RHEUMATOLOGISTS’ PERCEPTIONS OF THE CO-INCIDENCE OF TUBERCULOSIS ASSOCIATED WITH TNF-α INHIBITORS USED FOR THE TREATMENT OF RHEUMATOID ARTHRITIS IN SOUTH AFRICA.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in the part fulfilment of the requirements for the degree of Master of Science in Medicine (Pharmacotherapy).

Johannesburg, 2013
DEDICATION

To my mother, Kathy Leong, for her grounding of love and motivation and to the Lord for the strength in reaching the goalposts.
DECLARATION

I, Trudy Desirie Leong declare that this research report is my own work. It is being submitted in part fulfilment for the degree of Master of Science in Medicine (Pharmacotherapy) in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

______________________________________
Signature

_______ day of ______________ 2013
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ATC</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacille Calmette-Guerin</td>
</tr>
<tr>
<td>BSRBR</td>
<td>British Society for Rheumatology Biologics Register</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CDL</td>
<td>Chronic disease list</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>CMS</td>
<td>Council for Medical Schemes</td>
</tr>
<tr>
<td>DMARD</td>
<td>Disease modifying anti-rheumatic drug</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DTP</td>
<td>Diagnosis Treatment Pairs</td>
</tr>
<tr>
<td>HPCSA</td>
<td>Health Professions Council of South Africa</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon-gamma release assay</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IPT</td>
<td>Isoniazid preventive therapy</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent tuberculosis infection</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
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<tr>
<td>NDP</td>
<td>National Drug Policy</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PMB</td>
<td>Prescribed minimum benefit</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified protein derivative</td>
</tr>
<tr>
<td>Pyrs</td>
<td>Patient years</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SARAA</td>
<td>South African Rheumatism and Arthritis Association</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneously</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Tumour necrosis factor – α</td>
</tr>
<tr>
<td>XDR (TB)</td>
<td>Extensively drug resistant (TB)</td>
</tr>
</tbody>
</table>
ABSTRACT

Biological disease-modifying anti-rheumatic drugs (DMARDs) for the treatment of Rheumatoid Arthritis, particularly TNF-α inhibitors, have been shown to improve patient outcome by slowing or halting radiographic damage. However, similar to most immune-modulators, there is an increased risk of infections co-incident with Tumour necrosis factor (TNF)-α inhibitor use, particularly the risk of activated latent tuberculosis infection (LTBI). Therefore, local and international guidelines recommend pre-screening for tuberculosis (TB) prior to the initiation of TNF-α therapy in rheumatoid arthritis (RA) patients. Also of critical importance in South Africa is the need for clinicians to be aware of environmental risk factors such as TB being highly endemic.

Thus, a qualitative analysis was performed to investigate rheumatologists’ perceptions of TB co-incident with TNF-α inhibitors.

Method: Physicians (n=18) practising rheumatology in the private and public healthcare sectors in Gauteng were interviewed to obtain their perceptions and attitudes related to TB co-incident with TNF-α inhibitor use. Interviews were audio-recorded and the transcripts analysed using thematic content analysis.

Results: The determinants of health equity: Affordability, accessibility and availability of medicines (specifically TNF-α inhibitors) was reported to be different for the public care versus the private care patient. The high cost of TNF-α inhibitors warranted funding predominantly by the private medical schemes.
A higher occurrence of latent TB infection was reported by physicians practising in the public or combined practice compared to the occurrence of LTBI in the private sector (21.4% versus 1.5%).

The majority of study participants advocated pre-screening of TB, prior to the initiation of TNF-α inhibitors, in RA. However, it was suggested that because of the high occurrence of LTBI in the public sector, Isoniazid preventative therapy (IPT) should be compulsory, irrespective of the patient’s TB status, for the duration of TNF-α therapy.

Most study participants supported local South African Rheumatism and Arthritis Association (SARAA) guideline recommendation to re-screen for TB by chest x-ray (CXR), every 6 months. However, the value of re-screening using diagnostic tools, purified protein derivative (PPD) skin test or interferon-gamma release assays (IGRAs) was queried due to the possibility of false readings.

The occurrence of associated active TB in RA patients on TNF-α inhibitors was reported to be 0.07% in the private or combined practice versus 3.00% in the public sector. Forty percent of TB cases were reported to be extra-pulmonary. Despite active vigilance, some physicians reported that active TB month occurred months after the cessation of TNF-α inhibitor therapy. [Similar findings were observed from the British Society for Rheumatology Biologics Register (BSRBR)].

The majority of patients that developed TB co-incident with TNF-α inhibitors were treated successfully with TB chemotherapy. Only 1 of 12 patients died of extra-pulmonary TB,
following compassionate use of infliximab in public care.

**Conclusion:** Physicians practising rheumatology in Gauteng were of the opinion that there is a TB risk associated with the use of TNF-α inhibitors for the management of rheumatoid arthritis, as South Africa is a TB endemic country. Most acknowledged that these biological DMARDs were efficacious in slowing or halting radiographic progression in rheumatoid arthritis, but emphasised the need to take steps to prevent TB reactivation in the immuno-compromised RA patients and to remain overtly vigilant for active TB.

In clinical practice, physicians mentioned that the monitoring and management of TB associated with TNF-α inhibitors appears to follow the socio-economic status of the RA patient and that distinct recommendations should be made for the public healthcare as well as the private healthcare sectors.

Different opinions emanated from different physicians relating to the adequacy of local SARAA guidelines for the prevention of TB associated with TNF-α inhibitors. Some physicians mentioned that local guidelines were sufficient, whilst other physicians mentioned that the diagnostic tools were inadequate in the South African setting and that additional precautions should be taken in the form of IPT for the full duration of TNF-α therapy for all candidates, irrespective of TB status determined during pre-screening.

As the science of biological DMARDs evolves with the rapid development of new medicinal therapies, physicians showed a preference to consider alternative non TNF-α biological DMARDs that had a lower risk of associated TB, specifically in high-risk RA patients.
Physicians’ overall perception of the management of RA with TNF-α inhibitor therapy was that the risk-benefit assessment of these interventions, as well as patient preference and economic considerations should be taken into account.
CHAPTER 1: INTRODUCTION

1.1 RHEUMATOID ARTHRITIS AND TNF-α INHIBITORS

Rheumatoid arthritis (RA) is an auto-immune inflammatory disease that primarily affects the synovial membrane, which lines the joints of the body. The inflamed synovium progresses to erosions of the cartilage and bone and sometimes joint deformity. RA, though, is a systemic disease that can also manifest in other organs including the heart, lungs and eyes (Rudolf et al., 2009).

Pharmacological management aims to relieve symptoms (especially pain), and to modify the disease process. Disease modification slows or stops radiological progression. Conventional DMARDs are being advocated for people with early RA, ideally within 3 months of the onset of persistent symptoms (Rudolf et al., 2009).

Tumour Necrosis Factor (TNF) inhibitors are biological DMARDs that have shown to effect significantly improved clinical outcomes in RA patients. Cochrane systematic review evidence established the efficacy of TNF-α inhibitor therapy in RA. (Blumenauer et al., 2003; Blumenauer et al., 2002; Navarro-Sarabia et al., 2005).

In the public sector, management of RA is outlined in the Standard Treatment Guidelines (STG) produced by the National Essential Medicines List Committee for various levels of care; namely primary, secondary and tertiary level of care (Appendices VII, VIII, IX). The provincial Pharmacy and Therapeutics Committee (PTC) would decide if therapeutic
management of RA would deviate from the STGs. In the private sector, medical schemes are free to create formularies and managed care interventions, but are limited by the minima stipulated for Prescribed Minimum Benefit (PMB) conditions, as provided for by the Medical Schemes Act, Act 131 of 1988. Rheumatoid arthritis is one of the chronic disease list (CDL) conditions included as ambulatory care PMBs and as with other CDL conditions, is subject to a prescribed algorithm (Appendix VI). The list of DMARDs provided for, at a minimum, by all medical schemes is therefore limited to those in the PMB algorithm. Of note, is that both the STGs and PMB algorithm omits biological DMARDs from the list of pharmacological therapies for management of RA; precluding use of TNF-α inhibitors. (Refer to 3.3 for more detailed information).

However, if there is an adequate clinical reason why the STG treatments are ineffective, the PTC may authorise supply of TNF-α inhibitor on a named patient basis in the public sector. Similarly, in the private sector, if the PMB algorithm is inadequate for disease management in a specific RA patient, the Council for Medical Schemes (CMS) may rule that a medical scheme must fund the intervention under regulation 15.1 (c). Guidance regarding the therapeutic use of TNF-α inhibitors in RA is outlined in local SARAA Guidelines.

Currently three TNF-α inhibitors: infliximab, adalimumab (both monoclonal antibodies) and etanercept (soluble TNF receptor) are registered and marketed locally. A side effect of concern when using these Biological Disease Modifying agents includes the risk of reactivation of latent tuberculosis infection (LTBI). TNF-α not only has a pathogenic role in RA (Feldmann et al., 2008; Scott et al., 2006), but is an essential cytokine that protects against Mycobacterium tuberculosis infection (Newton et al., 2008). TNF-α develops and
maintains granuloma integrity which compartmentalizes the tubercule bacilli (Wallis et al., 2008; Kaplan et al., 1996; Chakravarty et al., 2008; Algood et al., 2005). Thus, TNF-α inhibitors may increase the risk of Tuberculosis (TB) infection.

1.2 MOTIVATION FOR THE STUDY

TB is an on-going concern, especially with the high incidence of TB in South Africa. WHO data of 2009, ranked South Africa as the third highest country of Tuberculosis incidence (0.40-0.59 million incident cases). The occurrence of multi-drug-resistant TB (MDR-TB) contributed to increased mortality and morbidity (World Health Organisation, 2009) and increases the seriousness of TB infections in the country.

Thus, SARAA developed a biologics registry, which was intended to register and monitor arthropathic patients initiating biologic therapy with particular focus on TB. Rheumatologists prescribing TNF-α inhibitors should submit pre-screening TB test results prior to initiating a patient on biologics to the SARAA biologics registry panel (that consists of rheumatologists). Patients diagnosed with LTBI (presenting with a diameter of TST reaction of > 5 mm, abnormal chest radiography results, and previous TB exposure history) are treated according to SARAA recommendations prior to commencement of biologics therapy. Chemoprophylaxis is defined as a 6-9 month course of isoniazid or a three month course of isoniazid/ rifampicin combination. The SARAA biologics registry panel is empowered to regulate the supply of these interventions to patients as well as to provide authorisation for funding of TNF-α inhibitors by various medical schemes. Thus, SARAA
applies risk evaluation and mitigation strategies (REMS) to assist with minimising the occurrence of TB co-incident with TNF-α inhibitors.

Most studies on RA patients exposed to TNF inhibitors have been conducted in countries with a low to intermediate burden of TB (USA, Sweden, United Kingdom, Korea, Portugal, and Spain). However, in South Africa, there is a lack of local robust data to analyse the incidence of TB co-incident with TNF-inhibitors.

Firstly, the SARAA biologics registry is not currently up to date and is lacking in accurate data because of administrative challenges and non-compliance of physicians reporting TB cases, once a patient has stopped TNF-α inhibitor therapy. Secondly, cost constraints and subsequent lack of inclusion of TNF inhibitors from the Department of Health’s (DOH) Essential Drug List limits use \textit{en grande partie} in the private sector, which represents 16,4% of the total population (DOH Essential Drug List, 2006; Council for Medical Schemes, 2010; Statistics South Africa, 2011). Thus, data may be sourced from private healthcare insurances, if TNF inhibitors are funded by the medical schemes. TB, a communicable disease may be managed in both the public and private healthcare sectors. However, many patients are referred to state facilities, despite being beneficiaries of medical schemes or being covered by workplace or occupational health programmes. Thus, patients treated with TNF inhibitors funded by a private medical scheme that developed TB, treated by the DOH will be lost to follow up. The tracking of a patient’s clinical course in the two separate stand-alone databases provided practical challenges.
This limited the utilisation of a quantitative approach to analyse the occurrence of TB infection in RA patients treated with TNF-inhibitors in South Africa, a TB endemic country. A qualitative survey researching rheumatologists’ perception, attitude and concerns regarding the risk of TB associated with TNF-inhibitors would be more meaningful. Additionally, this study will inform the proposed prospective study to be instituted by SARAA.

1.3 THE AIMS OF THE STUDY

The aim of this qualitative cross sectional descriptive study is to elicit perceptions of rheumatologists in the private and public healthcare sectors, with regard to the co-incidence of tuberculosis infection in RA patients treated with biological disease modifying agents for arthritis, specifically TNF-α inhibitors.

1.4 THE OBJECTIVES OF THE STUDY

To elucidate the perception of rheumatologists, in Gauteng region, on:

- Pre-screening and re-screening of TB
- the prevalence of latent TB infections in candidate biological patients
- The occurrence of TB infection after introduction of biological agents
- The success of treatment of TB in RA patients who developed TB co-incident with TNF inhibitors.
CHAPTER 2: LITERATURE REVIEW

2.1 IMMUNO-COMPROMISED PATIENTS’ RISK OF TB

Immuno-compromised patients are at greater risk of progression of latent tuberculosis infection (LTBI) to active disease and the detection and consequent treatment of LTBI, particularly in this patient population group, is key in controlling TB (The South African National Tuberculosis Control Programme Practical Guidelines 2004; American Thoracic Society Guidelines, 1999; British Thoracic Society Standards of Care Committee, 2005).

Dixon et al. (2010) reported an increase in the risk of serious infections (defined as causing hospital admission, the need for treatment with IV antibiotics or death) in RA patients compared with the general population in the United Kingdom. This may be due to immunomodulatory effects of RA or to agents with immunosuppressive effects used in its treatment (Doran et al., 2002).

Most published studies, conducted in other countries, have demonstrated an increased risk of TB associated with anti-TNF therapy. This TB incidence has been observed to increase fourfold after initiation of anti-TNF therapy with TNF inhibitors in patients in the United States of America, Spain and Sweden (Keane et al., 2001; Carmona et al., 2003; Askling et al., 2005). Higher infliximab-associated TB case rates were reported in countries with higher incidences of TB: Spain [1113 per 100 000 (post TB screening) for infliximab] (Gómez-Reino et al., 2003), Korea (2558 per 100 000 for infliximab) (Seong et al., 2007) and Portugal (1500 per 100 000 for infliximab) (Fonseca et al., 2006). Lower rates were reported in countries
that have a lower incidence of LTBI; such as the USA (61.9 per 100 000 for infliximab) (Wolfe et al., 2004) and Sweden (145 per 100 000 for infliximab) (Askling et al., 2005).

Data published indicates that the risk of TB is higher for the monoclonal antibodies (mAb’s) infliximab and adalimumab compared to etanercept (Tubach et al., 2009; Dixon et al., 2010). The British Society for Rheumatology Biologics Register (BSRBR) showed that the rate of TB was 144 events/100 000 patient years (pyrs) for adalimumab, 136 events/100 000 pyrs for infliximab and 39 events/100 000 pyrs for etanercept (Katikireddi et al., 2010). Of note is the structural and functional difference of the mAbs compared to the soluble TNF receptor, etanercept (Wallis, 2008; Keane et al., 2001). The mAb, Infliximab has been shown to have increased binding to transmembrane protein TNF on activated T-cells and greater apoptosis of inflammatory cells, neutralising TNF (Wallis, 2008; Keane et al., 2001; Katikireddi et al., 2010). Development of active TB once infliximab treatment is started, is rapid, with a median onset of 12 weeks, and 98% of cases occurring within 6 months of initiation of TNF blockade (Askling et al., 2005; Lalvani et al., 2008). Furthermore, a higher incidence of extra pulmonary and disseminated disease has been reportedly associated with anti-TNF therapy (Katikireddi et al., 2008; Lalvani et al., 2008; Crum et al., 2005; Keane, 2004; Royal College of Physicians, 2006).

2.2 RISK MINIMISATION STRATEGIES ASSOCIATED WITH PRESCRIBING TNF-Α INHIBITORS FOR RA PATIENTS

TNF-α inhibitors are contra-indicated in active TB and close monitoring of patients for infections, including TB, before, during and after treatment with TNF-α inhibitors are stipulated in Medicines Control Council (MCC) approved package inserts for TNF-α inhibitors.
(MSD, 2001; Wyeth Laboratories, 2002; Abbott Laboratories-SA, 2005). Active surveillance for a history of untreated or partially treated TB or LTBI has already been shown to be effective in reducing the number of incident TB cases (Lalvani et al., 2008; Ponce de León et al.; 2005; Millington et al., 2007).

2.3 THE HEALTH SYSTEM OF SOUTH AFRICA

South Africa’s health system has been labelled, “dysfunctional” with contributing factors including the HIV and TB epidemics, vast income equalities, racial and gender discrimination, migrant labour system, human resources crisis in the healthcare sector, failures in leadership and stewardship and weak management resulting in the inadequate implementation of what are often good policies. Although the post democratic constitution provides South Africans the right to health, the country still suffers from marked health inequities. Mortality, morbidity and other determinants of health varies between genders, races, provinces and socio-economic groups (Coovadia et al., 2009). The 2002 reported estimated infant mortality varied between 7 per 1000 compared to 67 per 1000 in white and black populations, respectively (Bradshaw et al., 2004). Mortality was reported to be 1.38 times higher in men than in women for the age groups 15 to 60 years, despite the fact that women have a higher rate of HIV infection.

Internationally, the term double burden of disease to describe the health transition of developing countries, where populations are burdened with diseases associated with unhealthy lifestyles or under development. In the 1980’s to 1990s, this was observed in South Africa. Of concern is that South Africa has been categorised as a country with a quadruple burden of disease with the challenge of HIV and AIDS. Furthermore, it was
reported that even within the country, there are variations of mortality rates, attributed to poverty and under-development (Bradshaw et al., 2006). For example, in the Eastern Cape, the age standardised death rate caused by TB was three times that of Gauteng (Bradshaw et al., 2007). However, even within provinces, there is a difference: In the Cape Town metropolitan area there is almost three times less infant deaths between middle-class cosmopolitan areas compared to poorer informal settlements (Groenewald et al., 2008).

Essential interventions to ensure essential healthcare for all South Africans includes minimising health inequities between provinces and the developed-underdeveloped areas. Coovadia et al. (2008) mention multi factorial interventions including increased government spending on not only health, but also education, and social services with adequate political leadership; efforts to reduce squalid urbanisation; employment creation; efforts to reduce violence, crime and AIDS.

Unquestionably, individual taxpayers underwrite the public healthcare systems and similar to other developing countries, both private and public health sectors co-exist (Ataguba et al., 2010). In post-apartheid South Africa even though the constitution (Republic of South Africa, 2010) mandates access to essential healthcare services, within the constraints of available resources for all, inequalities do exist. This is probably one of the manifestations of income inequity (Coovadia et al., 2009; Gilson et al., 2007). Poverty results in many South Africans having limited access to the low quality public healthcare services. Ataguba et al (2009) indicated that the assessment of the equity of healthcare benefit incidence pattern should be done relative to the need for healthcare. The highest income sector of the population receives most of the health benefits (36%), despite having a lower healthcare burden and subsequent lower ‘healthcare need share’ of less than 10%, compared to health
expenditure of 14% for the poorest in the public sector (that have a healthcare need of more than 25%) (Ataguba et al., 2009). Health funding is thus distorted, favouring the private care sector with private medical schemes (Mooney et al., 2008). The South African context is reflected globally, where more than a billion people, mainly in low- and middle-income countries cannot access essential health services because of unaffordability (World Health Organisation, 2004).

2.4 THE RIGHT TO HUMAN HEALTH

WHO and the Human Rights Council advocated the right of everyone to the highest attainable standard of physical and mental health (2002), essentially a human-rights approach to health (World Health Organisation, 2007). Furthermore, international law describes access to essential medicines as a principle of the right to health (Perehudoff et al., 2010; Hogerzeill et al., 2006). This principle is legally enforced in South Africa by inclusion in the national constitution (1996, section 27); that states that it is the right of every South African to have access to healthcare services, within the constraints of available resources. However, there is an uneven distribution of healthcare amongst the different socio-economic population groups within South Africa. This inequality and inequity of health is deemed to be unjust and unfair, (Dahlgren et al., 2001). The principle of moral equality asserts that we all have equal worth and should therefore be accorded equal basic rights, and as Sen (2004) mentioned that “equity in achievement and distribution of health gets incorporated and embedded in a larger understanding of justice”. A number of key aspects of rights to health have been described including inclusive rights, freedoms, entitlements, non-discrimination and the accessibility, acceptability and quality of services (World Health Organisation, 2007).
Vulnerable populations with past health disparities because of race, poverty, less than optimal healthcare caused by underlying social political, economic and legal systems are at greater risk of suffering catastrophe health outcomes (Whitehead, undated; Krieger, 2001). These patients would likely be restricted in practicing their freedom and rights and probably would lack the capacity to influence what happens to them in terms of health. Thus, fair distribution of health includes the concept of social justice (Sen, 2004). However, for purposes of this study the relationship and effect between health inequity and healthcare services will primarily be discussed. A brief description of these four elements follows below (World Health Organisation, 2007):

- **Accessibility** of health facilities, goods and services to all. (This topic includes elements of non-discrimination, physical, economic and information accessibility).
- **Availability** of a sufficient quantity of functioning public health and health care facilities, goods and services, and programmes.
- **Acceptability**: All health facilities, goods and services must be respectful of medical ethics and culturally appropriate as well as sensitive to gender and life-cycle requirements.
- **Quality** of health facilities, goods and services must be scientifically and medically appropriate and sound.

### 2.5 HEALTHCARE SERVICES

It was reported that in the sexual and reproductive health services in the South African public sector, services has generally not been user-friendly with strained relationships between nurses and reports of rudeness, arbitrary acts of unkindness, physical assault, and
neglect by nurses (Jewkes et al., 1998; Wood et al., 2006). This abuse of patients was probably due to nurses’ lack of accountability towards the public (Jewkes et al., 1998; Coovadia et al., 2009). However, data describing patients’ perceptions on services in rheumatology clinics in South Africa was not available.

In Sweden, a qualitative analysis (Bala et al., 2012) described RA patients’ experience of care provided by nurse led rheumatology outpatient clinics as instilling security, trust, hope and confidence. Patients’ perceptions was that nurse-led clinics were easily accessible and provided continuity of the care ensuring health care safety, facilitating daily life and creating positive emotions. In addition, the nurses’ professional approach, empathy, competence with specialist knowledge of rheumatology care was highly appreciated.

Similarly, a UK qualitative analysis of NHS care provided to RA patients (Lempp et al., 2006) identified that patients no longer see themselves as passive recipients of care. Furthermore, patients appreciated acknowledgement from healthcare professionals of their own contribution towards management of their chronic illness, and welcomed a more equal dialogue with health care workers.

2.6 PUBLIC SECTOR: ACCESSING TNF-α INHIBITOR THERAPY THROUGH CLINICAL TRIALS

As TNF-α inhibitors are expensive and are not affordable to be used in the public healthcare setting, other alternative routes may be considered to access these agents. This includes participation of the public care patient in clinical trials. Some background information regarding the general ethical guidelines for health researchers in South Africa follows.
The value of biomedical research to save human lives and ameliorate disease has been acknowledged and South Africa has been noted as a rich resource for clinical research due to scientific expertise, advanced infrastructure, developing country burden of disease and large number of vulnerable populations. UNAIDS definition of vulnerable communities includes those communities that are underdeveloped, economically, have inadequate protection of human rights with discrimination of health rights, inadequate knowledge of what scientific research entails, limited availability of healthcare and treatment options and low levels of education and literacy. Researchers are guided by the Health professions council of South Africa (HPCSA) general ethical guidelines for health researchers (on the premise of the Declaration of Helsinki and CIOMS guidelines) to protect the rights of these vulnerable patients and to take into consideration all negative impacts of their research. Furthermore, the principle of autonomy is described where the vulnerable study participant should be treated with respect and given the opportunity to make their own informed decision and not be subjected to harm or abuse. In addition, there needs to be justification for doing research in vulnerable communities (HPCSA, 2008).

2.7 PRIVATE SECTOR: PHARMACEUTICAL INDUSTRY ASSISTING MEDICAL SCHEME REMBURSEMENT PROCESSES

Bringing a new biotechnology (such as an anti-TNF medicine) to the market is a daunting project. Not only does the product require registration with Medicine Regulatory Authorities to test its safety and efficacy, prior to being released in the marketplace; but "who will pay for this new product?" and "at what price?" are questions posed early in the development phase of the new medicine. Pharmaceutical companies strategize to include reimbursement analysis as part of their early business-planning to identify attractive market opportunities.
Thus, to achieve sales success, pharmaceutical companies’ now actively participate in and even lead the reimbursement process (Gold, 2003).

2.8 PROVISION OF EVIDENCE FROM PHARMACEUTICAL SPONSORED CLINICAL STUDIES

A healthy scepticism of pharmaceutical commercial marketing is advocated for physicians to ensure that the provision of drug information and promotion by pharmaceutical companies does more good than harm. Some study participants acknowledged that pharmaceutical companies provide medicine information with a financial incentive (increasing sales of more expensive medicines regardless of the impact on health care). The general argument is that medicine prices include a premium for research, promotion, and education (Mansfield, 2006). With the spate of controversies surrounding biased reporting of pharmaceutical studies and a recent USA study describing physicians discrediting industry-funded research and accordingly greater credibility and import to NIH-funded research (Kesselheim et al., 2012); it has been proposed that pharmaceutical manufacturers be banned from researching their products (Godlee, 2006) and that pharmaceutical functions (including research) be funded separately by government agencies via open competitive public tender (Baker, 2004; Mansfield, 2004; Mansfield et al., 2005). Unethical behaviour with reporting of fraudulent clinical trial result or misleading medicine promotion would incur penalties and disqualification from participating in a tender. This could possibly make cost-effective medicines available to larger numbers of people. However, South Africa has only now been initiated in the development of a unified national health system. The 1997 White Paper for the transformation of the health system in South Africa, outlining policy objectives, principles and implementation strategies upon which the Unified National Health System of South Africa will be based; and the 2011 Green Paper on the National Health Insurance
(NHI) ensuring equity and efficiency of healthcare services for universal access by all South Africans to affordable, quality healthcare services regardless of their socio-economic status. This would require national standards with increased transparency and accountability to ultimately improve healthcare performance and health outcomes (as documented in the 2011 Green Paper on NHI). Conversely, there have been pharmaceutical sponsored studies that have been clinically significant (Dorsey et al., 2010) and excessive physician scepticism may prevent conversion of these study results into practice (Ridker et al., 2008; Kritek et al., 2009; Kesselheim et al., 2012).

2.9 DIAGNOSTIC TESTS USED FOR SCREENING AND PRESCREENING OF TB

Purified Protein Derivative (PPD) diagnostic testing for both LTBI and active TB has been the gold standard for over a century, but has been shown to have a number of limitations. Proper administration of the test is needed, patients are required to return to the healthcare worker to have the PPD test read, inaccuracies and subjective bias can occur when the test is read, and false readings can occur because of prior Bacille Calmette-Guerin (BCG) vaccination - as the PPD test contains antigens similar to the non-tuberculosis mycobacterium that is present in BCG vaccines (Edwards et al., 1960; Judson et al., 1974; Snider, 1985). Furthermore, immunocompromised patients, anamnestic responses boosted with repeated PPD tests can further influence the PPD test reading (Madariaga et al., 2007).

Subsequently, new interferon gamma release blood assays have been developed, available on the South African market as T-SPOT.TB® and QuantiFERON-TB-Gold®. These tests have better specificity that the Purified Protein Derivative (PPD) test, and thus does not interact with the BCG vaccines (Andersen et al., 2000) and does not require follow up patient visit.
However, the Centres for Disease Control and Prevention updated guidelines for using IGRAs to determine TB (Mazurek et al., 2010) recommend that a PPD test is preferred to diagnose TB in children aged <5 years, and acknowledge that further research is required to answer questions such as:

- “Are IGRAs better at predicting subsequent active tuberculosis than TST?”
- “Are persons with discordant TST and IGRA results at increased risk for active tuberculosis compared with persons with concordant negative results?”
- “Do IGRAs perform differently in children than in adults, in those with extrapulmonary versus pulmonary tuberculosis, in those with HIV infection versus those without HIV infection, in those recently infected as compared with those infected years earlier, and in those with latent infection as compared with those with active tuberculosis?”
- “What causes variation in IGRA results and to what extent?”
- “What magnitude of change in IFN-γ response indicates new infection?”
- “After exposure, how long does it take for an IGRA to become positive?”
- “Is there an association between lymphocyte count and IFN-γ response (with or without HIV infection)?”
- “What effect does treatment of *M. tuberculosis* infection have on IGRA results?”

The PPD test is the standard diagnostic test for screening for TB, but the use of IGRAs is increasing (Lalvani et al., 2008). The evidence is inconsistent in suggesting which test is better and some studies recommend using both tests (Lalvani et al., 2008; Chen et al., 2008; Bartalesi et al., 2009; Bocchino et al., 2008).
An alternative diagnostic tool that is available in public healthcare facilities is the Genexpert®, an automated cassette-based molecular assay that uses sputum for TB case detection and rifampicin resistance testing. Results can be provided within 2 hours and the test has a high specificity and sensitivity. However, current SARAA guidelines do not include the Genexpert® test to diagnose TB.

2.10 REGULATORY CONTROL OF MEDICINES IN SOUTH AFRICA

In South Africa, the Medicines Control Council, a statutory body, is mandated by the Medicines and Related Substances Control Act, (Act 101 of 1965) to promote and protect public health and safety by ensuring that medicines and healthcare products (including complementary and biological medicines) are therapeutically effective, safe, of good quality and are manufactured, distributed, sold, and marketed according to appropriate standards. Before a medicine is approved for commercial marketing, the MCC considers whether a medicine is suitable for use for its intended purpose by assessing the medicine’s risk-benefit profile. The MCC operates through external experts who come from various academic institutions, mainly medical and pharmacy schools. In addition, the MCC approves clinical trials (Geldenhuys et al., 2013).

Furthermore, the Pharmacovigilance technical Committee of the MCC oversees the safety monitoring of medicines that are available in the market place. The thalidomide disaster in the 1960s was the milestone for the origin and development of pharmacovigilance. Close to 10 000 babies developed congenital defects because of the adverse effects of thalidomide (United States Food and Drug Administration, 1979). Therefore, spontaneous reports of
suspected adverse drug reactions (ADRs), post-marketing safety studies and literature reports, vigilance for unwanted effects of medicines in establishing a drug’s adverse-effect profile assists the MCC to identify important safety issues. The MCC then collaborates with the marketing authorisation holder of a medicine to update the medicine’s package insert and communicate the updated safety information to healthcare professionals. Minimising ADRs may substantially affect hospitalisation, morbidity and mortality (Pirmohamed et al., 2004).

In addition, the MCC provides regulatory control over counterfeit medicines. Counterfeit medicines are a global health problem that has been reported to occur in both developed and developing countries. The WHO defines a counterfeit medicine as "one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging” (Forzley, 2006).

The international trade of pharmaceutical ingredients and medicines through countries where regulatory control of medicine is lacking or under developed, adds another dimension to the problem (WHO, 2012).

WHO recommends that judicial procedures and policies should indicate the seriousness of the problem and courts should speedily dispose of cases, imposing appropriately penalties reflecting the gravity of the offence (WHO, 1999).
The growing burden of healthcare expenditure on households universally led to government involvement with medicine price regulation. Controlling pharmaceutical pricing was necessary to limit spiralling expenditure on pharmaceuticals (U.S. Department of Commerce International Trade Administration, 2004). By allowing market forces to wholly dictate the financing and supply of drugs could also fail to achieve public health objectives (Quick et al., 1997).

Pricing regulation practices also occurs in most of the European and Middle Eastern countries, Australia, New Zealand, the Far East, and Canada (Wertheimer et al., 1992). Different countries use different price control processes. The first countries to use cost effectiveness data in decision-making regarding reimbursement was Australia and Canada (Bloor et al., 1996). The Australian Pharmaceutical Benefits Advisory Committee uses pharmaco-economic analyses and reference pricing to determine the prices of drugs subsidised by the government (Productivity Commission, 2001). The Canadian Patented Medicines Prices Review Board determines a maximum introductory price for newly patented medicines, and forecasts and controls the prices of medicines based on a consumer price index adjustment factor (Patented Medicines Prices Review Board, 2004; Lexchin, 2003).

Germany and Japan practice indirect medicine price controls by limiting reimbursement under social insurance schemes (Danzon, 2000). The Netherlands introduced reference pricing of medicines in 1991, and in 1996 wholesalers had to decrease their prices by approximately 20% (Gier, 2003). In India, essential drugs cannot cost more than twice the
cost of production, and the final printed price must indicate the maximum retail price including local taxes (Kumar, 2004). And, in South Africa, the mandatory offer of generic substitutions is a policy to improve affordability of medicines to patients, particularly in the private healthcare sector. In addition, a system of controlling the single exit prices for all medicines in the private sector in South Africa is implemented, with regulated maximal annual increases (Gray, 2009).

Effective medicine regulation essentially has a multifaceted approach, which if implemented efficiently may promote and protects public health.

2.11 RATIONAL DRUG PRESCRIBING

As Denzinet al., (1994) described that the word “clinic”, derived from the Greek word “klinikos”, meaning of a bed, and “kilinein” meaning to lean or recline; and the word “patient” is derived from the Latin word “patiens”, meaning to suffer and “paene”, meaning almost and “penuria” meaning need. So, patients go to clinicians because they are suffering and are in much need, they need help to move towards the state of “wholeness”. Furthermore, Orlowski et al. (1992) noted, “Patients have a right to expect that a service or product is recommended or prescribed because it is needed and because it is the best, most efficacious, safest, and most cost-effective, based on sound professional judgment unbiased by extraneous factors or inducements.”

There have been serious concerns pertaining to the high incidence of medication errors, associated with prescribing of medicines, including the death of some patients (Leape et al., 1991). This has been due to inadequate teaching of medical pharmacology and medical
graduates lacking skills in safe and rational drug prescribing. Lack of knowledge often leads to ignorance, causing pervasive and prevalent doctor-drug industry relationships that influence doctor’s knowledge of medicine and thus, their prescribing habits (Gwee, 2009).

The WHO definition of rational use of drugs is that the practice requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community. This includes adequate diagnosing of the patient’s condition, determining effective and safe treatments with selection of appropriate medicines (that are efficacious, safe, effective and affordable) for the correct indication for a specific patient with his/her unique profile. Furthermore, patients should be provided with relevant, accurate, important and clear information regarding the disease and the treatments prescribed. Lastly, treatment responses should be evaluated including the expected and unexpected adverse drug reactions of the prescribed medicines should be monitored (WHO, 2002).

However, in the real world, rational drug prescribing is not always practiced and examples of irrational prescribing includes the overuse of antibiotics and antidiarrheals for non-specific childhood diarrhoea, inappropriate prescribing of antibiotics for viral flu, treating malnutrition with tonics and multivitamins unnecessary use of expensive antihypertensives and polypharmacy. In addition, use of drugs with doubtful or unproven efficacy, use of drugs of uncertain safety status and incorrect administration, dosages, or duration results in medicine errors affecting patients’ health outcomes (Holloway et al, 2013).
There are a number of factors contributing towards irrational use of drugs, are affected by various attitudes that are prevailing among the prescribers and consumers:

**Consumers:** Patients are misinformed about medicines affecting their perceptions and beliefs and resulting in certain demand and expectations. Poor patient communication to relate their problem(s) to healthcare workers also results in inappropriate management of the patient’s condition. (The latter would prevail in vulnerable populations, where the patient is less educated and has a low socio-economic status).

**Prescribers** that have inadequate education and training, inadequate or no access to objective and relevant drug information, a heavy patient and work load, are pressurised to prescribe (by consumers or pharmaceutical industry), a misleading belief about a medicine’s efficacy, inappropriate mentors and a generalisation of limited experiences.

**Drug Regulators:** Approving the availability of unsafe or non-essential drugs onto the market place, authorising of inadequately trained non-formal prescribers to prescribe medicine and the lack of regulation enforcement.

**Drug suppliers:** Inefficient management causing medicine stock outs and the non-availability of essential medicines or the supplying expired medicines.

Pharmaceutical industry: Promotional activities and misleading claims affect prescribing habits (de Vries et al., 1994).
The impact of inappropriate use of drugs includes:

- Reduced quality of drug therapy leading to increased morbidity and mortality.
- Waste of resources leading to reduced availability of other essential drugs and increased costs of healthcare expenditure.
- Increased risk of unwanted effects such as adverse drug reactions and the emergence of drug resistance (particularly global antimicrobial resistance).
- Psychosocial impact, such as when patients come to believe that there is "a pill for every ill", which may cause an apparent increased demand for drugs (de Vries et al., 1994).

The WHO describes the rational use of medicines as prescribing and administering the right medicine, to the right patient, at the right dose, using the right route, at the right frequency (WHO, 2002).
CHAPTER 3: BACKGROUND TO THE STUDY

To understand the management of RA patients with TNF-α inhibitors, in the local South African context; the mixed private-public healthcare environment needs consideration. Unfortunately, as Mooney et al. (2008) pointed out, the legacy of apartheid, the AIDS epidemic, grave concerns regarding poverty and income inequality are main factors affecting health in South Africa. The extreme variance in income is manifest in the distinct split between private and public care, with the greater part of the healthcare funds financing the richer private sector whilst the poorer population have limited access to low quality healthcare (Mooney et al., 2008).

Furthermore, the different sectors of healthcare are managed differently, as previously described in section 1.1.

3.1 SOUTH AFRICAN GUIDELINES FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

THE WHO concept of Essential medicines is medicines that satisfy the priority health care needs of a population (World Health Organisation, 2010). The selection of appropriate medicines is based on disease prevalence, evidence of efficacy, safety, and comparative cost-effectiveness. In South Africa, the health objectives of the National Drug Policy (NDP)(1996) is aligned with the WHO principles to ensure that affordable, good quality essential medicines are available at all times in adequate amounts, in appropriate dosage forms, to all citizens. The NDP aims to “promote the rational choice of drugs and associated items to be used in South Africa”. The policy further describes the promotion of the rational use of drugs by prescribers, dispensers and patients through provision of the necessary
training, education and information and promoting the concept of individual responsibility for health, preventive care and informed decision-making (National Department of Health, 2012).

In order to achieve these objectives an Essential Drugs Programme has been implemented with STGs and essential medicines lists (EMLs) to guide the treatment of diseases prevalent to South Africa. The national essential medicines list will not only be used as the basic health care package of the National Health System, but also as a model for medical aid schemes. Essentially there are three sets of EMLs (Primary healthcare EML, Adult and Paediatric Hospital level EML and Tertiary and Quaternary level EML). For rheumatoid arthritis, the STG and EML recommend that conventional DMARDs be used in a step-wise therapy for the remission of RA. The unaffordability of biological DMARDs (including TNF-α inhibitors) precludes use in the public sector (Department of Health, 2012). However, as suggested by the Arthritis clinical guidelines 2003, issued by the South African Medical Association (SAMA), for the management of privately funded patients with refractory RA, biological agents (including TNF-α inhibitors) or leflunomide are recommended. These guidelines were developed by a nationally representative consensus group comprising of representatives of professional, government and consumer groups with an interest in the arthritis field and endorsed by the SAMA Guideline Committee. Funds provided by pharmaceutical companies, MSD and Searle were made in accordance with the SAMA code of sponsorship. These clinical guidelines, which are 10 years old are aligned to, but are an abridged version of the current SARAA guidelines. Furthermore, SARAA provides a more comprehensive guidance pertaining to biological DMARD therapy and the screening, monitoring and management of TB in the RA patients.
Figure 1: Treatment algorithm for treatment of RA

1. Confirmation of diagnosis
2. Definition of goals
3. Assessment of disease activity
4. Patient education

The following measures may be required at any stage of the disease:

- Drug therapy
  - Analgesics
  - DMARDs for active disease
  - Anti-inflammatory drugs NSAIDs or COXIBs
  - Low-dose corticosteroids (e.g., prednisone < 7.5 mg/d)

- Non-pharmacological measures
  - Physiotherapy
  - Occupational therapy
  - Assistive devices
  - Modification of footwear, etc.

- Intra-articular steroids

- Combination of above drugs

Further management depends on age, sex and severity of disease:

- Leflunomide* (also being used as combination therapy)
  *Other agents which are sometimes used include azathioprine, cyclosporine and penicillamine.

- Biological agents (e.g., anti-TNF agents)

- Experimental therapies

(Adapted from SAMA Arthritis Clinical Guidelines, 2003).
Table 1: Anti-rheumatic medicines’ usual doses and associated toxicities

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>TYPICAL DOSAGE</th>
<th>TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorquine</td>
<td>Oral: 200 mg once or twice daily</td>
<td>Macular damage, rash, diarrhoea</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Oral: 500 mg twice daily, increase to maximum dose of 1 g twice daily</td>
<td>Myelosuppression, rash</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Oral, IV, IM, IA, and soft-tissue injections: variable</td>
<td>Hypertension, hyperglycaemia, osteoporosis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Oral or IM: 7.5 – 15 mg/week</td>
<td>Myelosuppression, hepatic fibrosis, cirrhosis, pulmonary infiltrates or fibrosis, stomatitis, rash</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Dose varies per NSAID</td>
<td>Gastrointestinal ulceration and bleeding, renal damage</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Oral: 100 mg daily for 3 days, followed by 10-20 mg daily</td>
<td>Hepatitis, gastrointestinal distress, alopecia</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Oral: 50-150 mg daily</td>
<td>Myelosuppression, hepatotoxicity, lymphoproliferative disorders</td>
</tr>
<tr>
<td>Etanercept</td>
<td>25 mg SC twice weekly or 50 mg weekly</td>
<td>Local injection site reactions, infection</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>40 mg SC every 2 weeks</td>
<td>Local injection site reactions, infection</td>
</tr>
<tr>
<td>Infliximab</td>
<td>IV: 3mg/ kg at 0, 2 and 6 weeks, and then every 8 weeks</td>
<td>Immune reactions, infection</td>
</tr>
<tr>
<td>Abatacept</td>
<td>IV: At 0, 2 and 4 weeks, and then every 4 weeks Dose per weight: ▪ Adults &lt; 60 kg: 500 mg ▪ Adults 60-100 kg: 750 mg ▪ Adults &gt; 100 kg: 1 g</td>
<td>Infection, hepatitis B virus reactivation</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV: Initially: 2 infusions of 1 g, separated by 2 weeks in combination with methotrexatex. Subsequent doses administered every 16-24 weeks</td>
<td>Hypersensitivity reaction, thrombocytopenia, infusion related side effects (flushing, chills, fever, rigors, hypotension), bronchospasm, dyspnoea, angioedema</td>
</tr>
<tr>
<td>Tocilizumab.</td>
<td>IV: Initially 4 mg/kg once every 4 weeks; may increase to 8 mg/kg once every 4 weeks based on clinical response. Doses &gt; 800mg not recommended</td>
<td>Infection, gastrointestinal perforation, neutropaenia, thrombocytopenia, immune reactions, hyperlipidaemia</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Oral: 2.5 mg/kg/day</td>
<td>Hypertension, tremor, nephrotoxicity, hyperlipidaemia, gingival hyperplasia, gastrointestinal disorders, leukopaenia</td>
</tr>
</tbody>
</table>

IV: intravenous; IM: intramuscular; IA: intra-articular; SC: subcutaneous.

(Adapted from Di Piro et al., 2005; Pharmacotherapy: A pathophysiologic approach, 6 ed.).

### 3.2 SOUTH AFRICAN RHEUMATISM AND ARTHRITIS ASSOCIATION (SARAA) OF SOUTH AFRICA

The South African rheumatism and arthritis association (SARAA) is a voluntary association of members of the healthcare profession with an interest in the management of arthritic diseases. The main aim of the association is to promote, maintain and protect the honour and interest of the discipline of rheumatology as a medical specialty for the benefit of all. This is achieved through a number of objectives including the advancement of the science and practice of rheumatology by promoting research, education, awareness and knowledge, the promoting of the relationship between the Association and other groups or organisations with an interest in the rheumatic diseases; the promotion of the professional and legitimate interests of the Association and its members; to maintain standards in rheumatology through peer review; to promote and uphold the principles of human rights, dignity and ethics in the practice of rheumatology with the provision of health care services and adequate treatment for all affected by the rheumatic diseases, particularly the poor and needy; to oppose unfair discrimination in the field of rheumatology with the promotion of the care of persons physically disabled due to rheumatic diseases and to encourage research and publication in the field of rheumatology (SARAA, 2012).
Furthermore, the SARAA has developed guidelines for the use of TNF-α inhibitors in arthritic patients (Appendix X). This guideline sets the criteria which the biologics registry panel uses to authorise a patient supply and funding of TNF-α inhibitors, where applicable. The place in therapy of TNF-α inhibitors has been described as after failure or intolerance of an adequate trial of conventional DMARDs and the guideline also documents the contra-indications, infection risk and withdrawal criteria associated with TNF-α inhibitors (SARAA, 2012).

In addition, SARAA’s position regarding the infection risk of TB associated with TNF-α inhibitors in South Africa is documented in SARAA’s TB Guidelines (Appendix XI). The rationale provided is that South Africa has unique problems with many people having been exposed to TB at some time and the guidelines are supported by observational data from the Spanish register BIOBADASER of a 80% reduction rate of TB after a 9 month course of TB chemoprophylaxis in patients diagnosed with LTBI, prior to TNF-α therapy (Gómez-Reino et al., 2003). The TB guidelines outline the diagnosis, and treatment of LTBI. Furthermore, the guidelines emphasise the need for ongoing vigilance in all patients on TNF-α therapy (even if the TB diagnostic test, the PPD test) is negative as well as the absolute contraindication of TNF-α inhibitors in patients with active TB (SARAA, 2012).

### 3.3 PRESCRIBED MINIMUM BENEFITS IN THE PRIVATELY FUNDED HEALTHCARE SECTOR OF SOUTH AFRICA

The Regulations of the Medical Schemes Act (Act no 131 of 1998) mandates that all privately funded medical schemes provide all members access to minimum health services for a
defined set of conditions known as Prescribed Minimum Benefit Conditions (PMBs) (Department of Health, 1998). The Council for Medical Schemes defines PMBs as “... a set of defined benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected. The aim is to provide people with continuous care to improve their health and well-being and to make healthcare more affordable. PMBs are a feature of the Medical Schemes Act, in terms of which medical schemes have to cover the costs related to the diagnosis, treatment and care of:

1. any emergency medical condition;
2. a limited set of 270 medical conditions (defined in the Diagnosis Treatment Pairs or DTP); and
3. 25 chronic conditions (defined in the Chronic Disease List or CDL). (Council for Medical Schemes, 2010)"

The objectives for specifying PMBs are two-fold. Firstly, to ensure members have access to minimum benefits for treatment of serious illness, even where members have exceeded or depleted their plan benefits. The second is to encourage more efficient use of the limited health care resources in the public and private sectors (Department of Health, 1998).

Furthermore, to contain costs of healthcare, the Act makes provision for the medical scheme to set out the “scope and level of minimum benefits” in its rules. As mentioned previously, the national essential medicines list provides a model for minimum cover benefits for medical aid schemes. However, the Act also assures the financial viability of the scheme, protecting the membership base. Medical schemes may use risk management interventions to improve the efficiency and effectiveness of health. These tools include the
use of formularies or medicine lists, application of algorithms and treatment protocols (describing the minimum cover for diagnostic and laboratory tests), benefit confirmation for procedures and the use of designated service providers (Department of Health, 1998).

If a member prefers a more costly medication that is not enlisted on the medical scheme’s formulary, the medical scheme will reimburse the medicine claim up to the formulary medicine price and the member is liable for the difference, as an out-of-pocket payment (Department of Health, 1998).

The high costs of TNF-α inhibitors are described later in section 1.6.5. Interestingly, McIntyre et al. (2007) reported that out-of-pocket payments contribute to approximately 17% of private health expenditure. This implies that privately funded patients’ are willing to pay to receive healthcare services. However, this amount would be constrained by a patient’s wealth or socio-economic status.

3.4 CURRENT COSTS OF TNF-A INHIBITORS ON THE SOUTH AFRICAN MARKET

The TNF-inhibitors that have been registered in South Africa by the Medicines Control Council includes Revellex® (infliximab) in 2001, Enbrel® (etanercept) in 2002 and Humira® (adalimumab) in 2005, respectively. (MSD, 2001; Wyeth Laboratories, 2002; Abbott Laboratories-SA, 2005).

Although, the efficacy of TNF-α inhibitors in RA patients has been shown, with improved radiographic results (Moreland et al., 2012; Lie et al., 2011; Jobanputra et al., 2012), these modalities are expensive
In South Africa, an additional factor that determines accessibility to medication is affordability.

**Table 2: Costs of TNF Inhibitors approved for RA in South Africa**

<table>
<thead>
<tr>
<th>TNF-α inhibitor</th>
<th>TYPICAL DOSAGE</th>
<th>COST PER MONTH* (SINGLE EXIT PRICE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab 100 mg/10 mL, inj 3 mg/kg IV infusion at 0, 2 and 6 weeks; then 8 weekly maintenance</td>
<td>R 8015.56** (excluding IV administration costs)</td>
<td></td>
</tr>
<tr>
<td>Adalimumab 40 mg, inj (2) 40 mg, subcutaneously, fortnightly</td>
<td></td>
<td>R 7090.60</td>
</tr>
<tr>
<td>Etanercept 25 mg, prefilled syringe (4 doses) 25 mg subcutaneously, twice a week</td>
<td></td>
<td>R 7114.78</td>
</tr>
</tbody>
</table>

*IV: intravenous; inj: injection; SC: subcutaneous

**Costs based on ex manufacturer Single Exit Price (SEP), VAT exclusive (Department of Health, 2013).

**Infliximab cost based on approximate maintenance dose for a 70kg adult.

Interestingly, current evidence suggests that TNF-α inhibitors have not improved overall survival in RA patients compared to the general population (Thyagarajan et al., 2012; Watson et al., 2007). Infliximab has been precluded from the essential medicines list in the
The British Society for Rheumatology Biologics Register (n=9849) compared standardised mortality ratios of patients administered TNF-α inhibitor therapy to that of the general population in the UK. The reported mortality ratios of 2.0 for males and 1.7 for females on TNF-α inhibitor therapy were similar to that reported in the pre-biologic era, suggesting that TNF-α inhibitor therapy does not improve overall survival (Watson et al., 2007). Furthermore, a retrospective cohort study of RA patients in the USA reported that the incidence rates for all-cause mortality in RA patients treated with TNF-α inhibitors of 5.34 deaths/1000 pyrs were similar to the general population (including both fatal infection and fatal malignancy rates) (Thyagarajan et al., 2012).

The option for pharmaceutical industry to lower the costs of TNF-inhibitors would assist equitable access to all RA patients. Although, the development of lower priced biosimilars may be an alternate consideration to provide essential competition in the marketplace (Roger et al., 2007), required clinical trials confirming biosimilarity (pertaining to the medicine’s safety, efficacy and immunogenicity) would need to be submitted for evaluation to medicine regulatory authorities.

### 3.5 QUALITATIVE RESEARCH ANALYSIS

Essentially, quantitative data analysis is an objective, statistical measure of an observation that is investigated. Denzin et al. (1994) argued that the quantitative scientific approach is positivistic, based on testing a theory in a controlled manner in order to deduce whether the...
predictive generalisation of the hypothesis is true. Conversely, qualitative analysis follows a naturalistic approach as it is a subjective study where the contextual description and interpretation of events is crucial to understand the question from multiple perspectives. Qualitative studies investigate human behaviour in natural settings and theories emerge as the study unfolds and hypotheses are induced, requiring descriptive write-ups. (Borg et al., 1989).

As quantitative research analyses numbers, this mode of research was inappropriate for this study, due to the study limitations associated with accessing quantitative data. Qualitative research involves analysis of data in the form of words, pictures or objects. Therefore, a qualitative study was considered favourably to discover rheumatologists’ perceptions towards the management of TB associated with TNF-α inhibitor therapy in RA patients. The concepts used by the study participants to describe experiences in clinical practice would provide an initial understanding of the association of TB with TNF-α inhibitors in the South African RA population and could reveal underlying motivations and factors that influence rheumatologists’ decision making and opinions.
CHAPTER 4: METHODOLOGY

4.1 THEORETICAL FRAMEWORK

The concept of ethnographic observation forms the basis of the theoretical framework of this study. The systematic approach of ethnography emphasises the nature of rheumatologists’ perceptions on TB associated with TNF- in RA patients in SA, rather than the testing of a pre-formulated hypothesis (Le Compte et al., 2010). Thus, ethnography is a humanistic, interpretative approach with the hypothesis emerging as data is being progressively collected, rather than a scientific and positivist approach. The ethnographic observation takes place in the natural setting (physicians’ normal day-to-day clinical practice) and the researcher interprets the situation from the perspective of the study participants (Atkinson et al., 1994). Essentially, the researcher is the primary tool of data collection (LeCompte et al., 2010).

However, a limitation of ethnography is reliability, as it is often difficult to replicate ethnographic research seeing that the event occurs in a natural setting (Nurani, 2008). Nonetheless, the ethnographic methodology adopts the theory of constructivism to ensure trustworthiness, credibility, transferability and conformability of the data ensues. The paradigms assumed include ontological and epistemological, querying the nature of reality; and querying the relationship between the researcher and interviewed to co-create understandings, respectively (Guba, 1990). Validity may also be queried, as it is not possible to control external variables (Nurani, 2008). However, various rigorous research methods and data collection techniques are used to minimise bias and ensure data accuracy (Nurani, 2008). Validation of the data collected is performed using different data collection methods.
(namely in depth interviews of study participants, participant observations documented in researcher’s field notes and ethnographic interpretation of the data collected (Nurani, 2008)).

Generalisability is not the key focus (Atkinson et al., 1994; Savage, 2000). Rather, a small number of case studies are investigated in detail to explore the discontinuities, paradoxes and inconsistencies of social perceptions and action, evoking the development of hypotheses and interpretivism (Atkinson et al., 1994; LeCompte et al., 2010).

Analysis involves interpreting the observations of human actions and behaviours, including verbal narrations, descriptions and explanations (Atkinson et al., 1994). Narration includes interpretive case studies (created through audio-recorded interview dialogues and observations documented in journal field notes) and ethnographic accounts (Guba, 2010).

During the interviewing process, the researcher is guided by participation observation, to discern subtleties (including appearance, verbal behaviour and interactions, physical behaviours and gestures, personal space, etc.) within participant responses. This provides the researcher with cues to ask more appropriate follow-up questions and probes. The principal method used for participant observation is the collection of field notes. These unbiased objective observations are documented in the researcher’s journal notes, covering a range of observations (including informal conversations, body language, the general environment, moods, etc.) to generate insights (Nurani, 2008).

Ethnographic observation methodology may be applied to the healthcare setting by assisting healthcare professionals with problem solving beyond the reach of traditional
research approaches, particularly in understanding the context of events in the real world setting of clinical practice. Interestingly, Atkinson raised important concerns relating to the use of models and algorithms to make decisions in medical practice, and whether these approaches acknowledge the complexities of clinical practice. (Savage, 2000).

4.2 ETHICS STATEMENT

The Human Ethics Research Committee of the University of the Witwatersrand approved the study (Appendix 1). Study participants were provided with information sheets (Appendix 2) and written informed consent (Appendix III) was obtained from rheumatologists to participate in this survey and to audio record the interviews. According to the general ethical guidelines for health researchers of the Health Professions Council of South Africa (HPCSA) study participants have a right to privacy and confidentiality should be protected. Therefore, the audio-taped interviews will be stored and used in a way that will respect the confidentiality of the study participants. Of note is the allocation of study numbers to study participants to preserve confidentiality (refer to point 2.6). In addition, the tape recordings should be stored for a minimum of 2 years after publication or 6 years in the absence of publication (HPCSA, 2008).

4.3 SURVEY INSTRUMENT

Rheumatologists were interviewed face-to-face in a semi-structured manner, using a schedule of questions derived from the study protocol. The items on the schedule (Appendix IV) included both open (where the respondent composes a reply) and closed (where pre-coded responses are available) questions (Britten, 1995). The survey focused on the interviewee’s demographic details, TNF-inhibitor experience, TB experience in patients and
vigilance in the clinical setting. In addition, underlying factors that predispose to tuberculosis reactivation including concomitant immunosuppressants (azathioprine, methotrexate, cyclosporine, leflunomide and prednisone at a dose greater than 10mg per day) (Segal, et al., 1997; Joint statement of ATS & CDC, 2000; Jick, et al., 2006) and co-morbid diseases [asthma, chronic obstructive pulmonary disease (Shu et al., 2010) and diabetes mellitus (Jeon et al., 2008; Restrepo et al., 2011)] were assessed. The interviews were audio-recorded (Britten, 1995).

4.4 PILOT STUDY

A pilot study was used to refine the data collection strategies (Morse et al., 2002). Two medical doctors were interviewed to identify item ambiguities, level of understanding and other sources of error associated with the survey instrument. The interviewees were also requested to assess the flow of the survey, if the questions were clear and concise (not requiring to be repeated or leading to misinterpretation) and if questions appeared to be sensitive (Kelley et al., 2003). In addition, the pilot interviews provided training for the researcher in the different elements of the research process.

The first medical doctor had no speciality in rheumatology. The interview was not audio-recorded, but ambiguities and difficult questions that required rephrasing were identified. Open-ended questions were tested and re-worded where appropriate; to ensure that there would be an adequate range of responses. The outcomes of this interview resulted in the development of the interview schedule into a pictorial annotation format (Appendix IV). The refined research tool was used to collect data in order to answer the research questions. In
addition, the document provided the substrate for the researcher to record journal notes during the interview process.

The second pilot study interview of a practicing rheumatologist was audio-recorded. The time taken to complete the interview was monitored and the interview process was amended to ensure a reasonable interview session of 10-15 minutes. This initial audio-recorded interview was included in the main study data and the risk of data contamination (with interviewee bias and hence data distortion) was considered to be negligible, as qualitative data collection often evolves with subsequent interviews improving, as the researcher obtains more experience and insight as the study progresses (van Teijlingen et al., 2001). The second pilot interview was used to refine the interviewer's technique and to confirm the utility of the pictorial format for the researcher's journal.

4.5 STUDY PERIOD

Data were collected from July 2012 to October 2012 inclusive.

4.6 CONFIDENTIALITY

Confidentiality was maintained by anonymising the identity of each interviewee. A number was allocated to each study participant for the purposes of the transcripts. The identifiable data was coded and the links were kept separately. Linking data was stored on a Microsoft Excel spread sheet that was password protected. Access to this data was limited, which was kept at a locked location at the University of the Witwatersrand, Department of Pharmacy and Pharmacology.
4.7 DATA COLLECTION

4.7.1 Sample: Experts in the field of rheumatology were specifically selected as there is a paucity of empirical evidence and uncertainty associated with the prevalence of TB co-incident with TNF-α inhibitors in the South African rheumatoid patient population and thus rheumatologists were considered the best source of information for this study. To identify the specific population of rheumatologists for this survey, purposive sampling (Kelley et al., 2003) was utilised. Purposive sampling offer a degree of control, as the domain of rheumatology was specifically pursued. A list of all practicing rheumatologists in South Africa was sought. However, time, access and logistical constraints restricted this study to the Gauteng region. Thus, the sampling frame (Kelley et al., 2003) was limited to physicians that actively practiced rheumatology in the Gauteng region. This is noted as a limitation of the study since TB prevalence differs from region to region and the incidence of rural-urban variation in South Africa (Abdool Karim et al., 2009; Houlihan et al., 2010) may affect the data collection, as interviews are limited to rheumatologists practicing in the Gauteng region.

A list of rheumatologists practicing in Gauteng was downloaded from the South African Rheumatism and Arthritis Association (SARAA) website that included rheumatologists as well as physicians with an interest in rheumatology. However, it was ascertained that not all practicing rheumatologists were enlisted on the SARAA website. Therefore, an additional recruitment mechanism, the snowball sampling technique was incorporated; where one rheumatologist identified other rheumatologists practicing in the Gauteng region, who then identify other rheumatologists in a chain-referral process comparable to a snowball rolling down a hill. This semi-self-directed, snowball sampling ensured that all clinicians practicing
rheumatology in Gauteng could be accessed in a pragmatic and socially acceptable manner (Sadler et al., 2010), enabling rheumatologists who were not members of SARAA to be included in this study. The contact information for additional rheumatologists practicing in the Gauteng region was solicited from the clinicians that were interviewed in both the pilot study and in the survey. All rheumatologists were contacted for consideration to participate in this study. The audio-recorded interviews were generally conducted in the physicians’ consulting room.

4.7.2 Collecting data: Consenting study participants were interviewed and audio-recorded. The audio recorded interviews were saved in a MP3 file format. The files of data were labelled according to the code number that was assigned to each study participant. In addition, journal notes scribed during each interview that presented additional information was labelled with the unique study participant number (Lacey et al., 2007).

4.8 ANALYSIS OF QUALITATIVE DATA

The Qualitative Analysis Guide of Leuven (QUAGOL) and the National Institute for Health Research (NIHR) Qualitative Data Analysis Resource Pack (Dierckx de Casterlé et al., 2012; Lacey A et al., 2007) were used to determine the framework for the content analysis of the qualitative interview data.
CHAPTER 5: DATA ANALYSIS

5.1 TRANSCRIPTION OF AUDIO RECORDINGS

Audio recorded interviews were immediately (following the interview) transcribed verbatim and non-verbal cues and other elements of conversation (sourced from the interview transcripts and journal notes) were included (including laughter, sigh, hesitation, etc.) (Dierckx de Casterlé et al., 2012). Names and other identifiable material were removed from the transcripts and narrative data was numbered using line numbers. Back-up copies of the audio recordings and word processed copies of the transcripts were made and the data stored at a locked location at the University of the Witwatersrand, Department of Pharmacy and Pharmacology.

Interview transcripts were compared with the journal notes recorded during the interview. Furthermore, observations and relevant communication outside of the recording were documented in the researcher’s journal notes were attached to each relevant transcript.

5.2 ORGANISING THE DATA

The researcher summarised, indexed and organised the transcribed data into sections, according to themes (as described in points5.3 to 5.7, below).

5.3 FAMILIARISATION

Familiarisation with the data through, listening to the MP3 files, re-reading the transcripts, journal notes and summaries and appropriate memos were prepared, before starting the formal data analysis process (Dierckx de Casterlé et al., 2012).
5.4 PRELIMINARY CODING

As data became familiar and scripts were being reviewed, codes were identified that could be applied to ideas across all the interviews. Codes described different ways that respondents expressed an underlying concept. Constant comparison of different responses within individual cases and across cases further facilitated the development and refining of common themes, concepts or hypotheses. Codes were refined and re-coded, as required. A common list of concepts was compiled forming preliminary codes (Dierckx de Casterlé et al., 2012; Lacey A et al., 2007).

5.5 CODING

The summarised transcripts were read again critically, hand-in-hand with the preliminary list of codes to determine if the concepts could be identified in each interview case; and if not, whether valid explanations for missing concepts could be suggested. The quality of the codes was examined to ensure that the concepts were adequately described, capturing all significant ideas, messages or hypotheses in a well-defined manner. Codes that were too ambiguous or abstract were re-coded or omitted to develop an optimal list of codes. Each code with its corresponding citations from each interview case was critically analysed to verify comparable association (Dierckx de Casterlé et al., 2012).

5.6 THEMES AND CATEGORIES

Once all relevant fragments of the interviews were appropriately coded, across-case analysis was performed to explore common, integrated, relational or differences in messages or themes (Ayres et al., 2003; Sandelowski, 1996). In addition, themes were further refined: defining themes more clearly, dividing into sub themes or combining multiple concepts into
one theme, where applicable. It was noted that many units of data fell into more than one category (Dierckx de Casterlé et al., 2012). The development of the common ideas throughout the analytical process was charted, by case for each respondent across all themes using a data matrix to enable easy reading across the entire dataset (Mile et al., 1994). Data analysis was repeated with continuous data collection to further conceptualise the data and refine the coding schemes (Dierckx de Casterlé et al., 2012). After nine interviews, themes were identified and classification of the themes was done again after the eighteen interviews had been completed. From the fifteenth interview onwards, data saturation had been reached, as the study participants were not expressing any new significant views. However, all eighteen interviews were completed. Individual particular attention was placed on each case so as not to accentuate averages and aggregation that may have led to misinterpretation (Noblit et al., 1988; Miles et al., 1994).

5.7 CONCEPTUAL FRAMEWORK

Themes were further integrated and contextualized to answer the research question(s). A framework was developed to organise and structure all themes into a story-line, where all individual interviews could be described (Dierckx de Casterlé et al., 2012). Core findings were described, using ethnographic reporting, where applicable, to enrich the description of the data (Bazeley, 2009). The differences and similarities in the characteristics of themes across variations in context were noted and each element was related, and the emerging theory from the data was compared to current validated evidence. After describing the research findings, the transcripts were reread for accuracy and comprehensiveness of the story line. Thereafter, the results were checked for trustworthiness using triangulation,
deviant case analysis and the constant comparative method (Dierckx de Casterlé et al., 2012).

5.8 VALIDITY AND RELIABILITY (TRUSTWORTHINESS)

To attain rigour in this research, validity and reliability of the research findings were enhanced using triangulation and deviant case analysis. Validity in qualitative research refers to “truth” (Silverman, 2005), whilst reliability refers to the degree of consistency with which instances are assigned to the same category by different observers (Hammersley, 1992). Two external experts, who were not rheumatologists, but who were experienced in the treatment of RA with anti TNF’s were invited to debate the assignation of themes and categories in the dataset.

5.8.1 Triangulation

Patton (2001) advocated the use of triangulation by stating that “triangulation strengthens a study by combining methods (Golafshani, 2003). Two methods of triangulation were used to establish that the data was trustworthy: Methodological triangulation and theory triangulation (Guion et al., 2011). The former being the comparison of two different qualitative methods; to deduce if similar results are being found. Here, ethnographic observations documented on journal notes and the direct transcripts from audio-recorded interviews were compared for consistency and the findings from the two methods were compared to determine if similar conclusions were drawn. Theory triangulation was utilised to evaluate the audio-recorded transcripts, where the opinions of two experts (a medical doctor and a pharmacologist) were debated until consensus was reached on each point.
5.8.2 Deviant case analysis

Silverman (2005) described comprehensive data analysis as actively seeking out and addressing anomalies or deviant cases. Further analysis of deviant cases enables a richer, more-in-depth understanding of the data and strengthens the validity of the research. Therefore, during data analysis, cases identified as outliers were to be analysed to determine the reason for the difference in outcome.

5.8.3 Constant comparative method

An iterative process of analysis using the constant comparative method was used to continuously verify the data and to further develop ideas, enabling a deeper understanding of the meaning of the qualitative data in relationship to context as new data was collected (Froggatt, 2001; Sandelowski, 1995, 1996; Dierckx de Casterle et al., 2012). In addition, data analysis was not isolated from description and interpretation of the data (Sandelowski, 1995; Wolcott, 1994).
CHAPTER 6: RESULTS

Development of codes, themes and categories

Common preliminary codes, identified as data, became familiar and scripts were reviewed using the constant comparison method. Inequity of healthcare services between the private and public healthcare sectors in South Africa was a predominant code that emerged; and specifically that TNF-α inhibitors were too expensive for use in the public sector. Another common code that emerged was vigilance of TB associated with TNF-α inhibitors in RA patients.

Critical re-review of the transcripts further refined the codes and verified the common concepts that emerged. Once all data was appropriately coded, across-case analysis was done to explore common themes, using a data matrix to simplify review of the entire dataset. Preliminary defining of themes was done after nine interviews and reclassification of themes once all eighteen interviews were completed.

Discussion between the investigator/interviewer and two external experts resulted in the re-classification of the preliminary code, ‘Inequity of healthcare services’ to a theme with the creation of a sub theme, ‘The right to human health’ determined by four determinants that affects the right to universal access to medicine. These determinants that emerged as common categories across cases were, ‘Affordability and accessibility of TNF-α inhibitors’, ‘Availability of medicine, diagnostics, healthcare workers in the various healthcare settings’, ‘Inequity in health outcomes in the private versus public healthcare sectors’ and
‘Acceptability by patients in a patient-centred care model regarding treatment with and safety of TNF-α inhibitors in RA’.

The preliminary code, vigilance, was likewise redefined as theme once the complete dataset was reviewed. This was verified with the two external experts. The study objectives was answered on reviewing the data relating to this theme and categories that emerged from analysis of the dataset were, ‘Prevalence of active TB co-incident with anti-TNFs’, ‘Treatment outcomes of TB in RA patients co-incident with TNF-α inhibitors’, ‘SARAA biologics registry and TB surveillance’, ‘Re-screening for LTBI’, ‘Preference of anti-TNF molecule in LTBI’ and ‘Restarting anti-TNF therapy after active TB’.

Although the case analysis provided rich data pertaining to inequity of healthcare services in the public versus private sector that was not directly related to the study objectives, this data could not be discarded as rheumatologists’ perceptions of the co-incidence of TB associated with TNF-α inhibitors could not be truly determined if a rheumatologist did not have access to these agents.

**Triangulation**

The trustworthiness of the data was verified using triangulation and deviant case analysis. Theory triangulation between the investigator and two external experts (medical doctor and pharmacologist) was described in the section above; where constructive debate and discussion resulted in the finalisation of the themes, sub-themes and categories on examination of the coding of the dataset. Methodological triangulation with comparison of documented ethnographic observations on journal notes and audio-recorded interviews for
consistency of concepts and ideas. A prominent example was data pertaining to the incorrect ICD coding of arthritic diseases to ensure funding by Medical Schemes.

A study participant’s interview transcript provided the following data: “…um, my practice I think consists mostly of the spondylitic arthritic patients, sero-negative arthritis, psoriatic arthritis...Um, rheumatoid arthritis patients.....I do, it’s normally about 10% of patients who are refractory that need to go on biologics....Um, if you talk about rheumatoid arthritis per se. The moment you go on to the spondylo-arthritic diseases, especially the ankylosing spondylitis, obviously then it’s higher, the incidence of that.......with the axial spondylitis”.

The study participant was very ambiguous regarding the types of arthritic patients that are administered TNF-α inhibitors in his/her practice. However, once the audio-recorded interview was completed, the study participant mentioned that the data that is reported to the SARAA registry (that authorises TNF-α inhibitors for Medical Scheme funding) is skew as the patient’s condition is falsely reported as sero-negative RA, when the condition is actually psoriatic arthritis, as most Medical Schemes only fund PMB conditions. Sero-negative RA is a PMB condition, whilst psoriatic arthritis is not.

**Deviant case analysis**

Deviant or negative case analysis is based on the approach that analysis of outliers in the dataset would enable a richer, more-in depth understanding of the data and strengthens the trustworthiness of the research.

Examples include:

• “...if you have a look there are no placebo controlled trials...it is always an add on, and that is a bit of the hypocrisy with the TNF trials I always find, they’re now
refractory to methotrexate and now you put them on a biologic and they use it as a comparison, methotrexate versus methotrexate and a biologic and then the claims are that it works better, than what methotrexate it is alone. But, if you first choose the biologics and add the methotrexate, you’d probably get the same results; it would be methotrexate add on would be better than the biologic. So, from the very beginning the trails were designed like this. It has a lot of ethical implications. So, I’ve learnt very quickly that it is not a replacement DMARD, it’s an add-on DMARD. So, if you discontinued your other DMARDs, your chance of having no response is worrying as it is not documented in the literature. So, I don’t change the background medication, unless I’m really convinced it doesn’t work. If a patient has moderately active disease and is on methotrexate, you find often enough if you stop it, they’re much worse off. The drug is just not keeping them in remission, or keeping them at a level of low disease activity”;

- “...my patients are well educated. So, they go off and they do it. Um, even before they come and see me. So if at any point they are not happy; they’re not happy with a symptom – anything suggesting TB; they go straight off and have a culture sent off and have a CXR done”;

- “2 of the companies provide sponsorship of the state patients that I work with, in terms of getting them drugs that they wouldn’t have had access to in other ways”; “...in the public sector you are dealing with such poor people. If I give you something that costs you R8000 aren’t you more likely to sell it, instead of giving it to yourself?”;

- “Being in the private sector, and especially being logistically where I am; I think the patient’s in this area are well educated....a lot of the patients, before they even come here have been fully “googled” to everything. So they know a lot more....but from my
experience in State, State patients don’t ask questions – they just accept what you say. Here (private practice) you are obligated to go through every side effect, everything... as the patients ask questions and they’re informed”; “I do a combination of PPD and T-spot. And CXR”;

• “I am not convinced they need pre-screening. And, I think there is an approach taken by other countries where there is a high incidence of TB. For instance, in India where they give INH prophylaxis for a minimum of 6-9 months to all”.

6.1 FLOW DIAGRAMS OF RESULTS
It was postulated that the study participants would provide responses mostly pertaining to the vigilance of TNF-α inhibitors in relation to the occurrence of TB. However, issues relating to the unique healthcare landscape of South Africa and the challenges regarding inequitable access of healthcare were also voiced. The following flow diagrams attempts to contextualise the wealth of information retrieved from the qualitative analysis.
Figure 2: Flow diagram of results

RESULTS

6.1. FLOW DIAGRAM OF RESULTS

6.2. STUDY PARTICIPANTS

6.3 INEQUITIES IN HEALTHCARE

6.4 VIGILANCE
Figure 3: Flow diagram of results, pertaining to inequities in healthcare

6.3.1 The right to human health

6.3.2 Affordability and accessibility of anti-TNFs
  6.3.2.1 Geographical placing and income inequity
  6.3.2.2 State hospital access
  6.3.2.3 Privately funded access
    • 6.3.2.3.1 Med. schemes & SARAA biologic registry
    • 6.3.2.3.2 SAARA’s autonomy & accountability
    • 6.3.2.3.3 Med. schemes perceived power relationship
  6.3.2.4 Practitioner-Pharm. sales representative interaction
    • 6.3.2.4.1 Practitioner-Pharm. sales rep interaction in public sector
    • 6.3.2.4.2 Assisting Med. scheme re-imbursement process
    • 6.3.2.4.3 Evidence from Pharm. sponsored clinical trials
    • 6.3.2.4.4 Evolving information on biomedicines

6.3.3 Availability
  6.3.3.1 Medicine availability
  6.3.3.2 Human resource inequities
  6.3.3.3 Prescreening for LTBI and active TB
    • 6.3.3.3.1 Prevalence of LTBI during prescreening
  6.3.3.4 Availability of TB tests in the public-private care mix
    • 6.3.3.4.1 IGRA superior to PPD?
  6.3.3.5 Targeted IPT

6.3.4 Inequity in health outcomes
  6.3.4.1 Concomitant immuno-suppression, comorbid diseases & co-infection contributing to TB risk.
    • 6.3.4.1.1 Background info of RA patients: concomitant immuno-suppressants
    • 6.3.4.1.2 Background info of RA patients: concomitant immuno-suppressants
    • 6.3.4.1.3 Background info of RA patients: co-infection
  6.3.4.2 Different risk minimisation strategies for different population
  6.3.4.3 Extrapolation of the biologics registry to public care

6.3.5 Acceptability
  6.3.5.1 Patient centred care
  6.3.5.2 Participatory decision-making
  6.3.5.3 Concordance between patient & physician
  6.3.5.4 Adverse drug monitoring in patient centred care
  6.3.5.5 Patient support provided by pharm. industry
  6.3.5.6 Patient preferences in decision making & responsibility
  6.3.5.7 Physician beneficence & patient autonomy
6.4 VIGILANCE

6.4.1 Prevalence of active TB co-incident with TNF-α inhibitors
   • 6.4.1.1 Types of TB reported

6.4.2 Treatment outcomes of TB in RA patients co-incident with TNF-α inhibitors

6.4.3 SARAA’s biologic registry and TB surveillance

6.4.4 Rescreening for LTBI

6.4.5 Preference of anti-TNF molecule in LTBI

6.4.6 Restarting anti-TNF therapy after active TB
6.2 STUDY PARTICIPANTS

Audio-recorded interviews were conducted with 18 physicians. The interviews (generally conducted in the physicians’ consulting room) lasted 20 to 45 minutes. Interviews took place from July 2012 to October 2012 inclusive. A total of 25 physicians practicing in the Gauteng region of South Africa were approached to participate in this study. 2 did not participate due to time constraints and there were 5 non-responders. Technical problems due to a faulty recorder prevented one interview from being fully audio-recorded. However, the journal notes the researcher made during the interview forms part of the record. As the journal notes did not include verbatim comments and was less detailed, the record wasn’t considered equal to the transcriptions. Of note, though, is that the findings of this singular record were similar to the transcribed records.

The study participants practiced either in the public sector (n=9), or the private sector (n=15). Of these, six physicians practiced in both settings. Although, participants were located in the Gauteng region, some physicians provided healthcare to patients from other areas. This included patients from rural regions, Mpumalanga, Limpopo, KwaZulu-Natal, Free State and the Western Cape. Furthermore, 11 study participants participated in clinical trials of TNF-α inhibitors, which the majority practiced in State hospitals.

Amongst the study participants were those who had limited experience with anti-TNF therapy, as they were either newly qualified or did not have the opportunity to prescribe biological DMARDs regularly. The average years of experience in rheumatology was
approximately 13 years, with a recently qualified rheumatologist practicing rheumatology for 4 months. The most experienced study participant had 25 years of experience.

Table 3: Demographic details of study participants

<table>
<thead>
<tr>
<th>SPECIALITY</th>
<th>1 physician with an interest in rheumatology</th>
<th>17 rheumatologists</th>
</tr>
</thead>
<tbody>
<tr>
<td>SECTOR OF PRACTICE</td>
<td>3: public sector only</td>
<td>5: private sector only</td>
</tr>
<tr>
<td>PARTICIPATE IN CLINICAL TRIALS</td>
<td>9: participated</td>
<td>2: no participation</td>
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6.3 INEQUITY OF HEALTHCARE SERVICES

All study participants acknowledged that there is a mixed public-private healthcare system in South Africa. The difference in healthcare services was predominantly attributed to the mixed population characteristics. Hence, before even attempting to answer the research question of the perceptions of rheumatologists on TB associated with TNF-α inhibitors in RA patients in South Africa, one needs to understand the practitioners’ perspectives on the diverse population healthcare needs in South Africa. Questions identified by rheumatologists included: What’s happening in the private practice or government clinic or organisational body or healthcare systems that is a help or an encumbrance to patients’ care? How does the healthcare system in South Africa affect access to anti-TNF therapy, and ultimately the outcomes in refractory RA patients?

Severe, refractory rheumatoid arthritis that is not controlled by conventional DMARDs require step up therapy with biological DMARDs that includes TNF-α inhibitors. Douglas K et al. (2001) estimated that approximately 6.2% of rheumatoid arthritis patients were eligible
for treatment with anti–TNFs in Birmingham, United Kingdom; according to the British Society of Rheumatology guidelines. This percentage was comparative to the estimate provided by local rheumatologists. As one physician mentioned: “According to the British Guidelines about 5% of patients would qualify for TNF-α inhibitors”; whilst others mentioned that “it’s normally about 10%” of patients who are refractory that need to go on biologics”. Most study participants queried whether this target is met in South Africa because of the mixed public-private healthcare setting, which questions the provision of universal care across the country. Physicians described public sector patients as “very bad RA patients, who need TNF drugs but cannot afford it”; “they’re on clinical trials – that is the only way that we can get them” and “due to financial constraints-don’t have access to these drugs on a regular basis”. Interestingly, a physician practicing in the private sector mentioned additional challenges from privately funded Medical schemes, “I don’t have 5% on it, but in those 5%, I will always try. But, there are still refusals; or patients that are not a high scheme enough”.

6.3.1 The right to human health
Physicians were aware of the extreme variance in healthcare in the public-private healthcare mix causing inequitable healthcare across the South African population. Experiences in public care that were imparted included: “The trial had been stopped (the drug had been stopped) and she was in pain”; “The public sector has access to IGRAs only through clinical trials, as it is expensive”; “It depends on the socio-economic background, the education background of the parents and the patients”; “There would be a difference between the State patients and private patients. You would obviously give patients biologics who understand what you’re saying and the patients that you feel will comply”; “patients
seen in public care are a completely different patient population; with a much higher risk (socially disadvantaged and often living in crowded environments); and “public care patients don’t ask questions – they just accept what you say”. Thus, factors influencing access to healthcare probably include socio-economic status, education level and affordability of healthcare commodities. Physicians, however do attempt to ensure that patients do have access to healthcare: “where they can’t afford biologics and things like that....low dose prednisone, not more than 7.5 mg for short periods of time” is considered; and “2 of the companies provide sponsorship of the state patients that I work with, in terms of getting them drugs”. Responses and comments received from physicians relating to the four elements of the right to healthcare (accessibility and affordability, availability, acceptability and quality) follow on.

6.3.2 Affordability and accessibility of TNF-inhibitors

SARAA’s guidelines recommend that severe, refractory rheumatoid arthritis that is not controlled by conventional DMARDs require step up therapy with biological DMARDs that includes TNF-α inhibitors. The proportion of RA patients that would be eligible for anti-TNF therapy in South Africa was estimated by study participants to approximate 5-10%.

To achieve universal health cover across South Africa would require providing accessible, essential services to the entire population, accommodating differential needs (such as socio-economic, rural-urban and public versus private health sectors differentials) without imposing an unaffordable burden on individuals or households (Frenz et al., 2010). Study participants estimated that approximately 5.0% of rheumatoid arthritis patients funded by private Medical Schemes were administered TNF-α inhibitors compared to 0.4% in the
public sector. This bears witness of South Africa’s typical private-public sector split and the affliction of the poor (Ataguba et al., 2009). One physician described that “Private patients are quite privileged” as generally TNF-α inhibitors are “not available in public care, and it’s them that need it the most, by far”; and another mentioned that in the public sector there are “very bad RA patients, who need TNF drugs but cannot afford it”. Thus, it was observed that rationing of healthcare in the public sector thwarts clinicians in providing newer, expensive biotechnologies to RA patients. The physicians were of the opinion that these newer agents provide therapeutic relief to the patient and satisfaction to both the patient and clinician, and should be made available to all patients.

6.3.2.1 Geographical placing and income inequity

It should be noted that there are considerable inequities of access to healthcare between provinces and also within provinces due to the regional inequalities in socio-economic status (Mooney et al., 2009; Coovadia et al., 2009). Relatively well-off provinces (Western Cape and Gauteng) have less poverty, higher healthcare expenditure (medical scheme and public health funding) and more accessible, potable water in comparison to the relatively poorer provinces (Coovadia et al., 2009). These social determinants of health directly or indirectly impact overall health of South Africans. TB is a typical example of a social disease that is linked very closely to socio-economic conditions, with high-income countries reported to have a low incidence of TB, and inversely, low income countries, a high TB incidence (United Nations, 2006). However, the prevalence of TB across South Africa is not straightforward. As one study participant commented, “Everybody seems to talk about TB in South Africa and mix everything up, because the two settings are so different”. Study participants recognized
that South Africa has a “skewed patient population” with the public sector having “a different population with different risk factors” with more TB and that private sector patient profiles are “probably more close to first world of low endemic areas or a moderate endemic area”. According to WHO statistics, South Africa ranks among the worst afflicted countries in the world for TB infection (World Health Organisation, 2009). However, the significant disparity between the impoverished and richer income groups in South Africa causes different regions and communities to present with different TB prevalence rates - within the same country.

Most of South Africa’s TB has been reported to be HIV-associated (Abdool Karim et al., 2009). Before the emergence of HIV, the Western Cape reported the highest cases of TB. However, in 2006, KwaZulu-Natal reported a TB prevalence rate of 1,066 per 100,000 co-incident with the highest antenatal HIV prevalence of 39.1% and the worst National TB programme performance indicators (Abdool Karim et al., 2009). The National TB programme measures the performance of national and provincial TB control programmes, using surveillance data, to track progress towards national programme objectives. Furthermore, in a rural KwaZulu-Natal district in 2007, 266 cases of extensively drug-resistant (XDR) tuberculosis had been diagnosed with a mortality of 84% (Abdool Karim et al., 2009). It was reported that TB is the most common notified natural cause of death in South Africa (Barron et al., 2007) contributed by the increasing number of TB cases, HIV-TB co-infection and drug-resistant TB cases. Interestingly, TB prevalence in rural areas appears to be comparable to urban settings. Although, the TB prevalence rate was reported to be lower if rural patients had easier access to district hospitals (Houlihan et al., 2010). The
WHO report of TB prevalence rates for South Africa for 2011 was 770 per 100 000 (95 % CI 400 to 1250 per 100 000) (WHO, 2012).

A number of participants were of the opinion that the risk of TB associated with TNF-α inhibitors would be higher in the public sector and more predominant in certain provinces. Despite the fact that this study only involved participants from the Gauteng region, physicians mentioned that colleagues in the Western Cape are experiencing a greater number of TB cases. In addition, one study participant reported 2 cases of active TB co-incident with TNF-α inhibitors, one patient resided in Kwazulu-Natal and the other had relocated from the Western Cape. This demonstrates commendable communication within the discipline. However, there aren’t many rheumatologists in the country and SARAA provides the necessary domain for continuous interaction and knowledge sharing between physicians.

6.3.2.2 State hospital access of TNF-α inhibitors

Study participants generally perceived that TNF-α inhibitors are too expensive to be included (termed, “coding”) on State hospital formularies, and access of these agents occurred through clinical trials. It was previously observed that clinical trials included physicians practicing in the public sector (Refer to table 3). This was consistent with study participants’ description that “financial constraints” prevents TNF-α inhibitors being “on code”, “limiting access to these drugs on a regular basis”. Thus, RA patients “in the public sector are on clinical trials” as it is the “only way” to access this medicine. Furthermore, certain academic State hospitals have very limited use of TNF-α inhibitors which is accessed with specialist motivation, in a controlled fashion; as explained by a study participant, “at
the moment biologics are not on code as yet, so everything is on a named patient basis”. Nevertheless, physicians attempted a number of avenues to overcome this hurdle, and accessing anti-TNF medication through clinical trials and sponsorship from pharmaceutical companies describes the creative problem-solving characteristics inherent to experienced physicians who have been in clinical practice for a number of years. Less experienced physicians inclined to access TNF-α inhibitors for public care patients through clinical trials. It is important to note that infliximab for RA, had not been recommended for inclusion on the public sector’s essential medicines list as available evidence does not indicate a reduction of clinically significant endpoints (Department of Health, 2012). Furthermore, the NDP (1996) recommends that the provision of donated medicines must be relevant to the health needs of the country and therefore comply with STGs and EMLs. Thus, the Department of Health (DoH) is faced with the challenge of successfully implementing the NDP with continuous monitoring and evaluation of performance to identify problems and provide strategies to effectively solve operational issues.

6.3.2.3 Privately funded access of TNF-inhibitors

Private health care has disparities within its own system. Patients with private health insurance are not entirely covered by their medical schemes. In 2005, annual expenditure on medical schemes and out-of-pocket payments was approximately R9500 per beneficiary (McIntyre et al., 2007). This was reaffirmed by a recent study (Ataguba et al., 2012) which showed that medical scheme membership doesn’t provide sufficient financial protection to members, querying the value for money for membership. Payment of healthcare benefits from savings accounts is essentially paid from the patient’s medical scheme premium.
contributions, implying that there is no benefit from risk pooling. Disconcertingly, in 2010, expenditure for medicines, medical specialists and general practitioner visits accounted for 34.2%, 19.3% and 16% of patient’s savings account. (Council for Medical Schemes, 2012). McIntyre et al. (2007) so aptly described that South Africa has a situation where ‘you get what you pay for’. This is congruent with a study participant’s statement, “Medical Funders decline the funding of TNF-α inhibitors if the patient is not on a high option”. Thus, the choice of a medical scheme package will determine the extent to which a member is insured (Söderlund et al., 1998). So, even in the privately funded sector, healthcare accessibility is largely determined by cost and affordability. However, some economists argue that health care is not a common commodity and is categorised as a merit good, benefited according to the need for health care (Ataguba et al., 2009). Hence, defining health care according to need and anticipating universal healthcare and accessibility of TNF-α inhibitors for all South Africans will require social solidarity. This will assist income cross-subsidisation of the rich by the poor, as well as risk cross-subsidisation (of the sick by the healthy) (Ataguba et al., 2010).

The Medical Schemes Act of 1998 (South Africa, 1998) regulates that each medical scheme provide full cover, without any co-payment, for a prescribed minimum benefit (PMB) package for a wide range of conditions (Council for Medical Schemes, 2003). Although, rheumatoid arthritis is listed as a PMB condition, funding for expensive anti-TNF-α inhibitors are not included in the CMS algorithm for RA management. However, funding may be provided for members on higher benefit options, with higher medical scheme premiums, as the managed healthcare approach defines the private medical scheme sector. This process was introduced in the late 1990’s in South Africa together with legislation (Regulation 8
Medical Schemes Act 131 of 1998) in order to contain spiralling costs incurred by the private medical schemes, resulting in the financial collapse of a number of schemes. Regulation 8(4) allows for managed care interventions and the purpose of this provision, was to ensure schemes provide cost effective, evidence-based healthcare to members (Council for Medical Schemes, newsletter 2011). Managed healthcare comprises of a number of different measures such as pre-authorisation, treatment protocols, designated service providers, formularies, etc. Thus, medical schemes are allowed to use formularies to treat PMB conditions. Nonetheless, when a medicine on the formulary proves ineffective or causes harmful effects, the medical scheme must fund an alternative intervention on receipt of adequate motivation from the treating physician, in accordance with the Regulations of the Medical Schemes Act No. 131 of 1998 (Department of Health, 1998). Nonetheless, if a formulary drug is clinically appropriate and effective and the patient chooses an alternative medicine, the scheme may impose a co-payment. The managed healthcare concept specifically rations expensive medicines and thus, presumably provides cost containment to some degree. Physicians complained that the Medical Scheme process of authorising TNF-α inhibitors is cumbersome and time-consuming and appears to have constrained use in the private sector.

Physicians commented that: “Funder approval process is disorganised and laborious”; “Patients were treated” for LTBI, “but none of these went onto biologics....reason being....entirely funding issues”; and “generally by the time you diagnosed the patient as having latent TB; and by the time you actually get SAARA authorisation and medical aid authorisation; it’s more than likely 3 months after being diagnosed with latent TB”. Physicians acknowledged receiving help from pharmaceutical industry with the
administration process. This provides critical insight into the role of pharmaceutical manufacturers in easing access to biological DMARDs and the practitioner-pharmaceutical sales representative interaction in both the public sector and private sector is analysed in section 6.3.2.4.

6.3.2.3.1 Medical schemes and the SARAA biologics registry

To ensure appropriate dissemination of funds, the medical schemes collaborated with the SARAA biologic registry approval process for the re-imbursement of TNF-α inhibitors. There are three aims for SARAA’s biologic registry. These include:

- Prospective data collection about biologic use in South Africa;
- Focusing on TB, as South Africa is an endemic country and patients administered these biological DMARDs are at a higher risk of developing TB;
- Facilitating the funding of biologic therapies by assessing the eligibility for use and continued safety of use by a biologics registry panel, comprising of rheumatologists (SARAA, 2012).

SARAA had initially appointed the approval committee to oversee applications for biologic DMARDs to assist funding by medical schemes in 2007-2008 with the publication of guidelines for biologic therapy use (including entry and exit criteria for these interventions) in The Specialist Forum in May 2007. (The Specialist Forum is the official journal for the South African Private Practitioners Forum). However, to date no data has been forthcoming from the registry.

The SARAA biologics registry has been perceived by many as merely a processing system for approval for biologic use. One physician described the process as: “I find it cumbersome. I
find the whole tone of it ineffective. I find that the fellows are not allowed to write ....it has a childish policeman flavour to it, which should not be the way it should be and it actually makes me resist completing the forms. When in fact the idea of gathering data is not so that I can get permission to use the drug, gathering data is so that everyone can, you know and it is inefficient. Those papers and to get the papers off the internet has been one of my struggles, so it doesn’t work at all”. In addition, physicians reported that the SARAA approval process could take up to 3 months.

Other study participants’ responses included: “The SARAA approval and the registry is the same thing”. There were 5 respondents that mentioned that the SARAA registry primarily benefits the Funders as SARAA approval is conditional for Medical scheme funding. It appears that the biologics registry fundamentally serves the private sector of the healthcare system. Though, it may be argued that privately funded patients are most likely the end-users of anti-TNF therapy.

There are additional challenges faced to ensure accessibility to Medical scheme funds for the treatment of refractory RA with TNF-α inhibitors. Regulation 131 of the Medical schemes Act (1998) mandates that prescribed minimum benefits (PMBs) should be provided to beneficiaries. These benefits provide medical insurance against unforeseen catastrophic events and allow risk cross subsidisation, protecting the risk pool of the medical schemes. Amongst the arthritic conditions, only RA and Systemic Lupus Erythema are listed as PMB conditions, causing vague and non-specific diagnoses to be documented on SARAA application forms for biologic DMARDs. Thus, data on the SARAA registry may be skewed in terms of the diagnoses, the prevalence and the incidence of the different types of arthritic
disease; because of PMBs. Although, physicians are prescribing TNF-α inhibitors for the registered MCC indications that include rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and polyarticular juvenile idiopathic arthritis. This implies either that physicians are strongly motivated to provide the best healthcare to their patients and will attempt all means to access appropriate therapy; or that there may be underlying financial incentives that may influence doctors’ behaviour and possibly distort clinical judgement. Interestingly, Lescoe-Long et al., (1996) suggested in a USA-based study, that resource constraints improve physicians’ clinical decision-making and causes more vigilant problem-solving. However, this was only identified in areas of clinical practice where the physician could clearly identify that reductions in resource consumption clearly benefit clinical strategies. Therefore, understanding the value system of physicians as well as how they respond to economic incentives or disincentives will assist access to specific healthcare services (Chubin et al., 1990).

6.3.2.3.2 SARAA biologics registry’s autonomy and accountability

SARAA, like most professional associations, is an organisation that seeks to further rheumatology, maintain the standards and interests of rheumatologists and to safeguard the public’s interest regarding the practice of rheumatology in the South African marketplace (Harvey et al., 1995). Collectively, the participating physicians acknowledge the registry panel as gatekeepers to safe and appropriate use of biological DMARDs, especially with respect to the management of TB. As one study participant mentioned: “The registry is useful; I think it is an area that requires guarding”.

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The SARAA biologics registry Committee consists of rheumatologists that review applications to determine appropriateness in prescribing TNF-α inhibitors and other biological DMARDs for arthritic patients. It is a peer review process that preserves the professional autonomy of rheumatologists as a specialty, but simultaneously is accountable to society (with regards to TB risk, appropriate funding of Medical schemes’ funds, etc.). The expert panel aim to provide Medical schemes reliable and high quality information and the latter expects that if this trust is misplaced that the rheumatology profession, as a whole will take swift and decisive corrective action.

However, physicians mentioned that: “the actual data is incomplete and not very accurate for proper analysis”; “A lot of the registry data gets filled in because we have to fill it in. There is no real audit at a level of point of care”; “the data is a little bit more reliable if you have got certain focus points, like disease activity measures and information such as TB. The data is fairly accurate and reliable with regards to latent TB, where you have got specific questions with regards to CXR, PPD or Quantiferon®. These values can be corroborated with laboratory and so on”.

Therefore, the participants were of the opinion that the pre-screening data is relevant, but the reliability of the data that is entered is questionable. It was stated that internationally, registries provide data relating to the local contextual setting, “such as, how many patients have we got on therapy, how many of those patients developed TB, etc.; we do not have access to registry information, because the information isn’t being processed”.

However it was acknowledged that the registry is progressively improving. As one study participant mentioned, “It was also something that needed to be started from scratch and expected teething problems”. A physician who was part of the SAARA registry panel reviewing the applications for biologics mentioned that omissions and mistakes in the applications were being noted. So, “incorrect information went on to the registry. Though, as it is being developed; hopefully in time some of those problems will be sorted out”. The registry “was never set up to monitor TB. That is one of the shortcomings”, and “actual TB data is incomplete; as clinicians don’t always report”, but as one physician mentioned pertaining to TB surveillance, “I think the way they have been changing the system; hopefully it will be more beneficial”. Although, the old system did have follow up of patients where screening and x-rays are required, to monitor TB, it had been identified that, “Patients that stop anti-TNFs are lost to follow up” and “there is no lost to follow up on the true registry”. It was states that, “That’s where we fail as patients who fall off the registry are the ones who tend to stop their TNF for a complication”.

Therefore, the registry cannot currently provide robust data relating to TB associated with TNF-α inhibitors in RA patients, but “it will be if the data is more consistently collected”. So, measures have been taken as, “Now, there is a data manager who will trouble the clinicians until the missing data is provided”, “who is tasked to follow that up and says why are these patients no longer being renewed”. So, “the registry will provide very good information as well, in terms of trends and usage “going forward. In addition, SAARA is currently undertaking a project to look at “adverse events arising from the use of anti-TNFs”.

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Thus, the review process features peer control and autonomy with internalized standards of conduct, self-regulation and self-evaluation and is accountable to produce a validated product. The result is the democratic control of science (Chubin et al., 1990). As one study participant mentioned, “The most useful thing of the registry is having the Committee, because it backs up your application in terms of getting access of drugs to your patient” and “patients and funders have confidence in the peer review process of the biologics applications by the biological registry panel”. Therefore, SARAA, as a group, presumably act in the patient’s interest, and the behaviour of the individual rheumatologists is regulated by SARAA. However, at times rheumatologists may find themselves pressurised to adhere to best-practice guidelines due to the limits placed on them (Martimianakis et al., 2009). There may be specific situations where physicians may consider individual professional autonomy of more import than the domain autonomy of SARAA.

6.3.2.3.3 Medical scheme’s perceived power relationship

In the South African health system, it has been acknowledged that medical schemes are powerful stakeholders (Mooney et al, 2008). Study participants’ perception of the biologics registry is that it is the same as the approval process that authorises Medical scheme funding. This is reflected in study participants’ responses to questions related to starting or restarting RA patients on anti-TNF medicines or the choice of TNF-α inhibitors prescribed. “It has entirely gone down to funding issues” and “Well, it’s pretty much which anti-TNF molecule that the medical aids will pay for; I have TB on all three TNF-α inhibitors”, were some of the responses. Thus, the restrictive environment of Medical scheme controlled management of a patient’s disease can act as a deterrent to appropriate accessibility of TNF-α inhibitors. However, as mentioned previously Medical schemes are mandated by
regulation 8(4) to ensure that cost-effective, evidence-based healthcare is provided to members. Although, medical scheme clinical policies guiding this principle would require transparency and fairness to ensure democratic principles.

6.3.2.4 Practitioner-pharmaceutical sales representative interaction

There is much controversy over the regular contact of physicians with pharmaceutical sales representatives, who spend large sums of money on promotion and commercial marketing in the form of meals, travel subsidies to sponsored teachings and symposia, etc. (Wazana, 2000). The attitude of different study participants towards this interaction and the effect it has on accessibility of TNF-α inhibitors, is further described.

6.3.2.4.1 Practitioner-pharmaceutical sales representative interaction in the public sector

It follows that public sector physicians’ interaction with pharmaceutical industry would be focused on affordability and accessibility of TNF-α inhibitors for the less fortunate patients. Pharmaceutical sales representatives’ visits added value as they “keep us abreast of what is going in the industry; particularly pricing wise”, said one participant.

In addition, another participant mentioned that: “two of the companies provide sponsorship of the state patients that I work with, in terms of getting them drugs that they wouldn’t have had access to in other ways”. As mentioned previously, the latter describes the problem solving approaches of experienced physicians that tend to be more creative and inclusive of contextual information, rather than confined to disease symptoms (Grosswald, 2007).
6.3.2.4.2 Assisting Medical scheme re-imbursement processes

Of interest, is that four study participants that practice in the private sector mentioned that pharmaceutical representatives’ visits were beneficial as they provide administration support with the re-imbursement process, by assisting with the application process for TNF-α inhibitors and obtaining Medical scheme approval.

Furthermore, one study participant mentioned that “Funder approval process is disorganised and laborious”.

So, pharmaceutical companies have identified a need: assistance with medical insurance reimbursement paperwork which is time-consuming. The rules, regulations and processes by which physicians receive payment from third party Medical schemes, for their services and products they render to the patient are indeed complicated. Comments made by study participants relate to this: “When you do need to authorise the drug”, sales representatives help “with patient information and patient follow up; they have their use”.

Interestingly, some physicians are overtly conscious of maintaining their professional integrity. One study participant mentioned: “I do the applications myself; I don’t enlist the help of the pharmaceutical industry “to lodge applications for anti-TNF medicines with the SARAA biologics registry.

It has been universally recognized that the increased contact between physicians and pharmaceuticals sales representatives results in increased prescribing of the medicine, often unnecessarily and inappropriately (Lexchinin, 1989; Wallet al, 2007).
6.3.2.4.3 Evolving information on biomedicines

However, practicing biomedicine or medicine in general, often challenges physicians’ clinical knowledge. The majority of study participants valued pharmaceutical sale representative visits as they provided updated product information on TNF-α inhibitors, safety data, breaking news, literature articles and new clinical trial data. As one study participant commented, “It’s a steep learning curve for everybody; so anything new is valuable”.

Another study participant emphasised that: “It’s not always product marketing and they tend generally, especially in our area, do support a lot of rheumatology education programmes”.

Six study participants were sceptical about commercial marketing and acknowledged that commercial marketing is focussed on sales with selective provision of clinical literature; and that regular journal clubs (with fellow physicians to assess the literature) was important. Conversely, a survey done in Spain (Fernández et al., 2000) ranked peer review, key opinion leaders’ opinions, conferences, scientific literature, professional associations, academic institutions, internal audits, and professional associations as the most important factors influencing their professional practice. The least important factors were economic incentives and product information provided by pharmaceutical sales representatives. The authors did acknowledge a limitation in the study that the results were based on doctors’ opinions, rather than objective measurement of behaviours and practices. However, isolation from commercial marketing is most likely not the answer, and there should be confidence that physicians maintain a ‘healthy’ dose of scepticism when reviewing journal
articles and clinical studies presented by pharmaceutical representatives to affect positive patient outcomes.

This was reinforced by study participants’ acknowledgement that although pharmaceutical sales representatives provide value added services in the form of information updates or literature articles: “they do encourage you to prescribe their product”.

Furthermore, a physician mentioned: “I don’t pay particular attention to their detailing; we have regular journal clubs; we review the literature”, whilst another cautioned, “obviously people always give you what they want to take out of studies. So, I think it’s important to have your own journal club and your own academic input from that…”

6.3.3 Availability
There are other dimensions of barriers to accessing health care in middle to low-income countries besides affordability. The literature mentions availability, geographical access and acceptability (Penchansky, 1977). A discussion about the availability of medicine and physicians follows.

6.3.3.1 Medicine availability
Whether a medicine is available to the patient or not will no doubt have an effect on the patient’s healthcare. In response to the suggestion of ensuring that TNF-α inhibitors are made available in the public sector, respondents raised a number of concerns.
As one study participant mentioned: “You can’t skip one month, because you encourage resistance or antibodies to form; in the public sector we run out of methotrexate which is such a cheap drug”.

The continuous drug stock-outs at public care facilities is a reality and is a major concern (Thom et al., 2010; Fokazi et al., 2012). Gouge et al. (2009) reported that poor households attempting to access chronic care in a rural area of South Africa, complained about medicines being continually out of stock. This resulted in patients shopping around, self-treating or accessing alternative healthcare (such as traditional healers) rather than waste money on transport to the clinic. Or, patients purchase medicines without a prescription from their local pharmacy and those that cannot afford to visit the hospital or pharmacy are simply left untreated (Gouge et al., 2009).

Another concern that was voiced was that if anti-TNF subcutaneous pens are made available to the public sector the current cost would provide additional challenges: “In the public sector you are dealing with such poor people. If I have R8000 given to me and I am living in a shack; am I going to sell it or actually inject it into myself? So, infusional therapy would be more appropriate.” The previous study participant provided a solution of providing anti-TNF therapy in the form of in-patient infusions rather than out-patient subcutaneous self-administered pens. However, specialists are required to provide this service and one questions the availability of specialists in public care, which is discussed below.
6.3.3.2 Human resource inequities

To further achieve health equity for every South African, every person should have the opportunity to access physicians. However, one study participant described the strain felt by physicians in the public sector by commenting, “We are few enough rheumatologists”. Resource inequities in South Africa are acute and staffing crises have persisted, despite the investment of 60% of the health budget on human resources (Coovadia et al., 2009). Maldistribution exists, with the majority of doctors working in the private sector (Padrath et al., 2000; McIntyre et al., 2009). In 2005, one specialist treated less than 500 patients in the private sector, compared to 11 000 in the public sector (Mcintyre et al., 2007). The possible rationale for this includes the provision of more hospital beds in the private sector (McIntyre et al., 1995), the lobbying for specialists within medical schools (Coovadia et al., 2009) and the high levels of international migration of healthcare workers (Padarath et al., 2000). More specifically, it was estimated that in 2000 there were approximately 7000 South African doctors and over 4800 South African nurses that were abroad (Clemens et al., 2006). The differential in resources in the private-public mix is consistent with findings in this study (Table 4).

In addition, despite the substantial allocation of healthcare funds to human resource development, the country’s performance is currently poor; confirmed by poor health outcome indicators of high infant mortality rates, high HIV prevalence rates and low health service indicators such as vaccination coverage and TB cure rates. Millennium development goals agreed on by United Nations member states, including South Africa includes reducing child mortality rates and combating HIV/ AIDS by 2015. However, although South Africa is categorised as a middle-income country, health outcomes are worse than lower income
countries, with child mortality having increased, rather than declined (Coovadia et al., 2009).

6.3.3.3 Pre-screening for LTBI and active TB

All patients should be screened for both active and latent disease prior to initiating treatment (Furst et al., 2011). It has been shown that pre-screening for TB prior to treatment with adalimumab resulted in an 85% reduction in the rate of LTBI (Perez et al., 2005). Therefore, local and international guidelines recommend that RA patients that are candidates for TNF-α inhibitors should be pre-screened for LTBI using either the PPD or IGRAs.

However, it has been reported that immunosuppressant may cause currently available TB diagnostic tests to provide false readings, resulting in misdiagnosis (Madariaga et al., 2007). In addition, with the high incidence of TB in South Africa, the relevance of pre-screening is questioned. An alternative intervention that could be considered is targeted IPT co-administered with TNF-α inhibitors, irrespective of TB status. The direct cost comparison between pre-screening and targeted IPT would not fully inform this clinical decision, as there are additional indirect costs that need to be factored into the equation (healthcare professional’s time, lost wages, the cost of misdiagnosing TB, inconvenience, side effects experienced due to IPT, income forgone because of lost wages (morbidity) and premature death (mortality) (Sanchez, 2008). As IPT would be administered for at least 6 months, another factor that would consideration is patient adherence of taking this chronic course of medication.
The majority of study participants highlighted the importance of pre-screening, as per SARAA’s guidelines. However, a study participant advocated that as the TB risk in the public setting is so high, that all patients should be given INH prophylaxis for 6-9 months irrespective if the PPD test result is negative or positive. Thus, PPD testing for LTBI would not be necessary and would be used for baseline information purposes only. Active TB would mostly be ruled out by CXR.(However, it should be mentioned that there are challenges of low specificity in HIV–positive patients, particularly those with paucibacillary disease or in patients with extra-pulmonary TB; high expense and inter-observer variability may preclude the use of CXRs as a stand-alone diagnostic tool (Reid et al., 2009)). This approach is taken by other developing countries like India, where there is a high incidence of TB.

Currently, there are no formal guidelines regarding TB screening or TB prophylaxis with TNF-α inhibitors in India, but as data suggests that tuberculin testing has a limited role in India due to BCG vaccination at birth; the Indian Rheumatology Association initiated a dialogue that INH prophylaxis for 9 months be used in RA patients commencing treatment (Handa et al., 2006). Similarly, the Portuguese recommend that chemoprophylaxis be administered to all patients initiated on TNF-α inhibitors (Gomez-Reino et al., 2006). Thus, how valuable is pre-screening in the public healthcare setting, where TB prevalence mirrors high endemic TB countries. This was reinforced by a study participant suggesting that patients in the public sector setting will be co-administered INH prophylaxis whilst on anti-TNF therapy, irrespective of SARAA’s recommendations or the lack of local robust data supporting this intervention.
In contrast, the privately funded sector would probably benefit more from pre-screening. And, this was echoed by one study participant’s perception that the incidence of TB did decrease, since SARAA instituted pre-screening. However, no data has been provided by the registry to date. (Refer to section 6.2.3.1).

6.3.3.3.1 Prevalence of LTBI during pre-screening

Study participants provided estimates of the percentage of LTBI detected in RA patients in their respective practices, and more LTBI was reported in the public sector (Table 4). This re-confirms that the socio-economic status of a patient in South Africa has a major contribution to their TB status. And, one can describe that South Africa has an unequal distribution of TB within its borders.

Table 4: Responses regarding estimated percentage of RA patients diagnosed with LTBI during pre-screening

<table>
<thead>
<tr>
<th>SECTOR OF PRACTICE</th>
<th>NUMBER OF PHYSICIANS</th>
<th>AVERAGE PERCEIVED % OF LTBI DIAGNOSED RA PATIENTS (MIN to MAX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private sector only</td>
<td>5</td>
<td>3.40%(0.01% to 10%)</td>
</tr>
<tr>
<td>Public sector only</td>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>Combined private and public</td>
<td>10</td>
<td>5.54%(0.13% to 40%)</td>
</tr>
<tr>
<td>sectors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6.3.3.4 Availability of TB tests in the public-private care mix

Most study participants recognised the limitations associated with the PPD test causing false readings caused by previous BCG vaccination, immunocompromised patients, anamnestic responses boosted with repeated PPD tests and variability in reading and interpreting the test (Madariaga et al., 2007). The reliability of the PPD test was further dependent on patient compliance: patients have to return for a second visit for the interpretation of the test. The 100 year old PPD test is the gold standard for detecting LTBI and is required by the SARAA biologics registry (SARAA, 2010). It is inexpensive and does not require additional infrastructure such as laboratory testing. Indeed, PPD tests are used in the public sector and access to more expensive and newer laboratory tests, the IGRAs are only through clinical trials. IGRAs are newer modalities that are more specific than PPD tests and is unaffected by BCG vaccination or successive PPD tests. The IGRAs are mostly available to private sector patients. Currently there are two IGRAs on the South African market, the T-SPOT.TB® and QuantiFERON-TB-Gold® tests. However, there doesn’t appear to be consensus amongst the study participants regarding the sensitivity and specificity of the IGRAs. One study participant was doubtful about the IGRAs, when they are repeated frequently; another mentioned, “that if you repeat a Quantiferon after a PPD, you can get a false positive with the Quantiferon”; whilst another stated, “I prefer the Quantiferon®, because it does not expose the patient to a positive test later on, just because you did a PPD”.

6.3.3.4.1 IGRAs superior to PPD?

Although five study participants preferred the IGRAs, as they perceived them to be more objective laboratory tests, a few were unconvinced of the superiority of these tests over the
PPD tests. The literature is not very clear and it appears that current evidence indicates that neither test is superior. Two study participants preferred the T-SPOT.TB® test on the recommendation of expert opinion in the field of pulmonology and pathology.

Further diverse views were voiced: One study participant commented that there is lack of evidence supporting the combination of PPD and IGRAs, whilst another private practitioner preferred a combination of PPD, T-spot and CXR on each patient, as South Africa is a TB endemic country.

Further research is required in this area to determine the effectiveness of diagnostic TB testing in the South African context. More crucially, the issue of TB reactivation and prophylaxis in South Africa is very pertinent. As one study participant mentioned, “For what it’s worth, it is worthwhile doing a PPD or Quantiferon test, but we should accept that any patient that is going to go onto an anti-TNF drug...may develop TB at some point”.

6.3.3.5 Targeted INH prophylaxis therapy

As mentioned previously, one of the aims of the registry is TB surveillance (through assessment of TB pre-screening test results and the prospective collection of patient information on biological DMARDs relating to TB) (SARAA, 2010). SARAA mandates that pre-screening TB test results (CXR and PPD results) be submitted to the registry on application for a prescription of a biological. If LTBI (infection with no signs and symptoms of active TB disease) is detected, prophylactic medication of either INH for 6 - 9 months or INH with rifampicin for 3 months is recommended, prior to starting anti-TNF therapy. Data suggests that the risk of reactivation can be decreased by treating LTBI before initiating TNF-α
inhibitors (Winthrop et al., 2005). In addition, a recent randomised trial in South Africa, currently only available as a conference abstract, (n>24000) strongly supported targeted INH therapy for patients at risk. Gold miners, co-morbid HIV administered INH preventative therapy (IPT) for 9 months had 63% fewer cases of TB than miners who had no IPT. Of import is that this benefit was not seen in miners who had active TB. Thus, screening is important to exclude active TB prior to IPT (Create: Thibela study, 2012).

In addition, the duration of IPT is questioned. UK (British Thoracic Society, 2005) Guidelines recommends 6 months; though most countries such as Spain (Gomez-Reino et al., 2003), Ireland (Kavanagh et al., 2008) and Switzerland (Beglinger et al., 2007) recommend 9 months of IPT. This raises questions pertinent to the South African setting of whether 6 months of IPT monotherapy adequate; or should this be increased to 9 months?

Physicians’ responses included: “If they are positive and they have never been exposed, I put them on INH for 6-9 months. There is no prescribed protocol. If they had TB in the past, then I would add rifampicin for 3 months. Just, it’s purely not on data or on any information. It’s just I think, be prepared”; “We either use INH and pyridoxine for 9 months, or INH plus rifampicin for 3 months”; “we use the INH prophylaxis only for 6-8 months”; “9 months” and “I think there is an approach taken by other countries where there is a high incidence of TB. For instance, in India where they give INH prophylaxis for a minimum of 6-9 months to all”.

6.3.4 Inequity in health outcomes

It can be argued that other principles of health equity include equal health outcomes (Oliver et al., 2004). The impact of healthcare interventions on disease progression, morbidity and
mortality would need to be measured. This would include determining the risk-benefit ratio of providing anti-TNF therapy to the RA populace in South Africa in both the private as well as the public sectors.

6.3.4.1 Concomitant immunosuppression, comorbid diseases and co-infection contributing to TB risk.

Underlying factors that affect immunity includes concomitant immunosuppressants, comorbid diseases such as asthma, chronic obstructive pulmonary disease (Shu et al., 2010) and diabetes mellitus (Jeon et al., 2008; Restrepo et al., 2011) as well as co-infection (e.g. with HIV) which promotes reactivation of TB or increased susceptibility to infection.

6.3.4.1.1 Background information of RA patients: concomitant immunosuppression

The background concomitant immunosuppressant therapy reported to be used by RA patients using TNF-α inhibitors varied, but methotrexate was the predominant DMARD. As mentioned by one study participant and suggested by a number of clinical trials (Weinblatt et al., 2003; Breedveld et al., 2006; Lipsky et al., 2000; Weinblatt et al., 1999; Bathon et al., 2001; St. Clair et al., 2004) TNF-α inhibitor therapy is more effective combined with methotrexate in RA patients that are non-responders on methotrexate. If a patient was intolerant to methotrexate, alternatives included leflunomide or azathioprine. Of note was that leflunomide and azathioprine were restricted to patients in the private sector. Patients in the public sector were generally on concomitant methotrexate or methotrexate plus sulfasalazine.
Generally, study participants reported that patients were taking one additional DMARD. It was mentioned that “Methotrexate is the most common one, but if they can’t tolerate for whatever reason then you use another” immunosuppressant and another study participant commented “For anti-TNF therapy, it doesn’t really work if you don’t have concomitant methotrexate; so if you want to increase the response of anti-TNFs, most patients have to be on methotrexate”. This practice was supported by RCTs that suggest that TNF-α inhibitor with methotrexate is more effective than when compared with methotrexate, alone (Breedveld et al., 2006; Emery et al., 2008; Jobanputra et al., 2012; Kameda et al., 2010; Keystone et al., 2004; Klareskog et al., 2004; Lie et al., 2011; Moreland et al., 2012; Visvanathan et al., 2007; Weinblatt et al., 1999; Weinblatt et al., 2003; Weinblatt et al., 2006). In addition, infliximab is approved for RA in combination with methotrexate (MSD, 2001), in order to decrease antibodies to infliximab (thereby making infliximab less effective).

However, one study participant had doubts that TNF-α inhibitors are more beneficial than other conventional non biological DMARDs. It was mentioned that TNF-α inhibitors are not replacement DMARDs, but add-on DMARDs in refractory RA and that the clinical trials were designed, accordingly. Thus, the concern was raised that the chance of having no response, if the other DMARDs are discontinued is worrying as it is not documented in the literature. Therefore, the physician mentioned that the background medication is not changed, when an anti-TNF is added on as add-on therapy.

The physician stated that: “there are no placebo controlled trials as such, really; it is always an add on, and that is a bit of the hypocrisy with the TNF trials I always find, they’re now
refractory to methotrexate and now you put them on a biologic and they use it as a comparison, methotrexate versus methotrexate and a biologic and then the claims are that it works better, than what methotrexate it is alone. But, if you first choose the biologics and add the methotrexate, you’d probably get the same results; it would be methotrexate add on would be better than the biologic”. Of interest, is the various ways of interpreting the clinical and scientific evidence in the field of evidence based medicine. Nonetheless, questions that arise in clinical practice do provide motivation for further research to either reconfirm current evidence or to provide new answers.

Study participants did not report if any patients that developed active TB were taking concomitant immunosuppressants. Interestingly, one study participant mentioned that a RA patient developed TB co-incident with methotrexate monotherapy; whilst another on azathioprine monotherapy for dermacytosis. This is congruent with literature citations of TB cases co-incident with methotrexate (Binymin et al., 2001) and azathioprine (Meggitt et al., 2011). Immunosuppression generally increases patients’ risk of infections.

6.3.4.1.1.1 Corticosteroids

It is universally accepted that corticosteroids use predispose to the development of TB (Jick et al., 2006). However, a systematic review of the literature showed a paucity of data about the risk of infection in RA patients on low dose corticosteroids and that the risk seems low (Ruyssen-Witrand et al., 2010). In developing countries, corticosteroids are widely used because they are not expensive and are effective in reducing inflammation associated with RA (Mody et al., 2008). A retrospective study (n=182) observed that oral prednisone was used in 60.4% of South African Black patients at some time during their follow-up (Tikly et
al., 2003). This was confirmed by two study participants who mentioned that in the public sector, where biological DMARDs are unaffordable, bad RA is controlled on low dose corticosteroids.

Most study participants preferred not to use chronic corticosteroids, and where necessitated low dose (5-10 mg) pulse therapy was prescribed for relapses of RA disease. However, some study participants considered that if a patient needs adjunctive corticosteroids, that the TNF-α inhibitors have failed therapeutically. Furthermore, it was mentioned that only when RA patients are diagnosed with vasculitis are high corticosteroid doses considered. Two study participants indicated a preference of intra-articular corticosteroid administration rather than oral formulations. This results in more immediate pain relief, improved mobility with reduced inflammation (Stephens et al., 2008); whilst evidence suggests that (Weitoft et al., 2005) intra-articular corticosteroid treatment for knee synovitis may have a cartilage protective effect (improving RA) and a reversible suppression of bone formation (possibly not promoting osteoporosis, which is considered to be a general side effect of corticosteroids). The risk-benefit assessment and vigilance of corticosteroid therapy associated with serious infections was noteworthy amongst the study participants.

Study participants mentioned: “Patients seldom on prednisone greater than 10mg unless they are not controlled”; “Less problems with anti-TNFs, because I use less steroids”; “…some on low dose steroids”; Few on prednisone, “..not more than 7.5 mg a day”; “none of them are on high dose prednisone”; “No prednisone greater than 10 mg”; “We try and move away from the steroids as much as possible”; “I don’t think a single one of my biologic
"patients is on a corticosteroid”; “if you gain disease control on anti-TNFs, seldom use prednisone greater than 10mg” and one physician stated that there is a “failure in therapy, if a patient needs to be on a steroid”.

Besides immunosuppressants, RA is also associated with TB as suggested by surveys in Spain (Carmona et al., 2003), Korea (Seong et al., 2007) and Quebec (Brassard et al., 2009); where there was a respective 4-fold, 8-9 fold and 10-fold increased risk of TB infection in patients diagnosed with RA compared to the general population. Although, in Quebec, some of the risk was attributed to non-biologic DMARDs and corticosteroid therapies and the contribution by anti-TNF therapies could not be clearly determined. One study participant mentioned, “In this country there is about a 7% incidence of TB in rheumatoids who are not on biologic drugs, you know”. It was noted that the study participant probably reported an estimated 7% TB occurrence. Furthermore, although there is no published data for South Africa, it was suspected that the background incidence of TB in the RA population would be higher in the public sector than in the private sector. This was echoed by study participants, who mentioned that in State “…we have lots of TB; irrespective of the skin test”; that the State sector consists of a “…different population with different risk factors and we may see a lot more TB” and another expressed that, “I think the public sector is very aware of TB, as so many of their patients have TB”.
### Table 5: Summary of study participants’ background information of RA patients that are administered anti-TNF therapy

<table>
<thead>
<tr>
<th></th>
<th>PRIVATE PRACTICE</th>
<th>PUBLIC SECTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on TNF-α inhibitors</td>
<td>5%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Concomitant medicines</td>
<td>MTX, or</td>
<td>MTX, or</td>
</tr>
<tr>
<td></td>
<td>Leflunomide, or</td>
<td>MTX + Sulfasalazine</td>
</tr>
<tr>
<td></td>
<td>Azathioprine, or</td>
<td>Chloroquine, or</td>
</tr>
<tr>
<td></td>
<td>Chloroquine, or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combination of above</td>
<td></td>
</tr>
<tr>
<td>Concomitant steroids</td>
<td>Mostly low dose</td>
<td>Mostly low dose</td>
</tr>
<tr>
<td>Intra-articular route steroid</td>
<td>2 study participants</td>
<td>1 study participant</td>
</tr>
<tr>
<td>preferred</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Co-morbid diseases</td>
<td>State patients often have a number of co-morbidities; Clinical trials exclude patients with uncontrolled co-morbidities.</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Generally representative of the rest of the RA population</td>
<td>Not as a rule; Not different to general population.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Quite a common co morbidity in paediatrics</td>
<td>Not as a rule</td>
</tr>
<tr>
<td>Condition</td>
<td>Description</td>
<td>Commonality</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>COPD</td>
<td>Generally representative of what we see in the rest of the RA population</td>
<td>Not as a rule</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Commonest co-morbidity is hypertension; as high as 60-70% of the adults</td>
<td>Commonest co-morbidity is hypertension, about 60%</td>
</tr>
<tr>
<td>Other</td>
<td>Other auto-immune diseases: Psoriatic arthritis, inflammatory bowel diseases, oncological issues, recurrent infections.</td>
<td></td>
</tr>
</tbody>
</table>


6.3.4.1.2 Background information of RA patients: Co-morbidities

The most frequently observed co-morbid disease in RA patients was reported to be hypertension, as high as 60-70%. Adult diabetes, asthma and COPD were rarely seen and one study participant mentioned that asthma was common in children. Patients reported to have developed active TB associated with anti-TNF therapy had diabetes (n=2) and one patient had an additional autoimmune disease, ulcerative colitis. However, it is unknown whether these patients were on other immunosuppressants or corticosteroids.

Where patients in developing countries cannot access biological DMARDs and require long-term oral corticosteroids to control RA, pre-screening of TB is suggested (Mody et al., 2008). There is a lack of data supporting this, but in India, IPT in corticosteroid-treated systemic lupus erythematosus patients resulted in a reduced incidence of the incidence of active TB (Gaitonde et al., 2002). In addition, consideration of IPT is recommended in Latin American countries where patients use prednisone doses greater than 10 mg daily (Cardiel et al., 2006). Currently, there are no clear guidelines for pre-screening of TB in RA patients on non-biological immunosuppressants.

One can surmise that to reduce inequities in healthcare in South Africa, it is important to ensure that proposed interventions do no harm to the total population, by weighing the risks against the benefits. This practice was mentioned by study participants when considering TNF-α inhibitor therapy for RA patients.

Study participants pointed out that: “… it is important to stratify risk”; “I mostly warn about the infection risk. I make a big thing about the TB story. I’ve got graphs that I show them, to
give them an idea of what the increase in percentages would mean in terms of relative risk to develop serious infections”; and “...my initial pep talk about biologics; probably 3-4 months before I consider therapy, ...these drugs are very efficacious, but very expensive and they do come with a risk and the biggest risk is that of infection and in our country we are concerned about TB; and hence the requirement for TB screening”.

6.3.4.1.3 Background information of RA patients: Co-infection

No patient administered anti-TNF therapy was reported to have a co-infection. One study participant mentioned that “Generally speaking, we are very careful when putting HIV positive patients on methotrexate; the CD4 count must be over 400”.

6.3.4.2 Different risk minimisation strategies for different population groups

As TB rates were reported to be high in public care, study participants reinforced that different interventions are required to break the cycle of reactivation of LTBI in this setting. Suggested risk minimisation strategies included administration of IPT, irrespective of the results of the PPD test, or IPT “lifelong” for the duration of anti-TNF therapy. The expert opinion based on incidents encountered by ‘experienced’ physicians differs from the domain autonomy of SARAA’s current guidelines. Although, there is no local data to support these interventions, they follow Indian and Portuguese guidelines. However, most importantly the physicians detected signals and implemented strategies to minimise the risk of reactivation of TB associated with TNF-α inhibitors in the public sector, which are important concepts of pharmacovigilance.
As one study participant that practises in the public sector mentioned: “...it has almost become a question for us as to whether our patients here, in the first place, irrespective of the results of the skin test should be put on INH prophylaxis. And, that is how we are going to go about it. So, we’re going to ignore all of it and there are people in the field who say that is the way to go. The second possibility is to put these patients on lifelong INH prophylaxis for as long as they are on anti-TNF therapy. We don’t have data to support this, but the latter 2 patients kind of suggest to us they didn’t develop TB whilst they were on anti-TNFs, they developed it after it was stopped”.

6.3.4.3 Expansion of the function of the biologics registry to public care

Currently, SARAA’s biologics registry has been set up primarily to serve the needs of the private health sector as one of the aims of the registry is to facilitate Medical scheme funding of biologic therapies. This was recognised by some study participants, as the registry “probably gives us better information about the sector that is funded privately”; whilst another physician commented that, “I have never worked in private practice. So I am not too sure about the Biologics registry and how it functions”. The question is whether this function may be applied to the public sector, taking into consideration the geographical, economic and co-morbid disparities of TB across the country. The intent of the function of the SARAA Biologics registry is questioned, though. Currently, the registry is functional as a gatekeeper for the supply of TNF-α inhibitors by manufacturers to all patients and reimbursement from medical schemes in the private sector. It is currently dysfunctional as a true registry to gather data about usage and outcomes, specifically adverse outcomes related to TNF-α inhibitors in the RA population of South Africa.
Five study participants were confident that the Biologics registry could be applied to the public sector, specifically relating to TB surveillance. SARAA approval is required before permitting access to any biological DMARD, whether the patient is in the private or public sector and all patients will thus be thoroughly screened. In addition, SARAA requests annual progress reports allowing monitoring of TB associated with TNF-α inhibitors. One study participant mentioned that a high incidence of TB in a number of patients from underprivileged backgrounds on TNF-blockers has not been observed, as physician management and vigilance has been first-rate.

The majority responded that the registry would be inadequate for TB surveillance in the public sector. Firstly, it was mentioned that the registry was never set up to monitor TB. However, SAARA is currently undertaking a project to look at adverse events arising from the use of TNF-α inhibitors. Pre-screening data is relevant, but actual TB data is incomplete and not very accurate for analysis; as clinicians don’t always report and there are patients that are lost to follow up. The registry now has a data manager tasked to follow up with physicians to query why patients discontinue anti-TNF therapy. Secondly, the patient population is skewed in the public-private mix. As one respondent commented: “The registry is useless to address the TB in South Africa, because it’s the socio-advanced person that forms the registry, whereas patients seen in public care are a completely different patient population; with a much higher risk (socially disadvantaged and often living in crowded environments). It would have to be started completely from scratch, and by trial and error to see what is actually going on in the public sector”. Thirdly, the reliability of the registry data was questioned. It was mentioned that “…a lot of the registry data gets filled in because we have to fill it in and that there is no real audit at point of care”. Though, certain
aspects of the registry data were considered to be more reliable. However, it was acknowledged that as the registry is being developed, the teething problems will be sorted out.

Nonetheless, most study participants recognised the importance of the registry as information specific and relevant to South Africa would quantify the risk of TB (and other serious adverse drug reactions) in our patient population. As one study participant so aptly commented, “We swim in TB basically and it is important that we collect the data because it’s important for the patients”.

In addition, the need for additional systems or programmes to assist TB surveillance in the public sector was identified. These included a slightly separated area (compared to the general outpatients’ area, where all patients mingle). One study participant preferred to avoid TNF-α inhibitors completely and to opt for an alternative agent not associated with co-incident TB. “Because of the very, very high risk of tuberculosis in public sector patients, where possible they should probably be on Mabthera® (rituximab), because it’s an infusion, administered 6 monthly and “less of a burden on the hospital”. Additional risk minimisation was recommended for patients that do require an anti-TNF and that do not have latent TB: INH TB prophylaxis for the duration of anti-TNF therapy, though excessive vigilance is preferred, “I am very reluctant to have them on anti-TNF therapy, but patients can develop TB at any stage; patients may develop TB in the next 5 years, after INH prophylaxis is given for 6 months”.
6.3.5 Acceptability

Another important component of the quality of care is acceptability by the patient.

6.3.5.1 Healthcare services

One study participant acknowledged the need for dedicated clinic days and trained nurses, as in the UK, where only about 10% of their patients on IV infusions and the rest of them are on injectables. This emphasises the self-management approach of RA, as a chronic illness by the patient and their families in the UK.

6.3.5.2 Patient centred care

However, the latter two surveys were done in developed countries and one could argue that the scenarios most likely reflect the RA patients’ behaviour and attitudes in the privately funded healthcare sector in South Africa. Whithead (1985) mentioned that the more articulate members of the population and those with the most powerful representation tend to have more influence than others in a weaker position; whilst the disadvantaged and vulnerable groups tend to have the least say and the lowest participation rates in key decisions affecting their health and wellbeing.

As one study participant in private practice commented: “Before they even come here have been fully ‘googled’ to everything; you are obligated to go through every side effect”.

Another study participant from the private sector mentioned: "Patients are well informed and they comprehend remarkably well. The patient needs to make an informed decision, you don’t decide for them anymore. It is a long process you have to explain the medicine’s place
in therapy, what to expect, is it magic, is it different from other drugs, its safety profile. You have to inform them fully, providing the relevant websites to access additional information in order to make a rational decision and you have to guide them along. And, though in the beginning from the internet, they were often misled by misinterpretations and so on, it’s difficult for a layperson; they’re getting very good at it and are quite aware of it”.

Interestingly, patients appear to use the internet as an additional resource, rather than a means to challenge their physician’s position; encouraging physicians to use the internet as a tool in patient education and care (Stevenson et al., 2007)

Patient centred care, where healthcare is centred on individual patients, is a much discussed topic in healthcare (WHO, 2000; Picker institute, 2004; International Alliance of Patients’ Organisations 2007). Although, the literature does not document a universally accepted definition (International Alliance of Patients’ Organisations, 2007) patient-centred care may be defined as ‘respecting and responding to patients’ wants, needs and preferences, so that patients can make choices in their care that best fit their individual circumstances’ (Institute of Medicine, 2001). It has been shown that patient-centred care results in improved healthcare outcomes, specifically in patients with chronic diseases (Greenfield et al., 1986; Ong et al., 1995). Patients more readily follow medication regimens if they share their physicians’ belief about the cause and outcomes of their health (Christensen et al., 2010), and this often requires a long-standing relationship between patient and physician (Kon, 2010).Thus, key points of patient centred care includes patient participation, involvement; the patient - healthcare professional relationship and the context of healthcare delivery to improve the quality of healthcare delivery (Kitson et al., 2013).
In a survey in the USA, patient activation (i.e. a person’s ability to manage their health and health care) has been reported to be lower for people with low incomes, less education and people with poor self-reported health. Conversely, higher activation levels are associated with much lower levels of unmet need for medical care and greater support from health care providers for self-management of chronic conditions (Hibbard et al., 2007). Thus, a conclusion from these studies is that patients’ level of understanding about his /her health status and related medicine and non-medicinal interventions is determined by education and income level. In South Africa the inequality of economic means and levels of education are apparent between the private and public healthcare sector, that it may be considered a challenge to implement patient-centred care in State health facilities. When study participants were asked whether patients are well-informed and what is their perceived level of understanding, most recognised that socio-economic and education background of the patient were contributory factors.

Research by Stewart (1995) and Stewart et al. (2000) identified that effective communication between doctor and patient improves the doctor–patient relationship. Constructive interaction, enabling the doctor to understand the patient as a whole and empowering the patient to be more responsible and accountable about their health was identified as components of patient centred care. Thus, the quality of the doctor-patient relationship would essentially determine the therapeutic alliance between the doctor and patient to achieve realistic patient outcomes.
In South Africa, where there are 11 official languages, effective communication in the vernacular is important. Interestingly, a USA study of Spanish, Chinese and English speaking patients showed that patients with a low English proficiency demonstrated a poor understanding of their diagnoses, medications and disease management, on discharge from hospital (Karliner et al., 2012). Furthermore, Schenker et al. (2010) found that physician-patient interaction was suboptimal amongst patients with low English proficiency and language discordant physicians.

A study in Cape Town (Haque et al., 2005) identified doctor’s lack of knowledge, experience, use of guidelines and language barriers; and patients’ lack of understanding of their disease and their poor socioeconomic conditions as contributory factors that prevented step up management with initiation of insulin therapy in type 2 diabetic patients treated in public-sector primary health care facilities. Additional challenges in the healthcare system resulting in suboptimal care of these diabetic patients included insufficient time and resources, overcrowded clinics, poor patient records, lack of continuity of care and financial constraints (Daniels et al., 2000). The study concluded that education of doctors on initiation of insulin therapy and use of standardised guidelines, a patient-centred approach with improved communication between doctors and patient and the re-organisation of certain aspects of the health system, may improve mistaken perceptions and help overcome barriers (Haque et al., 2005).

6.3.5.3 Participatory decision-making

Study participants were of the opinion that the more educated patients from private practice are well informed and ask questions. Conversely, it was reported that public care
patients are a more passive population; “they don’t ask questions and just accept what you say”.

6.3.5.4 Concordance between patient and physician

The traditional physician – patient relationship is revolutionising. Research has shown that physicians, who encouraged patients’ active participation in treatment decisions about their RA disease, resulted in patients with better functional status and better arthritic control (Kaplan et al., 1993). Anti-TNF therapy has been proven to be highly efficacious in refractory RA. However, the serious and often life-threatening adverse drug reactions of anti-TNF therapy require both the physician and patient’s input to be exceptionally alert and vigilant. The patient’s compliance with respect to this requires concordance between patient and physician about the prescriber’s recommendations (NICE, 2011), where both parties are considered equals in reaching this therapeutic alliance (Bell et al., 2005). This concordant approach starts with physicians providing relevant information and knowledge regarding the patient’s disease, and the available interventions’ (both medicinal and non-medicinal) efficacy and safety profile applicable to the patient’s health. The patient actively partakes in the decision-making process and even though the individual patient’s value of the risk and benefits of the intervention may differ to that of the physician, the physician respects the patient’s decision regarding the intervention (Alaszewski, 2005). The importance of obtaining a patient’s trust and agreement was recognised by a number of study participants. A study participant considered the rate limiting step as “getting the agreement that I must have with the patient, because every patient must be aware of the fact that they may develop TB on their anti-TNF drug: you have to accept that there is a risk and you have to be prepared to undertake the risk”. The study participants acknowledge that the decision
ultimately lies with the patient with some patients declining the intervention due to their occupational hazard (teacher, medical doctor, or nurse), patients with active disease were known to opt for anti-TNF therapy; whilst patients with mildly active disease often had difficulty in making a decision, though an understanding between the physician and patient is required where the patient admits that her RA is interfering with mobility and functionality and the risk is warranted.

The process is often time-consuming, complex and is considered more of an art rather than a science. As one study participant commented, “Patients’ level of understanding depends on how much input you put into it”.

6.3.5.5 Adverse drug monitoring in patient centred care

Patient centred care requires further evolution to aspire to high quality level of patient care, where the focus is not merely the patient’s disease but includes their experienced health problems (Starfield, 2011). Astute physicians report, record and study adverse drug reactions. Therefore, not only are patients well informed of TNF-α inhibitors’ serious side effects verbatim and through print as described by a number of study participants, to ensure that the patients understand the risks associated with these biological DMARDs. In addition signal detection and strategising to incorporate additional risk minimisation steps (as discussed earlier) is practiced. A patient centric approach of handling an ADR was described by one study participant as recognising the patient’s vulnerability when they develop TB and their gratefulness when you walk with them through the process. This process includes the objective confirmation of TB through relevant tests (e.g. biopsies), providing empathy when patients realise they need to stop their anti-TNF, resulting in
flaring of their RA and being there when they get better. Interestingly, one study participant educates RA patients sufficiently well enabling them to proceed with TB diagnostic tests (CXR and TB sputum tests) “… I give them a blank CXR form and blank sputum form, and say to them if at any point their flu lasts more than a week or they are unhappy; to immediately go and have their sputum sent off and have a CXR”. This exhibits self-management of chronic diseases by the empowered patient.

Although study participants perceived that patient centred care predominates in the private sector, dedicated biological clinics occur in some public sector institutions, where a multi-disciplinary team approach and patient-centred care prevails. Adequate staffing allows sufficient consultation time for effective management and rheumatology nurses counsel the patients in the vernacular. As a study participant mentioned that the physician may have to make therapeutic decisions for patients in the public care, but patient centred care is possible considering that HIV clinics can be setup where patients comprehends the complexity of medicine compliance and routine monitoring. In addition, it was reported that patients in the public sector have been known to decline participating in a clinical trial because of the potential side-effects of TNF-α inhibitors; but they are few and far between. Bantered and Sandal (2012) examined the dynamics of doctor-patient relationships and suggested that good physician-patient concordance in India, leads to better trust in the physician resulting in better patient enablement, irrespective of the socio-cultural determinants such as socioeconomic status, level of education or speaking the same native language as the physician.
6.3.5.6 Patient support provided by pharmaceutical industry

Study participants acknowledged that pharmaceutical companies not only provided sponsorship to conferences, literature on their products, etc.; but also provided patient support in the form of patient ‘treats’, patient counselling, patient information and associated nurse education programmes. Therefore, even physicians practicing in private practice related to the importance of a patient-centred approach to care; although pharmaceutical industry services are used to accomplish this. The study participants did not express their opinions on how these value added services impacted on their professional medical behaviour.

6.3.5.7 Patient preferences in decision making and responsibility

A study advises physicians not to assume that all patients wish to participate in clinical decision making, but to assess individual patient preferences and tailor care accordingly (Levinson et al., 2005). This describes the paternalistic model (Charles et al., 2003; Charles et al., 1999) of physician-centred approach to care where patients prefer to rely on physicians to make therapeutic decisions rather than collaborating with the physician.

Patients may prefer the physician-directed style of care, as they may feel inadequate about managing their health or due to literacy barriers or different styles of communication (Rosen et al., 2001). In addition, according to a survey in Sweden, older patients preferred their physicians to make decisions regarding their health. (Rosen et al., 2001)

The study suggests that patients with poor health are more dependent on physicians to choose treatments (Levinson et al., 2005). On the other hand, patients knowledgeable
(Kaplan et al., 1989; Greenfield et al., 1985) about their disease(s) actively participate in therapeutic decision regarding their health care (Deber et al., 1996) making, resulting in improved health outcomes. The same patient are not happy when they are informed they have TB, but understand the situation as they are educated. It is apparent that physicians acknowledged that the more vulnerable, frail patient and those without family support are dependent on physicians to make decisions on their behalf regarding serious and life-threatening situations.

Study participants acknowledged that patients’ level of understanding is relatively low in the public sector and as “they are a fairly passive population they accept anything we offer them”. In addition, as one study participant commented, TB is rife in their community, TB is considered as part of the community’s circumstances. When patients are chosen for a clinical trial, a perquisite is to understand the English language. However, the practical reality is “It’s not truly informed consent, “as many patients rely on the physician to make the final decision.

Likewise, the reluctance to self-manage their RA was described in private practice. As was mentioned by a study participant, “What their level of understanding is, we sometimes get a fright when we hear people when people do actually get their biologics. I doubt that their level of understanding is as good as we want it. I sometimes think that patients don’t always link their arthritis treatment to serious infections and they sometimes do very silly things when they are on the sub cuts.” And, physicians feel the need to intervene because of patients’ poor level of understanding, their geographical placement and environmental circumstances, opting for alternate agents to ensure patient compliance. This echoes the
findings of the study by Banjeree et al., (2012) that suggested socioeconomic status and level of education were not major factors that contributed to patient-centred care, but rather physician-patient concordance enabling patient compliance and adherence.

6.3.5.8 Physician beneficence and patient autonomy

Physician beneficence is the duty of intervening on behalf of a patient in order to save or protect life, if the patient is compromised and cannot act in his own best interest at the moment (University of Washington School of Medicine, 1998). Beneficence is one of the four complementary principles of bioethics. The democratic processes of clinical decision making, where patients are expected to collaborate with their physicians to reach an agreement regarding their health and treatment, specifically describes patient autonomy. However, in developing countries, like South Africa, patients seem to be more than willing to relinquish decision-making about their health to physicians, physician beneficence is more likely to be pursued.

To conclude, resolving inequity in healthcare is not merely the ensuring universal access of medicinal interventions... To provide universal access of TNF-α inhibitors to all South Africans is not a straightforward process and has many contributory determinants. These determinants includes affordability and accessibility of these biological DMARDs, functionality of databases such as the SARAA biologics registry across the private-public healthcare mix, decreasing income disparities and minimising poverty to minimise the TB prevalence rate currently reported in poorer regions of the country, availability of good quality healthcare workers and services to all and ensuring good quality education for all to enable patients to partake in therapeutic decision making. This would probably be long-
term objectives for the country. However, immediate healthcare interventions are required to assist an ailing healthcare system, in the interim. This alternative would be to adapt medical interventions to the different socio-cultural and environmental inequities, in order to make equitable health outcomes possible for all South Africans.
6.4 PHARMACOVIGILANCE

6.4.1 Prevalence of active TB co-incident with TNF-α inhibitors

Study participants’ impressions was that there was a higher estimated incidence of active TB co-incident with TNF-α inhibitors that emerged from the public sector (Table 5). The majority of the physicians emphasized that the TB risk is greater in the public sector. However, it was reported that the awareness of TB is greater in this sector, as so many public care patients have TB. One study participant shared his/her TB safety concerns in the public sector, “One out of nine RA patients that I have treated with TNF-α inhibitors developed severe pulmonary TB, cavitary disease”.

Table 6: Responses regarding estimated cases of RA patients on TNF-α inhibitors that developed TB

<table>
<thead>
<tr>
<th>SECTOR OF PRACTICE</th>
<th>NUMBER OF PHYSICIANS</th>
<th>AVERAGE PERCEIVED TB CASES ASSOCIATED WITH TNF-α INHIBITORS (Min to Max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private sector only</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Public sector only</td>
<td>3</td>
<td>2 (1 to 3)</td>
</tr>
<tr>
<td>Combined private and public sectors</td>
<td>2</td>
<td>2.5 (2 to 3)</td>
</tr>
</tbody>
</table>

Interestingly, in a Korean study (Seong et al., 2007) investigated the incidence of TB in RA patients not exposed to biological DMARDs (n=1285), RA patients on TNF-α inhibitors (n=193) and the risk of TB was higher in the absence of biological DMARDs (8.9; 95% CI 4.6
to 17.2) and in those specifically treated with infliximab (30.1; 95% CI 7.4 to 122.3). This is alarming, as this experience in a country known to be moderately endemic to TB is likely to be similar in other developing countries, like South Africa that has an even higher background incidence of TB.

### 6.4.1.1 Types of TB reported

In addition, study participants reported both extrapulmonary and pulmonary TB cases. This aligns with the worldwide trend of cases of active pulmonary and extrapulmonary TB being reported in patients receiving anti-TNF therapy (Gardam et al., 2003). Furthermore, study participants mentioned that TB was also likely to develop in patients with ankylosing spondylitis (AS) using TNF-α inhibitors. The absolute risk of serious infections in patients on TNF-α inhibitors was reported to be higher compared to those not on TNF-α inhibitors in a meta-analysis of RCTs (Fouque Aubert et al., 2009). Though, continued monitoring was recommended as the difference was not significant (possibly through lack of power).

### 6.4.2 Treatment outcomes of TB in RA patients, co-incident with TNF-α inhibitors

Most of the study participants reported that patients that developed TB co-incident with TNF-α inhibitors were treated successfully with TB chemotherapy. One patient (who was a nurse in the public healthcare sector) reported to have died from extrapulmonary, peritoneal TB, within 3 months of compassionate use of infliximab. The study participant commented that this aligns with the evidence suggesting that the risk of reactivation of TB occurs within 3 to 6 months of initiating anti-TNF therapy (Askling et al., 2005; Lalvani et al., 2008).
Of interest is the concerns raised by study participants that 3 patients had developed TB after stopping anti-TNF therapy. One patient received IPT for 8 months prior to starting anti-TNF therapy and once anti-TNF therapy was stopped, developed florid pulmonary TB. The second patient received chemoprophylaxis for LTBI, was initiated on anti-TNF therapy for ankylosing spondylitis, and 3 months after stopping anti-TNF therapy developed TB. The third patient was on a clinical trial for 6 months and had developed TB within a few weeks of stopping the anti-TNF. These observations echo the findings from the analysis of the data from the national British Society for Rheumatology Biologics Register (BSRBR), where TB rates in 10,712 anti-TNF treated patients were compared to 3,232 patients with active RA treated with traditional DMARDs (Dixon et al., 2010). 40 cases of TB were reported, of which 13 cases occurred after stopping treatment. One case was diagnosed 6.0 months after stopping etanercept, one 11.5 months after stopping infliximab, and four cases after stopping adalimumab (3.6, 7.3, 12.9 and 13.8 months). These observations (both locally and in the UK) cautions physicians to remain vigilant for TB even after cessation of anti-TNF therapy, as recommended by the BTS guidelines (British Thoracic Society, 2005).

6.4.3 SARAA biologics registry and TB surveillance

It was mentioned that the registry assists TB surveillance in terms of pre-screening (through the application process) and monitoring of TB (submission of progress reports bi-annually). However, it was noted that minimising risk is a difficult thing to interpret in South Africa. As one study participant mentioned, “…if you have a patient with the Quanteferon® or PPD tested positive – in the South African setting, we’re not exactly sure – does it mean latent TB?” A number of study participants were of the opinion that the registry was inadequate for
TB surveillance, but acknowledged that SARAA has systems in place to ensure that data collection is more consistent and is currently undertaking a project, looking at adverse events associated with anti-TNF use. The perceptions of the reporting culture of physicians were divided. Some commented that physicians do not always report adverse drug reactions whilst another mentioned that rheumatologists are good at reporting, even if it is not immediately. A concern that was raised was that although patients are pre-screened for LTBI, and treated for IPT for 6 months, they may present with TB at a later stage (including extra-pulmonary TB). One study participant was satisfied that clinical practice in South Africa is aligning with international practice, whilst another was dissatisfied with the SARAA biologics registry as reporting process was not effective or user friendly. An additional concern was that data was not forthcoming from the registry, whilst internationally; registries provide data relating to the local contextual setting, such as, how many patients are on anti-TNF therapy, how many of those patients developed TB, etc.

6.4.4 Re-screening for LTBI

Study participants were divided in their opinion regarding re-screening for LTBI. Some regarded re-screening necessary, due to the high prevalence rate of TB in South Africa. However, although they felt that the principle of re-screening was worthy, the limitations of the diagnostic tools in South Africa were a concern. False readings are prevalent in RA patients that had tested positive before, are on current immunosuppressant therapy (including TNF-α inhibitors) and had previously had BCG vaccinations. Therefore, it was recommended that re-screening should be considered every 2-3 years for the subset of patients that tested negative for LTBI, previously. Interestingly, SARAA guides physicians to
do a CXR every 6 months, during anti-TNF therapy, which one study participant considered adequate as a re-screening procedure.

Other study participant did not consider routine re-screening necessary. Patients are monitored and watched clinically for systemic symptoms (loss of weight, chronic cough, etc.) to cause a high index of suspicion and aggressive investigation for TB. One study participant emphasised that clinical questions relating to TB are always asked at each patient visit, which would point to reactivation or new diagnosis of TB.

### 6.4.5 Preference of anti-TNF molecule in LTBI

Once a patient was diagnosed with LTBI, most study participants considered a conservative approach to anti-TNF therapy preferring etanercept, in concordance with international guidelines and literature. Where TB risk was considered greater (such as in public care) infliximab was avoided, as there is evidence that infliximab confers greater risk. One study participant associated adalimumab with a low risk for TB, though the British Society for Rheumatology Biologics Register (BSRBR) reported a three- to fourfold higher TB rate in RA patients receiving infliximab (136 events/100,000 person-years) and adalimumab (144/100,000 person-years) compared to etanercept (39/100,000 person-years) (Dixon et al., 2010).

In South Africa, TB has been reported with all 3 anti-TNF molecules. One study participant mentioned “…it’s pretty much which anti-TNF molecule that the medical aids will pay for. But, I have TB on all three anti-TNFs”. Two study participants expressed the opinion that
they would avoid anti-TNF therapy, altogether, and a number mentioned consideration of other biological DMARDs such as rituximab, abatacept or tocilizumab.

Three study participants had no preference of an anti-TNF, and choice was determined by efficacy, disease profile, RA category and risk-benefit ratio. Presumably, TB risks encountered by these physicians were low due to adequate TB surveillance and patient mobility, functionality and satisfaction were considered of import in patient care.

6.4.6 Restarting anti-TNF therapy after active TB

The majority of study participants opted not to restart anti-TNF therapy once a patient had experienced co-incident TB. Alternative biological DMARDs were considered more appropriate. Four study participants would consider restarting anti-TNF therapy, but only once the patient had completed TB chemotherapy and the risk and benefit had been stratified.

It is reassuring that rheumatologists are very aware of the endemic TB situation of South Africa and mostly concerned about the TB risk associated with anti-TNF therapy in RA patients.
CHAPTER 7: DISCUSSION

Triangulation and robust discussion between the investigator/interviewer and two external experts, resulted in the development of two predominant themes during data analysis of the dataset. The first theme generated was: ‘Inequity of access to healthcare’ with the expensive TNF-α inhibitors being inaccessible and unavailable in the public sector; and inequity in health outcomes with higher prevalence rates of TB occurring in the public versus private sector. ‘Vigilance’ was the second major theme that was identified and concepts relating to the physicians’ perceptions regarding the surveillance systems for the monitoring of TB ADRs associated with TNF-α inhibitors (MCC NADEMC surveillance system and the SARAA biologics registry) and the different risk evaluation and mitigation strategies (REMS) that is implemented; physicians perceptions of and attitudes towards ADR reporting; the option of using non TNF-α inhibitors in the public sector; and physicians opinion of guidelines and SARAA biologics registry to regulate access of TNF-α inhibitors.

Deviant case analysis to further test the trustworthiness of the data identified outliers pertaining to the categories, ‘Background information of RA patients: concomitant immunosuppression’ with different interpretations of published literature pertaining to the use of concomitant immunosuppressants with TNF-α inhibitors and the resultant rational/irrational prescribing of medicines; and the ‘Evolving information on biomedicines’ and the
methods which physicians keep up to date regarding current evidence-based medicine practices.

A more detailed discussion of the above-mentioned themes and categories follows.

7.1 DO WE HAVE A PUBLIC HEALTH RESPONSIBILITY TO CONTROL OR MONITOR TNF-α INHIBITORS IN SOUTH AFRICA.

Some physicians interviewed in this survey were not aware that the MCC had a National Adverse Event Monitoring Centre (NADEMC) to report post-market ADRs to. It had been acknowledged that ADRs are reported to pharmaceutical representatives, trusting that these would be reported to the NADEMC. Comments received included, “I wasn’t aware of the surveillance that was done on behalf of the MCC. So, we don’t have in this country; as in the UK, like the yellow card system”; “…if it’s really serious adverse effects, not talking about the mild ones. But, I don’t know about this…they [pharmaceutical companies] probably forward it to them…I wasn’t even aware…”; “I wasn’t aware of that and never reported to the MCC; even regarding other drugs. I reported to [pharmaceutical company] – I was not aware that I was also supposed to report to MCC….I hope it has got there”.

Even though it was considered an ethical obligation and responsibility to society as a whole to report ADRs to NADEMC, workload, lack of incentives to report and the poor reporting culture in South Africa, negatively impact what we should know about the safety status of TNF-α inhibitors, in context to our patient population. As one study participant mentioned: “if there is an adverse effect then you have to do the effort to [report]….. And, there is no incentive attached to it...if you want to act really ethical,
not only to your patient but to the whole community, you will inform the MCC about it. But, I’m not sure if without any incentive, you would have a reliable notification”.

Internationally, national registries have been set up to anticipate the serious ADRs associated with biological DMARDs. However, in the absence of a national registry in South Africa, SAARA has shouldered the responsibility. It was noted that physicians were of the opinion that MCC’s post-market safety monitoring was ineffective and that the SARAA registry process was at least functional to a degree and the process less painful.

Comments made by study participants included: “I’m very careful to tell any drug company that I had an event unless it was very odd, as the next thing you know I’ll get an SAE form on my desk and if it was an infection I’m not particularly interested in reporting it as an SAE, because it is expected. We know that these drugs are associated with a high risk of infection…I do find that I screen the question or phrase it very carefully if I put it to the drug companies, not particularly wanting to do an adverse event report if I can help it. I don’t mind doing it if it’s warranted or an odd situation, but for what is in my opinion a common expected side effect I don’t want to be bothered in filling out an SAE form. The SAARA process is rather pain free in that regard except that it is not a very robust system”, “It is very seldom that I report adverse events to the MCC. I send my reports to SAARA”; “SAARA progress report is usually a 6 monthly review and very vague allowing you to capture serious infections, changes in TB status, other hospitalisations and other adverse events in broad terms and one is not required to be very detailed or accurate. I think the more detailed you make it, the more you scare people to fill it out”; “…I don’t see that it is worthwhile to send
expected side-effects to the MCC, that’s a bit silly. But, I do think to get an idea of prevalence, it’s a good idea to...capture these and the SAARA database might be a good idea...the biggest problem is compliance with reporting, which is always a huge problem, I think with any system?”.

Similar findings were found in a systematic review (Lopez-Gonzalez et al., 2009) investigating under-reporting of ADRs and a survey (Robins et al., 1987) of 104 doctors practicing in privately in South Africa. Ignorance (unusual or serious ADRs were uncommon, whilst common, trivial ones did not require reporting) was the most common factor associated with under-reporting. Lethargy and indifference were the next most pertinent factors. Alarmingly, the South African survey reported that not one medical doctor had reported an ADR. Some medical specialists considered that reporting was relevant; whilst general practitioners were of the opinion that only medicines recently released on the South African market required ADR reporting. Interestingly, few of the doctors considered that ADR reporting was part of their practice in treating ADRs in clinical practice. Furthermore, the survey reported that criticism; medico-legal and uncertainty about what to report were relatively unimportant factors.

Therefore, the question arises whether our national drug authority is relevant, seeing that the safety monitoring of medicines in the marketplace seems dysfunctional. This is of critical importance to the risk of TB associated with TNF-α inhibitors in RA patients in our endemic country. However, other aspects need to be considered such as the MCC’s control of the prescribing and dispensing of medicines through the determination of schedules for various
medicines and substances. Restricting access to TNF-α inhibitors by medical prescription only could assist rational prescribing of these agents.

A typical analogy is the global problem of antibiotic resistance. Antibiotics are readily available as over the counter medicine in some countries and inappropriate use adds significantly to the resistance problem. National drug authorities can enforce laws restricting the purchase of antibiotics by prescription only. This regulatory measure was enforced by the Chilean Ministry of Health and for the period 1996 to 2000, it was reported that there has been 43% decrease in antimicrobial use in the outpatient setting (Bavestrello et al., 2002). However, in this age where information is readily available and patients take an active role in their help, misconceptions regarding the use of antibiotics have been noted in a Pan-European survey published in 2010, where 53% of Europeans still believe that antibiotics kill viruses and 47% that they are effective against colds and influenza (Read et al., 2011). Thus, a balanced approach between appropriate usage and access, with functional consumer education is needed for medicines that have dire healthcare effects such as antibiotics on global antibiotic resistance patterns and TNF-α inhibitors’ effect on the TB situation in South Africa.

Traditionally, the initial, regulator-mandated, benefit-risk assessment is determined when a medicine is approved by the MCC. This is supported by clinical research data with a consideration of uncertainties. Pharmacovigilance is now embedded in a medicine’s development and marketing lifespan including assessment of safety signals, strategies for risk minimisation and risk communications (Viljoen, 2011). Thus, from a regulatory perspective, the MCC mandates that pharmaceutical companies marketing biologicals have
to submit a formal risk minimisation strategy with the application for MCC registration. From a pharmacovigilance perspective, though, the MCC have not directly implemented a formal set of risk evaluation and mitigation strategies (REMS). However, SARAA has put a REMS in place. Although, record-keeping, data capturing and follow-up of patients that have stopped treatment with biologicals was not rigorously maintained, resulting in a poor quality data. Furthermore, it is unfortunate that the SARAA biologics registry lacks focus on ADR reporting.

Another consideration for regulatory control of medicines in South Africa is the problem of counterfeit medicines. It was reported that counterfeiting is greatest in regions where regulatory and enforcement systems for market control of medicines are weakest. Counterfeit medicines are a lucrative trade, and biological medicines are expensive and contribute substantially to the market share of pharmaceutical products.

In South Africa there is an extreme variance between the private and public healthcare sectors. The Department of Health has thus intervened by regulating pharmaceutical prices setting single exit prices (SEP), rather than leave this to market mechanisms most likely dictated by the private healthcare sector; as there is concern regarding the affordability of medicines for the general public. Therefore, the high cost of TNF-α inhibitors can be regulated to attempt universal access of healthcare to all. However, it is important to note that Revellex® (infliximab) was registered in 2001, Enbrel® (etanercept) in 2002 and the initial launch price into the market was thus not affected by the SEP regulations of 2003. SEP regulations were applicable to Humira® (adalimumab) that was registered by the MCC in 2005.
Therefore, there is unquestionably a public health responsibility to control the rational prescribing of TNF-α inhibitors in South Africa because of matters relating to safety and affordability.

### 7.2 ADVISABILITY OF WIDESPREAD TNF-α INHIBITOR USE IN SOUTH AFRICA

The question arises whether universal use of TNF-α inhibitors is appropriate in the South African setting. Although these biologicals have been proven to be efficacious in reducing the radiographic progression of RA, use of TNF-α inhibitors is associated with a high risk of TB. Currently, South Africa has a high mortality associated with TB. Some would argue that this intervention is inappropriate in our country, as mortality rates would invariably increase, which is already strained by the current TB and HIV epidemics. One study participant reiterated the contraindication documented in TNF-α inhibitors’ MCC registered package inserts: “...active TB – anti-TNFs are contra-indicated in those patients”.

Furthermore, in the public sector, there was a tendency for study participants favouring either etanercept (TNF-α inhibitor associated with the lowest risk of TB infection) or non TNF-α inhibitors.

Comments made included: “…in our setting where we have lots of TB; irrespective of the skin test – I will avoid infliximab, as there is strong data that infliximab confers greater risk. I’d probably go for the smaller molecule which is Enbrel® (etanercept) because that has been shown to have the least risk. Having said that, we have had a patient last week that developed TB on etanercept”; “I think there is evidence that etanercept is probably the least risky for TB and I know it is controversial. I know the competitors claim that they came late
to the area...”; ”The perception is that Enbrel® of the anti-TNFs has a lower TB risk, and I don’t normally go to things like rituximab, the CD-20 blockers, but that is a consideration it seems. If a patient has a definite history of TB, and then perhaps that becomes a bit of a consideration”.

The majority of study participants were reluctant to re-initiate TNF-α inhibitors in RA patients that had developed associated active TB. Responses included: “Restart patient on biological DMARDs, if they had had active TB previously associated with anti-TNF’s: I’d be very careful about that, obviously not use an anti-TNF biologic; probably choose a non-TNF biologic DMARD (rituximab or abatacept)”; “Avoid anti-TNFs, after patient initially contracted TB on an anti-TNF and was successfully treated for TB. Perhaps, go onto rituximab”; “Not restart anti-TNF therapy, probably another non-TNF inhibitor”; “Would I restart the anti-TNF?...Probably not”; “Opt for the ones which are less prone to TB, especially Mabthera®, where it works completely different; then I would start fairly soon.

Furthermore, current evidence suggests that TNF-α inhibitors have not improved overall survival in RA patients compared to the general population; rather improving morbidity and quality of life of the RA patient (Thyagarajan et al., 2012; Watson et al., 2007).

Others would promote restricted access, controlled by treatment algorithms or protocols. SARAA Guidelines and peer review process of the biologics registry panel was considered to be valuable by some study participants. Responses included: “I agree strongly with the process and feel that the fact that the applications are peer reviewed just strengthens our position on prescribing ability. So I am
quite a protagonist of the SAARA system, I think it is a good system”; “quite good, because you have to justify why the patient needs it”; “[The registry] is useful. I think it is an area that requires guarding, but the guarding can be quite severe”.

However, the actual implementation of these guidelines in clinical practice would need to be monitored and evaluated. One respondent was of the opinion that:

“A lot of the registry data gets filled in because we have to fill it in. There is no real audit at a level of point of care...I think a lot of the data gets filled in, what’s the quickest way to fill a form in”.

The SARAA biologics registry primarily caters for the private sector population, which accounts for only 16.4% of the total population. However, one questions the robust nature of the SARAA registry, though; as no data is forthcoming from the registry to describe the effect of TNF-α inhibitors on our local TB situation.

In addition, one study participant defended the SARAA registry as: “It was also something that needed to be started from scratch and expected teething problems”.

Additionally, the private healthcare sector population appears to have a different TB profile compared to the public healthcare sector. As indicated by this survey, a higher occurrence of LTBI was perceived by the physicians practicing in the public or combined practice compared the private sector (21.4% versus 1.5%). The literature reports that TB prevalence varies between regions within the country, following a pattern of higher prevalence in the less affluent regions (Abdool Karim et al., 2009; Coovadia et al., 2009; United Nations,
Therefore, providing TNF-α inhibitors to RA patients in the public healthcare sector warrants that additional functional systems and risk minimisation strategies be put in place for adequate TB surveillance as mentioned by a number of study participants.

Responses included: “...we have a different population with different risk factors and we may see a lot more TB. We may require additional programs”; “public patients, by just going to the clinics is a problem. They move in that physical area, where there are other patients. Perhaps, not in a RA specific clinic, but in the outpatient departments, you have TB there... [may need] physically just a slightly separated area”; “Your surveillance has to be top class when you are thinking of public sector”.

It follows that inequity of healthcare services in the public versus private sectors of South Africa is not only influenced by minimal access by public care patients as TNF-α inhibitors are expensive; as indicated by the following study participant responses, “Due to financial constraints – [public sector patients] don’t have access to these drugs on a regular basis”; “they’re on clinical trials – that is the only way that we can get them”; “2 of the companies provide sponsorship of the state patients... of getting them drugs that they wouldn’t have had access to in other ways”; “Private patients are quite privileged as generally not available in public care, and it’s them that need it the most, by far”.

However, additional factors such as the different HIV and TB prevalence rates in public versus private sectors may affect universal access of TNF-α inhibitors by all RA patients
7.3 PHYSICIANS’ PROFESSIONAL RESPONSIBILITIES IN RATIONAL DRUG PRESCRIBING

However, having adequate systems and processes in place are merely tools at the disposal of physicians to assist with the effective management of their patients. Physicians are professionals that practice medicine therapy to influence their patients’ health (Maxwell et al., 2003). Scripting is more than prescribing a medicine to treat a patient’s symptom; it involves good clinical judgement pertaining to effective diagnosis and therapeutic adeptness in prescribing the right medicine for the right indication for the right patient with consideration of the associated benefits and risks.

However, it is internationally recognised that prescribing errors are common. A study in the UK reported prescribing errors in 9% of hospital patients (Vincent et al., 2009). Approximately 1-2% of hospital patients are harmed by medication errors mostly associated with therapeutic errors in prescribing (Barber et al., 1998; Neale et al., 2001). A study in the UK (2001 to 2002) reported that about 6.5% of hospital admissions were caused by adverse drug reactions, with a 0.15% mortality rate costing approximately £466 million annually (Pirmohamed et al., 2004). Medication errors are harmful and a costly practice that may erode patients’ confidence in healthcare.

Medicine is continuously evolving. To accomplish rational drug prescribing this, physicians would need to keep their therapeutic knowledge up to date. However, informal education of medicine by pharmaceutical industry’s commercial activities should be regarded with scepticism so as not to irrationally practice medicine irrationally, causing possible harm to patients. Practicing evidence-based medicine may influence physicians to practice medicine rationally.
Study participants’ responses pertaining to this discussion includes: “...it’s a steep learning curve for everybody; so anything new is valuable”; “Products are coming on the market very quickly”; “…but obviously people always give you what they want to take out of studies. So, I think it’s important to have your own journal club and your own academic input from that”; “…don’t pay particular attention to their detailing”; “We have regular journal clubs”; “…we review the literature”.

Sacket et al. (1996) defines evidence based medicine as the conscientious, explicit, and judicious use of current best evidence in making about the care of individual patients. Therefore, evidence based medicine advocates the use of current, objective, good quality scientific evidence from healthcare research to inform medical decisions in clinical practice. This practice benefits public health as safe, efficacious and cost-effective medicine therapy would then be considered. However, a measure of clinical experience should be used with best available external evidence to manage an individual patient in a particular clinical setting.

An additional challenge is sourcing current accurate medicine information to support the principle of evidence based medicines. Physicians would need to critically appraise the published literature to determine validity and relevance to clinical practice. Although, assistance can be provided through drug information centres that provide independent and unbiased drug information, responsible prescribing ultimately lies with the physician, emphasising the ethical obligation that physicians have towards patients, society and the profession.
CHAPTER 8: LIMITATIONS OF THE STUDY

As the incidence of TB associated with TNF-α inhibitors in RA patients in South Africa has not been established, as yet, this qualitative survey provided insight into physicians’ perceptions and experiential phenomena relating to this subject.

However, the study participants that were interviewed were limited to only those practicing in the Gauteng province. This has a considerable implication on data collection, as the
prevalence of TB varies from province to province within the country. The views of physicians practicing in KwaZulu Natal (where TB is highly endemic) would probably vary from the responses received from those that participated in this survey. Therefore, the qualitative data produced from this survey would probably not generalise to other physicians in other provinces. Furthermore, as this survey was not generalisable, the outcomes of this study cannot provide unanimous recommendations. However, it may inform further research that would be needed to test the hypotheses that were generated.

As the concept of ethnographic observation formed the bases of the theoretical framework of this study, with emphasis on participant observation, the study results were more easily influenced by the researcher’s personal biases, interpretation and individuality. However, trustworthiness of the data during data analysis was confirmed through corroboration with multiple sources of information (interview transcripts and field notes) and external sources (pharmacologist and medical doctor) to establish that the participants’ viewpoints were reasonably interpreted. However, additional validation with objective information, such as individual patient files with supporting diagnostic test results, SARAA approvals, etc., would have further verified the study results.

In addition, the data was dependent on subject participants presenting candid and accurate responses to interview questions. A limitation of in depth interviews includes the provision of false information to hide embarrassment, or because of lapse of memory. Responses could likewise have been anticipated by study participants and could have provided in a theoretical frame, providing answers that are expected rather than real life patterns or incidences occurring in clinical practice. This limitation that would result in the
contamination of the data is termed social desirability bias (King and Bruner, 2000). Zerbe and Paulhus (1987) have attributed two factors to social desirability bias: self-deception (where the study participant is unaware of this behaviour) and impression management (where the study participant purposefully responds in line with norms and standards in order to present a favourable image). Using a validated scale to measure social desirability would verify the data.

The subjective nature of this analysis makes it difficult to make quantitative predictions. Rather, the detailed examination of a small number of in-depth interviews was done to explore paradoxes or inconsistencies in order to encourage further research. Furthermore, conventional theories regarding the management of the associated risk of TB were challenged based on physicians’ experiences in practice in the local South African setting (and more specifically in the mixed private-public healthcare setting).

CHAPTER 9: CONCLUSION

Physicians practising rheumatology in Gauteng perceived that there is a risk of TB coincident with TNF-α inhibitors in RA patients as South Africa is a TB endemic country. Most acknowledged biological DMARDs efficacy in slowing radiographic progression in RA, but emphasised that steps need to be taken to prevent TB reactivation in the immunocompromised RA patients, in addition to the importance of constant vigilance.
In clinical practice, physicians were of the opinion that prevalence of LTBI (determined at pre-screening prior to TNF-α inhibitor therapy) and active TB or TB reactivation associated with TNF-α inhibitors appears to follow the socio-economic status of the RA patient, with a higher prevalence in the public sector. Physicians reported that active TB manifested mostly as extra-pulmonary, with cases of pulmonary and cavitary TB were also reported. Despite active vigilance, physicians reported that active TB occurred months after cessation of TNF-α inhibitor therapy. [Similar findings were observed from the British Society for Rheumatology Biologics Register (BSRBR)]. The majority of patients who developed TB co-incident with TNF-α inhibitors were treated successfully with TB chemotherapy. Only 1 of 12 patients died of extra-pulmonary TB, following compassionate use of infliximab in public care.

It was suggested that distinct recommendations be made within the public healthcare versus the private healthcare sectors. Different opinions emanated from different physicians relating to the adequacy of local SARAA guidelines for the prevention of TB associated with TNF-α inhibitors. Some physicians mentioned that local guidelines were sufficient, whilst other physicians stated that the diagnostic tools were inadequate for pre-screening of TB in the South African setting and that additional precautions should be taken in the form of IPT for the full duration of TNF-α therapy for all candidates, irrespective of TB status determined during pre-screening. The majority of study participants were uncertain of the value of rescreening for TB; and some questioned the sensitivity and specificity of the current diagnostic tools in RA patients that have been previously tested and are on immunosuppressants (including TNF-α inhibitors). Currently, the SAARA guidelines recommend that patients on TNF-α inhibitors should be routinely screened for TB by CXR.
As the science of biological DMARDs evolves with the rapid development of new medicinal therapies, physicians showed a preference towards considering alternative non TNF-α biological DMARDs that had a lower risk of associated TB, specifically in high-risk RA patients. Physicians’ overall perception of the management of RA with TNF-α inhibitor therapy was that the risk-benefit assessment of these interventions, as well as patient preference and economic considerations should be taken into account.

This survey opens up further avenues for research, but this preliminary qualitative data analysis may possibly suggest implications that would require further investigation.

### 9.1 IMPLICATIONS FOR PRACTICE AND POLICY

The qualitative study doesn’t provide robust recommendations for changes in policy and guidelines but opens up further research questions.

#### 9.1.1 Clinical practice perspective

Two immediate challenges were expressed by the physicians participating in this study. The first challenge was the unique situation of managing TB in the immunocompromised patient in South Africa, which is a TB endemic country; and secondly the lack of local robust safety data to inform decision making in clinical practice.

- *Establish distinct policies and guidelines for private sector and public care:*
- Feedback from physicians indicated that the monitoring and management of TB associated with TNF-α inhibitors appears to follow the socio-economic status of the RA patient in South Africa. An inter variance of TB incidences between provinces,
and between the private and public care patient groups were reported, which is merely a manifestation of the extreme discrepancy in income between private and public care. The unique TB situation in South Africa, patterning both high and low endemic TB situations in one country, should probably be acknowledged to direct distinct policy recommendations for the public healthcare versus private healthcare sectors. Two study participants were of the opinion that IPT should be considered for all public care RA patients that are candidates for TNF-α inhibitor therapy, irrespective of TB status for the duration of biological DMARD therapy, as opposed to private sector patients.

- **Promote pharmacovigilance culture amongst healthcare workers and continuous development of systems to promote safety monitoring processes**: Local policies and guidelines to manage TB associated with TNF-α inhibitors in the RA patient have been developed and implemented, through extrapolation from studies that have been conducted in countries with a low to intermediate burden of TB, namely United Kingdom, United States, Sweden, Spain and Korea. The survey revealed that most physicians were frustrated with the registry process as no safety data was forthcoming to inform local clinical practice. However, it was acknowledged that the registry was progressively improving and that the data required to be validated prior to release. In addition, the peer review process of the SARAA biologics registry panel was esteemed by most physicians. Interestingly, the registry is maintained by a private body in South Africa and it follows that the primary function was initially to be the gate-keeper for private medical aid funding. The study suggests that there is a definite need to promote safety monitoring on a national policy level. Furthermore,
as time and incentives were obstructions for healthcare workers voluntary reporting adverse drug reactions, a culture of the importance of pharmacovigilance could be initiated, emphasised and practiced at relevant schools (pharmacy, medical, nursing, dental, etc.). However, direct patient reporting of ADRs would not be a viable option in this clinical setting as TNF-α inhibitors are associated with serious ADRs and patients are mostly not medically aware of ADRs that are being experienced.

- **Encourage participatory patient-centred practices:** The study presents a challenge to physicians to progress from a physician-centred practice to a patient-centred practice. This would empower patients to collaborate with their physicians in the management of their health. As the current TB epidemic persists, RA patients on immunosuppressant therapy should ideally be counseled about the importance of vigilance and should be educated to take responsibility for their health, reacting when presented with TB symptoms.

- **9.1.2 South African healthcare policy perspective**

During the course of this study, it became apparent that some study participants could not answer certain interview questions. The reason was that none of their RA patients were being managed with TNF-α inhibitors, as access to these agents were restricted, specifically in the public sector.

- **Universal access, the ultimate goal of equitable healthcare should be an integral theme of policy:**
The implication is that this opens up the discussion on more affordable interventions, such as biosimilars. The study exposed the inequitable access of TNF-α inhibitors for RA in the private versus public healthcare sectors, because these interventions were expensive. Universal access cover across South Africa would require providing accessible, essential services to the entire population, without imposing an unaffordable burden on patients or households. Biosimilar medicines are similar versions of innovator biological medicines. They are developed after the original biological patent protection has expired and are expected to be slightly less costly than the innovator product. As biotechnology processes involves recombinant DNA or controlled gene expression methods, biosimilars are similar but not identical copies of the original biological medicine and are intended to have the same mechanism of action and indication as the originator. However, as the safety profiles may vastly differ and “biosimilarity may not necessarily imply interchangeability” (Declerck, 2013).

9.2 IMPLICATIONS FOR THEORY

Published literature pertaining to the incidence of RA patients exposed to TNF-α inhibitors have been conducted in American, English, Swedish, Spanish and Korean patient populations where there is a low to intermediate burden of TB. No data has been published for the local South African context, to date.

Parallel to international consensus guidelines, study participants were of the opinion that TNF-α inhibitors increases the risk of TB. Quantitative data is needed to further explore this problem.
9.3 IMPLICATIONS FOR FURTHER RESEARCH

The study has provided a snapshot of the perceived situation in South Africa relating to TNF-α inhibitors and co-incident TB in RA. It has captured dynamic physicians, processes, strategies, and activities as a one-dimensional image. Essentially, the ethnographic observations is a pre-design stage of research that generates further research questions for follow up by additional study methods. In addition, there were a number of limitations of this study which would warrant further investigation; namely, the subjective nature of the data and the restriction of the study to physicians in Gauteng region, only.

- **Continuous review and updating of treatment algorithms:** The study revealed an important matter pertaining to the use of algorithms and decision making models within medicine. Continuous review and updating of treatment algorithms (STGs and EMLs, CMS PMB Algorithms and SARAA Guidelines) are essential taking into account the pragmatic complexities in clinical practice.

- **Local studies need to be performed regularly, to inform clinical decision making for adequate health management for our South African population:**

- Research needs to be directed towards understanding the local complexities of the South African RA patient. Studies pertaining to the topic of this survey includes:
  - The incidence of TB associated with TNF-α inhibitors in the different healthcare settings (i.e. the private healthcare sector and the public healthcare sector);
TB diagnostic tools relevant to the South African setting (Due to the high exposure of South Africans to *Mycobacterium tuberculosis*, false readings are ubiquitous with current diagnostic tools);

Hopefully, this preliminary qualitative study will inform the findings of the prospective study to be undertaken by SARAA.

We currently hear the inharmonius music of physicians, patients, insurance companies, professional bodies, pharmaceutical industry and government healthcare systems. But, hopefully once the data from the SARAA biologics registry is forthcoming, we will have the local data regarding prevalence rates of TB co-incident with TNF-α inhibitors that will further guide the management of RA.

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