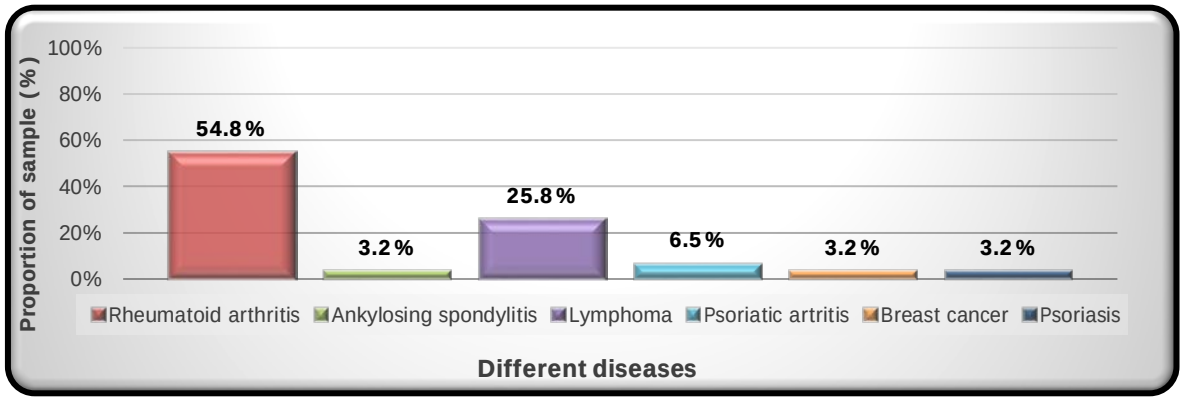


Figure 4.16: The disease or disorder of patients

Ninety comma three percent (n = 31) of the patients could explain their disease to someone else (cf. Appendix D, Table D13); 83,9% knew what Biological Medicines were (cf. Appendix D, Table D14) and 96,4% (n = 28) received information/explanation regarding the disease from their doctor (cf. Appendix D, Table D15). Ninety comma three percent of the patients pointed out that they were informed about Biological Medicines (cf. Appendix D, Table D16), and ninety-six comma four percent indicated they were informed by their doctor (cf. Appendix D, Table D17). Eighty-nine comma seven percent (n = 29) of the patients

indicated that Biological Medicines were improving their condition (cf. Appendix D, Table D18). Of the three patients that indicated Biological Medicines were not improving their condition, 33,3% (n = 3) indicated that the reason for it is that the level of pain and discomfort were not getting better; the other 33,3% (n = 3) indicated that they had not been for a scan yet to see how they would react to the treatment; and the other 33,3% indicated that they had received only one treatment yet, and that it was therefore too early to tell (cf. Appendix D, Table D19). Eighty-seven comma one percent (n = 31) of the patients went for frequent clinical check-ups (cf. Appendix D, Table D20) and of the 12,9% (n = 31) who did not go for frequent clinical check-ups, 25% (n = 4) indicated that a reason might be that “the doctor who has the knowledge and ability to treat me is too busy and the others have no clue about Biological Medicines”; 25% (n = 4) stated a reason might be living outside Bloemfontein and there was no rheumatologist; 25% (n = 4) pointed out that they did not experience any problem before the next treatment, and 25% mentioned from then onwards, check-ups would be more frequent (cf. Appendix D, Table D21).

4.30 SUMMARY

- Few patients used Biological Medicines.
- Most of the patients were private patients.
- Religious beliefs may influence the acceptance of Biological Medicines by patients.
- The majority were female and non-smoking.
- Patients knew their diagnosis that had led to the use of Biological Medicines.
- Most patients had other chronic conditions - mainly hypertension; thyroid disorders; gastric and duodenal ulcers; and depression.
- Most patients on Biological Medicines were using other drugs – hypertension, pain and thyroid medication, antidepressants and antimetabolites.
- Many patients experienced mild side-effects of Biological Medication.
- Most patients knew their Biological Medicines and were told by their doctor.
- Most patients went for frequent check-ups.
- Some patients indicated that check-ups failed because doctors were too busy or they needed to travel too far to the specialist.
- Most patients benefited from Biological Medicines.

CHAPTER 4

PART 4: FACTORS INFLUENCING THE USE OF BIOLOGICAL MEDICINES

The overall conclusion of the factors influencing the use of biological medicines after compiling survey results:

4.31 CONCLUSION REGARDING NEWLY QUALIFIED DOCTORS

From the results, the following can be regarded as important factors for the prescribing of Biological Medicines by young doctors. There was a general lack of knowledge on Biological Medicines among newly qualified doctors. Due to limitations on the prescribing of Biological Medicines, whereby young doctors are not allowed to, they were not well exposed to the use of Biological Medicines.

There is a need to educate newly qualified doctors about Biological Medicines, and support them in the form of guidelines on the use of Biological Medicines to ensure that current patients benefit. All doctors must know the available Biological Medicines and their respective indications. Furthermore, there is a need for more emphasis on Biological Medicines during undergraduate training.

4.32 CONCLUSION REGARDING THE SPECIALIST

From the results of the Specialist doctors, the following can be regarded as important factors for the prescribing of Biological Medicines. Although there was an increased use of Biological Medicines, it was only prescribed by a few specialists and used by a few patients. The procurement process, special motivation, as well as increased cost limited the use of Biological Medicines. Biological Medicines are commonly used after other medication have failed. If Biological Medicines are used at the correct time for the respective diseases, they are effective.

Doctors' knowledge about Biological Medicines needs continuous professional education, specialized training - including pharmacology of Biological Medicines and improvement via seminars, CPD events, and workshops. The procurement process to obtain Biological Medicines is complex, and dependent on financial advisory services. Furthermore, a

framework should be available to guide Doctors concerning the necessary work-up (investigation) before the administering of Biological Medicines.

4.33 CONCLUSION REGARDING THE PATIENTS

From the data collected, most of the patients were female private patients who benefited from Biological Medicines. While Biological Medicines improve the quality of life of patients, many experienced mild side-effects and most of them used other drugs concomitantly with their Biological Medicines. Thus, co-morbidities and complications need to be considered when Biological Medicines are prescribed.

Frequent patient reviews to check for infections, malignancies and other adverse effects of Biological Medicines are necessary. Most of the patients went for frequent check-ups, but some of them indicated that check-ups failed because doctors were too busy or they needed to travel too far to the specialist.

Most of the patients knew their Biological Medicines as the Doctor told them. Patient education on Biological Medication is of paramount importance, as patient understanding of the information promotes use.

Individuals' beliefs also limit the use of Biological Medicines. Therefore, staff that administer Biological Medicines must have appropriate training about Biological Medicines, to explain it to the patient in a way that the patient will understand it.

The above factors led to an in-depth study utilizing the Delphi technique in Chapter 5.

CHAPTER 5

DEVELOPMENT OF A FRAMEWORK FOR THE USE OF BIOLOGICAL MEDICINES

5.1 INTRODUCTION

In this Chapter, it is described how the Delphi technique was used to enable a panel of experts on Biological Medicines to reach a consensus on how to address the factors that affect the use of Biological Medicines in South Africa. A Delphi questionnaire was successfully used to obtain the opinions of a panel of experts on the different aspects of Biological Medicines in South Africa that were identified by the young doctors, prescribers and patients (refer to Chapter 4). These opinions were used to draft the South African proposal framework for the use of Biological Medicines.

5.2 METHODS

5.2.1 Preparation: Development of the Delphi questionnaire and related documents

A Delphi questionnaire was structured to seek the opinion of experts on the importance of the different 'factors affecting the use of Biological Medicines' that were identified by the young doctors, patients and prescribers.

The Delphi Questionnaire was divided into four sections, A, B, C & D. Section A addressed the use of Biological Medicine - more specifically, how to prescribe them. Section B was on the use of information resources on Biological Medicines, while section C addressed issues on patient care and management, and section D was on the availability, prescription, and the dispensing and procurement processes.

Each question was presented as a 'statement' to be evaluated by the respondent (expert) in respect of its importance for inclusion in the 'South African guidelines for use of Biological Medicines, using a three-point Likert scale (Likert, 1932), whereby 1 = Essential (must definitely be included); 2 = Useful (can be included); and 3 = Unnecessary (can definitely be excluded). Each section had space at the end of the section for the respondents to write comments on the issues raised or add new suggestions (cf. Appendix E2).

5.2.2 Evaluation of the questionnaire

The draft questionnaire was evaluated by four independent experts. They consisted of a medical specialist in community or public health with vast experience in the use of the Delphi method, two medical specialists (haematologist and oncologist) with vast experience in the use (prescribing) and care for patients on Biological Medicines; and a clinical pharmacologist with vast experience in the pharmacology, therapeutics at hospital level and the regulation of Biological Medicines in South Africa. These experts advised on the structure and type of questions/statements in the questionnaire that would ensure trustworthiness, reliability and validity of the study, as well as making the questionnaire user friendly. The questionnaire was modified according to the experts' inputs. Of note, these individuals did not take part in the subsequent Delphi study.

5.3 SELECTION OF THE DELPHI PANEL OF EXPERTS: THE PROCESS

Members of the Delphi panel were selected through a nationwide and international search for experts in the different aspects of Biological Medicines. These included specialists in haematology, medical microbiology, gastroenterology, clinical haematology, internal medicine, clinical pharmacology, rheumatology, clinical oncologist, oncology, pharmaceutical science, and medicines regulation. Information about the experts was sought from peers as well as literature and Internet searches.

5.3.1.1 *Inclusion criteria*

- A higher degree or specialist qualification in the respective field
- Current occupation or post designation is commensurate with continuous service in the field dealing with Biological Medicines
- Experts who gave consent.

5.3.1.2 *Exclusion criteria*

- Experts who did not give consent to participate
- Experts who had already provided advice in the study, included the experts who evaluated the questionnaire
- Experts with conflict of interest in the study.

5.3.1.3 *The Delphi panel*

Overall, a team of 20 experts was selected (marked for invitation) to form a Delphi panel. As part of the ethics non-disclosure of study participants, members of the Delphi panel cannot be disclosed. However, these experts can be described as follows:

- All had extensive experience regarding Biological Medicines;
- Some were members of the MCC expert committees, i.e., the Central Clinical Committee, and the Biological Medicines Committee of South Africa;
- Some were specialists in the following fields: Oncology, Haematology, Gastroenterology, Rheumatology, Internal Medicines, Pharmaceutical Sciences, and Medical Microbiology;
- There were two international experts in the field of Biological Medicines; and
- The team included 60% (n= 12) males, and 40% (n= 8) females.

Please note that the 20 experts (national as well as international) were nominations earmarked to be part of the Delphi panel of experts. To avoid complexity of the process, confirmation of the panel membership was only for those experts who responded to the invitation and consent.

5.4 ETHICS

A consent form (cf. Appendix E2), and the letter of invitation (cf. Appendix F1) were drafted. The Ethics Committee of the Faculty of Health Sciences, University of Free State (Project number: HSREC 154/2016) approved the study. The concept of quasi-anonymity by Keeney *et al.,* (2006:209) was utilised in the Delphi survey where the individual panel members or respondents were unknown to each other. A coding system was used to track respondents and their responses from the first to the second Round.

5.4.1 The Delphi survey and/or data collection

The flowchart in Figure 5.1 presents a summary of the two-Rounds of Delphi process used. The consent form (cf. Appendix E2), as well as letters of invitation (cf. Appendix F1) were e-mailed to 20 members of the selected expert panel. When the respective expert accepted the invitation and e-mailed the signed consent form back to the researcher, then the Delphi questionnaire was sent to the expert by e-mail; this was called Round 1 of the survey.

Consensus is assumed to exist when there is **80%** or more agreement among the members of the panel. The responses of Round 1 were analysed and statements on which a consensus had been reached (>80% agreement) were removed from the questionnaire. A new questionnaire was compiled on statements where there was no consensus or to address new suggestions from the experts. The second questionnaire was then sent back to the experts that submitted the first questionnaire. This was called Round 2 of the survey. The responses of Rounds 1 and 2 were analysed for consensus on each statement.

In this study, out of the 20 experts who were invited, only 15 responded. As per protocol, the 15 experts were confirmed as members of the Delphi panel of experts for this study. Therefore, consensus was assumed to have been achieved when at least 12 of the 15 participants agreed on a statement.

In Round 2, one of the participants indicated that he was not working in a clinical practice anymore and therefore decided to withdraw from the Delphi. Thus, there were 14 participants in Round 2 (and not 15 as in Round 1). Because of this change in the denominator (lowered), consensus was assumed to exist when there was **86%** or more agreement among the members of the panel in Round 2.

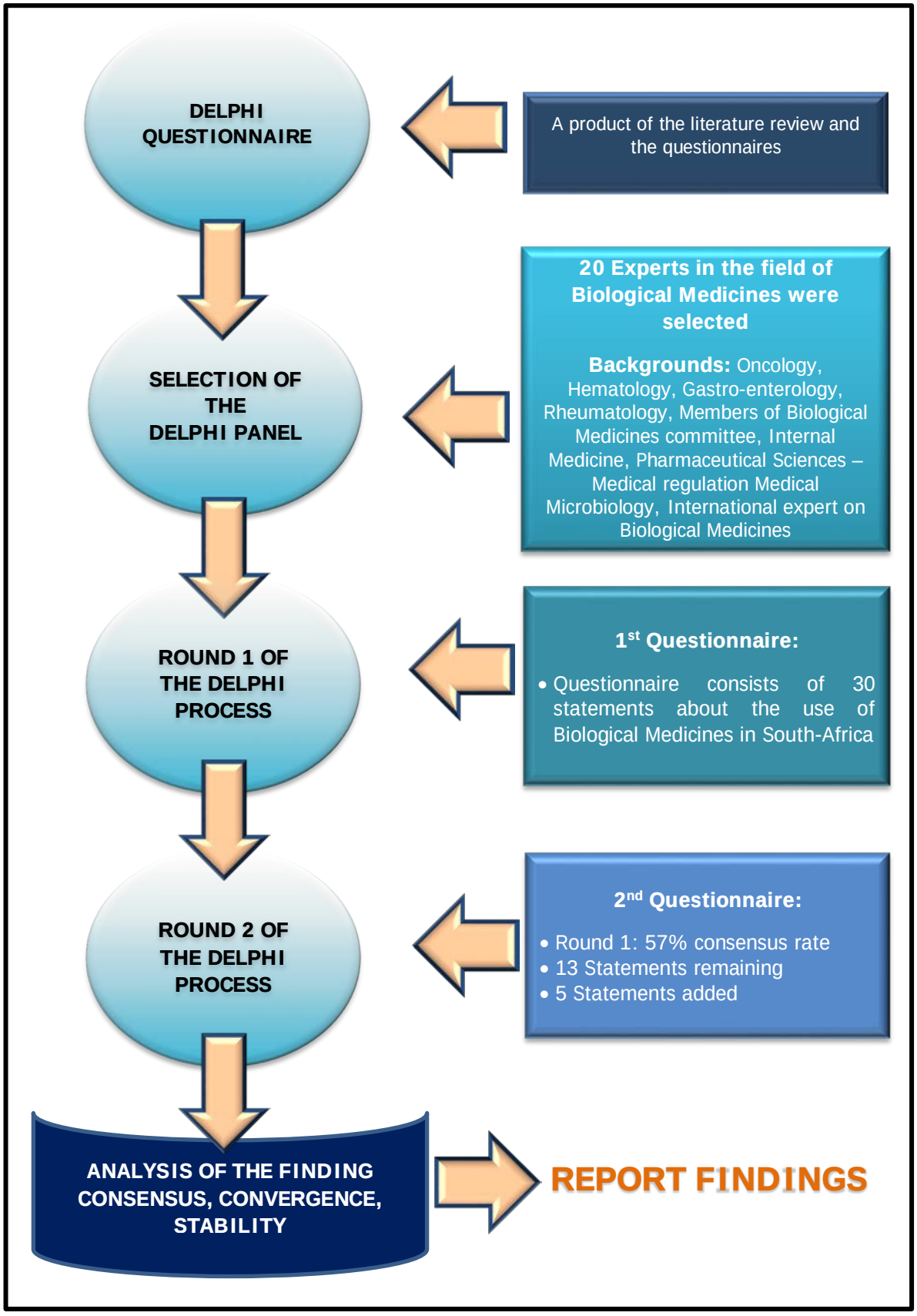


Figure 5.1: A flow chart of the two Round Delphi process utilized in the present study (Compiled by the researcher, Mocke-Richter 2018)

5.5 THE PROPOSAL FRAMEWORK

To compile such a framework, the following role players will be involved and the availability, prescribing, dispensing, and procurement need to be recognised:

- The health professional – specialist who prescribed Biological Medicines, general practitioners, and the newly qualified doctors, in the maintaining and acquiring of new and updated levels of knowledge, prescribing and dispensing of Biological Medicines
- Lecturers at the different medical institutions in South Africa have to educate skilled, competent and caring practitioners regarding Biological Medicines
- Role-players in the procurement of Biological Medicines in developing policy proposals for a uniform but flexible system
- Medical staff for providing the necessary information regarding Biological Medicines to patients
- South African Biological Medicines Committee in the administering and monitoring the prescribing and use of Biological Medicines in the South-African health care system.

5.6 RESULTS

5.6.1 Responses to the questionnaire, Round 1

Section A - contained thirteen statements focusing on the use of Biological Medicines and how to prescribe them.

5.6.2 A need for a framework

Statement A1 was '*There is a need for a framework for the use of Biological Medicines in South Africa*'. The responses were 14 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (14/15) in Round 1. This was supported by comments from some of the panel members who said that Biological Medicines are life-changing medication, and that there is therefore a need for a guideline to practitioners.

5.6.3 Biological Medicines that may not be used with coexisting diseases

Statement A2 was '*Some Biological Medicines may not be used with coexisting diseases such as TB or the presence of serious infections or organ failure'*.

The responses were 12 = essential, 2 = useful and 1 = unnecessary. This gave a response consensus score of 80% (12/15) in Round 1. This finding is in line with comments from some panel members that medicines that affect the immune system of the patient pose a definite risk and co-morbidities and complications need to be considered.

5.6.4 Administration of Biological Medicines

Statement A3 was *'The staff that administer Biological Medicines must have appropriate training about Biological Medicines, to explain it to the patient in a way that the patient will understand it'*. The responses were 14 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (14/15) in Round 1. This is also supported by comments of the panel that it is in the interest of transparency, education and good practice.

5.6.5 Availability of Biological Medicines

Statement A4 was *'Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria'*. The responses were 13 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (13/14) in Round 2. This is supported by comments from the Delphi panel received on the statement that this would be the ideal, but that costs prevent it, although it is the right of every patient to have access to it.

5.6.6 Treatment monitored by specialists

Statement A5 was *'Treatment should be initiated and monitored by specialists'*. The responses were 13 = essential, 2 = useful and 0 = unnecessary. This gave a response consensus score of 87% (13/15) in Round 1. These products require highly specialized knowledge and judgement. Biological Medicines are target specific and mimic the physiological actions of the respective endogenous compounds; they require appropriate patient selection, which involves preliminary and continuous testing for monitoring response and safety during therapy (Heinen-Kammerer *et al.,* 2007; Banacloche & Weinberg 2006).

5.6.7 Biological Medicines must be given early in disease process

Statement A6 was *'Biological Medicines must be given early in the disease process for it to be effective'*. The responses were 2 = essential, 12 = useful and 0 = unnecessary. This

gave a response consensus score of 85% (12/14) in Round 2. Consensus was reached after Round 2 that it can be useful to give Biological Medicines early in the disease. This was supported by the comment that is generally true of all medicine, but if there are other medications that are effective, biologics are not needed.

5.6.8 Patients should undergo appropriate laboratory tests

Statement A7 was *'Patients should undergo appropriate laboratory tests before Biological Medicines is administered'*. The responses were 14 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (14/15) in Round 1. The panel were in agreement during Round 1 that patients should undergo appropriate laboratory tests before Biological Medicines are administered; this will help to assess the disease activity and complications. The statement was supported by a comment from the panel members, mainly in the case of TNF blockers, which can unmask chronic infections, e.g. TB.

5.6.9 Frequent patient review

Statement A8 was *'Frequent patient review to check for infections, malignancies and other adverse effects of Biological Medicines is necessary'*. The responses were 14 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (14/15) in Round 1. The panel were in agreement during Round 1 that frequent patient reviews to check for infections, malignancies and other adverse effects of Biological Medicines is necessary as this will help to assess the disease activity and complications, and particularly for neutralising antibodies.

5.6.10 Guidelines can help in determining when a patient should be given Biological Medicines

Statement A9 was *'Guidelines can help in determining when a patient should be given Biological Medicines'*. The responses were 14 = essential, 1 = useful and 0 = unnecessary. This gave a response consensus score of 93% (14/15) in Round 1. It was interesting to note that the majority of the expert panel members indicated that guidelines could help in determining when a patient should be given Biological Medicines. It was highlighted by comments from the expert panel that this will also support good patient care.

5.6.11 Plasma concentrations of Biological Medicines

Statement A10 was *'Plasma concentrations of Biological Medicines are useful to know in patients with poor response because it is helpful to understand the lack of response/measure and adherence'*. The responses were 0 = essential, 12 = useful and 2 = unnecessary. This gave a response consensus score of 86% (12/14) in Round 2. The panel felt that it is not essential but useful to know the plasma concentrations of Biological Medicines in patients with poor response, because it is helpful to understand the lack of response/measure and adherence. Poor response could also be due to immunogenicity reactions and depends on the Biological Medicines.

5.6.12 Framework should be available to guide Doctors

Statement A11 was *'Framework should be available to guide Doctors concerning the necessary work-up (investigation) before the administering of Biological Medicines'*. The responses were 12 = essential, 3 = useful and 0 = unnecessary. This gave a response consensus score of 80% (12/15) in Round 1. Consensus was achieved in Round 1 that a framework should be available to guide doctors concerning the necessarily work-up (investigation) before the administering of Biological Medicines. It was supported by a comment from the expert panel that poor response could also be due to immunogenicity reactions – which require checking for neutralising antibodies.

5.6.13 Medicines that affect the immune system of the patient pose a definite risk

Statement A12 was *'Medicines that affect the immune system of the patient pose a definite risk'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. This gave a response consensus score of 86% (12/14) in Round 2. This was a new statement suggested for inclusion in Round 2 by a panel member. In Round 2, 12 of the 14 participants indicated that it is essential to add that medicines that affect the immune system of the patient pose a definite risk in the guidelines. The side-effects of some Biological Medicines are still not well understood. Whereas some of the side-effects are immunologic in nature, and some are related to the actions of the respective Biological Medicines, they are more complex than initially thought. The side-effect profile of Biological Medicines does not fit into the current pharmaceutical-based paradigm (Lee & Kavanaugh 2005).

5.6.14 Co-morbidities and complications need to be considered

Statement A13 was *'Co-morbidities and complications need to be considered when Biological Medicines are prescribed'*. The responses were 14 = essential, 0 = useful and 0 = unnecessary. This gave a response consensus score of 100% (14/14) in Round 2. This is a new statement that was added in Round 2. The statement was formulated out of the feedback received from Round 1, and consensus was achieved that co-morbidities and complications need to be considered when Biological Medicines are prescribed.

5.7 RESPONSES TO SECTION B

Section B - contained nine statements focusing on the information resource of Biological Medicines.

5.7.1 A step-by-step approach is needed in the development of a framework for the use of Biological Medicines

Statement B1 was *'A step-by-step approach is needed in the development of a framework for the use of Biological Medicines'*. The responses were 12 = essential, 3 = useful and 0 = unnecessary. This gave a response consensus score of 80% (12/15) in Round 1. Panel members agreed in Round 1 that a step-by-step approach is needed in the development of a framework for the use of Biological Medicines.

5.7.2 Guidelines for the use of Biological Medicines

Statement B2 was *'Guidelines for use of Biological Medicines should be readily available in a written format'*. The responses were 12 = essential, 3 = useful and 0 = unnecessary. This gave a response consensus score of 80% (12/15) in Round 1. Most of the panel members felt in Round 1 that guidelines for the use of Biological Medicines should be readily available in a written format.

5.7.3 Biological Medicines promotion programs

Statement B3 was *'Biological Medicines' promotion programs must be included in the set of guidelines'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. This gave

a response consensus score of 86% (12/14) in Round 2. A comment received on this statement was that this would facilitate industry bias.

5.7.4 Specialist knowledge of Biological Medicines

Statement B4 was *'Specialist knowledge of Biological Medicines must be improved'*. The responses were 12 = essential, 3 = useful and 0 = unnecessary. Consensus was achieved in Round 1 (12/15) with 80% that indicated that specialist knowledge of Biological Medicines must be improved as this will be in the interest of patients. Appropriate use of Biological Medicines requires cautious selection of suitable patients and identification of risk groups in order to reduce the incidence of adverse events among patients (Weber 2004).

5.7.5 Undergraduate students must be exposed more to Biological Medicines during their studies

Statement B5 was *'Undergraduate students must be exposed more to Biological Medicines during their studies'*. The responses were 12 = essential, 2 = useful and 0 = unnecessary. Consensus on the above statement was only achieved in Round 2 with 86% (12/14). This finding is supported by a comment from the panel members that this is important, because it will probably become the most commonly used medicine in future.

5.7.6 More education about Biological Medicines

Statement B6 was *'There must be more education about Biological Medicines in lectures'*. The responses were 12 = essential, 3 = useful and 0 = unnecessary. Consensus on the above statement was achieved in Round 1 with 80% (12/15). This finding is supported by a comment that it should be part of the general pharmaceutical curriculum, because it will probably become the most commonly used medicine in future.

5.7.7 All doctors must know the available Biological Medicines

Statement B7 was *'All doctors must know the available Biological Medicines and their respective indications'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. Consensus was achieved in Round 2, with (12/14), 86% participants supporting the idea that all doctors must know the available Biological Medicines and their respective indications. It was also in line with a comment received that doctors and other specialists need to know the basics about biologics and when and what to monitor in their patients.

5.7.8 Doctors' knowledge about Biological Medicines

Statement B8 was *'Doctors' knowledge about Biological Medicines needs continuous professional education / improvement via seminars / CPD evenings / workshops'*. The responses were 12= essential, 2 = useful and 0 = unnecessary. By the end of Round 2, 12 of the 14 (86%) panel members were in agreement that doctors' knowledge about Biological Medicines need continuous professional education/improvement via seminars, CPD evenings and workshops. This view ties in with that of Lee and Arthur (2005) that clinicians need to develop a better understanding of the spectrum and types of reactions of Biological Medicines, as well as the mechanisms primary to such reactions.

5.7.9 Medical students must know Biological Medicines

Statement B9 was *'Medical students must know the Biological Medicines available and their respective indications'*. The responses were 12 = essential, 2 = useful and 0 = unnecessary. It is noteworthy that during Round 1, merely 27% of the participants indicated that it is essential that medical students must know the Biological Medicines available and their respective indications, but that during Round 2, a majority of (12/14) 86% of participants indicated that it is essential.

5.8 RESPONSES TO SECTION C

Section C – Contained five statements regarding patient care and management.

5.8.1 Biological Medicines are difficult to use

Statement C1 was *'Biological Medicines are difficult to use because they are administered parentally (IV, IM or SC), hence require close monitoring'*. The responses were 0 = essential, 12 = useful and 2 = unnecessary. This gave a response consensus score of 86% (12/14) in Round 2. This was supported by comments from some of the panel members that indicated it is useful to know that Biological Medicines are difficult to use, because they are administered parentally (IV, IM or SC), hence require close monitoring.

5.8.2 Religious or cultural objection using Biological Medicines

Statement C2 was *'There may be a religious or cultural objection to using Biological Medicines*. The responses were 1 = essential, 12 = useful and 2 = unnecessary; (12/15)

80% participants indicated that it is useful to add that there may be a religious or cultural objection to using Biological Medicines.

5.8.3 Biological Medicines improve quality of life

Statement C3 was *'Biological Medicines improve the quality of life of patients'.* The responses were 13 = essential, 1 = useful and 1 = unnecessary. Thirteen of the 15 participants (87%) agreed in Round 1 that it is essential to know that Biological Medicines improve the quality of life of patients.

5.8.4 Patient understanding of information regarding Biological Medicines promotes use

Statement C4 was *'Patient understanding of information regarding Biological Medicines promotes use'*. The responses were 12 = essential, 2 = useful and 1 = unnecessary. Twelve of the 15 participants (80%) agreed in Round 1 that patient understanding of information regarding Biological Medicines promotes use is essential for the framework.

5.8.5 Patient education on Biological Medication is of paramount importance

Statement C5 was *'Patient education on Biological Medication is of paramount importance'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. Consensus was achieved during Round 2 with 12 of the 14 participants agreeing that patient education on Biological Medication is of paramount importance; this statement was added in the second Round from the feedback that was received from Round 1. It would help to improve compliance.

5.9 RESPONSES TO SECTION D

Section D – contained eight statements that focus on the availability, prescription, dispensing and procurement process.

5.9.1 The use of Biological Medicines is limited because of the procurement process

Statement D1 was *'The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex'*. The responses were 12 = essential,

1 = useful and 1 = unnecessary. Consensus was reached in Round 2 with (12/14) 86% that indicated the use of Biological Medicines was limited because the procurement process to obtain Biological Medicines was complex. This finding is in line with comments from the panel members that lack of knowledge of service providers and procurement play a role.

5.9.2 Financial advisory services are important

Statement D2 was *'Financial advisory services are important in the procurement process of Biological Medicines'*. The responses were 12 = essential, 2 = useful and 1 = unnecessary. Twelve out of the fifteen (80%) panel members agreed during Round 1 that financial advisory services are important in the procurement process of Biological Medicines. This finding is in line with comments from the panel members that it is a limiting factor for the foreseeable future, as very expensive medicines with often marginal benefit only, are involved.

5.9.3 Guidelines for the use of Biological Medicines should create a better relationship

Statement D3 was *'Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. Consensus on the above statement was achieved only in Round 2 with (12/14) 86% of the panel members agreeing that guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier.

5.9.4 Procurement process of Biological Medicines must be improved

Statement D4 was *'The procurement process of Biological Medicines is as a slow process that could be streamlined'*. The responses were 12 = essential, 2 = useful and 0 = unnecessary. This gave a response consensus score of 86% (12/14) in Round 2.

5.9.5 Limited access due to funding

Statement D5 was *'Limited access due to funding'*. The responses were 13 = essential, 1 = useful and 1 = unnecessary. In Round 1, consensus was reached with (13/15) 87%

participants that indicated that there is limited access due to funding, because it is very expensive medicine.

5.9.6 Limited access due to availability/registration

Statement D6 was *'Limited access due to availability/registration'*. The responses were 12 = essential, 2 = useful and 0 = unnecessary. Consensus on the above statement was achieved only in Round 2 with (12/14) 86% of the panel members agreeing that there is limited access due to availability/registration; in Round 1, only 47% of the panel members agreed with this statement.

5.9.7 Lack of knowledge of service providers and procurement play a role in the availability of Biological Medicines

Statement D7 was *'Lack of knowledge of service providers and procurement play a role in the availability of Biological Medicines'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. The Delphi panel reached consensus about this statement in Round 2 and (12/14) 86% of the respondents felt that lack of knowledge of service providers and procurement play a role in the availability of Biological Medicines. This statement was added in Round 2 after feedback was received from Round 1. The process of registration is complex and time consuming; and still lacks expertise.

5.9.8 Complex regulatory requirements play a role in the availability of Biological Medicines

Statement D8 was *'Complex regulatory requirements play a role in the availability of Biological Medicines'*. The responses were 12 = essential, 1 = useful and 1 = unnecessary. This statement was added in Round 2 after feedback was received from Round 1. Consensus on the above statement was achieved in Round 2 with (12/14) 86% of the panel members indicating that complex regulatory requirements play a role in the availability of Biological Medicines.

5.10 SUMMARY OF EXPERTS' RECOMMENDATIONS

In Round 1, the experts reached consensus on the following statements:

- There is a need for a framework for the use of Biological Medicines in South Africa.

- Some Biological Medicines may not be used with coexisting diseases such as TB or the presence of serious infections or organ failure.
- The staff that administer Biological Medicines must have appropriate training about Biological Medicines, in order to explain it to the patient in a way that the patient will understand it.
- Treatment should be initiated and monitored by specialists.
- Patients should undergo appropriate laboratory tests before Biological Medicines are administered.
- Frequent patient reviews to check for infections, malignancies and other adverse effects of Biological Medicines are necessary.
- Guidelines can help in determining when a patient should be given Biological Medicines.
- Plasma concentrations of Biological Medicines are useful to know in patients with poor response, because it is helpful to understand the lack of response/measure and adherence.
- A step-by-step approach is needed in the development of a framework for the use of Biological Medicines.
- Guidelines for use of Biological Medicines should be readily available in a written format.
- Specialist knowledge of Biological Medicines must be improved.
- There must be more education about Biological Medicines in lectures.
- There may be a religious or cultural objection to using Biological Medicines.
- Patient understanding of information regarding Biological Medicines promotes use
- Biological Medicines improve the quality of life of patients.
- Limited access due to funding.

In Round 2, the experts reached consensus on the following statements:

- Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria.
- Biological Medicines must be given early in the disease process for it to be effective.
- Biological Medicines promotion programs must be included in the set of guidelines.
- Undergraduate students must be exposed more to Biological Medicines during their studies.
- All doctors must know the available Biological Medicines and their respective indications.

- Doctors' knowledge about Biological Medicines needs continuous professional education / improvement via seminars / CPD evenings / workshops.
- Medical students must know the Biological Medicines available and their respective indications.
- Biological Medicines are difficult to use because they are administered parentally (IV, IM or SC), hence require close monitoring.
- The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex.
- Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier.
- Limited access due to availability/registration.

New statement added in Round 2 received from comments in Round 1, where consensus was reached in Round 2:

- Medicines that affect the immune system of the patient pose a definite risk.
- Co-morbidities and complications need to be considered when Biological Medicines are prescribed.
- Patient education on Biological Medication is of paramount importance.
- Lack of knowledge of service providers and procurement play a role in the availability of Biological Medicines.
- Complex regulatory requirements play a role in the availability of Biological Medicines.

5.11 DESIGN OF THE FRAMEWORK FOR THE USE OF BIOLOGICAL MEDICINES IN SOUTH AFRICA

The proposed framework for the use of Biological Medicines is hereby set by classifying the experts' recommendations into five categories, namely, Training, Resources, Regulations, the Patient, and the Community. Of note, some of the recommendations may appear in more than one category.

5.11.1 Training

Appropriate training focus on undergraduate and postgraduate (Specialists) programmes and refer to follow up on patients and provide patient information to students, manage

patients and drawing up guidelines for Biological Medicines use (cf. Figure 5.2). The experts in the field of Biological Medicines support it with the following statements.

- There must be more education about Biological Medicines in lectures;
- Undergraduate students must be exposed more to Biological Medicines during their studies;
- All doctors must know the available Biological Medicines and their respective indications;
- Medical students must know the Biological Medicines available and their respective indications;
- Frequent patient reviews to check for infections, malignancies and other adverse effects of Biological Medicines are necessary;
- Biological Medicines promotion programs must be included in the set of guidelines;
- Guidelines can help in determining when a patient should be given Biological Medicines;
- The staff that administer Biological Medicines must have appropriate training about Biological Medicines, in order to explain it to the patient in a way that the patient will understand it; and
- Biological Medicines are difficult to use because they are administered parentally (IV, IM or SC), hence require close monitoring.

5.11.2 Information resources

Pharmacology of Biological Medicines must be covered well in standard medical textbooks, and use for seminars, continuing medical education programme and expert groups (cf. Figure 5.2B). It is supported by the following statements of the expert opinions.

- Some Biological Medicines may not be used with coexisting diseases such as TB or the presence of serious infections or organ failure;
- Guidelines for use of Biological Medicines should be readily available in written format;
- A step-by-step approach is needed in the development of a framework for the use of Biological Medicines specialist knowledge of Biological Medicines must be improved;
- There must be more education about Biological Medicines in lectures;
- All doctors must know the available Biological Medicines and their respective indications; and
- Doctors' knowledge about Biological Medicines needs continuous professional education / improvement via seminars / CPD evenings / workshops.

5.11.3 Availability: Regulations

Biological medicines must not be the last resort; therefore, there should be more approved Biological Medicines on the market; the government should improve funding; it should be put on the standard medicine code list of Department of Health; it must be given in time for the patient to benefit (cf. Figure 5.2C). The following expert statements support these points:

- Treatment should be initiated and monitored by specialists;
- Limited access due to funding;
- Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria;
- Biological Medicines must be given early in the disease process for it to be effective;
- The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex;
- Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the suppliers;
- Limited access due to poor availability, restricted registration;
- Complex regulatory requirements play a role in the availability of Biological Medicines; and
- Lack of knowledge of service providers and procurement plays a role in the availability of Biological Medicines.

5.11.4 Patients need adequate information

Patients need adequate knowledge to improve compliance; to know what to do when they experience side-effects; and to guide them when there is a religious or cultural objection (cf. Figure 5.2D). The following expert statements support these points:

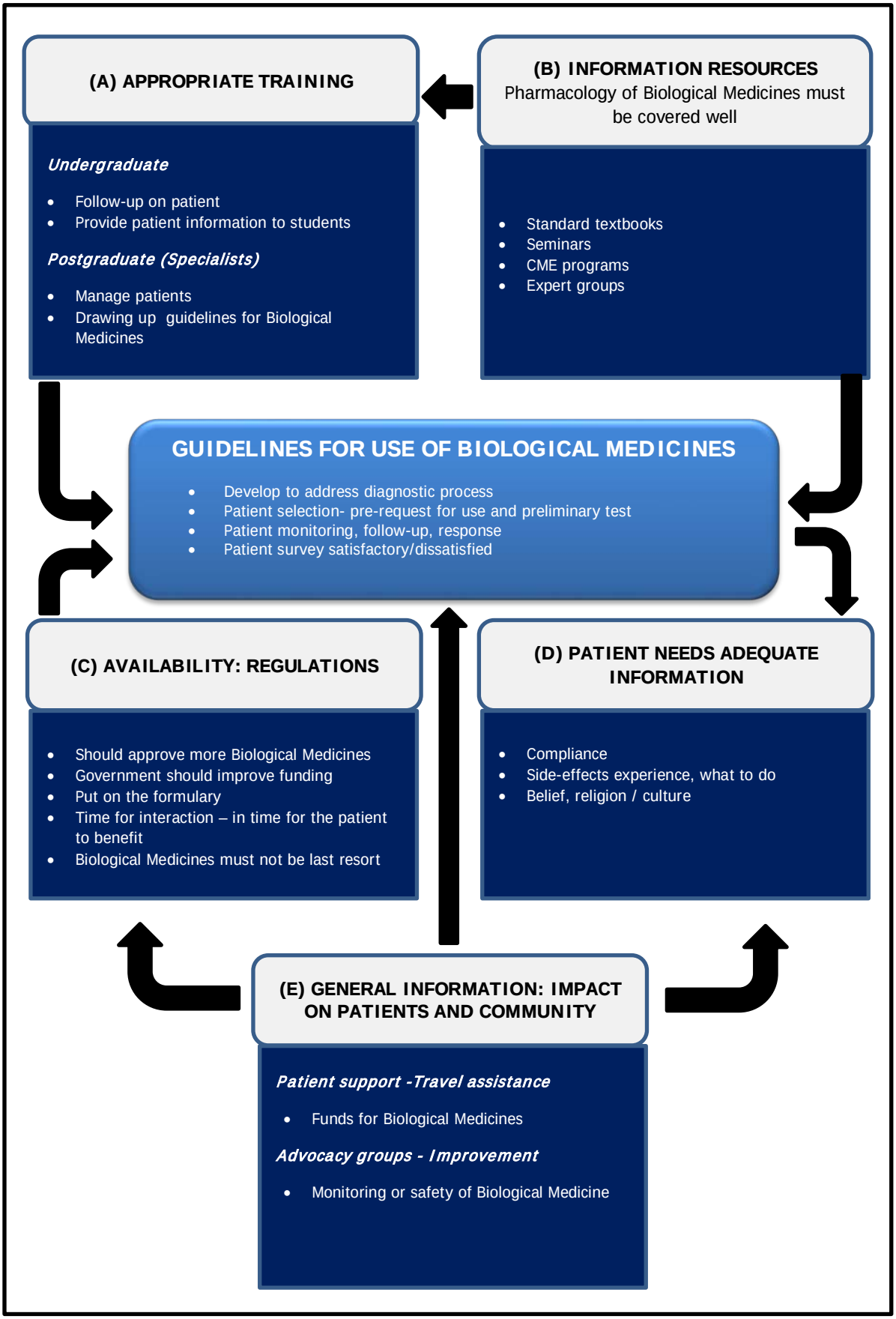
- Individuals' belief limits the use of Biological Medicines;
- Patient understanding of information regarding Biological Medicines promotes use;
- There may be a religious or cultural objection to using Biological Medicines; and
- Frequent patient reviews to check for infections, malignancies and other adverse effects of Biological Medicines are necessary.

5.11.5 General information: Impact on patients and community

Patient support in the form of travel assistance and funds for Biological medicines and advocacy group improvement is needed (cf. Figure 5.2.E). The following expert statements support it:

- Biological Medicines improve the quality of life of patients;
- Medicines that affect the immune system of the patient pose a definite risk;
- Co-morbidities and complications need to be considered when Biological Medicines is prescribed;
- Patient education on Biological Medication is of paramount importance; and
- Patients should undergo appropriate laboratory tests before Biological Medicines are administered.

Figure 5.2 illustrates the framework for guidance in the use of Biological Medicines in South Africa divided into five different categories. The different stakeholders in these categories ought to draft the appropriate guidelines and monitoring mechanisms for use of Biological Medicines.



CME – Continuing Medical Education

Figure 5.2: Framework: Findings of the research

5.12 FRAMEWORK CONTAINING FINDINGS OF THE RESEARCH

The framework containing the findings of the research will be brought to the attention of the Biological Medicine Committee of South Africa, the Medicine Control Council, as well as the National Department of Health. It will furthermore be recommended that the framework that was developed may be adapted by the health care professionals who prescribe Biological Medicines. The research findings will be submitted to academic journals with a view to publication, as well as presented at conferences.

5.12.1 Discussion

According to the Business Dictionary (2019) a framework is a broad overview, outline, or skeleton of interlinked items which support a particular approach to a specific objective, and serves as a guide that can be modified as required by adding or deleting items. The American Heritage dictionary of the English language defines a framework as “a set of assumptions, concepts, values and practices that constitutes a way of viewing reality”. This proposed framework is evidence based and unique since it was developed through a process. The literature review was used to compile the questionnaires for newly qualified doctors, specialists who prescribed Biological Medicines as well as the patients who received Biological Medicines. The data was captured and thereafter a Delphi questionnaire was compiled; this was sent to 20 experts in the field of Biological Medicines and finally the framework was developed through a process of consensus achievement of stakeholders by the Delphi questionnaire.

There is a definite need for this framework to become a reality. Adapting the elements of the framework will address the challenges of Biological medicines regarding ease of access and rational use.

The provision of information resources of Biological Medicines is limited, therefore information of Biological Medicines is not well covered in medical textbooks - compared to the information that is available on pharmaceutical agents. This is clearly noticeable when you compare the information of Biological Medicines and pharmaceutical agents in Pharmacology (cf. Appendix H) (Bremer & Stevans 2018) as well as Harrison’s principles of Internal Medicines (Jameson *et al.* 2018).Therefore textbooks need to be revised to increase covering. There is a need to develop a modified training curriculum to include information on Biological medicines to meet the needs of patients and prescribers. Improved knowledge

of Biological Medicine leads to improved care of patients on these agents; therefore, the doctors will be better equipped to serve the community.

The framework will be presented to the following role players involved in the availability, prescribing, dispensing and procurement for implementation.

- The health professional – specialists who prescribe Biological Medicines, general practitioners, and the newly qualified doctors, in the maintaining and acquiring of new and updated levels of knowledge, prescribing and dispensing of Biological Medicines.
- Lecturers at the different medical institutions in South Africa who have to educate skilled, competent and caring practitioners regarding Biological Medicines. Role players in the procurement of Biological Medicines in developing policy proposals for a uniform but flexible system.
- Medical staff for providing the necessary information regarding Biological Medicines to patients; to improve patients' education of Biological Medicines.
- The South African Biological Medicines Committee in the administering and monitoring the prescribing and use of Biological Medicines in the South African health care profession.
- The South-African Health care department.

CHAPTER 6

CONCLUSION, CHALLENGES AND RECOMMENDATIONS

6.1 CONCLUSION

The two-fold aim of the study was to identify the factors influencing the utilization of Biological Medicines in the Free State (South Africa), and to develop a framework for the use of Biological Medicines in South Africa. In pursuit of this aim, the following were achieved:

1. First, the factors that might influence the utilization of biological medicines by young doctors (practice ≥ 2) in the Free State province were identified and are summarised here as follows:

a) Regarding Knowledge of biological medicines:
   - The young doctors demonstrated a general lack of knowledge on biological medicines.
   - The young doctors indicated that they found biological medicines difficult to use.

b) Regarding availability of study resources on biological medicines.
   The young doctors indicated that:
   - Biological Medicines were not adequately covered in standard medical textbooks
   - Their undergraduate training on Biological Medicines was not adequate
   - Currently, they get information on Biological Medicines from the Internet or colleagues
   - There was a need for more training, seminars and guidelines on biological medicines.

c) Regarding their readiness to prescribe Biological Medicines:
   - The young doctors concurred that their current knowledge of Biological Medicines was not adequate for the prescribing and management of patients on Biological Medicines, including follow up.

d) Regarding limitations of their access to Biological Medicines, the young doctors indicated that, by policy, in their health facilities:

- They are generally not allowed to prescribe Biological Medicines
- Biological medicines are used only when other medication has failed
- Biological medicines are very expensive to use
- There is a lack of information resources on Biological Medicines.

2. Secondly, the factors that might influence the prescribing of Biological Medicines by the prescribing specialists in the Free State province were identified and are summarised here as follows:

a) Regarding the type of biological medicines used or on the market in the Free State province, the prescribing specialists observed that:
   - A wide variety of biological medicines are available and used in the province, even though those used for treatment of cancer and inflammatory or rheumatic disorders featured most. This implies that our clinicians will need to be knowledgeable on all types of Biological Medicines produced.
   - There was an increase in use of Biological Medicines, even though patients do not demand Biological Medicines.
   - Biological Medicines should be prescribed by specialists only.

b) Regarding availability of study resources on Biological Medicines, the prescribing specialists indicated that:
   - They were taught on Biological Medicines during their specialist training.
   - Currently, they get information on Biological Medicines from peer-reviewed articles.
   - Information on Biological Medicines was not adequately covered in standard medical textbooks.
   - There is a need for more education and lectures on Biological Medicines.

c) Regarding their knowledge of Biological Medicines, the prescribing specialists indicated that:
   - Their current knowledge on the respective Biological Medicines is sufficient.
   - At the same time, almost all (91%) agreed that they had limited knowledge of the pharmacology of Biological Medicines.

d) Regarding their readiness to prescribe of Biological Medicines, the prescribing specialists indicated that:

- Biological Medicines are currently used appropriately for the respective diseases.
- Specialized training including pharmacology of the use of Biological Medicines is needed.
- Availability of guidelines is essential to the prescribing of Biological Medicines.
- When Biological Medicines are used at the correct time, they are effective.
- Biological Medicines should be available to all clinicians who need to use them.
- Plasma concentrations of Biological Medicines are useful to know in patients with poor response.

e) Regarding limitations on the use of Biological Medicines, the prescribing specialists indicated that, by policy, in health care facilities:

- The procurement process to obtain Biological Medicines is difficult (owing to the need for special motivations, paper work involving line-managers' and committee reviews, informed consent, etc.).
- The high cost of Biological Medicines versus limited funds to the health facilities or patients limits their utilization.
- Requirements for special screening tests or patients' selection, treatment and monitoring of patients on Biological Medicines increase costs.
- Few specialists are allowed to prescribe Biological Medicines in each facility.
- Few patients are using Biological Medicines.
- Most Biological Medicines are commonly used after other medication have failed.

3. Thirdly, the factors that might influence patients use compliance with Biological Medicines in the Free State Province were identified and are summarised here as follows:

a) Regarding the patient population utilising Biological Medicines:

- Overall, very few patients used Biological Medicines.
- Most of the patients were private patients.
- The majority were female and non-smoking.
- Most of the Biological medicines were administered intravenously.

b) Regarding patient knowledge on Biological Medicines:
   - Most patients knew (could explain) their diagnosis that had led to the use of Biological Medicines.
   - Most of the patients had Rheumatoid Arthritis or Cancer.
   - Most patients knew about the Biological Medicine they were using, i.e., they could name the medicine and/or give a layman's explanation of the mechanism of action.
   - Most patients were informed about their Biological Medicines by their doctor.

c) Confounding factors to the use of Biological Medicines:
   - Most patients had other co-morbid conditions: mainly hypertension, thyroid disorders, gastric and duodenal ulcers and depression.
   - Most patients on Biological Medicines were using other drugs: mainly for hypertension, pain, thyroid disorders, antidepressants and antimetabolites.
   - Most patients experience side-effects (mainly headaches and GIT disturbances) while using Biological Medicines, but they were considered mild or manageable, as they did not lead to stopping of treatment with the Biological Medicine.

d) Meeting the treatment requirements:
   - Most patients went for frequent check-ups as scheduled.
   - A few indicated that their check-ups failed because doctors were too busy or they needed to travel too far to the specialist.

e) Benefits of Biological Medicines:
   - Most patients indicated that the Biological Medicines were improving their condition.

f) Limitations to use of biological medicines:
   - Religious beliefs may influence the acceptance of Biological Medicines by patients as some patients' religion is against use of biological therapies.
   - Please note, in these patients, cost and supply (stock availability) were not a limiting factor because they had already procured the medicines.

3. Lastly, using a team of experts on Biological Medicines to evaluate and integrate the opinions from the three stakeholders (i.e., the young doctors, prescribing specialists, and patients) by the Delphi method, a framework for the use of Biological Medicines in

the Free State province was developed. The framework proposes that appropriate use of Biological Medicines requires establishment of '**guidelines for use of Biological Medicines'** but only after successful implementation of the following five factors:

i. Ensuring **appropriate training of health professionals** (medical practitioners and specialists) on Biological Medicines by revising the training syllabus to improve coverage on Biological Medicines.
ii. Improved coverage and availability of **study resources** on biological medicines (standard textbooks, journals, seminars, CME, and other).
iii. Improving the **availability of Biological Medicines** to clinicians who need to use them. This includes the drug regulatory authority processes, availability of funds and the easing of procurement processes, etc.
iv. Promoting **appropriate patient information** to ensure compliance and timely response in case of problems.
v. Promoting a **well-informed community** about Biological Medicines, with the aim of improving appropriate patient support and pharmaco-vigilance on biological medicines.

6.2 CHALLENGES WITH THE STUDY

The challenges experienced with this study were:

- To stay in the timeframe; due to the fact that questionnaires were used, it took a lot of energy and was time consuming to receive it back.
- A further openness was the Delphi method; due to the fact that experts were used to complete the questionnaire, they had busy programs and did not observe the deadline of the Delphi questionnaires.

6.3 RECOMMENDATIONS

In order for the study to yield valuable and significant results, the researcher takes the liberty to recommend the following:

- The framework should be presented to the South-African Biological Medicines Committee, the Medicine Control Council of South Africa as well as the National Department of Health, for adaption and implementation.

- Using the data and results of the findings to publish several articles in accredited subject journals.
- The framework should be presented to all experts who participated in the Delphi method as collection of the data might have raised this expectation from them.
- To present the framework at National as well as International conferences.
- The framework should be available to guide Doctors concerning the necessary work-up (investigation) before the administering of Biological Medicines.
- To present the factors that influence the use of Biological Medicines at CPD evenings.
- The framework will be submitted to the different medical institutions in South Africa. Lectures at the different medical institutions in South Africa have to educate skilled, competent and caring practitioners regarding Biological Medicines.

REFERENCES

Aberer, W., Bircher, A. Romano, A., Blanca, M. Campis, P., Fernande, Z., Brockow, K. & Pichler, W.J. 2003. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy* (58):854-863.

Adams, G.P. & Weiner, L.M. 2005. Monoclonal antibody therapy of cancer. *Nature biotechnology*. 23(9):1147-1157.

Ali, A.K. 2005. Using the Delphi technique to search for empirical measures of local planning agency power. *The Qualitative Report* 10(4):718-744.
http://www.nova.edu/ssss/QR/QR10-4/ali.pdf
Accessed: 10 June 2018.

Aubin, F., Carbonnel, F. & Wendling, D. 2013. The complexity of adverse side-effects to biological agents. *Journal of Crohn's and Collitis* 7(4):257-262.

Banacloche, G.J.C. & Weinberg, G.A. 2007. Monoclonal Antibody Therapeutics and Risk for Infection. *Paediatric Infectious Disease Journal* (26):1049-1052.

Barbaud, A., Granel, F., Waton, J. & Poreaux, C. 2011. How to manage hypersensitivity reactions to Biological Medicines. *Eur J Dermatol* (21):667-674.

Bremer, M.G. & Stevans, W.C. 2018. Pharmacology. 5th Edition. Elsevier. 343 -353 & 507-519.

Chawla-Sarkar, M., Lindner, D.J., Liu, Y.F., Williams, B., Sen, G.C., Silverman, R.H. & Borden, E.C. 2003. Apoptosis and interferons: role of interferon-stimulated genes as mediators of apoptosis. *Apoptosis* 8(3):237-249.

Child, K. 2015. Biologics' sickening cost. https://www.timeslive.co.za/news/south-africa/2015-01-26-biologics-sickening-cost/
Accessed: 17 June 2019.

Clarke-Farr, P.C. 2005. The development of a post-graduate education and training programme for health care workers for the prevention and management of ocular complications in diabetic patients. Bloemfontein: University of the Free State. 226-228.

Clayton, M.J. 1997. Delphi: A technique to harness opinion for critical decision-making tasks in Education. *Educational Psychology* 17(4):373-386.

Critcher, C. & Gladstone, B. 1998. Utilising the Delphi technique in policy discussion: A case study of a privatized utility in Britain. *Public Administration* 76:431-449.

Daïen, C & Morel, J. 2014. Predictive factors of response to Biological Disease Modifying Antirheamatic Drugs: Towards personal medicine. Mediators of Inflammation. http://dx.doi.org/10.1155/2014/386148
Accessed: 22 April 2016.

Dalkey, N.C. 1969. The Delphi Method: An Experimental Study of Group Opinion. Santa Monica, CA: The Rand Corporation.

De Villiers, M.R., De Villiers, P.J.T. & Kent, A.P. 2005. The Delphi technique in health sciences education research. *Medical Teacher* 27(7):639-643.

Descotes J. & Gourand A. 2008. Clinical immunotoxicity of therapeutic proteins. *Expert Opinion Drug MetabToxicol* 4:1537-1549.

Donzeau, M. & Knappik, A. 2007. Recombinant Monoclonal Antibodies. Chapter 2. In: Monoclonal antibodies: Methods and Protocols. 1st Edition. Totowa NJ: Humana, 15-32.

Drummond, M.D., Brixner, D., Gold, M., Kind, P., McGiure, A. & Nord, E. 2009. Toward a consensus on the QALY. *Value health* 12(1):1281-1290.

Framework. 2019. BusinessDictionary.com. Web Finance, Inc.
http://www.businessdictionary.com/definition/framework.html
Accessed: 3 June 2019.

Gad, S.G. 2007. Growth Factors, Cytokines, and Chemokines: Formulation, Delivery and Pharmacokinetics. Chapter 8.2. In: Handbook of Pharmaceutical Biotechnology. Eds: Cao, H. & Lin, R. Hoboken NJ: Wiley & Sons, 149-168.

Goodman, C.M. 1987. The Delphi technique. A critique. *Journal of Advanced Nursing* 12:729-734.

Gunasekaran, K., Pentony, M., Shen, M., Garrett, L., Forte, C., Woodward, A., Bin Ng, S., Born, T., Retter, M., Manchulenko, K., Sweet, H., Foltz, I., Wittekind, M. & Yan, W. 2010. Enhancing antibody Fc heterodimer formation through electrostatic steering effects. Applications to bispecific molecules and monovalent IgG. *The journal of Biological chemistry* 285(25): 19637-19646.

Harris, L.J.S.B., Larson, K.W., Hasel, J., Day, A., Greenwood & Mcpherson, A. 1992. The three-dimensional structure of an intact monoclonal antibody for canine lymphoma. *Nature* 360:369-372.

Heinen-Kammerer, T., Daniel, D., Stratman, L., Rychlik, R. & Boekncke, W.H. 2007. Cost effectiveness of psoriasis therapy with entanercept in Germany. *J DtschDermatolGes*. (5):762-768.

Holilinger, P. & Hudson, P.J. 2005. Engineered antibody fragments and use of single domains. *Nature Biotechnology* 23:1126-1136.

Hsu, C.C. & Sandford, B.A. 2012. Encyclopedia of Research Design. Delphi Technique. http://dx.doi.org/10.4135/9781412961288
Accessed: 28 February 2016.

Imai, K. & Takaoka, A. 2006. Comparing antibody and small-molecule therapies for cancer. *Nature Reviews Cancer* 6:714-727.

Jameson, J.L., Kasper, D.L., Longo, D.L., Fauci, A.S., Hauser, S.L., & Loscalzo, J. 2018. Harrisons Principles of Internal Medicine. *Oncology & Hematology* 4:465-498.

Joensuu, J.T., Huoponen, S., Aaltonene, K.J., Konttinen, Y.T., Nordstrom, D. & Blom, M. 2015. The Cost-Effectiveness of Biologics for the Treatment of Rheumatoid Arthritis: A Systemic Review. *PLOS One*. 10(3):e0119683.

Jones, J. & Hunter, D. 1995. Consensus Methods for Medical and Health Services Research. *BMJ* 311(7001):376–380.

Keeney, S., Hasson, F. & McKenna, H. 2006. Consulting the oracle: Ten lessons from using the Delphi technique in nursing research. *Journal of Advanced Nursing* 53(2):205-212.

Kennedy, H.P. 2004. Enhancing Delphi research: Methods and results. *Journal of Advanced Nursing* 45(5):504-511.

Kohler, G. & Milstein, C. 1975. Continuous cultures of focused cells secreting antibody of predefined specificity. *Nature* 256:495-497.

Lee, S.J. & Kavanuagh, A. 2005. Adverse reactions to biological agents: focus on autoimmune disease therapies. *J Allergy ClinImmunolm* 116:900-905.

Likert, R. 1932. A technique for the measurement of attitudes. *Archives of Psychology* 22(140):1–55.

Linstone, H.A. & Turoff, M. 2002. The Delphi method: techniques and applications. http://www.is.njit.edu/pubs.php
Accessed: 5 June 2018.

Loo, R. 2002. The Delphi method, a powerful tool for strategic management. *Policing. An International Journal of Policy Strategies & Management* 25(4):762-769.

Mayer, G. 2017. Immunoglobulins – structure and function. Chapter 4. University of South Carolina School of Medicine. Microbiology and Immunology On-line.
https://www.microbiologybook.org/mayer/IgStruct2000.htm
Accessed: 20 June 2019.

McKenna H. 1994. The Delphi technique: a worthwhile approach to nursing. *J Adv Nurs* 19: 1221-1225.

Michigan State University. 1994. Delphi Technique. Extension Information Management Program. http://www.msue.msu.edu/msue/imp/modii/iii00006.html
Accessed: 6 June 2018.

Murry, J.W. & Hammons, J.O. 1995. Delphi: A versatile methodology for conducting qualitative research. *The Review of Higher Education* 18(4):423-436.

Naisbitt, D.J., Gordon, S.F., Pirmohamed, M. & Park, B.K. 2000. Immunological principles of adverse drug reactions: the initiation and propagation of immune responses elicited by drug treatment. *Drug Saf* 23:483-507.

Oldham, R.K. & Dillman, R.O. 2009. Cytokines. Chapter 8. In: Principles of Cancer Biotheraphy. 5th Edition. Springer, 155-276.

Perez-Solar, R. & Saltz. L. 2005. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? *J ClinOncol* (23):5235-5246.

Pichler, M.D. 2006. Adverse side-effects to Biological agents. *Allergy* 61(8):901-920.

Powell, C. 2003. The Delphi technique. Myths and realities. *Journal of Advanced Nursing* 41(4):376-382.

Prosser, H., Almond, S. & Walley, T. 2003. Influences on GPs' decision to prescribe new drugs – the importance of who says what. *Family Practice* 2003 (20):61-68.

Protein Design LaboratoryBioPharma Inc. Technology and Products. What are monoclonal antibodies? (PDL) BioPharmaInc 2015 [online].
http://pdl.com/technology-products/what-are-humanized-monoclonal-antibodies/
Accessed: 15 August 2015.

Rodney, J.Y.H. 2014. Antibodies and Derivates. Chapter 9. In: Biotechnology and Biopharmaceuticals: Transforming Proteins and Genes into Drugs. 2nd Edition. Hoboken NJ: Wiley & Sons, 139-211.

Rogge, M.C., Liu, Y. & Galluppi, G.R. 2014. Interferon Beta Assessment in Non-Chinese and Chinese Subjects: Pharmacokinetics and Pharmacodynamic Activity of an Endogenous Cytokine Are Not Race Dependent. *The Journal of Clinical Pharmacology* 54(10):1153-1161.

Salvana, E.M.T. & Salata, R.A. 2009. Infectious Complications Associated with Monoclonal Antibodies and Related Small Molecules. *Clinical Microbiology reviews* 22(2):274-290.

Scherer, K., Spoerl, D. & Bircher, A.J. 2010. Adverse drug reactions to biologics. *JDtschDermatolGes* 8(6):411-426.

Tang, P. Hung, M.C. & Klostergaard, J. 1996. Human pro-tumor necrosis factor is a homotrimer. *Biochemistry* (35):8216-8225.

Tangaratinam, S & Redman, C.W.E. 2005. The Delphi technique. *The Obstetrician & Gynaecologist* 7:120-125.

Vasquez, E.M., Fabrega A.J. & Pollak R. 1995. OKT3-induced cytokine-release syndrome: occurrence beyond the second dose and association with rejection severity. *Transplant Proc* 27:873-874.

Walsh, G. 2003. Biopharmaceuticals: biochemistry and biotechnology, 2nd Edition. Ireland: John Wiley & Sons. 55(1): 3-10

Weber, R.W. 2004. Adverse reactions to biological modifiers. *Current Opinion in Allergy & Clinical Immunology* 4(4):277-283.

Wink, M. 2011. An introduction to Molecular Biotechnology: Fundamentals, methods and application. In: Glossary. 2nd Edition. Weinheim, Germany: Wiley and Blackwell, 559.

Wisniacki, N., Amaravadi, L., Gerald, R., Gallupi, G.R., Zheng, T.S., Zhang, R., Kong, J. & Burkly, L.C. 2013. Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Anti-TWEAK Monoclonal Antibody in Patients with Rheumatoid Arthritis. *Clinical Therapeutics* 35(8):1137-1149.

APPENDICES

APPENDIX A1

RESEARCH INFORMATION LEAFLET

STUDY TITLE: FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN SOUTH AFRICA

Ethics number of study: HSREC 154/2016 (UFS-HSD2016/1329)

Dear _____

I am Martlie Mocke-Richter and am doing a study under supervision of Prof. A. Walubo entitled, FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN SOUTH AFRICA.

I am inviting you to participate in this research study. Participation is voluntary, and refusal to participate will involve no loss of benefits to which you are otherwise entitled.

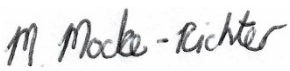
The two-fold aim of this study is to identify the major factors that influence the utilization of Biological Medicines (excluding vaccines) in South Africa, whereafter guidelines will be set to improve the use of Biological Medicines in South Africa.

For this study, ongoing surveys will be done with patients and doctors to establish what they know about the effects of Biological Medicines. This will involve patients who have been treated with such medicines; doctors who have prescribed them; and newly qualified doctors. There are no physical risks involved in this study. It will not cost you anything to participate and you will also not be paid to participate in this study. You can change your mind concerning taking part in the study at any time.

If you decide to take part in the study, you will be given a questionnaire about Biological Medicines to fill in. This will take about 5 minutes to do. All the information we collect will be kept confidential.

Confidentiality will be obtained in accordance with the Promotion of Access to Information Act (Act no. 2 of 2000). Your personal information will be kept confidential. Organizations may inspect research records for quality assurance and data analysis include groups such as Biostatistics and the Ethics Committee for Medical Research. Request for information will have to be submitted according to the provision of the said act and may be refused if the disclosure may lead to the exposure of an individual. Results may be published. Your name will not be mentioned in such a publication. For any further questions or remarks, please contact me on 082 489 1166.

Kind regards



Martlie Mocke-Richter

APPENDIX A2

CONSENT TO PARTICIPATE IN RESEARCH

PROJECT TITLE: FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH AFRICA)

You have been asked to participate in a research study.

You may contact Martlie Mocke-Richter at 082 489 1166 at any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4017794/5 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate.

I understand what my involvement in the study means and I voluntarily agree to participate.

_____ _____

Signature of Participant Date

APPENDIX A3

DATA SURVEY OF NEWLY QUALIFIED DOCTORS IN MANGAUNG DISTRICT BLOEMFONTEIN

NEWLY (≤ 2 years) QUALIFIED DOCTORS						
Instruction:	Mark the appropriate block with an X or write your answer in the space provided.					
What is your Intern number:						
SECTION A: PRESCRIBER'S PARTICULARS						
4.1	Completion date of questionnaire:				.....(dd)/ .....(mm) / 2017	
4.2	What is your gender?				Male	Female
4.3	What is your age?				.....years	
4.4	How many years of work experience do you have?				.....years	
4.5	Where did you study?					
SECTION B: USE OF BIOLOGICAL MEDICINES (EXCLUDING VACCINES)						
4.6	Do you know anything about Biological Medicines?				Yes	No
4.7	If your answer is yes to 4.6, what do you know about Biological Medicines?					
4.8	Do you prescribe Biological Medicines at your institution?				Yes	No
4.9	If your answer is no in 4.8, do you want to prescribe Biological Medicines?				Yes	No
4.10	Do patients sometimes demand to use Biological Medicines?				Yes	No
4.11	At what stage of a disease do you prescribe Biological Medicines?					
	Mild	Moderate	Severe	Not allowed to prescribe Biological Medicines at institution		
4.12	What is the determining factor indicating when a patient should be given Biological Medicines? (for example, stage, guidelines)					
4.13	List the Biological Medicines you know that can be prescribed for Cancer and Rheumatoid arthritis?					
	Biological Medicines			Condition		
SECTION C: INFORMATION RESOURCE						
4.14	Were you taught about Biological Medicines at any time during your medical (under- and post-graduate) training?				Yes	No
4.15	Do you think Biological Medicines were adequately covered in the standard medical textbooks you used or lectures you attended?				Yes	No
4.16	How relevant was it to your current requirement to prescribe these drugs?				Sufficient	Insufficient
4.17	Where do you currently get information (literature, etc.) that enables you to prescribe and care for patients using Biological Medicines?					
	Textbooks	Internet	Colleagues	Peer-reviewed articles	Other: Don't get information at this stage	
4.18	Do you think information on Biological Medicines is readily available to all clinicians?				Yes	No
	If your answer is no to 4.18, suggest ways to make this information more readily available:					
4.19	What steps must be followed when you decide to prescribe Biological Medicines for a patient?					
	(1)	I am not allowed to prescribe Biological Medicines at my institution and will refer the patient to some one senior or to a specialist.				
	(2)	Other, please specify:				

SECTION D: PATIENT CARE/MANAGEMENT					
4.20	How do your approaches, requirements, or criteria to prescribe Biological Medicines differ from your prescribing of pharmaceutical agents?				
4.21	How does the care of patients on Biological Medicines differ from that of patients on pharmaceutical medicines?				
4.22	On average, when do you start giving your patient Biological Medicines?				
	Too late	On diagnosis	In time for it to be effective	Not allowed to prescribe Biological Medicines	
SECTION E: CLINICIAN'S PERCEPTION					
	Select your preferred option/s with an X. You are more than welcome to select more than one block				
4.23	Biological Medicines are difficult to use because:				
	(1)	They are time-consuming in that patient selection may involve special tests.			
	(2)	They are administered parentally hence require close monitoring.			
	(3)	Adverse reactions are more common in that patients need more review than in the case of pharmaceutical agents			
	(4)	I have limited knowledge of the pharmacology of biological agents			
	(5)	They are expensive			
	(6)	Other (specify):			
4.24	Use of Biological Medicines is limited because of:				
	(1)	Attitudes and perceptions towards Biological Medicines: I consider genetically derived products as unsafe, hence may not recommend them to patients.			
	(2)	Beliefs: especially religions that do not allow the use of human derivatives.			
	(3)	Availability/affordability of specialized tests for monitoring efficacy are difficult and expensive.			
	(4)	Procurement process to obtain Biological Medicines is difficult.			
	(5)	Lack of monitoring safety: adequate knowledge to enable detection of side-effects, clinical exam and lab tests.			
	(6)	Availability of knowledge/information about Biological Medicines is limited.			
	(7)	Prescribing practice: use of guidelines or individual's ethos can limit the use of Biological Medicines.			
4.25	When will you NOT prescribe Biological Medicines?				
	(1)	Coexisting disease: TB or presence of serious infections or organ failure			
	(2)	Previous treatment, especially with Biological Medicines, is associated with poor response to another biological medication			
	(3)	Presence of drug antibodies: contribute to Biological Medicines ineffective.			
4.26	Do Biological Medicines have more adverse effects than pharmaceutical medicines?			Yes	No
4.27	Please indicate if you agree with the statement/s:				
	(1)	Biological Medicines are more effective than pharmaceutical agents			
	(2)	There is still much to be learned about the adverse effects of biological agents			
	(3)	Biological Medicines should be prescribed by specialists only			
	(4)	My patients on Biological Medicines have reported more adverse side-effects than those on pharmaceutical medicines.			
	(5)	I consider prescribing Biological Medicines as a last resort when pharmaceutical medicines have failed			
4.28	Indicate the factors that play a role in the efficacy and safety of Biological Medicines?				
	(1)	Plasma concentrations of Biological Medicines: are useful to know in patients with poor response.			
	(2)	Presence of neutralizing antibodies: likely in patients who lose response after showing good response.			
	(3)	Genetics: some SNP polymorphism associated with better response to TNFa inhibitors in RA			
	(4)	Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNFa			

SECTION F: PROCUREMENT				
4.29	What channel do you use to obtain Biological Medicines for your patients?			
4.30	Is the process satisfactory?	Yes	No	Have not had exposure to the process
4.31	If your answer is no to question 4.30; suggest how it should be improved:			

APPENDIX A4

DATA SURVEY OF THE SPECIALIST PRESCRIBING BIOLOGICAL MEDICINES IN THE FREE STATE

PRESCRIBERS OF BIOLOGICAL MEDICINES					
	Instructions:	Mark the appropriate block with an X or write your answer on the space provided.			
	How are you currently employed?	Private	Both		
	What is your MP number?	Nr:			
SECTION A: PRESCRIBER'S PARTICULARS					
(1)	Completion date of questionnaire:	(dd)/ (mm) / 2017			
(2)	What is your gender?	Male	Female		
(3)	What is your age?	..... years			
(4)	How many years of work experience do you have?	..... years			
(5)	Did you do a Master's or fellowship?	Master's	Fellowship	Both	None
(6)	What is your field of specialization?				
SECTION B: USE OF BIOLOGICAL MEDICINES (EXCLUDING VACCINES)					
(7)	When was the first time you started prescribing Biological Medicines?				
(8)	For which condition?				
(9)	In the past two years, have you prescribed more Biological Medicines?	Yes	No		
(10)	Do patients sometimes demand to use Biological Medicines?	Yes	No		
(11)	At what stage of a disease do you prescribe Biological Medicines?	Mild	Moderate	Server	Any
(12)	What is the determining factor indicating when a patient should be given Biological Medicines? (for example, stage, guidelines)				
(13)	List the Biological Medicines you prescribe and associated conditions?				
	Biological Medicines	Condition			
SECTION C: INFORMATION RESOURCE					
(14)	Were you taught about Biological Medicines at any time during your medical (under- and post-graduate) training?	Yes	No		
(15)	Do you think Biological Medicines were adequately covered in the standard medical textbooks you used or lectures you attended?	Yes	No		
(16)	How relevant was it to your current requirement to prescribe these drugs?	Sufficient	Insufficient		
(17)	Where do you currently get information (literature, etc.) that enables you to prescribe and care for patients using Biological Medicines?				
	Textbooks	Internet	Colleagues	Other	Peer-reviewed articles
(18)	Do you think information on Biological Medicines is readily available to all clinicians?	Yes	No		
	If your answer is no in 18, suggest ways to make this information more readily available				
(19)	What steps must be followed when you decide to prescribe a patient Biological Medicines?				
SECTION D: PATIENT CARE/MANAGEMENT					
(20)	How do your approaches, requirements or criteria to prescribe Biological Medicines differ from your prescribing of pharmaceutical agents?				

(21)	How does the care of patients on Biological Medicines differ from that of patients on pharmaceutical medicines?			
(22)	What are the common problems you encounter in patients on Biological Medicines?			
	Side-effects	Patient concern	Plasma concentration of BM: is useful to know in respect of patients with poor	Other
	If you indicate other, please specify:			
(23)	When is the most suitable time to prescribe Biological Medicines?			
(24)	On average when do you start administering your patient Biological Medicines?			
	(1) Too late	(2) On diagnosis	(3) In time for it to be effective	(4) Other
(25)	If your answer in 24 was no.1, please provide reason for it:			

SECTION E: CLINICIAN'S PERCEPTION

	Select your preferred option/s with an X. You are more than welcome to select more than one block			
(26)	Biological Medicines are difficult to use because:			
	(1)	Time-consuming in that patient selection may involve special tests		
	(2)	They are administered parenterally, hence require close monitoring		
	(3)	Adverse reactions are more common in that patients need more review than in the case of pharmaceutical agents		
	(4)	I have limited knowledge of the pharmacology of biological agents		
	(5)	They are expensive		
	(6)	Other (specify)		
(27)	Use of Biological Medicines is limited because of:			
	(1)	Attitudes and perceptions towards Biological Medicines: I consider genetically derived products as unsafe, hence may not recommend them to patients.		
	(2)	Beliefs: especially religions that do not allow use of human derivatives.		
	(3)	Availability/affordability of specialized tests for monitoring efficacy are difficult and expensive.		
	(4)	Procurement process to obtain Biological Medicines is difficult.		
	(5)	Lack of monitoring safety: adequate knowledge to enable detection of side-effects, clinical exam and lab tests.		
	(6)	Availability of knowledge/information about Biological Medicines is limited		
	(7)	Prescribing practice: use of guidelines or individuals' ethos can limit the use of Biological Medicines		
(28)	When will you NOT prescribe Biological Medicines?			
	(1)	Coexisting disease: TB or presence of serious infections or organ failure		
	(2)	Previous treatment, especially with Biological Medicines, is associated with poor response to another biological medication		
	(3)	Presence of drug antibodies: render Biological Medicines ineffective.		
(29)	Do Biological Medicines have more adverse effects than pharmaceutical medicines?		Yes	No
(30)	Please indicate if you agree with the statement/s:			
	(1)	Biological Medicines are more effective than pharmaceutical agents		
	(2)	There is still much to be learned about the adverse effects of biological agents		
	(3)	Biological Medicines should be prescribed by specialists only		
	(4)	My patients on Biological Medicines have reported more adverse side-effects than those on pharmaceutical medicines.		
	(5)	I consider prescribing Biological Medicines as a last resort when pharmaceutical medicines have failed		

(31)	Indicate the factors that play a role in efficacy and safety of Biological Medicines?			
	(1)	Plasma concentrations of Biological Medicines: are useful to know in patients with poor response		
	(2)	Presence of neutralizing antibodies: likely in patients who lose response after showing good response.		
	(3)	Genetics: some SNP polymorphism associated with better response to TNFa inhibitors in RA		
	(4)	Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNFa		
SECTION F: PROCUREMENT				
(32)	Does the company (supplier or sponsor) play a role in the use of Biological Medicines?		Yes	No
(33)	If your answer is yes in 32 please indicate what role?		Limited	Recommended
(34)	What channel do you use to obtain Biological Medicines for your patients?			
(35)	Is the process satisfactory?		Yes	No
(36)	If your answer is no in question 35, suggest how it should be improved:			

APPENDIX A5

DATA SURVEY OF THE PATIENTS USING BIOLOGICAL MEDICINES IN THE FREE STATE

PATIENTS USING BIOLOGICAL MEDICINES			
Instructions	**Mark the appropriate block with an X or write your answer in the space provided**		
Patient or Um number?		Nr:	
Which doctor do you consult?		Public	Private
Section A: Patient demographics			
1a. Date questionnaire was completed?		_(dd)/ (mm) / 2017	
2a. What is your gender?		Male	Female
3a. Do you smoke?		Yes	No
4a. What is your height?			.....m
5a. What is your weight?			.....kg
6a. Does your religion allow you to use human derivates?		Yes	No
Section B: Medical history			
1b.Do you know the diagnosis leading to biological medicine being used?		Yes	No
2b. When were you first diagnosed with the disease named in 1b?		_(dd)/ (mm) /	
3b. Names of Biological Medicines that you use			

Biological medicine	**Date of treatment Start**	**Stop**	**Dosage**	**Frequency**

4b. Indicate any pre-qualification test for selection to use the biological medicine.				
5b. What route of administration is used?	Subcutaneous	Intravenous	Intramuscular	Intralesional
6b. What other chronic diseases do you have?				
7b. Do you use any other medicines apart from the Biological Medicine?			Yes	No
8b. If yes to question 7b, please indicate the other medicines in table below				

Medicine	**Date**	**Dosage and Frequency**	**Indication**

Medicine	Date	Dosage and Frequency	Indication

9b. Do you experience any side-effects while you are taking Biological Medicine?	Yes	No

10b. If your answer is yes to question 9b, please indicate which of following side-effects you experience:

(If any other, please write it down)

Side-effect:		Side-effect:		Side-effect:	
Abdominal pain		Back pain		Depression	
Infection		Headache		Allergic reaction	
Fever		Pharyngitis		Diarrhea	
Nausea		Constipation		Rash	
Chills		Night sweat		TB	

Other:

11b. What is the worst experience (side-effect) you have had while being treated with drug X?

Section C: Patient knowledge and experience.

1c. Indicate the disease or disorder you are suffering from? (If it is cancer, what type of cancer)	Cancer	Ulcerative colitis	Rheumatoid arthritis	Ankylosing spondylitis	Other

2c. Can you explain your disease to somebody else?			Yes	No
3c. Do you know what Biological Medicines are?			Yes	No
4c. From whom do you receive information / explanation regarding the disease indicated in question 1c?	Doctor	Nurse	Pharmacist	Other
5c. Have you been informed about Biological Medicine?			Yes	No
6c. If your answer is yes to question 5c, who informed you?	Doctor		Pharmacist	Nurse
7c. Do you think biological medicine is improving your condition?			Yes	No

8c. If your answer is no to question 7c, what are the main reasons for this?

9c. Do you go for frequent clinical check-ups?	Yes	No

10c. If your answer is no to question 9c, what is the main reason for this?

APPENDIX A6

ETHICAL APPROVAL LETTER FROM THE UNIVERSITY OF THE FREE STATE

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

30 November 2016

MS M RICHTER
DEPT OF PHARMACOLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Ms Richter

HSREC 154/2016 (UFS-HSD2016/1329)
PROJECT TITLE: FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH-AFRICA)

1. You are hereby kindly informed that, at the meeting held on 29 November 2016, the Health Sciences Research Ethics Committee (HSREC) approved the above project after all conditions were met.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval and annually for long term studies.

5. A final report should be submitted at the completion of the study.

6. Kindly use the **HSREC NR** as reference in correspondence to the HSREC Secretariat.

7. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

DR LE GRANGE
CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | F: +27 (0)51 444 4359 | E: ethicsfhs@ufs.ac.za
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za

APPENDIX A7

APPROVAL LETTER FROM FREE STATE DEPARTMENT OF HEALTH

health
Department of
Health
FREE STATE PROVINCE

30 January 2017

Ms. M Richter
Dept. of Pharmacology
Faculty of Health Science
UFS

Dear Ms. M Richter

Subject: Factors influencing the utilization of Biological medicines in the Free State (South Africa).

- Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participants must be obtained
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of the facilities nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to sebeelats@fshealth.gov.za before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 31/01/2017

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikolvup@fshealth.gov.za
www.fs.gov.za

APPENDIX B

NEWLY QUALIFIED DOCTORS DATA FROM SURVEY

Table B1: Gender of newly qualified doctors (n=63)

Gender	Quantity	Percentage
Male	25	39,7%
Female	38	60,3%

Table B2: Average age of newly qualified doctors (n=63)

Age	Quantity	Percentage
23	2	3,2%
24	17	27,0%
25	12	19,0%
26	13	20,6%
27	7	11,1%
28	6	9,5%
29	2	3,2%
30	1	1,6%
33	2	3,2%
36	1	1,6%

Table B3: Years of work experience (n=63)

Years	Quantity	Percentage
0,5	4	6,3%
1	46	73,0%
1,5	5	7,9%
2	8	12,7%

Table B4: Knowledge of Biological Medicines (n=63)

Description	Quantity	Percentage
Yes	29	46,0%
No	34	54,0%

Table B5: Do you prescribe Biological Medicines at your institution? (n=63)

Description	Quantity	Percentage
Yes	16	25,4%
No	47	74,6%

Table B6: Do you want to prescribe Biological Medicines? (n=43)

Description	Quantity	Percentage
Yes	24	55,8%
No	19	44,2%

Table B7: Do patients demand to use Biological Medicines? (n=63)

Description	Quantity	Percentage
Yes	3	4,8%
No	60	95,2%

Table B8: Were you taught about Biological Medicines at any time during your medical training? (n=63)

Description	Quantity	Percentage
Yes	52	82,5%
No	11	17,5%

Table B9: Do you think Biological Medicines were adequately covered in the standard medical textbooks you used or lectures you attended? (n=61)

Description	Quantity	Percentage
Yes	14	23,0%
No	47	77,0%

Table B10: How relevant was it to your current requirement to prescribe these drugs? (n=62)

Description	Quantity	Percentage
Sufficient	22	35,5%
Insufficient	40	64,5%

Table B11: Do you think information on Biological Medicines is readily available to all clinicians? (n=53)

Description	Quantity	Percentage
Yes	9	17,0%
No	44	83,0%

Table B12.1: What steps must be followed when you decide to prescribe Biological Medicines to a patient? (n=58)

Description	Quantity	Percentage
I am not allowed to prescribe Biological Medicines at my institution and will refer the patient to someone senior or to a specialist.	55	94,8%
Other, please specify	3	5,2%

Table B12.2: Refer to Table B12.1 other please specify (n=3)

Description	Quantity	Percentage
Follow appropriate guidelines	2	66,7%
Uncertain	1	33,3%

Table B13: Do Biological Medicines have more adverse effects than pharmaceutical agents? (n=57)

Description	Quantity	Percentage
Yes	20	35,1%
No	37	64,9%

Table B14: What channel do you use to obtain Biological Medicines for your patients? (n=51)

Description	Quantity	Percentage
I have not yet prescribed these drugs, uncertain	31	60,8 %
I have to get consent from a specialist	20	39,2%

Table B15.1: Is the process satisfactory? (n=58)

Description	Quantity	Percentage
Have not had exposure to the process	54	93,2%
Yes	2	3,4%
No	2	3,4%

Table B15.2: If the process is not satisfactory, suggest how it should be improved? (n=58)

Description	Quantity	Percentage
Process take very long	2	3,4%

APPENDIX C

SPECIALIST DATA FROM SURVEY

Table C1: Gender of Specialist (n=12)

Description	Quantity	Percentage
Male	5	41,7%
Female	7	58,3%

Table C2: What is your age? (n=12)

Description	Quantity	Percentage
32	2	16,7%
36	1	8,3%
37	1	8,3%
39	1	8,3%
45	2	16,7%
47	1	8,3%
51	1	8,3%
56	1	8,3%
62	1	8,3%
69	1	8,3%

Table C3: How many years of work experience do you have? (n=12)

Work experience	Quantity	Percentage
9	3	27,3%
12	1	9,1%
16	1	9,1%
19	1	9,1%
24	1	9,1%
28	1	9,1%
30	1	9,1%
35	1	9,1%
45	1	9,1%

Table C4: Did you do a Master's or fellowship? (n=12)

Description	Quantity	Percentage
Master's	9	75,0%
Fellowship	0	0,0%
Both	3	25,0%

Table C5: What is your field of specialization? (n=12)

Description	Quantity	Percentage
Dermatology	1	8,3%
Clinical-Radiation Oncology	7	58,3%
Breast cancer	1	8,3%
Rheumatologist (Physician)	1	8,3%
Clinical Haematology	1	8,3%
Gastroenterology	1	8,3%

Table C6: When was the first time you started prescribing Biological Medicines? (n=10)

Description	Quantity	Percentage
9-10 years ago	4	40,0%
5-8 years ago	6	60,0%

Table C7: For which condition? (n=12)

Description	Quantity	Percentage
Psoriasis	1	8,3%
Melanoma	2	16,7%
Neutropenia	1	8,3%
Non-Hodgkin's lymphoma	6	50,0%
Breast cancer	1	8,3%
Rheumatoid Arthritis	1	8,3%

Table C8: In the past two years have you prescribed more Biological Medicines? (n=5)

Description	Quantity	Percentage
Yes	9	81,8%
No	2	18,2%

Table C9: Do patients sometimes demand to use Biological Medicines? (n=12)

Description	Quantity	Percentage
Yes	2	16,7%
No	10	83,3%

Table C10: At what stage of a disease do you prescribe Biological Medicines? (n=12)

Description	Quantity	Percentage
Mild	0	0,0%
Moderate	0	0,0%
Severe	3	25,0%
Any	9	75,0%

Table C11: Were you taught about Biological Medicines at any time during your medical (under- and post-graduate) training? (n=12)

Description	Quantity	Percentage
Yes	10	83,3%
No	2	16,7%

Table C12: Do you think Biological Medicines were adequately covered in the standard medical textbooks you used or lectures you attended? (n=11)

Description	Quantity	Percentage
Yes	5	45,5%
No	6	54,5%

Table C13: How relevant was it to your current requirement to prescribe these drugs? (n=9)

Description	Quantity	Percentage
Sufficient	7	77,8%
Insufficient	2	22,2%

Table C14: Do you think information on Biological Medicines is readily available to all clinicians? (n=12)

Description	Quantity	Percentage
Yes	9	75,0%
No	3	25,0%

Table C15: If your answer is no to the question mentioned in table C14, suggest ways to make this information more readily available? (n=3)

Description	Quantity	Percentage
Education with lectures is needed	3	25,0%

Table C16: How does the care of patients on Biological Medicines differ from that of patients on pharmaceutical medicines?

Description	Quantity	Percentage
Close monitoring during administration because side effect profile differ of each patient, allergic reactions are more common	9	75,0%
Check endocrine effects, monitoring for viral replication, example hepatitis B for Rituximab and cytomegalovirus for Alentuzumab, regular follow up and evaluation for adverse events and complications (3-6 monthly) needed	5	41,7%

Table C17: If your answer in 5d was no.1, please provide reason for it? (n=2)

Description	Quantity	Percentage
As indicated by registration	1	50%
Too much Paperwork	1	50%

Table C18: Do Biological Medicines have more adverse effects than pharmaceutical medicines? (n=12)

Description	Quantity	Percentage
Yes	0	0%
No	12	100%

Table C19: Does the company (supplier or sponsor) play a role in the use of Biological Medicines? (n=12)

Description	Quantity	Percentage
Yes	8	66,7%
No	4	33,3%

Table C20: If your answer is yes in 1a please indicate what role (n=8)

Description	Quantity	Percentage
Limited	5	62,5%
Recommended	3	37,5%

Table C21: What Channel do you use to obtain Biological Medicines for your patients? (n=12)

Description	Quantity	Percentage
Motivation to dermalogical society, or motivation to PTC in Department of Health	4	33,3%
Dispense by pharmacy, sent and order from company. Depends on the supplier, but if available the current institution works well	7	58,3%
South African oncology guidelines	1	8,3%

Table C22: Is the process satisfactory? (n=12)

Description	Quantity	Percentage
Yes	9	75,0%
No	3	25,0%

Table C23: If your answer is no in Description 2, suggest how it should be improve? (n=3)

Description	Quantity	Percentage
Administrative burden should be reduced	1	33,3%
Financing from National Department of Health	2	66,7%

APPENDIX D

PATIENTS' DATA FROM SURVEY

Table D1: Which doctor do you consult? (n=31)

Description	Quantity	Percentage
Public	9	29,0%
Private	22	71,0%

Table D2: What is your gender? (n=31)

Description	Quantity	Percentage
Male	7	22,6%
Female	24	77,4%

Table D3: Do you smoke? (n=31)

Description	Quantity	Percentage
Yes	6	19,4%
No	25	80,6%

Table D4: What is your height in meter? (n=31)

Description	Quantity	Percentage
1.52	2	6,5%
1.53	1	3,2%
1.59	1	3,2%
1.62	1	3,2%
1.65	3	9,7%
1.67	1	3,2%
1.68	5	16,1%
1.69	3	9,7%
1.7	2	6,5%
1.71	1	3,2%
1.73	1	3,2%
1.74	1	3,2%
1.75	2	6,5%
1.77	2	6,5%
1.78	1	3,2%
1.8	1	3,2%
1.82	1	3,2%
1.83	1	3,2%
1.85	1	3,2%

Table D5: What is your weight in kilogram? (n=31)

Description	Quantity	Percentage
53	1	3,2%
59	1	3,2%
62	2	6,5%
64	1	3,2%
65	2	6,5%
66	1	3,2%
68	1	3,2%
71	1	3,2%
72	1	3,2%
77	1	3,2%
79	2	6,5%
80	1	3,2%
81	1	3,2%
82	1	3,2%
85	2	6,5%

Description	Quantity	Percentage
85,5	1	3,2%
89	1	3,2%
90	3	9,7%
93	1	3,2%
96	1	3,2%
98	1	3,2%
100	1	3,2%
106	1	3,2%
109	1	3,2%
150	1	3,2%

Table D6: Does your religion allow you to use human derivatives? (n=31)

Description	Quantity	Percentage
Yes	31	100,0%
No	0	0,0%

Table D7: Do you know the diagnosis leading to the Biological Medicines being used? (n=31)

Description	Quantity	Percentage
Yes	29	93,5%
No	2	6,5%

Table D8: When were you first diagnosed with the disease named in D7? (n=31)

Description	Quantity	Percentage
1958	1	3,2%
1997	1	3,2%
1999	2	6,5%
2000	1	3,2%
2002	1	3,2%
2003	1	3,2%
2005	2	6,5%
2006	3	9,7%
2007	1	3,2%
2009	2	6,5%
2010	2	6,5%
2012	1	3,2%
2013	3	9,7%
2014	1	3,2%
2015	3	9,7%
2016	2	6,5%
2017	4	12,9%

Table D9: What is the duration of Biological Medicines use per patient? (n=31)

Description	Quantity	Percentage
1 Month	1	3,2%
2 Months	1	3,2%
4 Months	1	3,2%
5 Months	2	6,5%
6 Months	1	3,2%
9 Months	2	6,5%
10 Months	3	9,7%
12 Months	1	3,2%
19 Months	2	6,5%
24 Months	1	3,2%
29 Months	2	6,5%
33 Months	2	6,5%
35 Months	3	9,7%

Description	Quantity	Percentage
36 Months	1	3,2%
39 Months	1	3,2%
41 Months	1	3,2%
69 Months	3	9,7%
71 Months	1	3,2%
105 Months	1	3,2%
119 Months	1	3,2%

Table D10: What route of administration is used? (n=31)

Description	Quantity	Percentage
Subcutaneous	4	12,9%
Intravenous	27	87,1%
Intramuscular	0	0,0%
Intralesional	0	0,0%

Table D11: Do you use any other medicine apart from the Biological Medicines? (n=31)

Description	Quantity	Percentage
Yes	28	90,3%
No	3	9,7%

Table D12: Do you experience any side-effects while you are taking Biological Medicines? (n=29)

Description	Quantity	Percentage
Yes	15	51,7%
No	14	48,3%

Table D13: Can you explain your disease to somebody else? (n=31)

Description	Quantity	Percentage
Yes	28	90,3%
No	3	9,7%

Table D14: Do you know what Biological Medicines are? (n=31)

Description	Quantity	Percentage
Yes	26	83,9%
No	5	16,1%

Table D15: From whom do you receive information – explanations regarding the disease indicated in question 6.20 (n=31)

Description	Quantity	Percentage
Doctor	30	96,8%
Nurse	6	19,4%
Pharmacist	0	0,0%
Other	1	3,2%

Table D16: Have you been informed about Biological Medicines (n=31)

Description	Quantity	Percentage
Yes	28	90,3%
No	3	9,7%

Table D17: If your answer is yes to Question 6.22, who informed you (n=28)

Description	Quantity	Percentage
Doctor	27	96,4%
Pharmacist	1	3,6%
Nurse	0	0,0%

Table D18: Do you think Biological Medicines is improving your condition (n=29)

Description	Quantity	Percentage
Yes	26	89,7%
No	3	10,3%

Table D19: If your answer is no to question 6.24, what are the main reason for this (n=3)

Description	Quantity	Percentage
My level of pain and discomfort is not getting better.	1	33,3%
I didn't go for a scan yet, to see how did I react to the treatment	1	33,3%
Received only one treatment, too early to tell	1	33,3%

Table D20: Do you go for frequent clinical check-ups (n=31)

Description	Quantity	Percentage
Yes	27	87,1%
No	4	12,9%

Table D21: If your answer is no to question 6.26, what is the main reason for this (n=4)

Description	Quantity	Percentage
Doctor who has the knowledge and ability to treat me is too busy and the others have no clue about Biological Medicines	1	25,0%
Living outside Bloemfontein - No Rheumatologist	1	25,0%
Do not experience any problems before next treatment	1	25,0%
As from now check-ups will be more frequent	1	25,0%

APPENDIX E1

DELPHI METHOD: ROUND 1: INVITATION LETTER

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

[redacted]

Dear Sir/Madam

REQUEST TO PARTICIPATE IN DEVELOPING A STRATEGY FOR APPROPRIATE USE OF BIOLOGICAL MEDICINES

Introduction

As part of my PhD project on the 'factors influencing the use of biological medicines', I am conducting a study that uses the DELPHI technique to produce a consensus guideline on the use of Biological Medicines (BM). We have obtained opinions of the young doctors (< 2 years in practice) and prescribing consultants for the different BM. At this stage, we would like to use these views and your expertise to set guidelines for the use of biological medicines in South Africa.

Delphi technique

The Delphi technique seeks to obtain consensus on the opinions of experts, through structured questionnaires. This is an independent process that involves different experts in the field of biological medicines. It may involve several rounds of taking opinions, depending on the how the opinions differ. The responses from each round are fed back in brief form to the participants (experts) who are then given a chance to respond again. For this study, we hope there will be only two rounds, but if need be we shall request your participation for a third round. The Delphi is designed to convert expert opinions into group consensus.

Request

Here, I am requesting you to participate in this study because you are one of the experts in the use of BM. We believe that you contribution in important towards improvement in the use of biological medicines in South Africa. The study will be conducted via email, and will not take more than 30 minutes of your time, spread out over two separate occasions.

Should you wish to discuss the study or your participation in more detail, please feel free to contact me on +27 82 489 1166, or via email martlie.mocke@gmail.com

Thank you in advance for your time.

Yours sincerely

Martlie Mocke
(B.Pharm, M.Pharm)
(PhD student, Department of Pharmacology, University of the Free State)

Approved by:

PROF A WALUBO
Head: Department of Pharmacology

Prof. A. Walubo
SUPERVISOR AND HEAD OF DEPARTMENT

Department of Pharmacology
Departement Farmakologie

APPENDIX E2

DELPHI METHOD: ROUND 1: QUESTIONNAIRE

DEVELOPING A FRAMEWORK FOR PROMOTING THE USE OF BIOLOGICAL MEDICINE IN SOUTH AFRICA BY CONSENSUS USING THE DELPHI METHOD

1. The Electronic Consent form

Request to give consent to participate in the Delphi process in a study entitled: FACTORS INFLUENCING THE UTILISATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH AFRICA).

I hereby give my consent to participate in the Delphi Process. My particulars are as follows:

Title:	
Full initials:	
Surname:	
Email address:	
Telephone no:	
Cellular number:	
Date:	

Please return this form to me via e-mail as soon as possible.

My contact details are as follows:

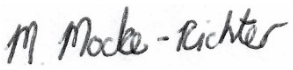
Cellular phone: 082 489 1166
Email address: martlie.mocke@gmail.com
Fax: 051 522 8337

Please note the following:

- The information you provide here will be treated with high confidentiality
- There will be no references to any of the participants' names in any communication, including publication, of the results.
- During evaluation of the data, participants will be identified by numbers
- You may withdraw from the study at any time.

Thank you in advance for your kind cooperation.

Kind regards



Ms M. Mocke-Richter
University of the Free State
Bloemfontein

ETOVS no: HSREC154/2016

DEVELOPING A FRAMEWORK FOR PROMOTING THE USE OF BIOLOGICAL MEDICINE IN SOUTH AFRICA BY CONSENSUS USING THE DELPHI METHOD

2. DELPHI QUESTIONNAIRE – ROUND 1

Participant no: _____

GENERAL INFORMATION FROM PARTICIPANT:

Field of specialization:	
Institution:	

List the Biological Medicine you use generally:

Biological Medicine	Indication

INSTRUCTIONS ON HOW TO COMPLETE THE QUESTIONNAIRE

Please indicate (mark with **X**) the degree of importance each statement is for inclusion in the framework for the use of biological medicines in South Africa according to the following scales or grades:

1 = Essential - **Must definitely be included**
2 = Useful - **Can be included**
3 = Unnecessary - **Must definitely be excluded**

Note:

a) Mark the option you choose with an **X**
b) Mark one option only
c) Add your comments where you feel that it is necessary.
d) Additional comments can be added using the space provided at the end of each section

EXAMPLE
QUESTIONNAIRE - 1

		1	2	3	Comments
1.	Trastuzumab is approved for the treatment of early stage breast cancer	X			This is an important treatment method and should definitely be included

Fill in the sections of the questionnaire (A, B, C and D) as per instructions on the previous page

SECTION A:
USE OF BIOLOGICAL MEDICINES (HOW TO PRESCRIBE BIOLOGICAL MEDICINES)

A		1	2	3	Comments
1.	There is a need for a framework for the use of Biological Medicines in South Africa				
2.	Some Biological Medicines may not be used with coexisting diseases such as TB or the presence of serious infections or organ failure				
3.	The staff that administer biological medicines must have appropriate training about Biological Medicines, to explain it to the patient in a way that the patient will understand it				
4.	Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria				
5.	Treatment should be initiated and monitored by specialists				
6.	Biological Medicines must be given early in the disease process for it to be effective				
7.	Patients should undergo appropriate laboratory tests before Biological Medicines is administered				
8.	Frequent patient review to check for infections, malignancies and other adverse effects of biological medicines is necessary				
9.	Guidelines can help in determining when a patient should be given Biological Medicines				
10.	Plasma concentrations of Biological Medicines are useful to know in patients with poor response				
11.	Framework should be available to guide Doctors concerning the necessarily work-up (investigation) before the administering of Biological Medicines				
12.	*Any additional comments for the framework for the use of Biological Medicines in South Africa:*				

SECTION B:
INFORMATION RESOURCE

B		1	2	3	Comments
1.	A step-by-step approach is needed in the development of a framework for the use of Biological Medicines				
2.	Guidelines for use of Biological Medicines should be readily available in a written format				

B		1	2	3	Comments
3.	Biological Medicines promotion programmes must be included in the set of guidelines				
4.	Specialist knowledge of Biological Medicines must be improved				
5.	Undergraduate students must be exposed more to Biological Medicines during their studies				
6.	There must be more education about Biological Medicines in lectures				
7.	All doctors must know the available Biological medicines and their respective indications				
8.	Doctors' knowledge about Biological Medicines needs continuous professional education/ improvement via seminars/ CPD evenings/workshops				
9.	Medical students must know the Biological Medicines available and their respective indications.				
10.	*Any additional comments for a framework for the use of Biological Medicines in South Africa:*				

SECTION C:
PATIENT CARE / MANAGEMENT

C		1	2	3	Comments
1.	Biological medicines are difficult to use because they are administered parenterally, hence require close monitoring				
2.	There may be a religious or cultural objection to using Biological Medicines				
3.	Biological medicines improve the quality of life of patients				
4.	Patient understanding of information regarding Biological Medicine promotes use.				
5.	*Any additional comments for a framework for the use of Biological Medicines in South Africa:*				

SECTION D:
AVAILABILITY, PRESCRIPTION, DISPENSING and PROCUREMENT

D		1	2	3	Comments
1.	The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex				
2.	Financial advisory services are important in the procurement process of Biological Medicines				
3.	Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier				
4.	The procurement process of Biological Medicines must be improved				

D		1	2	3	Comments
5.	Limited access due to funding				
6.	Limited access due to availability/registration.				
7.	*Any additional comments for a framework for the use of Biological Medicines in South Africa:*				

Thank you

This first stage of Delphi survey is now complete. In two weeks you will receive the second phase of the survey, which will summarise all the responses we received anonymously and request some further comments.

APPENDIX E3

DELPHI METHOD: ROUND 1: SUMMARY OF RESULTS

	001			002			003			004			005			006			007			008			009			010			011			012			013			14			15			TOTAL		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
A1	1			1			1			1			1			1			1			1			1			1				1		1			1			1			1			14	1	0
A2	1			1			1			1			1			1			1					1	1			1			1				1			1			1			1			12	2	1
A3	1			1			1			1				1		1			1			1			1			1			1			1			1			1			1			14	1	0
A4		1		1			1				1			1				1		1			1		1				1		1			1			1			1			1			8	6	1
A5	1			1			1			1			1			1			1				1		1			1			1				1		1			1			1			13	2	0
A6			1		1		1				1			1			1			1			1		1				1		1			1				1			1			1			5	9	1
A7	1			1				1		1			1			1			1			1			1			1			1			1			1			1			1			14	1	0
A8	1			1				1		1			1			1			1			1			1			1			1			1			1			1			1			14	1	0
A9	1			1			1			1			1			1			1			1			1			1				1		1			1			1			1			14	1	0
A10	1			1			1				1				1			1		1			1				1		1			1				1			1			1			6	6	3
A11	1			1				1		1			1			1			1			1				1		1				1		1			1			1			1			12	3	0
B1	1			1			1			1				1		1			1			1				1		1				1		1			1			1			1			12	3	0
B2	1			1			1			1				1		1			1			1				1		1				1		1			1			1			1			12	3	0
B3			1			1		1			1				1	1			1			1				1		1				1			1			1			1			1			6	6	3
B4	1				1			1		1			1			1			1			1				1		1			1			1			1			1			1			12	3	0
B5	1				1			1			1			1			1		1			1					1	1				1			1					1	1			1			6	7	3
B6	1				1		1			1			1			1			1			1				1			1		1			1			1			1			1			12	3	0
B7	1			1			1				1				1			1		1		1					1			1			1				1			1			1			6	5	4
B8	1			1			1				1			1			1		1			1				1			1			1			1			1			1			1			7	7	1
B9	1			1				1			1				1			1		1		1					1		1			1				1			1				1			4	8	3
C1			1		1			1			1			1			1		1			1				1				1		1				1			1				1			3	10	2
C2			1			1			1			1			1			1			1			1			1			1			1			1			1			1		1	1	1	13
C3		1		1			1					1	1			1			1			1			1			1			1			1			1			1			1			13	1	1
C4			1	1				1			1			1				1		1		1				1			1			1			1			1			1			3	10	2
D1		1		1					1	1				1			1			1			1			1				1	1			1			1			1			6	7	2
D2	1			1					1	1			1			1			1				1		1			1				1		1			1			1			1			12	2	1
D3			1		1		1				1		1					1	1			1					1	1						1	1			1			1			9	2	4
D4		1		1					1	1				1		1			1			1			1				1		1				1			1			1			9	5	1
D5			1	1			1			1			1				1		1			1			1			1			1			1			1			1			1			13	1	1
D6			1	1			1			1				1				1		1		1			1				1				1	1			1			1			1			7	4	3

APPENDIX F1

DELPHI METHOD: ROUND 2: LETTER AND QUESTIONNAIRE

DEVELOPING A FRAMEWORK FOR PROMOTING THE USE OF BIOLOGICAL MEDICINE IN SOUTH AFRICA BY CONSENSUS USING THE DELPHI METHOD

Dear Delphi Participant

Thank you for participating in the Delphi survey of this study and the effort to complete the First round questionnaire. This is the survey for the Second round. Your answers in Round one were analysed. Statements where there were 80% consensus will not feature in Round 2. All the answers where consensus were **NOT** reached (having less than 80% agreement) in the First round, must be answered again **please**, and you need to reconsider your original rating. **19 out of 32 consensus was reached in Round 1.** This is the reason why Round 2 will go much faster.

Completing the Round 2 questionnaire

Each statement will have a score below the rating scale. That is the number of experts rating the statement. The **asterisk** "*" expresses the answer you (personally) indicated in Round 1.

INSTRUCTIONS ON HOW TO COMPLETE DELPHI ROUND 2

Please indicate (mark with **X**) the degree of importance each statement is for inclusion in the framework for the use of biological medicines in South Africa according to the following scales or grades:

1 = Essential - **Must definitely be included**
2 = Useful - **Can be included**
3 = Unnecessary - **Must definitely be excluded**

Note:

a) Mark the option you choose with an **X**
b) Mark one option only
c) Add your comments where you feel that it is necessary
d) Additional comments can be added using the space provided at the end of each section.

EXAMPLE

QUESTIONNAIRE - 1

		1	2	3	Comments
1.	Round 1: Trastuzumab is approved for the treatment of early stage breast cancer	**10**	**2 ***	**3**	
	Round 2				

Ten of the *fifteen* experts rated this statement as essential (must definitely be included).
Two of the *fifteen* experts decided this statement is useful (can be considered), the asterisk "*" indicates that you are one of the two experts rating this as a "2".

Round 2 gives you the opportunity to reconsider your opinion on each statement where consensus was not reached in the First round. During Round 2, you are allowed to change your opinion and choose a different option; however, you may also retain your original choice if you feel it is appropriate. All information will be treated confidentially; the identity of the respondents is not known to the other experts in the study and will only be known by the researcher.

It should not take longer than 10 minutes to complete the questionnaire.
Please return the completed questionnaire as soon as possible.

Thank you once again for your participation

Kind regards, *Martlie Mocke*

DEVELOPING A FRAMEWORK FOR PROMOTING THE USE OF BIOLOGICAL MEDICINE IN SOUTH AFRICA BY CONSENSUS USING THE DELPHI METHOD

Delphi questionnaire – Round 2

Participant no:

Fill in the sections of the questionnaire (A, B, C and D) as per instructions on the previous page

SECTION A:
USE OF BIOLOGICAL MEDICINES (HOW TO PRESCRIBE BIOLOGICAL MEDICINES)

A		1	2	3	Comments
	Round 1: Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria	**8**	**6**	**1**	
1.	**Round 2:**				
	Round 1: Biological Medicines must be given early in the disease process for it to be effective	**5**	**9**	**1**	
2.	**Round 2:**				
	Round 1: Plasma concentrations of Biological Medicines are useful to know in patients with poor response because it is helpful to understand lack of response /measure and adherence	**6**	**6**	**3**	
3.	**Round 2:**				
4.	(New) Medicines that affect the immune system of the patient pose a definite risk				
5.	(New) Co-morbidities and complications need to be considered when Biological Medicine is prescribed				
6.	*Any additional comments for the framework for the use of Biological Medicines in South Africa:*				

SECTION B:
INFORMATION RESOURCE

B		1	2	3	Comments
	Round 1: Biological Medicines promotion programmes must be included in the set of guidelines	**6**	**6**	**3**	
1.	**Round 2:**				
	Round 1: Undergraduate students must be exposed more to Biological Medicines during their studies	**6**	**7**	**2**	
2.	**Round 2:**				
	Round 1: There must be more education about Biological Medicines in lectures, because it will probably become the most commonly used medicine in future	**8**	**7**	**0**	

3.	**Round 2:**				
	Round 1: All doctors must know the available Biological Medicines and their respective indications	**6**	**5**	**4**	
4.	**Round 2:**				
	Round 1: Doctors' knowledge about Biological Medicines needs continuous professional education/ improvement via seminars/ CPD evenings/workshops	**7**	**7**	**1**	
5.	**Round 2:**				
	Round 1: Medical students must know the basics about Biological Medicine, should be part of the general pharmacology curriculum	**4**	**8**	**3**	
6.	**Round 2:**				
7.	*Any additional comments for a framework for the use of Biological Medicines in South Africa:*				

SECTION C:
PATIENT CARE / MANAGEMENT

C		**1**	**2**	**3**	**Comments**
	Round 1: Biological Medicines are difficult to use because they are administered parentally(IV,IM or SC), hence require close monitoring	**3**	**10**	**2**	
1.	**Round 2:**				
2.	**(New)** Patient education on Biological Medication is of paramount importance				
3.	*Any additional comments for a framework for the use of Biological Medicines in South Africa:*				

SECTION D:

AVAILABILITY, PRESCRIPTION, DISPENSING and PROCUREMENT

D		**1**	**2**	**3**	**Comments**
	Round 1: The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex	**6**	**7**	**2**	
1.	**Round 2:**				
	Round 1: Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier	**9**	**2**	**4**	
2.	**Round 2:**				
	Round 1: The procurement process of Biological Medicines must be improved	**7**	**6**	**2**	

3.	**Round 2:**				
	Round 1: Limited access due to availability/registration	**8**	**4**	**3**	
4.	**Round 2:**				
5.	**(New)** The procurement of biological medicine is a slow process that could be streamlined				
6.	**(New)** Lack of knowledge of service providers and procurement play a role in the availability of Biological Medicine				
7.	**(New)** Complex regulatory requirements play a role in the availability of Biological Medicine				
8.	***Any additional comments for a framework for the use of Biological Medicines in South Africa:***				

Thank you

This second stage of the Delphi survey

APPENDIX F2

DELPHI METHOD: ROUND 2: SUMMARY OF RESULTS

	001			002			003			004			005			006			007			008			009			010			011			012			013			014			015			TOTALS		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
A1	1			1							1		1			1			1			1			1			1			1			1			1			1			1			13	1	0
A2		1			1						1			1			1			1			1			1			1			1			1			1			1			2	12	0
A3	1				1						1			1		1				1			1			1			1			1			1			1			1			2	12	0
A4	1			1						1			1					1	1			1			1			1			1			1			1			1			12	1	1
A5	1			1						1			1			1			1			1			1			1			1			1			1			1			14	0	0
B1	1			1							1				1	1			1			1			1			1			1			1			1			1			12	1	1
B2		1		1						1			1			1			1			1					1	1			1			1			1			1			12	1	1
B3		1		1						1			1				1		1			1			1			1			1			1			1			1			12	2	0
B4	1			1						1			1			1				1		1			1				1		1			1			1			1			12	2	0
B5	1			1							1		1				1		1			1			1			1			1			1			1			1			12	2	0
B6	1			1						1				1		1				1		1			1			1			1			1			1			1			12	2	0
C1		1				1					1			1			1			1			1			1				1		1				1			1				1		0	12	2
C2	1			1						1					1	1			1				1		1			1			1			1			1			1			12	1	1
D1	1			1						1			1			1			1			1				1				1	1			1			1			1			12	1	1
D2	1			1							1		1			1			1			1			1			1			1					1	1			1			1			12	1	1
D3	1			1						1			1				1		1			1			1				1		1			1			1			1			12	2	0
D4	1			1						1				1			1		1			1			1			1			1			1			1			1			12	2	0
D5	1			1						1			1			1			1			1			1					1		1		1			1			1			12	1	1
D6	1				1					1			1			1			1			1			1			1			1					1	1			1			1			12	1	1
D7	1					1				1			1			1			1			1			1			1				1		1			1			1			1			12	1	1

APPENDIX G

SUMMARY OF RESPONSES TO THE DELPHI QUESTIONNAIRE

Responses to the questionnaire, Round 1

Section A - contained thirteen statements focusing on the use of Biological Medicines and how to prescribe them.

		Essential	Useful	Unnecessary	Responses
		1	**2**	**3**	
A1.	There is a need for a framework for the use of Biological Medicines in South Africa	14	1	0	**Round 1: (1) 93%**
A2.	Some Biological Medicines may not be used with coexisting diseases such as TB or the presence of serious infections or organ failure	12	2	1	**Round 1: (1) 80%**
A3.	The staff that administer Biological Medicines must have appropriate training about Biological Medicines, to explain it to the patient in a way that the patient will understand it	14	1	0	**Round 1: (1) 93%**
A4.	Biological Medicines should be made available to all patients fulfilling the currently recommended eligibility criteria	13	1	0	**Round 1: (1) 53%** **Round 2: (1) 93%**
A5.	Treatment should be initiated and monitored by specialists	13	2	0	**Round 1: (1) 87%**
A6.	Biological Medicines must be given early in the disease process for it to be effective	2	12	0	**Round 1: (2) 60%** **Round 2: (2) 85%**
A7.	Patients should undergo appropriate laboratory tests before Biological Medicines is administered	14	1	0	**Round 1: (1) 93%**
A8.	Frequent patient review to check for infections, malignancies and other adverse effects of Biological Medicines is necessary	14	1	0	**Round 1: (1) 93%**
A9.	Guidelines can help in determining when a patient should be given Biological Medicines	14	1	0	**Round 1: (1) 93%**
A10	Plasma concentrations of Biological Medicines are useful to know in patients with poor response because it is helpful to understand the lack of response/measure and adherence	0	12	2	**Round 1: (2) 40%** **Round 2: (2) 86%**
A11.	Framework should be available to guide Doctors concerning the necessarily work-up (investigation) before the administering of Biological Medicines	12	3	0	**Round 1: (1) 80%**
A12.	Medicines that affect the immune system of the patient pose a definite risk	12	1	1	**Round 2: (1) 86%**
A13.	Co-morbidities and complications need to be considered when Biological Medicines is prescribed	12	3	0	**Round 2: (1) 100%**

RESPONSES TO SECTION B

Section B - contained nine statements focusing on the information resource of Biological Medicines.

B1. A step-by-step approach is needed in the development of a framework for the use of Biological Medicines

		Essential	Useful	Unnecessary	Responses
		1	**2**	**3**	
B1.	A step-by-step approach is needed in the development of a framework for the use of Biological Medicines	12	3	0	**Round 1: (1) 80%**
B2.	Guidelines for use of Biological Medicines should be readily available in a written format	12	3	0	**Round 1: (1) 80%**
B3.	Biological Medicines promotion programs must be included in the set of guidelines	12	1	1	**Round 1: (1)40%** **Round 2: (1) 80%**
B4	Specialist knowledge of Biological Medicines must be improved	12	3	0	**Round 1: (1) 80%**
B5	Undergraduate students must be exposed more to Biological Medicines during their studies	12	2	0	**Round 1: (1) 40%** **Round 2: (1) 86%**
B6	There must be more education about Biological Medicines in lectures	12	3	0	**Round 1: (1) 80%**
B7	All doctors must know the available Biological Medicines and their respective indications	12	1	1	**Round 1: (1) 42%** **Round 2: (1) 86%**
B8	Doctors' knowledge about Biological Medicines needs continuous professional education / improvement via seminars / CPD evenings / workshops	2	12	0	**Round 1: (1) 42%** **Round 2: (1) 86%**
B9	Medical students must know the Biological Medicines available and their respective indications.	12	2	0	**Round 1: (1) 29%** **Round 2: (1) 86%**

RESPONSES TO SECTION C

Section C – Contained six statements regarding patient care and management.

Biological Medicines are difficult to use

		Essential	Useful	Unnecessary	Responses
C		**1**	**2**	**3**	
C1.	Biological Medicines are difficult to use because they are administered parentally (IV, IM or SC), hence require close monitoring	0	12	2	**Round 1: (2) 67%** **Round 2: (2) 86%**
C2.	There may be a religious or cultural objection to using Biological Medicines.	1	12	1	**Round 1: (2) 87%**
C3.	Biological Medicines improve the quality of life of patients	13	1	1	**Round 1: (1) 86%**
C4.	Patient understanding of information regarding Biological Medicines promotes use	12	1	1	**Round 1: (2) 67%** **Round 2: (2) 86%**
C5.	Patient education on Biological Medication is of paramount importance	12	1	1	**Round 2: (2) 86%**

RESPONSES TO SECTION D

Section D - contained eight statements that focus on the availability, prescription, dispensing and procurement process

The use of Biological Medicines is limited because of the procurement process

		Essential	Useful	Unnecessary	Responses
D		**1**	**2**	**3**	
D1	The use of Biological Medicines is limited because the procurement process to obtain Biological Medicines is complex	12	1	1	**Round 1: (1) 40 %** **Round 2: (1) 86 %**
D2	Financial advisory services are important in the procurement process of Biological Medicines	12	2	1	**Round 1: (1) 86 %**
D3.	Guidelines for the use of Biological Medicines should create a better relationship between the prescribers and the supplier	12	1	1	**Round 1: (1) 60 %** **Round 2: (1) 86 %**
D4.	The procurement process of Biological Medicines is as a slow process that could be streamlined	12	2	0	**Round 1: (1) 60 %** **Round 2: (1) 86 %**
D5.	Limited access due to funding	13	1	1	**Round 1: (1) 87 %**
D6.	Limited access due to availability/registration	7	4	3	**Round 1: (1) 47 %** **Round 2: (1) 86 %**
D7	Lack of knowledge of service providers and procurement play a role in the availability of Biological Medicines	12	1	1	**Round 2: (1) 86 %**
D8	Complex regulatory requirements play a role in the availability of Biological Medicines	12	1	1	**Round 2: (1) 86 %**

CHAPTER 45

Anticancer and Immunomodulating Drugs

CLASSIFICATION OF ANTICANCER AND IMMUNOMODULATING DRUGS

DNA Synthesis Inhibitors

- Methotrexate
- Mercaptopurine[a]
- Fluorouracil[b]

DNA Cross-linking and Intercalating Drugs

- Cyclophosphamide[c]
- Carmustine[d]
- Cisplatin[e]
- Busulfan[f]
- Bleomycin
- Doxorubicin[g]

DNA Topoisomerase Inhibitors

- Etoposide
- Irinotecan[h]

Mitotic Inhibitors

- Paclitaxel
- Vincristine[i]

Enzyme and Proteasome Inhibitors

- Bortezomib
- Imatinib[j]
- Vemurafenib

Cancer Immunotherapy Agents

- Rituximab
- Trastuzumab[k]
- Interferon alfa

Immunosuppressant Drugs

- Azathioprine
- Mycophenolate
- Basiliximab
- Daclizumab[l]
- Cyclosporine
- Sirolimus
- Tacrolimus[m]

[a]Also cladribine, clofarabine, fludarabine, nelarabine, and thioguanine.
[b]Also azacitidine, capecitabine, cytarabine, floxuridine, and gemcitabine; also uridine triacetate (VISTOGARD), an antidote for fluorouracil or capecitabine overdose and toxicity.
[c]Also ifosfamide, chlorambucil, mechlorethamine, and melphalan.
[d]Also lomustine and streptozocin.
[e]Also carboplatin and oxaliplatin.
[f]Also dacarbazine, mitomycin, and temozolomide.
[g]Also daunorubicin, idarubicin, mitoxantrone, and dactinomycin.
[h]Also teniposide and topotecan.
[i]Also docetaxel, cabazitaxel, vinblastine, vinorelbine, and ixabepilone.
[j]Also dasatinib, gefitinib, ibrutinib, lapatinib, nilotinib, pazopanib, sorafenib, and sunitinib.
[k]Also alemtuzumab, bevacizumab, cetuximab, daratumumab, elotuzumab, ipilimumab, nivolumab, panitumumab, ^{90}Y-ibritumomab, and ^{131}I-tositumomab.
[l]Also belatacept and palivizumab.
[m]Also available as tacrolimus extended-release (ENVARSUS XR).

OVERVIEW

Cancer is the second most common cause of death in the United States and other developed countries. Currently, about 1,685, 000 new cancer cases and 595,000 cancer deaths are projected to occur each year in the United States. Worldwide, an estimated 9 million people die of cancer each year. There are two main types of cancer: (1) **solid tumors** that begin as abnormal tissue growths and often spread to other tissues and (2) **hematologic malignancies** that arise in the **bone marrow or lymph nodes** and produce large quantities of **abnormal blood cells.** The most common solid tumor malignancies are those of the **lungs, colon, breast, and prostate**. The hematologic malignancies include **leukemias** consisting of malignant white blood cells (leukocytes), **lymphomas** comprised of malignant lymphocytes, and **multiple myeloma.**

Cancer results from the **transformation** of normal cells into **malignant neoplastic cells** that exhibit **loss of normal function** (de-differentiation), **uncontrolled cell division, invasiveness,** and **metastasis.** The invasiveness of cancer cells enables them to spread into surrounding tissues, while metastasis enables them to spread to other sites in the body through blood vessels and the lymphatic system (lymph nodes). The invasiveness and metastasis of cancer cells depends on the expression of growth factors that promote the formation of new blood vessels to supply the growing tumor. This process is called **angiogenesis** and is a target of several newer anticancer drugs.

Malignant transformation is caused by **genetic mutations** that convert **proto-oncogenes to oncogenes** (cancer forming genes). These genes express proteins that **promote uncontrolled cell proliferation** or that **inactivate tumor suppressor**

Vinca Alkaloids. **Vincristine** and **vinblastine** are alkaloids obtained from the periwinkle plant, formerly designated *Vinca rosea*. Despite their structural similarity and similar mechanisms of action, the two drugs have different antitumor activities and toxicities. Both drugs are administered intravenously and are extensively metabolized before undergoing biliary excretion. Vinca alkaloids do not enter the CNS in significant amounts.

Vincristine is often used to treat **hematologic cancers,** including acute lymphocytic leukemia and Hodgkin and non-Hodgkin lymphomas, and to treat **solid tumors** such as rhabdosarcoma, neuroblastoma, and Wilms tumor. Vinblastine is a component of the ABVD regimen described earlier for **Hodgkin disease** and is also used for treating breast cancer (see Table 45.2). **Vinorelbine** is a semisynthetic derivative of vinblastine that is used to treat **non–small cell lung cancer,** breast cancer, and ovarian cancer.

Vincristine produces dose-limiting neurotoxicity in the form of a **peripheral neuropathy** that affects both sensory and motor function. Suppression of deep tendon reflexes is usually the earliest sign of neuropathy, and paresthesias of the hands and toes are common. Cranial nerve damage can cause hoarseness, facial palsies, or jaw pain, whereas autonomic neuropathies can cause orthostatic hypotension, abdominal pain, and constipation. These effects are usually reversible and do not require discontinuation of vincristine therapy unless they are disabling. Vincristine causes little myelosuppression, whereas vinblastine produces **myelosuppression** but little neurotoxicity.

Taxanes. The taxanes are alkaloids obtained from the bark **(paclitaxel)** or needles **(docetaxel** and **cabazitaxel)** of yew trees. The taxanes are given intravenously and are eliminated via metabolism and biliary excretion.

The taxanes have good activity against several types of cancer (see Table 45.1). **Paclitaxel** is indicated as first-line therapy for metastatic **ovarian cancer,** in combination with cisplatin; treatment of **non–small cell lung cancer;** and treatment of **metastatic breast cancer** unresponsive to first-line therapy. **Docetaxel** is approved for locally advanced or metastatic breast cancer and for metastatic non–small cell lung cancer after failure of cisplatin-based chemotherapy. **Cabazitaxel** is indicated as second-line treatment of metastatic **hormone-refractory prostate cancer.**

The major dose-limiting toxicity of taxanes is **myelosuppression,** particularly neutropenia. Taxanes can also cause alopecia and neurotoxicity.

Ixabepilone is a microtubule inhibitor for the treatment of metastatic or locally **advanced breast cancer** resistant to treatment with other drugs. Ixabepilone has low susceptibility to efflux transporters such as Pgp and multi-drug resistance pump (MRP) and is active against tumors resistant to taxanes, vinca alkaloids, and anthracyclines. The drug is given intravenously and is extensively metabolized before fecal and renal excretion.

Enzyme and Proteasome Inhibitors

A number of newer drugs inhibit molecular pathways involved in cancer cell transformation and proliferation as shown in Table 45.3. Many of these drugs **inhibit tyrosine kinase enzymes** that phosphorylate and thereby activate these pathways leading to continuous cell proliferation. Other drugs inhibit **proteasomes** that serve to degrade and recycle proteins.

Imatinib, dasatinib, and **nilotinib** inhibit the BCR-ABL (breakpoint cluster region–Abelson) tyrosine kinase expressed by the **Philadelphia chromosome** in **CML** cells (Fig. 45.6). BCR-ABL kinase is an oncoprotein resulting from a reciprocal chromosomal translocation (swap) between chromosomes 9 and 22 designated t(9;22). This swap inserts *ABL* from chromosome 9 adjacent to *BCR* on chromosome 22, forming the *BCR-ABL* fusion gene and leading to expression of an abnormal tyrosine kinase and the malignant transformation of hematopoietic stem cells. Inhibition of the BCR-ABL kinase reduces cell proliferation and induces apoptosis.

Imatinib has produced remarkable rates of hematologic and cytogenetic remission in CML and is a first-line treatment for this disease. **Imatinib** also inhibits **c-kit,** a tyrosine kinase stem cell receptor, and has been used to treat **gastrointestinal stromal tumors** associated with c-kit mutations. Both **dasatinib** and **nilotinib** are effective in patients with imatinib-resistant tumors, and they appear to and achieve greater cytogenetic responses with less cancer progression in newly diagnosed patients than did imatinib.

Erlotinib and **gefitinib** are specific inhibitors of the **epidermal growth factor receptor** tyrosine kinase. They are used as second-line therapies for **non–small cell lung cancer** and achieve modest increases in survival. Erlotinib is metabolized by CYP3A, and other drugs that inhibit or induce this enzyme can alter its plasma levels.

Sunitinib and **sorafenib** inhibit several **receptor tyrosine kinases,** including **vascular endothelial growth factor (VEGF) receptors** and **platelet-derived growth factor receptors** that promote **angiogenesis.** Both drugs are indicated for advanced **renal cell carcinoma.** Sunitinib is also used for gastrointestinal stromal tumor (GIST), while sorafenib is used to treat hepatocellular carcinoma. **Lapatinib** inhibits the human epidermal growth factor–2 (HER2/neu) receptor kinase in breast cancer cells and is used to treat HER2 receptor-positive breast cancer.

The combination of **drabrafenib** and **trametinib** is now available to treat inoperable and metastatic melanoma. Drabrafenib inhibits the **B-raf kinase** expressed by the *BRAF* gene having the **V600E mutation.** This mutation occurs in about 60% of melanomas and results in continuous B-raf kinase activity, leading to continuous cell proliferation. Trametinib is a MEK (mitogen-activated protein kinase) inhibitor that acts synergistically with drabrafenib to block melanoma cell proliferation. Another B-raf kinase/MEK inhibitor combination for treating metastatic melanoma consists of **vemurafenib** and **cobimetinib.** The most common side effects of this treatment are fever, nausea, vomiting, and diarrhea, though severe adverse effects have also occurred.

The treatment of relapsed CLL has advanced with the introduction of **ibrutinib,** the first inhibitor of **Bruton's kinase** to be developed for cancer treatment. This kinase plays a crucial role in B-lymphocyte maturation. An early study found that the drug reduced disease progression by 80% compared with the standard treatment for relapsed CLL of bendamustine plus rituximab.

Bortezomib is the first **proteasome inhibitor** to be developed for cancer treatment. The drug prevents the degradation and recycling of proteins by the proteasome of cancer cells, leading to protein accumulation and cell death. Bortezomib is used to treat **multiple myeloma** and **mantle cell lymphoma.**

TABLE 45.3 Pharmacology of Enzyme Inhibitors and Monoclonal Antibodies

DRUG	TARGET INHIBITED	MECHANISM	EFFECTS
Protein Kinase Inhibitors			
Imatinib, dasatinib, nilotinib	BCR-ABL tyrosine kinase	Prevents activation of RAS/RAF/MAP and other pathways	Inhibits proliferation and promotes apoptosis of myeloid leukemia cells
Erlotinib, gefitinib	Epidermal GFR kinase	Prevents MAP kinase and k-ras GTPase activation of DNA synthesis and cell proliferation	Reduces proliferation of nonsmall cell lung and other cancer cells
Sunitinib, sorafenib	Vascular endothelial GFR kinases, platelet-derived GFR kinases	Inhibits proliferation of vascular endothelial cells	Inhibits invasion and metastasis of solid tumor cancer cells
Lapatinib	HER2/neu receptor tyrosine kinase	Prevents activation of MAP kinase, STAT, and phospholipase C	Inhibits proliferation of breast cancer cells
Drabrafenib, vemurafenib	B-raf kinase (mutated)	Prevents MAP kinase activation of cell division	Inhibits proliferation of melanoma cells
Trametinib, cobimetinib	Mitogen-activated protein (MAP) kinase	Disrupts pathway leading to DNA transcription	Inhibits growth of BRAF-mutated melanoma
Ibrutinib	Bruton's tyrosine kinase	Prevents phospholipase C activation of B-cell signaling pathways	Leukemic B-cell apoptosis
Proteasome Inhibitor			
Bortezomib	Catalytic site of 26S proteasome	Prevents degradation of proapoptotic proteins	Destroys myeloma and mantle lymphoma cells
Monoclonal Antibodies			
Alemtuzumab	CD52 surface glycoprotein	Induces complement-mediated cytolysis	Destroys leukemic B-cell lymphocytes and lymphoma cells
Bevacizumab	Vascular endothelial GF	Inhibits proliferation of vascular endothelial cells	Inhibits invasion and metastasis of solid tumor cancer cells
Cetuximab, panitumumab	Epidermal GF receptor	Prevents MAP kinase/k-ras GTPase activation of cell proliferation	Decreases colon cancer cell replication
Daratumumab	ADP ribose hydrolase (CD38)	Blocks overexpressed CD38 on myeloma cells	Reduces myeloma cell proliferation
Elotuzumab	SLAM-F7 protein	Modulates myeloma and NK lymphocyte activity	Destroys myeloma cells and enhances NK antitumor immunity
Rituximab	CD20 antigen	Recruits complement	Lysis of non-Hodgkin lymphoma cells
^{90}Y-ibritumomab, ^{131}I-tositumomab	CD20 antigen	Emit β-radiation	Destroys non-Hodgkin lymphoma cells
Ipilimumab	Cytotoxic T-lymphocyte antigen 4	Releases inhibition of T-lymphocyte tumor immunity	Increases CD8 T-cells and melanoma immunity
Nivolumab	Programmed death-1 protein (PD-1)	Blocks PD-1 inactivation of T cells	Enables T-cell destruction of melanoma cells
Trastuzumab	HER2/neu receptor	Prevents MAP kinase, STAT, and phospholipase C activation	Reduces breast cancer proliferation

ADP, Adenosine diphosphate; *BCR-ABL,* break cluster region-Abelson; *CD,* cell differentiation; *GF,* growth factor; *GFR,* growth factor receptor; *GTPase,* guanosine triphosphatase; *Her2/neu,* human epidermal growth factor 2/neural; *k-ras,* Kirsten rat sarcoma viral oncogene homolog; *MAP,* mitogen-activated protein; *NK cell,* natural killer cell; *RAS/RAF/MAP,* rat sarcoma/ rapidly activated fibrosarcoma/mitogen-activated protein; *SLAM F7,* signaling lymphocytic activation molecule F7; *STAT,* signal transducer and activator of transcription; *T-lymphocyte (cell),* thymus-derived lymphocyte.

Immunotherapy Agents

Monoclonal Antibodies. **Monoclonal antibodies** are a fast-growing class of anticancer immunotherapy agents. The fragment antigen binding (Fab) portion of these antibodies binds to a specific antigen on a particular type of cancer cell, leading to blockade of an oncogenic pathway. Some antibodies target growth factors or their receptors, whereas others release a cytotoxic isotope or enhance host immunity (Table 45.3). Because of their protein structure, these agents must be given **intravenously.** Many monoclonal antibodies cause hypersensitivity reactions and impair immune function.

The names of monoclonal antibodies end in *mab* or *monab*. The letters before *mab* indicate the source of the antibody: *o* for mouse, *u* for human, and *xi* for chimeric. An internal letter or syllable identifies the therapeutic use of the antibody, for example, *tu* for tumor, *vi* for virus, and *c* or *ci* for circulation. For example, rituximab is a chimeric (*xi*) human-murine

CHAPTER 30 Drugs for Pain, Inflammation, and Arthritic Disorders

CLASSIFICATION OF DRUGS FOR PAIN, INFLAMMATION, AND ARTHRITIC DISORDERS

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

Nonselective Cyclooxygenase Inhibitors
- Acetaminophen (TYLENOL)[a]
- Aspirin and other salicylates
- Ibuprofen (MOTRIN, ADVIL)[b]
- Ketoprofen (ORUDIS)
- Meloxicam (MOBIC)[c]
- Naproxen (NAPROSYN, ALEVE)[d]

Selective Cyclooxygenase-2 Inhibitors
- Celecoxib (CELEBREX)

Disease-Modifying Antirheumatic Drugs (DMARDs)

Gold Salts
- Auranofin (RIDAURA)
- Aurothioglucose (SOLGANAL)
- Gold sodium thiomalate (MYOCHRYSINE, AUROLATE)

Glucocorticoids
- Prednisone (DELTASONE)[e]

Other Disease-Modifying Antirheumatic Drugs
- Etanercept (ENBREL)[f]
- Hydroxychloroquine (PLAQUENIL)
- Leflunomide (ARAVA)
- Methotrexate (RHEUMATREX)
- Penicillamine (CUPRIMINE)
- Sulfasalazine (AZULFIDINE)[g]

Drugs for Gout

Drugs to Prevent Gout Attacks
- Allopurinol (ZYLOPRIM)
- Febuxostat (ULORIC)
- Pegloticase (KRYSTEXXA)
- Rasburicase (Elitek)
- Lesinurad (ZURAMPIC)

Drugs to Treat Gout Attacks
- Colchicine (COLCRYS)
- Indomethacin and other NSAIDs

[a]Also injectable form of acetaminophen (OFIRMEV).
[b]Also injectable form of ibuprofen (CALDOLOR)
[c]Meloxicam also available in a microparticle formulation (VIVLODEX).
[d]Also indomethacin in oral and injection formulations (INDOCIN) and in oral only (TIVORBEX), sulindac (CLINORIL), ketorolac (TORADOL, ACUVAIL, SPRIX), piroxicam (FELDENE), nabumetone (RELAFEN), etodolac (LODINE), diclofenac (FLECTOR, VOLTAREN GEL, ZIPSOR, DYLOJECT), and combination formulations such as ibuprofen with famotidine (DUEXIS) and naproxen with esomeprazole (VIMOVO).
[e]Also available in a prednisone delayed-release formulation (RAYOS).
[f]Also infliximab (REMICADE), adalimumab (HUMIRA), anakinra (KINERET), abatacept (ORENCIA), tocilizumab (ACTEMRA), certolizumab (CIMZIA), and golimumab (SIMPONI).
[g]Also apremilast (OTEZLA).

OVERVIEW

A variety of medical disorders and injuries are characterized by **pain** and **inflammation.** This chapter describes the pharmacologic properties of **nonsteroidal antiinflammatory drugs (NSAIDs),** which are widely used to alleviate the symptoms of rheumatoid arthritis (RA), osteoarthritis (OA), and gout, as well as to relieve the pain and fever that accompany many nonarthritic disorders. They are also used by millions on a daily basis for the occasional headache. The chapter also discusses **disease-modifying antirheumatic drugs (DMARDs)** and drugs for the prevention and treatment of gout.

RHEUMATOID ARTHRITIS

RA is an autoimmune disorder of unknown cause. The hallmark symptom of RA is joint inflammation, and most patients with RA experience a chronic, fluctuating course of disease that, despite therapeutic measures, can result in progressive joint destruction, deformity, disability, and premature death. RA affects 2% to 3% of the U.S. population, making it the most common systemic inflammatory disease (Box 30.1). It is three times more common in women than in men. RA is characterized by **symmetric joint inflammation** that most frequently affects the small joints of the hands, wrists, and feet, but also the joints of the ankles, elbows, hips, knees, and shoulders. Cardiopulmonary, neurologic, and ocular inflammation are also often found in patients with RA, and many patients develop rheumatoid nodules on the extensor surfaces of the elbows, forearms, and hands. In addition, many patients have extraarticular manifestations, such as vasculitis, lymphadenopathy, and splenomegaly.

As shown in Fig. 30.1, RA is triggered by **autoimmune mechanisms** that lead to the destruction of synovial tissue and other connective tissue. Both humoral and cellular immune mechanisms are involved in the pathogenesis of the disease. These mechanisms include the cytokine-mediated activation of T and B lymphocytes and the recruitment and activation of macrophages. The inflammatory leukocytes then release a variety of prostaglandins, cytotoxic compounds, and free radicals that cause joint inflammation and

synthesis. It also **inhibits lymphocyte proliferation** and the production of cytokines and rheumatoid factor. In addition, it interferes with polymorphonuclear leukocyte chemotaxis and **reduces the production of cytotoxins** and free radicals that damage the synovial membrane and bone.

Methotrexate is considered the DMARD of choice for most patients with RA. The drug can be given orally or intramuscularly and has a fairly rapid onset of action, with benefits observed as early as 2 to 3 weeks after therapy is started. From 45% to 55% of patients continue therapy for at least 5 to 7 years, and sustained efficacy for up to 15 years has been demonstrated in some patients. The combined use of methotrexate and other DMARDs is often more effective than single-drug therapy.

Treatment with methotrexate is generally well tolerated by patients with RA, but it can cause adverse GI, hematologic, hepatic, and pulmonary reactions. Elevated liver enzyme levels are found in up to 15% of patients treated with methotrexate, but serious hepatotoxicity is rare. The administration of folic acid supplements does not reduce the drug efficacy and may prevent some of these adverse effects. The use of **methotrexate is** contraindicated in pregnancy.

Leflunomide

Leflunomide is a newer immunosuppressive drug that acts as a powerful **inhibitor of leukocyte** and **T-cell proliferation.** The active metabolite of leflunomide inhibits a key enzyme in pyrimidine synthesis, dihydroorotate dehydrogenase, and thereby prevents replication of DNA and synthesis of RNA and protein in immune cells. Leflunomide is converted to its active metabolite, **teriflunomide,** in the intestinal wall and liver. Teriflunomide is further metabolized and excreted in the urine and feces, with an elimination half-life of about 2 weeks. Teriflunomide is also marketed and indicated for the treatment of multiple sclerosis (see Chapter 24).

Leflunomide is marketed as an **alternative to methotrexate** for the first-line management of RA. In a controlled trial, 41% of patients treated with leflunomide showed significant improvement in tender and swollen joints, compared with 35% of those treated with methotrexate and 19% given a placebo.

The adverse effects of leflunomide include **diarrhea** and **reversible alopecia** (baldness). The drug can increase serum levels of hepatic enzymes and increase the risk of hepatotoxicity alone and when it is used in combination with methotrexate. The active metabolite of leflunomide inhibits CYP2C9 and may thereby increase the serum level of many drugs, including ibuprofen and some of the other NSAIDs. Leflunomide is **teratogenic,** so its use is **contraindicated in pregnancy.**

Hydroxychloroquine

Hydroxychloroquine, an **antimalarial drug related to chloroquine,** is extensively used as a DMARD. It reduces the chemotaxis and phagocytosis of polymorphonuclear leukocytes and decreases the production of superoxide radicals by these cells. The drug has a slow onset of action and can require 6 months of therapy before benefits are observed. It does not produce the myelosuppressive, hepatic, and renal toxicities that many other DMARDs produce. Hydroxychloroquine occasionally causes GI disturbances, and patients undergoing hydroxychloroquine treatment must be monitored for **adverse ocular effects,** including blurred vision, scotomas, and night blindness.

Immunomodulators

Tumor Necrosis Factor α (TNFα) Blocking Agents. **TNFα blocking agents** are immunomodulating agents that exert their effects by binding to and **inactivating** TNFα. TNFα is one of the proinflammatory cytokines produced by macrophages and activated T cells. Elevated levels of TNFα are found in the synovial fluid of joints of RA patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of RA. Newer agents have novel mechanisms of action such as preventing interleukin binding and T-cell activation, and are introduced later (see Fig. 30.1).

Etanercept is a protein formed by recombining human **soluble TNFα receptors** with Fc fragments of human immunoglobulin G1 (IgG1). In comparison with the original protein, the **recombined protein** can antagonize TNFα to a greater extent and has a longer half-life. Experimental studies in several animal models of RA have found etanercept treatment to be effective, as have subsequent clinical trials in patients with this disease. According to a 3-month clinical study, 75% of patients with RA had a significant improvement in the signs and symptoms of their disease. The drug was generally well tolerated, although **injection site reactions** were common. The drug is currently intended for use in patients whose RA is refractory to treatment with methotrexate or other DMARDs. Etanercept can be used alone or in combination with methotrexate in these patients.

Infliximab is a **chimeric human-murine (mouse) monoclonal antibody** that **inactivates** TNFα. It is used in the treatment of **Crohn's disease** and **RA.** In one clinical trial, infliximab treatment resulted in an improvement of RA manifestations in 80% of patients whose disease was refractory to other drugs. In another study, infliximab was found to be **more effective when combined with methotrexate** than when used alone. Infliximab is administered intravenously at 4- to 12-week intervals.

Adalimumab is a human **IgG1 monoclonal antibody specific** for human TNFα. It is made by recombinant DNA technology in a mammalian cell expression system and purified to exclude viral particles. For adult patients, adalimumab is administered every other week as a subcutaneous injection. During adalimumab treatment, administration of methotrexate, glucocorticoids, salicylates, NSAIDs, analgesics, or other DMARDs can continue safely. Some patients not taking concomitant methotrexate may see additional benefits by increasing the frequency of adalimumab to 40 mg every week.

Certolizumab is a **pegylated, monoclonal antibody** directed against TNFα. By combining the active molecule with polyethylene glycol (PEG), the resulting product remains in the body longer and provides sustained activity.

Golimumab is a human monoclonal antibody that binds to **both the soluble and transmembrane** forms of human TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biologic activity of TNFα. Golimumab, in **combination with methotrexate,** is indicated for the treatment of adult patients with moderately to severely active RA.

All TNFα-blocking agents produced **serious infections and sepsis,** some fatal, during clinical trials. Many of the

serious infections were seen in patients on concomitant immunosuppressive therapy that, in addition to their RA, could predispose them to infections. Tuberculosis and invasive opportunistic fungal infections were also noted during treatment with TNF blockers. In September 2011, the FDA mandated a **new block box warning** on the prescribing information for all TNF blockers that warns specifically of the risk of *Legionella* pneumonia (also known as *Legionnaire disease*) and *Listeria* infections.

Lymphomas were also reported in patients treated with TNFα-blocking agents. In clinical trials, patients with RA, particularly those with highly active disease, were at increased risk for the development of lymphoma. The role of TNFα blockers in the development of this malignancy is not known.

Other Immunomodulating Agents. **Anakinra** is a recombinant form of the human **interleukin-1 receptor antagonist (IL-1Ra),** differing only by the addition of a single methionine residue at its amino terminus. It blocks the biologic activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI). IL-1 production is induced in response to inflammatory stimuli and mediates inflammatory and immunologic responses. IL-1 has a broad range of activities, including cartilage degradation by its induction of the rapid loss of proteoglycans, as well as stimulation of bone resorption. The levels of the naturally occurring IL-1Ra in synovial fluid of patients with RA are not sufficient to compete with the increased production of IL-1. The recommended dose of anakinra is 100 mg/day administered daily by subcutaneous injection. The adverse effects are the same as for the TNF blockers, with serious infections and lymphoma of most concern.

Abatacept is a selective **costimulation modulator** and **inhibits T-cell activation** by binding to cell surface markers (proteins) on leukocytes. Activated T lymphocytes are involved in the cause of RA and are found in the synovial fluid of patients with RA. Abatacept is a recombinant protein made by joining the extracellular domain of human cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) to the modified Fc portion of human IgG1. It is the CTLA part of the molecule that binds to specific cell surface proteins of T lymphocytes to prevent their activation. Abatacept is the first and only biologic for the treatment of RA available in a self-injectable subcutaneous formulation.

Tocilizumab is a humanized **anti–IL-6 receptor monoclonal antibody.** It binds selectively to IL-6 receptors and blocks IL-6 activity. IL-6 is a proinflammatory cytokine produced by a variety of cell types, including T and B cells, lymphocytes, monocytes, and fibroblasts. Tocilizumab is indicated for the treatment of RA and uniquely indicated for the treatment of active systemic **juvenile idiopathic arthritis** in patients 2 years of age and older.

Apremilast is an **inhibitor of phosphodiesterase type 4** (PDE_4), which is the isozyme primarily expressed on immune cells and is specific for breaking down cyclic adenosine monophosphate (cAMP). PDE_4 inhibition by apremilast increases cAMP levels, which **decreases expression of TNFα,** and other proinflammatory cytokines.

Sulfasalazine and Penicillamine

Sulfasalazine was originally used in the treatment of RA in the 1930s, but only recently was it approved for this indication by the FDA. In the 1920s and 1930s, scientists theorized that RA was an inflammatory disease caused by an infection in the GI tract. Consistent with that hypothesis, sulfasalazine was developed and is a formulation combining an antiinflammatory drug, 5-amino salicylic acid, with an antibacterial drug, sulfapyridine. Recent experiments suggest that sulfapyridine is active against RA, but the exact mechanism is not known. Because **sulfasalazine is a sulfa drug,** people who are allergic to sulfa compounds should not take it.

D-Penicillamine is a penicillin-derived compound used frequently in the past, but its use today has declined with the increasing use of other DMARDs (e.g., methotrexate). It is not understood exactly how penicillamine provides a benefit in RA, but it is known to reduce the blood levels of inflammatory cytokines. Penicillamine effects can take up to 3 months to manifest; however, if no effect is seen in a year, it should be stopped. Penicillamine is also used as a **copper chelating agent** in the treatment of Wilson's disease (see Chapter 5).

DRUGS FOR THE TREATMENT OF GOUT

Drugs for Preventing Gout Attacks

Gout attacks can be prevented by lowering the serum concentration of uric acid. **Probenecid** and **lesinurad** accomplish this goal by increasing the excretion of uric acid, whereas allopurinol and other agents do so by inhibiting the synthesis of uric acid. A third class of agents provides catabolic enzymes to reverse hyperuricemia. Uric acid metabolism and sites of drug action are depicted in Fig. 30.5.

Uricosuric Drugs

A **uricosuric drug,** such as **probenecid,** is used to prevent gout attacks in persons who **underexcrete uric acid,** as indicated by a 24-hour uric acid excretion that is less than 800 mg.

Probenecid is a weak acid that **competitively inhibits the reabsorption of uric acid** by renal tubules and thereby increases the excretion of uric acid. The drug is taken orally and should be swallowed with a full glass of water to ensure adequate fluid intake. Treatment should begin with a low dose, and the dosage should be gradually increased until an adequate uricosuric effect is obtained or the maximal dosage is reached. Probenecid treatment is usually well tolerated.

The use of aspirin and other **salicylates can alter or interfere with the** uricosuric effect of probenecid, so patients should avoid concurrent use of these agents. High doses of salicylates inhibit uric acid reabsorption and exert a uricosuric effect. Low doses of salicylates, however, inhibit uric acid secretion by renal tubules and thereby increase serum concentrations of uric acid.

Lesinurad reduces serum uric acid levels by inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidney. Lesinurad inhibited the function of two apical transporters responsible for uric acid reabsorption, uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4). URAT1 is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen.

Xanthine Oxidase Inhibitors

Allopurinol is used to prevent gout attacks in persons who **overproduce uric acid,** as indicated by a 24-hour uric acid excretion greater than 800 mg. It is also sometimes used to

ABSTRACT ACCEPTANCE LETTER

Abstract submitted to: WCP2018 KYOTO 18th World Congress of Basic and Clinical Pharmacology

KYOTO WCP2018

WCP2018 KYOTO
18th WORLD CONGRESS
OF BASIC AND CLINICAL PHARMACOLOGY

Pharmacology for the Future
Science, Drug Development and Therapeutics

July 1 (Sun) - 6 (Fri), 2018
Kyoto International Conference Center Kyoto, Japan

March 30, 2018

Mrs. Martlie Mocke-Richter,
, Department of Pharmacology, University of the Freestate, South-Africa, South Africa

Subject: [WCP2018] Acceptance Notification

Dear Mrs. Martlie Mocke-Richter,

Thank you for submitting your abstract for the 18th World Congress of Basic and Clinical Pharmacology (WCP2018) to be held from July 1 to 6, 2018, in Kyoto, Japan.
We are pleased to inform you that your abstract below has been selected as a Poster presentation:

Abstract Submission Number: 21039
Abstract Title: Perception and Knowledge of Biological Medicines by Newly Qualified Doctors (< 2 Years of Practice)

Presenting Author: Martlie Mocke-Richter
Presentation Style: Poster

Thank you again for your participation in the WCP2018.
We are looking forward to seeing you in Kyoto in July.

Very truly yours,

Shuh Narumiya
President
The 18th World Congress of Basic and Clinical Pharmacology (WCP2018)

For inquiries:
Program Secretariat of WCP2018
c/o Congress Corporation
Kohsai-kaikan Bldg., 5-1 Kojimachi, Chiyoda-ku, Tokyo 102-8481, Japan
Tel: +81-3-5216-5318 / Fax: +81-3-5216-5552
Email: abs-wcp2018@congre.co.jp
Official site: http://www.wcp2018.org/index.html

P04-10-6

Perception and Knowledge of Biological Medicines by Newly Qualified Doctors (< 2 Years of Practice)

Martlie Mocke-Richter, Andrew Walubo and Cornel van Rooyen*
Faculty of Health Sciences, Department of Pharmacology and *Biostatistics,
University of the Free State, Bloemfontein, South Africa

INTRODUCTION

Biological medicine (BM) use has grown worldwide[1] & is paralleled with improved quality of life in patients due to better management of many disorders, particularly inflammatory diseases & cancer[2]. However, in South Africa (SA) access to BM remains limited. Therefore, there was a need to investigate possible factors that influence the utilization of BM in SA, of which the prescribers (doctors) are a major component.

OBJECTIVE

The objective of the study was to evaluate, perception and knowledge, (training & experience) in the prescribing of BM by newly qualified doctors (<2 years in practice).

METHODS

- This was a retrospective study.
- Study population: newly qualified doctors (<2 years of practice), identified at their point of work.
- Ethical approval: obtained from the University of the Free State (UFS) Health Sciences Research Ethics Committee (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee.
- Participants received an information leaflet about the study & consent form before completing the questionnaire.
- Questionnaires were completed by doctors practicing in the Mangaung district (Bloemfontein) in the Free State, SA.
- *Information obtained:* Questionnaire, divided into different categories;
  Section A: Prescriber particulars
  Section B: Use of BM, specifically, the doctor's knowledge about BM; determining factors indicating when a patient should be given BM.
  Section C: Available medical information resources on BM; whether the doctors were taught about BM during their medical training; whether they think BM were adequately covered in the standard medical textbooks used / lectures they attended.
  Section D: Patient care & management; how doctors approach these aspects; how requirements / criteria for prescribing BM differ from that of pharmaceutical agents.
  Section E: Doctors' perception; more specifically, the reason why BM is difficult to use; the perception that BM use is limited; & factors that play a role in the efficacy & safety of BM.
  Section F: Procurement process – specifically, whether satisfactory & suggestions of how it should be improved.
- *Statistical analyses:* Data was captured in Excel, & imported into SAS (Statistical Analysis Software). Analysis was done using SAS 9.4. Descriptive statistics, namely means, medians, standard deviations, percentages & frequencies were calculated for continuous data. Percentage (%) evaluations of responses were based on the 'study population' whereby non-response to a question was regarded as negative.

RESULTS

Prescriber's particulars:

- Out of the 79 doctors identified, 63 (80%) completed the questionnaire, hence, the study population = 63.
- Gender & age: 60% females & 40% males with a mean age of 26.01 ± 2.4 years old.
- Experience: 46 (73%) had worked for 1 year while 17 (27%) had worked for 1.5 – 2 years.
- Training: Most doctors (20 (32%)) were trained at the UFS (Fig. 1).

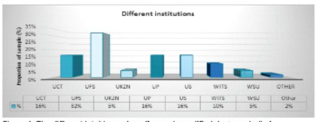


Figure 1: The different intuitions where the newly qualified doctors studied

UCT = University of Cape Town; UFS = University of the Free State; UKZN = University of Kwazulu Natal, UP = University of Pretoria, WITS = University of Witwatersrand

Regarding the doctors' knowledge on BM:

- Over half of the doctors (34 (54%)) did not know what BM are.
- Of the (29 (46%)) who indicated that they knew what BM are, only (17 (59%)) provided an example of the indication, treatment of rheumatoid arthritis (RA) & cancer (Fig. 2).
- Table 1 illustrates the doctors' knowledge on the use of some BM. Overall, (30 (48%)) cited Infliximab & almost all (28 (44%)) noted its use in RA. Thereafter, the proportion reduced for the other products.

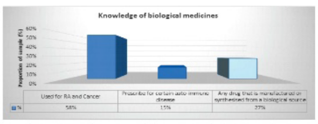


Figure 2: Knowledge of the newly qualified doctors about biological medicine
RA = Rheumatoid arthritis

Table 1: Biological medicine and condition

Biological medicine	n=63	Percentage	Condition	n=63	Percentage
Infliximab	30	48%	Rheumatoid arthritis	28	44%
Rituximab	15	24%	Rheumatoid arthritis	14	22%
Adalimumab	2	3%	Rheumatoid arthritis	2	3%
Interferon	3	5%	Cancer	3	5%
Trastuzumab	2	3%	Breast cancer	1	2%

Regarding prescribing of BM:

- An overwhelming majority of the doctors (60 (95%)) indicated that patients do not demand to be treated with BM.
- Thirty-seven (59%) indicated they are not allowed to prescribe BM.
- Thirty-two (51%) indicated that BM are only prescribed in severe cases.
- Figure 3 shows that (20 (32%)) indicated that the regular determining factor when a patient should be given BM is when a patient is not responding to other treatment (pharmaceutical agents).
- About half (32 (51%)) indicated they did not know how the approaches, requirements or criteria to prescribe BM differ from that of pharmaceutical agents (Fig. 4).
- Also, (25 (40%)) indicated that they were unsure regarding the differences in care of patients on BM & those that use pharmaceutical agents, while (22 (35%)) indicated that frequent follow-ups, close monitoring & good screening are required (Fig. 5).

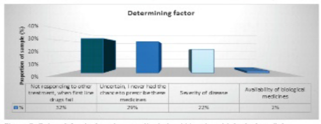


Figure 3: Determining factor when a patient should be given biological medicine

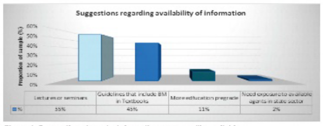


Figure 4: Suggestions to make information more readily available

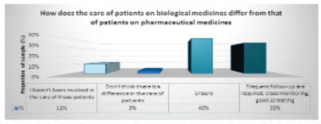


Figure 5: Indication of how the care of patients on biological medicines differs from that of patients on pharmaceutical medicines?

Regarding the available Information resource:

- Fifty-two (83%) indicated they were taught about BM during their medical training.
- Forty-eight (76%) indicated that BM were not adequately covered in standard medical textbooks.
- Forty (63%) indicated that the current requirements to prescribe BM is insufficient.

Regarding availability of BM:

- Forty-four (70%) indicated that BM are not readily available to all clinicians.
- Figure 3 shows that (24 (38%)) suggested that there should be more lectures & seminars on BM; while some (20 (32%)) suggested that there should be more specific guidelines for use of BM in textbooks.

Regarding the multiple-choice questions:

- The majority (76%) of doctors found BM difficult to use because they had limited knowledge of the pharmacology thereof, but (67%) indicated that it was because BM are expensive (Table 2). Furthermore, many of them (56%) indicated that BM use is limited due to the unavailability of information thereof, while 46% indicated that it was due to the unavailability / unaffordable (expensive) specialized tests required for monitoring efficacy (Table 3).
- In fact, only half (51%) of the doctors were able to correctly state when they would not prescribe BM, and a similar number (51%) agreed correctly that plasma concentrations of BM are useful to know in patients with poor response (Table 5). Accordingly, the majority (75%) agree that there is still much to be learned about the adverse effects of BM (Table 4).

Table 2: BM are difficult to use because:

Description	Quantity	Percentage
They are time-consuming in that patient selection may involve special tests	9	14%
They are administered parenteral, hence require close monitoring	15	24%
Adverse reactions are more common in that patients need more review than in the case of pharmaceutical agents	15	24%
I have limited knowledge of the pharmacology of biological agents	48	76%
They are expensive	42	67%

Table 3: Use of BM is limited because of:

Description	Quantity	Percentage
Attitudes & perceptions towards BM: I consider genetically derived products as unsafe, hence, may not recommend them to patients	4	6%
Beliefs, especially religions that do not allow the use of human derivatives	10	16%
Availability/affordability of specialized tests for monitoring efficacy is difficult and expensive	29	46%
Procurement process to obtain BM is difficult	21	33%
Lack of monitoring safety, adequate knowledge to enable detection of side-effects, clinical exam and lab tests	10	16%
Availability of knowledge/information about BM is limited	35	56%
Prescribing practice: use of guidelines / individual's ethics can limit the use of BM	12	19%

Table 4: Do the newly qualified doctors agree with the statement(s) below?

Description	Quantity	Percentage
BM are more effective than pharmaceutical agents	26	41%
There is still much to be learned about the adverse effects of BM	47	75%
My patients on BM have reported more adverse side-effects than those on pharmaceutical medicines	0	0,0%
I consider prescribing BM as a last resort when pharmaceutical medicines have failed	20	32%

Table 5: The factors that play a role in the efficacy and safety of BM

Description	Quantity	Percentage
Plasma concentrations of BM: are useful to know in patients with poor response	32	51%
Presence of neutralizing antibodies: likely in patients who lose response after showing good response	29	46%
Genetics: some SNP polymorphism associated with better response to TNFα inhibitors in RA	17	27%
Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNFs	7	11%

CONCLUSION

There is a general lack of knowledge on BM among the newly qualified doctors; therefore, there is a need to educate these young doctors about BM, and support them in the form of guidelines on the use of BM to ensure that current patients benefit. Furthermore, there is a need for more emphasis on BM during undergraduate training.

REFERENCES

1. Aubin, F., Carbonnel, F., and Wendling, D. 2013. The complexity of adverse side-effects to biological agents. *Journal of Crohn's and Colitis*, 7(4):257-262.
2. Rodney, J.Y.Ho. 2013. Antibodies and Derivates. Chapter 9. In: Biotechnology and Biopharmaceuticals: *Transforming Proteins and Genes into Drugs*. 2nd edition. Hoboken NJ: Wiley & Sons, 139-211.

ACKNOWLEDGEMENTS

The National Research Fund, for financial support.

T.: +27 82 4891 166 | martlie.mocke@gmail.com | www.ufs.ac.za
UFSUV | UFSweb | UFSweb | ufsuv

Inspiring excellence. Transforming lives.
Inspireer uitnemendheid. Verander lewens.

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE
SCHOOL OF MEDICINE
SKOOL VIR GENEESKUNDE
PHARMACOLOGY
FARMAKOLOGIE

APPENDIX J

ABSTRACT ACCEPTANCE LETTER

Abstract submitted to: First Conference of Biomedical and Natural Sciences and Therapeutics (CoBNeST), Spier Estate, Stellenbosch (September 2018)

Perception and Knowledge of Biological Medicines by Newly Qualified Doctors (< 2 Years of Practice)

Presenting Author: Martlie Mocke-Richter
Affiliation: University of the Free State
E-mail: martlie.mocke@gmail.com
Co-Author(s): Andrew Walubo
Affiliation(s): Department of Pharmacology, University of the Free State, Bloemfontein, South Africa

Abstract
Introduction: The use of biological medicines pauses challenges with regard to appreciating the minimum requirements for appropriate therapeutic response. Hence, it is envisaged that clinicians need to understand the major determinants of response and toxicity to biological medicines in their local population of patients to ensure cost-effective use of biological medicines. Therefore, the aim of this study was to investigate for factors that influence the utilization of biological medicines in South Africa.
Methods: Using a questionnaire, a prospective survey was conducted on newly qualified doctors. Information sought included; experience in the use of biological medicines, available medical information resource on biological medicines, their role in patient's care/management using biological medicines, their perception of biological medicines with regard to efficacy, toxicity or other, any problems with obtaining biological medicine, and procurement processes.
Results: Out the 79 newly qualified doctors that were identified, 79,7% (n=63) completed the questionnaire. From these, 63% (n=63) did not know what biological medicine are, 83,0% (n=53) indicated that biological medicine are not readily available to all clinicians, 65,9 % (n=44) suggested that there should be more lectures and seminars on biological medicines, 52,3% (n=44) suggested that there should be more specific guidelines for use of biological medicines in textbooks and 76,2% (n=63) indicated that biological medicine is difficult to use because they do not have adequate knowledge on the pharmacology of biological medicines.
Conclusion: There is a general lack of knowledge on biological medicines, therefore, there is a need to educate these young doctors about biological medicines, and support in form of guidelines on the use of biological medicines to ensure that current patients benefit. Furthermore, there is a need for more emphasis on biological medicines during undergraduate training.

Table of contents

APPENDIX K

ABSTRACT ACCEPTANCE LETTER

Abstract submitted to: The South African Association of Hospital and Institutional Pharmacists (SAAHIP) 2019

THE SOUTH AFRICAN ASSOCIATION

OF HOSPITAL AND INSTITUTIONAL PHARMACISTS

33rd Annual Conference (7-9 March 2019)

and 62nd Annual General Meeting (AGM)

12 October 2018

Dear M Mocke-Richter

Thank you for submitting the following abstract for the SAAHIP 2019 Conference:

"Knowledge and Attitudes concerning use of Biological Medicines by South-African Health Professionals"

This abstract has been accepted for a podium presentation. Further information on the format of your presentation will be sent in due course.

If you are a SAAHIP member, please notify your local SAAHIP Branch Chairperson of your intention to present at Conference 2019. If you are not a SAAHIP member, please submit an Observer Booking Form to attend conference as an observer.

Please let me know urgently if you no longer intend attending or presenting at conference.

If you require any further information, please don't hesitate to contact me on saahip.conference@gmail.com

Kind regards

Chantell Hayward-Zeelie

Academic Programme Organiser

SAAHIP Conference 2019

ARTICLE SUBMITTED FOR PUBLICATION

PERCEPTION AND KNOWLEDGE ON BIOLOGICAL MEDICINES BY NEWLY QUALIFIED DOCTORS IN THE FREE STATE (SOUTH-AFRICAN)

Martlie Mocke and Andrew Walubo
Department of Pharmacology, University of the Free State, Bloemfontein, 9300

Corresponding author:
Martlie Mocke-Richter
Department of Pharmacology, University of the Free State,
P.O. Box 339 (G6),
Bloemfontein 9300, South Africa,
Phone: 27-51-401-3090;
E-mail: martlie.mocke@gmail.com

ABSTRACT

Introduction: The clinical effectiveness of BM has been extremely significant and this success has driven the development of increasing numbers of BM. Unfortunately, the use of BM has presented challenges. Clinical response to drugs usually varies between patients and depends on disease characteristics including presence of autoantibodies, disease activity and severity. Pharmacokinetics and drug concentrations are influenced by characteristics of the patient such as gender, age, liver- and renal functions, smoking status and body mass index. However, in South Africa, access to BM remains limited. The objective of the study was to evaluate the perception and knowledge (training and experience) in the prescribing of BM by newly qualified doctors.

Methods: A carefully constructed and trailed questionnaire sought the following outcome measures: doctors' particulars; experience in the use of BM; available medical information sources on BM; their role in patients' care/management using BM; their perception of BM with regard to efficacy, toxicity or other; problems with obtaining BM; undergraduate training on BM; and procurement processes. 79 doctors were identified, of which 63 (38 females and 25 males) completed the questionnaire. For purposes of this study, only newly qualified doctors, i.e. those with less than two years of practice, were selected.

Results: Out of 79 doctors, 63 (80%) completed the questionnaire. More than half of the doctors, 34 (54%), did not know what BM are. The majority (76%) of doctors found the use of BM difficult because they had limited knowledge of the pharmacology of BM, but 67% indicated that it was because BM are expensive.

Conclusion: In conclusion, there is a general lack of knowledge on BM among newly qualified doctors. This implies that medical students do not know the basics of BM, and that it should be part of the general pharmacology curriculum. Furthermore, for newly qualified doctors, this gap can be bridged by continuous professional education on BM via seminars, CPD events, as well as workshops.

Funding: The research project was supported by the National Research Fund.

Keywords: Biological Medicines; Cross-sectional study; Knowledge and Attitudes, Doctors perception.

INTRODUCTION

Biological medicines (BM) are therapeutic substances (monoclonal antibodies, cytokines, peptides, etc.), derived from biological sources that are used to treat, diagnose or prevent disease. Over the past two decades, there has been an increased use of BM owing to their effectiveness in a wide variety of chronic diseases such as autoimmune disorders, intractable cancers, cardiovascular diseases and allergy [1] [2]. Unfortunately, the use of BM has not been without challenges [3] [4]. The response to BM is influenced by many factors which include, to mention but a few, disease activity and severity, cytokine levels, immune cell genotype and phenotypes, and presence of autoantibodies, and this is in addition to the patient characteristics such as gender, age, body mass index and the concomitant use of other drugs [5]. Their use is also limited by the heightened fear for host rejection and/or tolerance, which can exhibit, respectively, as hypersensitivity (immune) reactions and failure of response due to drug antibodies. Some BM require preliminary screening tests because they only work in patients who express specific endogenous structures such as receptors or cell-subclasses or genotype. Trastuzumab acts on tumours expressing HER-2 receptors, while rituximab is more effective in B-cells with the CD20 protein, and natalizumab inhibition of α4-integrin is best in endothelial cells expressing the vascular cell adhesion molecule 1 (VCAM-1) gene. Also, because most BM are targeted at interfering with the physiological actions of their respective endogenous compounds, they may predispose patients to related adverse events. For instance, infliximab inhibits TNF-α which is required for normal inflammation and other processes, leading to infections as a complication. As such, these BM require continuous testing to monitor response and safety during therapy [3] [4] and this makes them more costly, particularly with the additional tedious procurement requirements and designation to particular prescribers [3] [7] [8]. Furthermore, the side-effects profile of BM does not fit into the current pharmaceutical medicines' adverse drug reaction (ADR) paradigm [2]. Whereas the ADR of pharmaceutical medicines are classified into 5 types (A, B, C, D and E), those of BM are differently classified into 5 new types (α, β, γ, δ and ε).

Therefore, appropriate use of BM requires a clinician with adequate knowledge on the selection of suitable patients to ensure maximum benefit, and avoiding high-risk groups in order to reduce the risk of adverse events [6]. This includes appropriate training not only on the pharmacology of BM, but also on the population factors that determine response and safety of BM [7] [8] [10]. Such knowledge would empower clinicians to identify the major determinants of response and toxicity of BM in the local South African patient population, to enable appropriate modifications in the guidelines for the use of BM in our patients. Unfortunately, this information (knowledge) is still not generally available in standard textbooks or general literature, hence is not accessible to most clinicians. Worse still, in South Africa, prescribing of BM is limited to specific specialists in central hospitals who, unfortunately, are not in reach of all patients that need them. As such, there was a need to investigate the factors that influence the utilization of BM in South Africa, and the doctor's knowledge on the respective medicines is a major factor in this respect.

METHODS

This was a cross-sectional study of newly qualified doctors (doctors with less than two years of practice) who were practicing in the Free State. The University of the Free State Health Sciences Research Ethics Committee (HSREC 154/2016) as well as the Free State Department of Health Ethics Committee granted ethical approval. The doctors were identified and recruited from their place of work at which they completed the questionnaires.

The questionnaire sought for the prescriber's particulars (gender, age, years of work experience and where they studied); information that enable doctors to prescribe BM (the doctor's knowledge about BM, at what stage of the disease they prescribe BM, the determining factor indicating when a patient should be given BM); available medical information resources on BM (whether the doctors were taught about BM during their medical training; whether they think BM were adequately covered in the standard medical textbooks they used); patient care and management (how doctors approach these aspects, how requirements or criteria for prescribing BM differ from prescribing pharmaceutical agents, how the care of patients on BM differ from those on pharmaceutical medicines, when the doctors will start giving BM to the patients); the doctors' perceptions (the reason why BM are difficult to use, the perception that BM use is limited, when the doctor should not prescribe BM, and the factors that determine the efficacy and safety of BM); procurement process (whether the current process is satisfactory and suggestions of how it should be improved).

Statistical analysis

Data was transferred on to an Excel data sheet, after which it was imported into SAS (Statistical Analysis Software) 9.4 and analysed and expressed as descriptive statistics. The proportion (%) of responders was calculated using the 'study population sample' as the denominator, whereby non-response to a question was regarded as a negative response.

RESULTS

Out of the 79 doctors that were identified, 63 doctors (38 females and 25 males) completed the questionnaire. The mean age (±sd) was 26.01 ± 2.4 years, and 46 (73%) had worked for one year, while 17 (27%) had worked for 1.5 to 2 years. Most of the doctors 20 (32%), were trained at the University of the Free State. Participation of other institutions were as follows; University of Cape Town 16%, University of KwaZulu Natal 5%; University of Pretoria 16%, University of the Witwatersrand 10%, University of Stellenbosch 10%, Walter Sisulu University 5% and others 2%.

Regarding the doctors' knowledge on BM, over half of the doctors (34; 54%) did not know what BM are. Even then, of those who indicated that they knew what BM are (29; 46%), only 17 (59%) cited a BM with a correct indication, which were mainly rheumatoid arthritis and cancer. Specifically, 58% indicated rheumatoid arthritis and cancer, and 15% said it was for certain autoimmune disorders. Further evaluation showed that infliximab was the most known BM (**Table 1**); it was cited by 29 (48%) and almost all of them (28; 44%) correctly noted its use for rheumatoid arthritis. Thereafter, the proportion of doctors with knowledge of other BM products was drastically low.

Table 1: Examples of biological medicines and their respective indications provided by the doctors (N=63)

Biological medicine	Responders	Percentage	Indication	Responders	Percentage
Infliximab	30	48%	Rheumatoid arthritis	28	44%
Rituximab	15	24%	Rheumatoid arthritis	14	22%
Adalimumab	2	3%	Rheumatoid arthritis	2	3%
Interferon	3	5%	Cancer	3	5%
Trastuzumab	2	3%	Breast cancer	1	2%

On the prescribing of BM, an overwhelming majority of doctors (60; 95%) indicated that patients do not demand to be treated with BM. Most of the doctors 59% (37) indicated they are not allowed by their hospital authorities to prescribe BM, while 32 (51%) indicated that BM are prescribed only in severe cases, and only 20 (32%) indicated that the regular determining factor when a patient should be given BM is when a patient is not responding to other treatment (pharmaceutical medicines).

Over half of the doctors (32; 51%) indicated that they did not know how the prescribing of BM differed from the prescribing of pharmaceutical medicines because they have never used them. In the same perspective, 40% (25) indicated that they were unsure of the differences in care of patients on BM compared to patients using pharmaceutical medicines, and only 35% (22) indicated that frequent follow-ups, close monitoring and good screening are required for BM.

On the training and availability of information resources, the majority of doctors (52; 83%) agreed that they were taught about BM during their medical training, and most of them (48; 76%) confirmed that BM were not adequately covered in the standard medical textbooks they used. Again, the majority of doctors (40; 63%) indicated that the current requirements or criteria to prescribe BM are insufficient for them, while 70% (44) agreed that BM are not readily available to all clinicians. Some doctors (24; 38%) suggested that there should be more lectures and seminars on BM, while others (20; 32%) suggested that there should be more specific guidelines for use of BM in the textbooks, and others called for exposure to the available agents in the state health sector.

The responses to direct questioning by multiple-choice questions are shown in **Table 2**. The majority (76%) of doctors found BM difficult to use because they had limited knowledge of the pharmacology of BM, but 67% indicated that it was because BM are expensive (Table 2, question 1). Furthermore, many of them (56%) indicated that the use of BM is limited because of the unavailability of information about BM, while 46% indicated that it was due to the unavailability or unaffordable specialized tests required for monitoring efficacy (Table 2, question 2). In fact, only half (51%) of the doctors were able to correctly state when they would not prescribe BM (Table 2, question 3), and a similar number (51%) agreed correctly that knowledge of plasma concentrations of BM may be useful to know in patients with poor response (Table 2, question 4). Accordingly, the majority (75%) agreed that there is still much to be learnt about the adverse effects of biological agents (Table 2, question 5).

Table 2: The doctors' (N =63) responses to multiple choice questions on the different aspects of the use of Biological medicines (BM)

The doctors' response	Responders	Percentage
Question 1: BM are difficult to use because:		
a) They are time-consuming in that patient selection may involve special tests	9	14%
b) They are administered parenteral, hence require close monitoring	15	24%
c) ADR are more common in that patients need more review than in the case of pharmaceutical agents	15	24%
d) I have limited knowledge of the pharmacology of biological agents	48	76%
e) They are expensive	42	67%
f) Other (specify)	0	0,0%
Question 2: Use of BM is limited by:		
a) On attitudes and perceptions towards biological medicine: I consider genetically derived products as unsafe; hence, may not recommend them to patients	4	6%
b) Beliefs: especially religions that do not allow the use of human derivatives	10	16%
c) Availability/affordability of specialized tests for monitoring efficacy is difficult and expensive	29	46%
d) Procurement process to obtain BM is difficult	21	33%
e) Lack of monitoring safety: adequate knowledge to enable detection of side-effects, clinical exam and lab tests	10	16%
f) Availability of knowledge/information about BM is limited	35	56%
g) Prescribing practice: use of guidelines or individual's ethos can limit the use of biological medicine	12	19%
Question 3: When will you NOT prescribe biological medicine?		
a) Coexisting disease: TB or presence of serious infections or organ failure	32	51%
b) Previous treatment, especially with BM, is associated with poor response to another biological medication	19	30%
c) Presence of drug antibodies: render BM ineffective	14	22%
Question 4: How do the following factors influence the efficacy and safety of BM?		
a) Plasma concentrations of biological medicine: are useful to know in patients with poor response	32	51%
b) Presence of neutralizing antibodies: likely in patients who lose response after showing good response	29	46%
c) Genetics: some SNP polymorphism associated with better response to TNFa inhibitors in RA	17	27%
d) Higher level of cytokines (or immune activity) at the time of intervention with BM was associated with good response to TNFa	7	11%
Question 5: Do the newly qualified doctors agree with the statement(s) below?		
a) BM are more effective than pharmaceutical agents	26	41%
b) There is still much to be learned about the adverse effects of biological agents	47	75%
c) My patients on BM have reported more adverse side-effects than those on pharmaceutical medicines	0	0,0%
d) I consider prescribing BM as a last resort when pharmaceutical medicines have failed	20	32%

DISCUSSION

This study has demonstrated a lack of knowledge of newly qualified doctors on BM, which further emphasises the concern that information on BM is not generally available/accessible to clinicians who need it in order to treat their patients to ensure maximum benefit. The "knowledge" evaluated by the questionnaire included the prescriber's particulars; information that enable doctors to prescribe BM; available medical information resources on BM; patient care and management; the doctors' perceptions; and procurement process.

Given the young age of the doctors, the majority did not know what BM are, most likely due to a short period of medical practice. The minority could at least identify a BM with a correct indication. Another limiting factor of these doctors' exposure to BM utilisation is that most of them are not allowed by their hospital authorities to prescribe BM. Even so, some of the doctors knew that BM are prescribed only in severe cases when a patient is not responding to standard treatment with pharmaceutical medicines. That said, the majority did not know that the prescribing of BM differed from that of pharmaceutical medicines, since they have never been confronted with the prescription of BM. Consequently, their knowledge on the care of a patient on BM were also minimal, although some knew that frequent follow-ups, close monitoring and good screening are required.

The majority of doctors confirmed that the topic of BM was not adequately covered in standard medical textbooks. Furthermore, it was identified that current requirements to prescribe BM are insufficient. There are a number of publications that characterize the pharmacokinetics and pharmacodynamics of monoclonal antibodies in Asian versus non-Asian populations, and the biological effects of cytokines in Chinese and non-Chinese patients [9], but no similar studies have been done in South Africa.

The majority agreed that BM are not readily available to all clinicians, especially in the public health sector. Here, the high cost of BM could be identified as the limiting factor. Lastly, the side-effects associated with BM differ from that of chemical drugs (xenobiotics) [7], therefore most of the doctors acknowledged that there is still much to be learnt about the adverse effects of biological agents.

The appropriate utilisation of any BM requires adequate knowledge of not only their pharmacology, but also factors that determine appropriate response and safety [7] [8]. It is therefore of utmost importance for a clinician to take all available information into consideration before prescribing BM in order for his/her patients to fully benefit [10]. Unfortunately, as supported by findings of this study, information and guidelines on BM is still not generally available in standard textbooks or literature [2]. As such, it is suggested that more lectures and seminars on BM should be held, and that specific guidelines for the use of BM should be made available in textbooks. Furthermore, undergraduate medical students should be better educated and trained on the basics of BM, which should be part of the general Pharmacology curriculum. Overall, the knowledge of young doctors on BM could only benefit from continuous professional education/improvement via seminars, CPD events as well as workshops.

CONCLUSION

There is a general lack of knowledge on BM among newly qualified doctors; therefore, there is a need to educate these young doctors about BM, and support them in the form of

guidelines on the use of BM to ensure that current patients benefit. Furthermore, there is a need for more emphasis on BM during undergraduate training.

ACKNOWLEDGEMENTS

The National Research Fund, for financial support, the University of the Free State for their technical support and the newly qualified doctors who completed the questionnaire.

COMPETING INTERESTS

The authors confirm that there are no possible conflict of interests in the manuscript.

REFERENCES

[1] Aubin, F., Carbonnel, F., Wendling, D. 2013. The complexity of adverse side-effects to biological agents. *Journal of Crohn's and Collitis*, **7(4):** 257-262.

[2] Lee, S.J., Kavanuagh, A. 2005. Adverse reactions to biological agents: focus on autoimmune disease therapies. J Allergy ClinImmunolm **116**:900-905.

[3] Heinen-Kammerer, T., Daniel, D., Stratman, L., Rychlik, R., Boeknoke, W.H. 2007. Cost effectiveness of psoriasis therapy with entanercept in Germany. *J DtschDermatolGes*. **(5)**:762-768.

[4] Banacloche, G.J.C., Weinberg, G.A. 2007. Monoclonal Antibody Therapeutics and Risk for Infection. *Paediatric Infectious Disease Journal*, **(26):** 1049-1052.

[5] Benson III, et al 2018: Colon Cancer, Version 2.2018: Featured Updates to the NCCN Guidelines. Natl. Compr. Canc. Netw., 2018; 16 *(4):359–369*

[6] Weber, RW. 2004. Adverse reactions to biological modifiers. *Current Opinion in Allergy & Clinical Immunology*. **4(4)**:277-283.

[7] Pichler, M.D. 2006. Adverse side-effects to Biological agents. *Allergy* **61(8)**: 901-920.

[8] Rodney, J.Y. Ho. 2013. Antibodies and Derivates. Chapter 9. In: *Biotechnology and Biopharmaceuticals*: *Transforming Proteins and Genes into Drugs*. 2nd edition. Hoboken NJ: Wiley & Sons, 139-211.

[9] Rogge, M.C., Liu, Y. and Galluppi, G.R. 2014. Interferon Beta Assessment in Non-Chinese and Chinese Subjects: Pharmacokinetics and Pharmacodynamic Activity of an Endogenous Cytokine Are Not Race Dependent. *The Journal of Clinical Pharmacology* **54(10)**: 1153-1161.

[10] Salvana, E.M.T., Salata, R.A. 2009. Infectious Complications Associated with Monoclonal Antibodies and Related Small Molecules. *Clinical Microbiology reviews* **22(2)**: 274-290.

APPENDIX M

TURN-IT-IN REPORT

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA
UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

11 June 2019

TO WHOM IT MAY CONCERN

DECLARATION ON PLAGIARISM

According to the University of the Free State's Policy on the Prevention of Plagiarism and Dealing with Academic Writing Misconduct defenition:

Plagiarism implies direct duplication of the formulation and insights of a source text with the intention of presenting it as one's own work. Plagiarism cannot be confirmed as a result of mere similarities of words between the source text and the borrowed text as in the case of terminology, commonly used phrases and known facts. If plagiarism is suspected it must also be provable. The source text and borrowed text must therefore be placed side by side. The mere suspicion of plagiarism cannot form the basis of an accusation. Plagiarism is distinguished from forms of academic writing misconduct such as:

- cribbing in tests and examinations;
- collusion and fabrication or falsification of data;
- deliberate dishonesty;
- purchasing assignments, dissertations and/or theses on the Internet and presenting such documents as one's own work;
- presenting the same work for more than one course or in consecutive years; and
- the submission of another person's work as one's own original work.

To check for plagiarism the UFS uses software programmes like TURNITIN. The programme does not show plagiarism but rather focus on similarity in text against certain criteria.

In this spirit the promoter is satisfied that in the report following this letter it shows a **16%** similarity in chapters 1-6. When comparing text with text from the two works it is evident that there are no plagiarism. Where text are similar it is properly referenced or quoted and referenced. See report attached.

The full report is electronically avialable on request from examiners (assessors).

Yours sincerely

PROF A WALUBO
HEAD: DEPARTMENT OF PHARMACOLOGY

Department of Pharmacology
Departement Farmakologie
T: +27 (0)51 401 3090 | F: +27 (0)51 444 1523
205 Nelson Mandela Drive/Rylaan | Park West/Parkwes | Bloemfontein 9301 | South Africa/Suid-Afrika
P.O. Box/Posbus 339 (G6) | Bloemfontein 9300 | South Africa/Suid-Afrika | www.ufs.ac.za

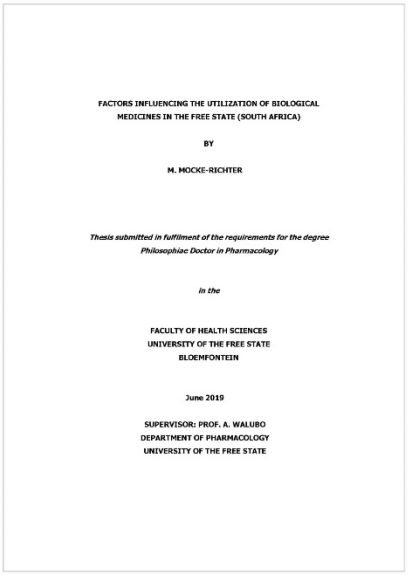
turnitin

Digital Receipt

This receipt acknowledges that Turnitin received your paper. Below you will find the receipt information regarding your submission.

The first page of your submissions is displayed below.

Submission author:	Martie Mocke
Assignment title:	Chapter 1
Submission title:	Thesis
File name:	PHD_-_Martlie_-_combined_final_-..
File size:	13.12M
Page count:	167
Word count:	33,472
Character count:	193,556
Submission date:	20-May-2019 11:42AM (UTC+0200)
Submission ID:	1133253448



FACTORS INFLUENCING THE UTILIZATION OF BIOLOGICAL MEDICINES IN THE FREE STATE (SOUTH AFRICA)

BY

M. MOCKE-RICHTER

Thesis submitted in fulfilment of the requirements for the degree Philosophiae Doctor in Pharmacology

In the

FACULTY OF HEALTH SCIENCES
UNIVERSITY OF THE FREE STATE
BLOEMFONTEIN

June 2019

SUPERVISOR: PROF. A. WALUBO
DEPARTMENT OF PHARMACOLOGY
UNIVERSITY OF THE FREE STATE

Thesis

ORIGINALITY REPORT

16%	9%	8%	9%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	etd.uovs.ac.za Internet Source	3%
2	Ho, . "ANTIBODIES AND DERIVATIVES", Biotechnology and Biopharmaceuticals Transforming Proteins and Genes into Drugs, 2013. Publication	1%
3	scholar.ufs.ac.za:8080 Internet Source	1%
4	Ho, . "CYTOKINES AND INTERFERONS", Biotechnology and Biopharmaceuticals Transforming Proteins and Genes into Drugs, 2013. Publication	1%
5	Kathrin Scherer. "Adverse drug reactions to biologics", JDDG Journal der Deutschen Dermatologischen Gesellschaft, 02/03/2010 Publication	1%
6	Submitted to University of the Free State Student Paper	1%

LANGUAGE EDITING

Dynamic Language & Translation Specialists

Antoinette Bisschoff
71 Esselen Street,
Potchefstroom
Tel: 018 293 3046
Cell: 082 878 5183
Language@dlts.co.za
CC No: 1995/017794/23

Tuesday, 11 June 2019

To whom it may concern

Re: Confirmation of language edit and technical precision

The PhD thesis **Factors influencing the utilization of biological medicines in the Free State (South Africa)** by **M. Mocke-Richter** was edited for language and technical precision. The referencing and sources were also checked. Final, last minute corrections remain the responsibility of the author.

Antoinette Bisschoff

BA Languages (UPE – now NMU); MBA (PU for CHE – now NWU); Translation and Linguistic Studies (NWU)

Officially approved language editor of the NWU since 1998
Member of SA Translators Institute (no. 100181)

SUMMARY

Keywords: Biological Medicines, Monoclonal antibodies, Delphi method, Factors influencing the use of Biological Medicines, Framework for use of Biological Medicines

Biological Medicines are substances derived from animal or other biological origin, and are used to treat, diagnose or prevent mainly inflammatory diseases and cancer. The use thereof has grown worldwide and is aimed at improving the quality of life of patients. However, in South Africa access to Biological Medicines remains limited. Unfortunately, the use of Biological Medicines has presented challenges with regard to the requirements for appropriate therapeutic responses and their side-effects. In order to obtain an appropriate therapeutic response, appropriate patients have to be selected and continuously monitored during therapy.

The two-fold aim of the study was to identify the factors influencing the utilization of Biological Medicines in the Free State (South Africa), and to develop a framework for the use of Biological Medicines in South Africa. Therefore the objective of the study was to determine perception, knowledge of and training in Biological Medicines by clinicians who have been practising for two years or less since graduating and to identify the factors that might influence the prescribing of Biological Medicines by some doctors in the Free State. It was also important to evaluate patient knowledge and experience with Biological Medicines and identify the factors (age, gender, race, disease, patient perception, and adverse effects) that might influence patient compliance with Biological Medicines in some institutions in South Africa. The abovementioned helped to develop a framework for the use of Biological Medicines in South Africa.

A cross sectional study design was used. The literature review was used as the foundation to compile the questionnaires. The study consists of three different questionnaires, one for the newly qualified doctors; one for the specialists who prescribed Biological Medicines as well as the one for the patients who used Biological Medicines. The Delphi survey consisted of the data generated through the previous phases of the study, which consisted of literature cited, as well as three different questionnaires. For the purpose of this study, the Delphi method was used as a tool for achieving consensus, where experts validated some of the aspects and criteria with the view to draft a framework.

As it was, out of the 79 newly qualified doctors in the Mangaung district (Bloemfontein) in the Free State, 79,7% (n = 63) completed the questionnaire. There were 17 specialists that prescribed Biological Medicines in the Free State, and 70,6% (n = 12) of them completed the questionnaire. Biological Medicines do not have more adverse effects than pharmaceutical agents. As it was, out of the 38 patients that used Biological Medicines and were identified by the clinicians, 81,6% completed the questionnaire. In the Delphi questionnaire study, there were 15 panel members that responded out of 20 who received the invitation.

In conclusion, there was a general lack of knowledge on Biological Medicines among newly qualified doctors; therefore, there was a need to educate these young doctors about Biological Medicines, and to offer support in the form of a framework on the use of Biological Medicines to ensure that current patients benefit. The clinicians have limited knowledge of the pharmacology of Biological Medicines and therefore there is still much to be learned about the adverse effects of Biological Medicines. Furthermore, there is a need to educate the prescribers, and to offer support in the form of a framework on the use of Biological Medicines to ensure that current patients benefit and also to improve the procurement process to obtain Biological Medicines. It was established that Biological Medicines are improving the quality of life of patients. Seen from above, Biological Medicines have so far had a positive impact on patient lives; therefore, there was a need expressed to make Biological Medicines more available to patients who need it.

The framework containing the findings of the research will be brought to the attention of the Biological Medicine Committee of South Africa, the Medicine Control Council, as well as the National Department of Health. It will furthermore be recommended that the framework that was developed may be adapted by the health care professionals who prescribe Biological Medicines. The research findings were submitted to academic journals with a view to publication, as well as presented at conferences.

OPSOMMING

Sleutelwoorde: Biologiese Medisyne; Monoklonale teenliggaampies; Delphi-metode; faktore wat die gebruik van Biologiese Medisyne beïnvloed; Raamwerk vir die gebruik van Biologiese Medisyne

Biologiese Medisyne is middels wat van diere of ander biologiese oorsprong is, en word gebruik om hoofsaaklik inflammatoriese siektes en kanker te behandel, diagnoseer of te voorkom. Die gebruik daarvan het wêreldwyd toegeneem met die doel om die lewenskwaliteit van pasiënte te verbeter. In Suid-Afrika is toegang tot hierdie middels beperk. Ongelukkig het die gebruik van Biologiese Medisyne tot dusver uitdagings gebied met betrekking tot die vereistes vir geskikte terapeutiese response en hul newe-effekte. Ten einde geskikte terapeutiese response te bekom, word geskikte pasiënte geselekteer, en deurlopend gemonitor gedurende terapie.

Die tweevoudige oogmerk van die studie was om die faktore wat die gebruik van Biologiese Medisyne in die Vrystaat provinsie van Suid-Afrika beïnvloed, te identifiseer en om ‘n raamwerk daar te stel vir die gebruik van Biologiese Medisyne in Suid-Afrika. Derhalwe was die doelwit van die studie om Vrystaatse dokters wat die afgelope twee jaar gegradueer het, se persepsie, kennis en opleiding aangaande Biologiese Medisyne te bepaal, sowel as om die faktore wat die dokters moontlik kan beïnvloed in die voorskryf van Biologiese Medisyne, te identifiseer. Dit was ook noodsaaklik om pasiënte se kennis en ervaring van Biologiese Medisyne te identifiseer sowel as die faktore (ouderdom, geslag, ras, siekte, pasiëntpersepsie en nadelige gevolge) te identifiseer ten opsigte van pasiënt-inwilliging om Biologiese Medisyne in sommige instellings in Suid-Afrika te gebruik.

’n Kruisdeursnee studie-ontwerp is in hierdie studie gebruik. Die literatuuroorsig is gebruik as die fondasie om die vraelyste op te stel. Die studie bestaan uit drie verskillende vraelyste: een vir die nuut gekwalifiseerde dokters, een vir die spesialiste wat Biologiese Medisyne voorskryf sowel as een vir die pasiënte wat Biologiese Medisyne gebruik. Die Delphi-metode het bestaan uit die data wat ingesamel is deur die vorige fases van die studie, wat bestaan het uit die literatuuroorsig sowel as die drie vraelyste. Vir die doeleindes van hierdie studie is die Delphi-metode gebruik as ‘n instrument om konsensus te bereik, waar kundiges sommige van die aspekte en kriteria valideer met die oog om ‘n raamwerk daar te stel. Vanuit die 79 nuut gekwalifiseerde dokters in die Mangaung-distrik (Bloemfontein) in die Vrystaat, het 79,7% (n = 63) die vraelyste voltooi. Daar was 17 spesialiste wat Biologiese

Medisyne in die Vrystaat voorskryf, en 70,6% (n = 12) van die spesialiste het die vraelys voltooi. Biologiese Medisyne het nie meer newe-effekte as farmaseutiese middels nie. ′n Totaal van 81,6% van die 38 pasiënte wat Biologiese Medisyne gebruik het en deur die spesialiste uitgewys is, het die vraelys voltooi. Die Delphi-vraelys is deur 15 van die uitgenooide 20 paneellede voltooi.

Laastens was daar ‘n gebrek aan kennis oor Biologiese Medisyne onder nuutaangestelde dokters en was dit nodig om hierdie jong dokters onderrig te gee in die gebruik van Biologiese Medisyne en om ondersteuning te bied in die vorm van ‘n raamwerk vir die gebruik van Biologiese Medisyne en derhalwe huidige pasiënte te bevoordeel. Dokters het nog heelwat onkundigheid ten opsigte van Biologiese Medisyne en derhalwe te leer van die newe-effekte van hierdie soort medisyne. Voorts is dit belangrik dat dokters meer te wete kom van die farmakologiese eienskappe van Biologiese Medisyne. Selfs verskaffers van Biologiese Medisyne moet opleiding ontvang en moet die raamwerk ontvang om hulle by te staan om huidige pasiënte te bevoordeel sowel as om verkrygingsprosesse te leer. Biologiese Medisyne het ‘n positiewe impak op pasiënte se lewens. Gesien in hierdie lig, was daar ‘n behoefte om Biologiese Medisyne meer toeganklik vir pasiënte te maak wat dit nodig het.

Die raamwerk bestaan uit die bevindinge van die navorsing en sal beskikbaar gestel word aan die Biologiese Medisynekomitee van Suid-Afrika. Ook die Medisynebeheerraad en die Departement van Gesondheid sal dit ontvang. Daar word voorts aanbeveel dat die raamwerk aangepas mag word vir professionele gesondheidswerkers wat Biologiese Medisyne voorskryf. Die navorsingsresultate is aan akademiese joernale gestuur met die oog op publikasie, of om as referate by konferensies te dien.