# Health-related Quality of Life and its Association with Medication Adherence in Active Pulmonary Tuberculosis in South Africa – an Integrated Patient-centred Outcomes Approach

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# Summary

**Introduction:** Tuberculosis (TB) is a leading cause of morbidity and mortality in South Africa. Whilst clinical parameters are important objective outcomes in TB, they are often not directly correlated with the subjective well-being of the patient which can be assessed using patient-reported outcome (PRO) measures. Health-related quality of life (HRQOL) is a specific PRO of multi-dimensional nature, which includes physical, mental and social health domains. Furthermore, HRQOL may be associated with medication adherence. The thesis evaluates HRQOL and its association with medication adherence in TB in South Africa.

**Methods:** A systematic review on HRQOL and adherence in TB was conducted. Based on the findings, a conceptual framework for HRQOL in TB was developed as a basis for identifying PRO measures, and to generate an endpoint model. The two generic measures SF-12 and EQ-5D-5L, the respiratory-specific measure St. George´s Respiratory Questionnaire (SGRQ), the condition-specific measure Hospital Anxiety and Depression Scale (HADS) for HRQOL and well-being assessment and the Morisky Medication Adherence Scale (MMAS) for adherence assessment were finally selected. All these measures were applied in an observational, longitudinal, multicentre study at five data collection time points during the six-month standard TB treatment. Eligible patients were older than 18 years, new TB cases and were diagnosed without HIV co-infection. Change over time in the Physical Component Score (PCS-12) of SF-12 was defined as primary endpoint. Sample size estimation based thereupon has led to a recruitment target of 96 patients. Statistical analysis included significance testing, correlations, univariable and multivariable analysis, and repeated measures ANOVA.

**Results:** A total of 131 patients participated in the study. Whilst HRQOL was impaired in all physical, mental and psycho-social health domains at the start of standard TB treatment, it improved significantly, and in a clinically meaningful manner, during the course of treatment. The greatest improvement in average mean score from baseline to six-month treatment (+95%) was observed in mental health. Younger patients with higher education and in employment reported a better HRQOL. Adherence mean scores stayed constant with participants attaining a medium average level throughout the treatment course. Associations between HRQOL and adherence were mainly weak, and included a positive relationship with improvements in anxiety and depression, pain and discomfort, and psycho-social health aspects after six months of treatment.

**Discussion:** This was the first longitudinal study in South Africa which evaluated HRQOL and its association with medication adherence in TB following a patient-centred and integrative approach. The study demonstrated the need for an integrative understanding of TB with HRQOL as one of the core elements to inform gaps in current TB management. In addition to an adequate drug treatment, the management of TB should also include services that focus on mental and psycho-social needs of the patient.

**Conclusion:** An understanding about patient-reported HRQOL in TB treatment should support the identification of sustainable health innovations in TB, help determining the value of new products, and support decision making with regard to health policy and pricing. In addition, an integrative patient-centred approach can contribute towards supporting the Sustainability Development Goal 3 target and the End TB strategy of the World Health Organization.

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# List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| AFB | Acid-fast bacilli |
| ANOVA | Analysis of Variance |
| ARV | Antiretroviral |
| BDI | Beck Depression Inventory |
| BL | Baseline |
| CEA | Cost-effectiveness Analysis |
| CER | Comparative Effectiveness Research |
| CES-D | Center for Epidemiologic Studies Depression Scale |
| COA | Clinical Outcomes Assessment |
| COPD | Chronic Obstructive Pulmonary Disease |
| DAI-10 | Drug Attitude Inventory 10 items |
| DOT | Direct Observed Treatment |
| DOTS | Direct Observed Treatment Short Course |
| DR-12 | Dhingra Rajpal 12 items |
| EKNZ | Ethik Kommission der Nord- und Zentralschweiz |
| EMA | European Medicines Agency |
| EOT | End of Treatment |
| EQ-5D | European Quality of Life 5 Dimensions |
| ERIQA | European Regulatory Issues on Quality of Life Assessment |
| FACIT-TB | Functional Assessment of Chronic Illness Therapy Tuberculosis |
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and Depression Scale |
| HIV/AIDS | Human Immunodeficiency Virus / Acquired Immune Deficiency Syndrome |
| HRQOL | Health-related Quality of Life |
| HTA | Health Technology Assessment |
| HUI | Health Utility Index |
| ICH | International Conference on Harmonization |
| K-10 | Kessler-10 |
| LTBI | Latent Tuberculosis |
| MDG | Millennium Development Goals |
| NDoH | National Department of Health |
| MDR-TB | Multi-Drug Resistance Tuberculosis |
| M(C)ID | Minimal (Clinically) Important Difference |
| NCD | Non-communicable disease |
| MCS-12 | Mental Component Score of SF-12 |

| | |
|---|---|
| NDA | New Drug Application |
| NHI | National Health Insurance |
| NICE | National Institute for Health and Care Excellence |
| MMAS | Morisky Medication Adherence Scale |
| PCR | Polymerase chain reaction |
| PCS-12 | Physical Component Score of SF-12 |
| PICOS | Population Intervention Comparator Outcomes Study design |
| PRO | Patient-reported Outcome |
| PROQOLID | Patient-reported Outcomes and Quality of Life Instruments Database |
| PTSD | Post-traumatic Stress Disorder |
| QALY | Quality Adjusted Life Year |
| SAP | Statistical Analysis Plan |
| SDG | Sustainable Development Goals |
| SF-12 | Short Form 12 items |
| SF-36 | Short Form 36 items |
| SG | Standard Gamble |
| SGRQ | St. George´s Respiratory Questionnaire |
| SOP | Standard Operating Procedure |
| STAI-6 | State-trait Anxiety Short Form |
| STROBE | Strengthening The Reporting of Observational Studies in Epidemiology |
| Swiss TPH | Swiss Tropical and Public Health Institute |
| TB | Tuberculosis |
| TTO | Time-trade Off |
| UCT | University of Cape Town |
| UK | United Kingdom |
| UN | United Nations |
| USA | United States of America |
| US FDA | United States Food and Drug Administration |
| VAS | Visual Analogue Scale |
| WHO | World Health Organization |
| WHOQOL-BREF | World Health Organization Quality of Life - brief |
| XDR-TB | Extensively Drug-Resistant Tuberculosis |
| Zim | Zimbabwe |

# Preface

In 2016, the United Nations (UN) introduced the Sustainable Development Goals (SDGs) to replace the Millennium Development Goals (MDGs) (WHO, 2015d). The MDGs were established during a Millennium Summit at the turn of the century to address global inequalities in wealth, health, gender, and education and promote environmental stability and greater global partnership for development, with the target to reach these goals by 2015. The SDGs comprise 17 goals, among them the third SDG (SDG3), a specific goal with focus on health including 13 targets. SDG3 aims to ensure healthy lives and promote well-being for all at all ages and aims to reach this goal by 2030 (WHO, 2015d). One of the ambitious targets within SDG 3 is to end the epidemic of tuberculosis (TB) by 2030 (WHO, 2015d). Another equally ambitious target focuses on universal health coverage, including access to safe, effective, quality and affordable essential medicines. Providing access to affordable medicines requires an understanding of the efficacy and cost-effectiveness in order to allow efficient decision-making in a health system. Evidence of both efficacy and cost-effectiveness are required for the evaluation of the benefit of treatment for the patient which should also consider the patient´s perspective. Further to this, the World Health Organization (WHO) has stated that patient involvement in their health care is a social, economic and technical necessity (Doward et al., 2010).

The disciplines of Pharmacoeconomics and Outcomes Research engage in the evaluation of patient-reported perspectives of disease. They contribute to a comprehensive understanding of the burden of disease and the effectiveness of treatment. One specific patient-reported outcome is health-related quality of life (HRQOL). The concept of HRQOL is applied in developed countries such as the UK to assess the performance of the National Health Service (NHS) (Appleby, 2005). The improvement in HRQOL is an important outcome for the NHS patient-centred approach to monitor performance. Furthermore, the concept of HRQOL is often considered in cost-effectiveness analysis. A challenge in applying a patient-centred approach in healthcare is the lack in standardization of the application of patient-reported outcomes. However, knowledge of HRQOL assessment can support the health system with information on health needs, quality of care, effectiveness of healthcare products under real-life conditions, and clinical thresholds. For developing countries such as South Africa, efficient health system performance is essential in order to handle the burden of diseases. With the introduction of a National Health Insurance (NHI) system in South Africa providing universal health coverage for all there is a need for an evidence-based approach to evaluate cost-effective and patient-valued medical interventions to be included in the NHI.

This work is structured in eight chapters. Chapter 1 introduces the topics of patient-reported

outcomes, HRQOL and adherence in general, followed by information on tuberculosis and its treatment. The overall research aim and specific research objectives are presented in chapter 2. Chapter 3 provides a brief overview on South Africa as country this work is focused on. Chapter 4 presents a systematic review on HRQOL and adherence in TB. Based on the findings from the systematic review, the study design and methodology of a longitudinal study were developed as described in chapter 5. Chapter 6 and 7 report the results of the longitudinal study. A chapter summarizing all references and an appendix including supplementary information complete the thesis.

# 1. Introduction

## 1.1 Patient-reported outcomes measures – an evidence-based tool

### 1.1.1 Introduction and definition

Demonstrating clinical efficacy, safety and quality of new treatments have been the three hurdles in the pharmaceutical drug development process in order to gain regulatory approval and market authorization. They have also been the basis for pricing and reimbursement discussions. Although clinical endpoints, such as arterial blood pressure in hypertension and blood sugar in diabetes, are informative they may not clearly translate to patient meaningful outcomes such as symptom benefit, improved emotional functioning, improved health-related quality of life (HRQOL) and overall well-being (Deshpande, 2011). Outside of the clinical trial environment, comprehensive healthcare and disease management should not only include physiological indicators but also an assessment of subjective well-being. Disease and treatment of disease influence the perception of health and well-being (Dhuria et al., 2009). Different stakeholders of a health system such as regulatory agencies, payers, pharmaceutical companies and healthcare professionals have realized this issue and have added a focus on real-world effectiveness and cost-effectiveness. These additional requirements are directly related to a patient-centered approach in healthcare. The difference between efficacy and effectiveness is that efficacy observes a treatment under artificial and controlled clinical conditions while effectiveness assess a treatment under real-life circumstances; therefore, effectiveness often leads to different outcomes compared to efficacy results. The patient perspective is observed with patient-reported outcomes (PRO) measures which provide evidence that the outcome is important to the patient with regard to survival, function and feelings (Patrick, 2013). The data obtained from PROs generate value propositions beyond clinical, physiological, and biochemical data to inform about disease and treatment impact on functioning and overall well-being (Deshpande, 2011, Doward et al., 2010, Acquadro C, 2003b). This follows a humanistic approach in health. The terminology PRO was first introduced in 2000 at the US Food and Drug Agency (US FDA); the term was later formalised in 2006 when the FDA released draft guidance on PROs and later in 2009 with the final guidance which provided their definition of PROs:

"*Any report of the status of a patient's health condition that comes directly from the patient,*

*without interpretation of the patient's response by a clinician or anyone else."* (FDA, 2009)

However, earlier than the U.S. FDA, the European Medicines Agency (EMA) provided following definition of PROs:

"*Any outcome based on a patient's perception of a disease and its treatment(s) scored by the patient himself is called a Patient-Reported Outcome (PRO). PROs are a large set of patient-assessed measures ranging from single item (e.g., pain VAS, overall treatment evaluation, and clinical global improvement) to multi-item tools. Multi-item tools can be mono-dimensional (e.g., measuring a single dimension such as physical functioning, fatigue, and sexual function) or multi-dimensional questionnaires measuring several of the following: symptoms, functional status, satisfaction, well-being, or health-related quality of life (HRQL). In general terms, PROs provide information on the patient's perspective of a disease and its treatment.*" (European Medicines Agency, 2005).

### 1.1.2 Application of PROs

PROs can be applied at many different stages in the drug development process and evaluation. For example, PROs are often included in clinical trials and real world evidence studies to assess efficacy, effectiveness and efficiency in order to evaluate the benefit and utility of medical treatment from the patient perspective. The evidence from PRO data can therefore be used for regulatory approval, pricing and reimbursement discussions and post-marketing.

#### Drug Development

PROs are often used during drug development and in particular during the clinical phase, to evaluate efficacy. During the translational or pre-investigational phase of the development of a new drug they can be used to gain better understanding of the natural history and characteristics of a disease and of disease symptoms; to define sub-populations, as well as to support the planning of clinical trial design and data analysis and interpretation of trial data (Patrick, 2013). Before PROs are applied in clinical trials, they can be used to support the recruitment process of eligible participants for clinical trials (Patrick, 2013).

#### Clinical trials (Phases I-III of clinical drug development)

Although PROs can be implemented in any of the three phases of clinical drug development, they are generally reserved for Phase II and Phase III clinical trials. During the clinical trial design and development phase, PROs can be incorporated into the endpoint strategy as clinical endpoint to support efficacy and safety. Some studies include PROs as primary or co-

primary endpoint. However, most studies implement PROs as a secondary or exploratory endpoint to generate evidence for the added value of a drug or device and to support biochemical endpoints (Doward et al., 2010). Information obtained from clinical studies is mainly used to define a medical need, meaningful treatment benefit, to demonstrate superiority against a comparator treatment or current standard care; and to gain more information on adverse events related to the intervention (Doward et al., 2010). Therefore, PROs are often applied in comparator studies rather than in placebo controlled trials, where the investigational treatment is compared against an active comparator/standard care rather than against placebo. Active comparator studies are known as comparative effectiveness research (CER).

## Regulatory Approval

The clinical data and results obtained from clinical trial efficacy evaluation are compiled in a pharmaceutical dossier for regulatory evaluation and approval for market authorization, and act thereby as an evidence-based approach for labeling claims. Some countries such as Germany require clear definition of superiority of new drug application (NDA) compared to standard care in order to grant market approval (Ruof et al., 2014). Guidance on the use of PRO instruments to support product label claim has also been issued by U.S. FDA (FDA, 2009). Unlike the U.S. FDA, the European Medicines Agency (EMA) has not issued a formal guidance but has released a reflection paper providing recommendations on the use of HRQOL PRO instruments and supplementary guidance in context of disease-specific guidance documents (European Medicines Agency, 2005); best practice and industry guidelines on the development and use of PRO instruments (Rothman, 2009, SACMOT, 2002) are also available (Patrick, 2007, Acquadro C, 2003b, Doward et al., 2010).

In 2011, the U.S. FDA introduced the term clinical outcome assessment (COA) to underline the importance of PROs but also of clinician (ClinRO) and observer reported outcomes (ObsRO) and performance outcome (PerfO) measures (Patrick, 2013). Regulatory qualification of clinical outcome assessments (COA) has been undergone at U.S. FDA known as U.S. FDA *Clinical Outcome Assessment Qualification Program*. The COA qualification program concludes if the COA is reliable and well-defined and if it measures a specific concept. The EMA has introduced the *European Regulatory Issues on Quality of Life Assessment* (ERIQA) (Acquadro C, 2003b). Both agencies are currently attempting to have greater harmonization in their process of qualitative review of clinical outcomes assessments (COAs) (Patrick, 2013). In 2013 the U.S. FDA has further expanded the role of the patient in the drug development process by the term patient-centered outcome and committed to the *Patient-Centered Drug Development Initiative* (Patrick, 2013). Between 2013 - 2017 the agency will obtain patient perspective on different therapies and disease areas (Patrick, 2013).

**Post-marketing Phase (IV)**

Effectiveness is usually assessed in post-marketing studies under real-life conditions and is often used to inform treatment guidelines (Acquadro C, 2003b). However, efficiency can be evaluated during efficacy studies by including self-reported utility PROs capturing the economic aspects of a treatment and modeling the economic effects resulting in cost-effectiveness outcomes. Evidence-based PRO data inform healthcare providers and payer about qualitative effective and affordable treatment options and support them in their decision making e.g. in pricing & reimbursement (FDA, 2009, European Medicines Agency, 2005).

### 1.1.3 Value of PROs for Key Stakeholders

PROs are of interest to a variety of different stakeholders within the health system. Each stakeholder applies and/or draws different information out of PRO data. The pharmaceutical industry uses PRO information for differentiation strategies and for label claims (Gnanasakthy, 2013). Regulatory agencies apply PRO data for granting approval and market authorization of healthcare products which show an added benefit to the patient. Based on adequate PRO data, health technology assessments (HTA) agencies can determine benefits and added value of medical interventions for health policy making as well as for establishment of medical guidelines (Bresnahan and Rundell, 2014); Australia, Canada and a number of European countries such as Germany and UK have local HTA agencies and a number of emerging countries are considering the introduction of formal HTA bodies to support health policy decisions. PRO data are considered in reimbursement decisions with regard to cost-effectiveness and inform payers. On a global level, 65% of the payers see data derived from peer-reviewed publications as more critical in their decision making process than PRO label claims (Reasner, 2015). In addition, the validation of PRO measures in country specific populations is of importance for payers. For example, in Germany, a new healthcare product has to show an additional benefit to achieve a price premium (Reasner, 2015). Physicians and health care professionals interpret treatment efficacy and effectiveness differently than a patient, as physicians and health care professionals may underestimate severity and overestimate treatment improvement. PRO allow an understanding of level of impairment, disability and patient satisfaction (Doward et al., 2010).

### 1.1.4 Psychometric properties of PROs and their conceptual framework

The impact of disease and treatment on a patient´s daily life can only be observed when PROs

reflect meaningful aspects which are relevant to the patient (Acquadro C, 2003b). Such information goes beyond counting of events and in combination with clinical data it provides valuable and unique information about disease and treatment impact (Acquadro C, 2003b). These meaningful aspects reflect the face and content validity, as well as the psychometric properties of the PRO instrument within a specific concept and context of use. The underlying concept measured in the PRO covers different health-related domains, dimensions and items in a conceptual framework. The conceptual framework is a graphical description of relationships among concepts, domains and items (Burke, 2008, Doward et al., 2010), as shown in figure 1. An example for a conceptual framework is given in 1.2:

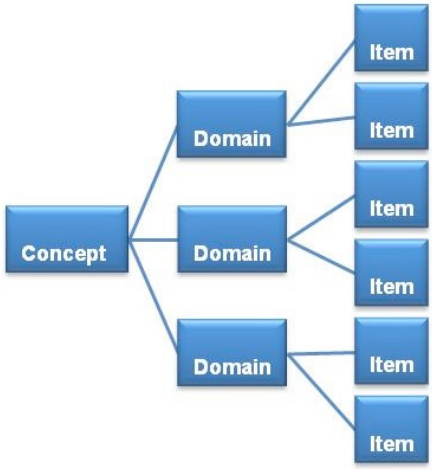


**Figure 1:** General conceptual framework of PRO measures. The general conceptual framework consists of concept, domains and items.

The conceptual framework of a PRO instrument is mirrored in the endpoint model of clinical studies by mapping endpoints to treatment benefit and appropriate claims (Burke, 2008).

Depending on the type of instrument, the concept of interest may vary. Such concept of interest may comprise physical functioning, symptoms, psychological well-being, social well-being, cognitive functioning, role activities, work productivity, personal constructs, patient satisfaction, patient preferences, adherence to treatment, clinical trial outcomes, and health-related quality of life (PROQOLID, Deshpande, 2011, Doward et al., 2010, Acquadro C, 2003b).

## 1.2 Health related Quality of Life (HRQOL) as PRO concept

The concept of health-related quality of life (HRQOL) is strongly related to the definition of health by the World Health Organization (WHO) defining health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (WHO 1948). A health system should aim to improve health and HRQOL of a population

(eunethta, 2013). One specific PRO concept which is more widely applied in clinical trials is HRQOL.

HRQOL is a multi-dimensional concept which may include physical, psychological and social domains (figure 2). Each domain consists of dimensions (such as physical functioning, emotional distress, and social interactions). Each domain being measured may comprise of single or multiple items (single question, statement or task). These domains, individually and collectively, evaluate the impact of a health condition and its treatment in daily life as well as health perception by the patient (eunethta, 2013, Apalone, 2001). It is thereby also a patient-relevant endpoint (eunethta, 2013). HRQOL assessment allows thereby an integrated evaluation of treatments beyond clinical parameters; physical health includes physical functioning, mobility, self-care, and usual activities; psychological health comprises cognitive functioning, emotional distress and anxiety and depression; social health focuses on the quality and quantity of social interactions and contacts (eunethta, 2013).

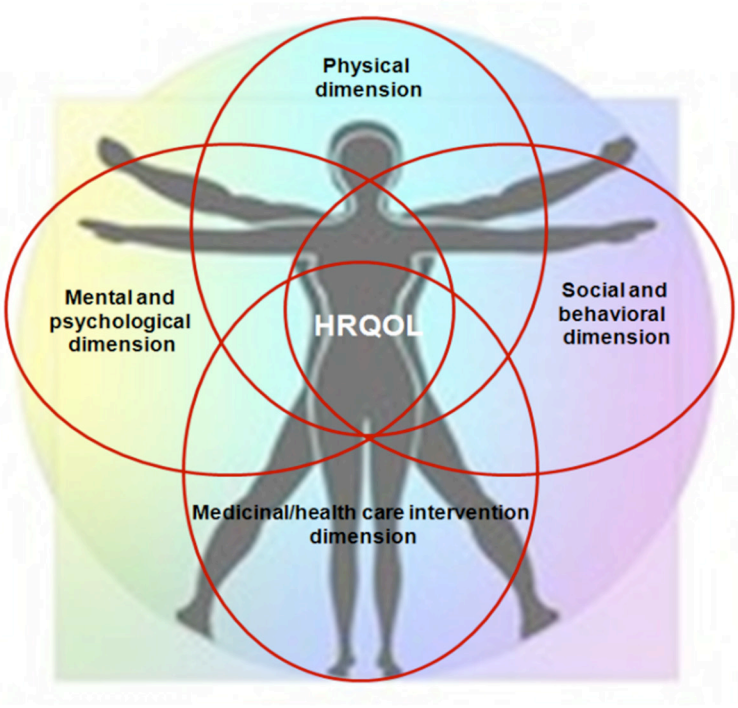


**Figure 2:** Health-related quality of life (HRQOL) concept. HRQOL concept comprises physical, mental, social domains and a domain for the health care intervention.

Clinical parameters, such as mortality and morbidity, are seen to delivery insufficient information about the full impact of a medical intervention (Aggarwal et al., 2013, eunethta, 2013). The integration of health perception through the patient respects the subjective health status perceived independently from objective disease parameter (Apalone, 2001). When a medical intervention does not target survival, an intervention-related improvement in HRQOL may have comparable importance as efficacy endpoints (eunethta, 2013). Health-related

emotional and social burden can be equal or even exceed the physiological impact of a disease (Dhuria et al., 2009). Consequently, HRQOL allows a benefit assessment (gains and losses) during clinical and epidemiological studies (eunethta, 2013). According to the European Network for Health Technology Assessment (eunetHTA) and its published guideline on HRQOL and utility measures (2013), the objectives of HRQOL assessment include (1) epidemiology of HRQOL (description of health status of a population), (2) assessment of relative effectiveness of a product, (3) cost-utility assessment of a product, and (4) informing clinical decision making (eunethta, 2013).

Together with morbidity and mortality, HRQOL is one of the patient-relevant endpoints in clinical trials and pharmacoeconomic evaluations (eunethta, 2013). Both the USA (through US FDA) and the UK (through the National Institute of Health and Care Excellence / NICE) incorporate HRQOL as a PRO in their decision-making process when appraising new technologies. The EMA disease-specific guidelines frequently request PRO endpoints ranging from symptoms to quality of life data to be included as key secondary end-points. From 81 final clinical guidance documents, available from EMA in 2010, 39 guidelines specified PRO inclusion as either primary (n=5), secondary (n=22) or both (n=12) trial endpoints (Doward et al., 2010, European Medicines Agency, 2005). The U.S. FDA approved 11 drug products and EMA 18 drug products based on HRQOL as primary endpoint, only 3 products used HRQOL as non-primary PRO label claim in the US (Gnanasakthy, 2013). A majority of these products were approved prior to the release of the PRO guidance through the U.S. FDA.

HRQOL measures have to be based on an appropriate framework which includes relevant health-related domains (Bottomley et al., 2009). This approach ensures that clinical variables are linked to HRQOL outcomes in an *a priori* hypothesized manner (Apalone, 2001). The conceptual framework of HRQOL includes physical, mental and social domains, which consist of single items depending on the respective HRQOL instrument. Figure 3 shows the general conceptual framework of HRQOL.

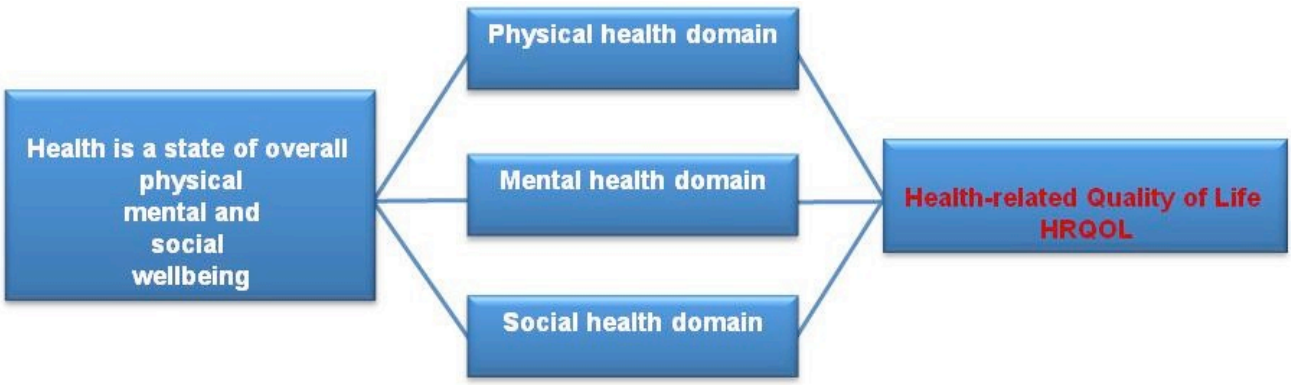

**Figure 3:** Conceptual framework of health-related quality of life (HRQOL) based on the definition of health by WHO**.**

HRQOL can be applied as tool for public health surveillance systems. The U.S. Department of Health and Human Services has implemented the initiative Healthy People 2020 and uses HRQOL to monitor the public health surveillance in order to reach their goals for Healthy People 2020 (CentersforDiseaseControlandPrevention, 2016). HRQOL can be applied to generate a spectrum of information to support health systems in their performance. It is an indicator for health service needs and for intervention outcomes. HRQOL supports the measurement of health insurance coverage and of the quality of health services and health care, and supports the identification of health policy and legislation needs. HRQOL facilitates the allocation of healthcare resources based on unmet needs. Using HRQOL for monitoringeffectiveness of different interventions can guide the development of strategic plans and can track efforts to promote equity in health (CentersforDiseaseControlandPrevention, 2016).

### 1.2.1 Critical aspects about HRQOL

There are some critical aspects about HRQOL. HRQOL reflects the subjective perception of health. Since patients with the same health status value their HRQOL differently, there may be high inter-individual variability within a defined group of patients. Furthermore, different HRQOL measures may give different results and make a comparability of outcomes between different instruments not always possible. Additionally, outcomes vary with different population groups. One of the methodological issues is that a number of different HRQOL measures have been developed, evaluated and applied with little standardization. Different types of HRQOL measures differ in their objective of application such as generic, disease-specific and utility measures.

### 1.2.2 Types of HRQOL measures

Different types of HRQOL measures are known: profile and summary measures, generic, disease-specific or condition-specific, and utility measures. Profile or summary measures are descriptive and apply a scoring system in form of a scale: binary (yes/no), ordinal (7 point-Likert) or continuous (visual analogue scale) (eunethta, 2013). Generic HRQOL instruments are applied to a broad range of indications and health problems, since they cover general aspects of HRQOL (eunethta, 2013, Deshpande, 2011, Doward et al., 2010). Generic HRQOL

measures allow comparison of HRQOL across different disease populations and general population norms (where they exist) and are often applied to inform health policy maker about allocation of resources (eunethta, 2013). Disease-specific or condition-specific measures are applied in a specific disease or health condition and thereby allow comparison within a specific indication. A systematic use of generic HRQOL instruments in all diseases supports consistent value judgment and transparency, for example in reimbursement decisions (eunethta, 2013). Disease-specific measures are more sensitive to changes than generic instruments and of greatest interest for patients and clinicians because of their increased relevance. Disease-specific HRQOL information is complementary to generic HRQOL measures, also when no effect was observed with generic measures.

A specific type of generic or disease-specific measures is used for health state preferences (utility) measurement. Such measures generate utilities by preference-based or choice-based methods representing patient or general population preferences for a health state. Utilities can be generated directly or indirectly; direct methods generate utilities from patients directly using time-trade off (TTO, choice-based), standard gamble (SG, choice-based) or visual analogue scale (VAS, preference-based). Utilities generated are used to calculate common-used utility outcomes such as quality-adjusted life years (QALYs) for cost-effectiveness and cost-utility evaluations. A commonly used basis for the calculation of utilities measure is the European Quality of Life-5 Dimensions instrument (EQ-5D) (eunethta, 2013).

## 1.3 Medication adherence

The World Health Organization has defined inadequate medication as a major problem for management of chronic diseases (WHO, 2003). Non-adherence to treatment of chronic diseases has a negative effect on clinical effectiveness, morbidity, causes medical and psycho-social complications, increases health care costs (direct and indirect costs) and reduces HRQOL (Cramer, 2008, WHO, 2003). The WHO have stated that increased medication adherence might have a greater impact on a populations health than any improvement in specific medical treatments (WHO, 2003).

Medication adherence is a complex, multi-dimensional, dynamic phenomenon comprising the patient behavior with regard to taking a drug at the prescribed interval, dose, and dosing regimen as well as quality of how medication is taken (Cramer, 2008, Hughes, 2007). Medication adherence is “the process by which patients take their medications as prescribed” (Vrijens et al., 2012). It comprises the initiation of the treatment (first dose), implementation of the prescribed dosing regimen, discontinuation of the therapy (end of therapy), and persistence (time from initiation until discontinuation) (Vrijens et al., 2012, Lam and Fresco, 2015). Medication adherence is crucial to reach clinical targets and the causes of non-adherence are

multi-factorial (Lam and Fresco, 2015, Fairman, 2000). Since adherence affects the effectiveness of medical interventions and their outcomes, effective and efficient treatment requires the identification of factors that contribute to non-adherence (Saleem, 2012). Major factors impacting medication adherence behavior are known (figure 4); these factors include therapy-, condition-, health system- and patient-related factors (Wilke et al., 2011, WHO, 2003).

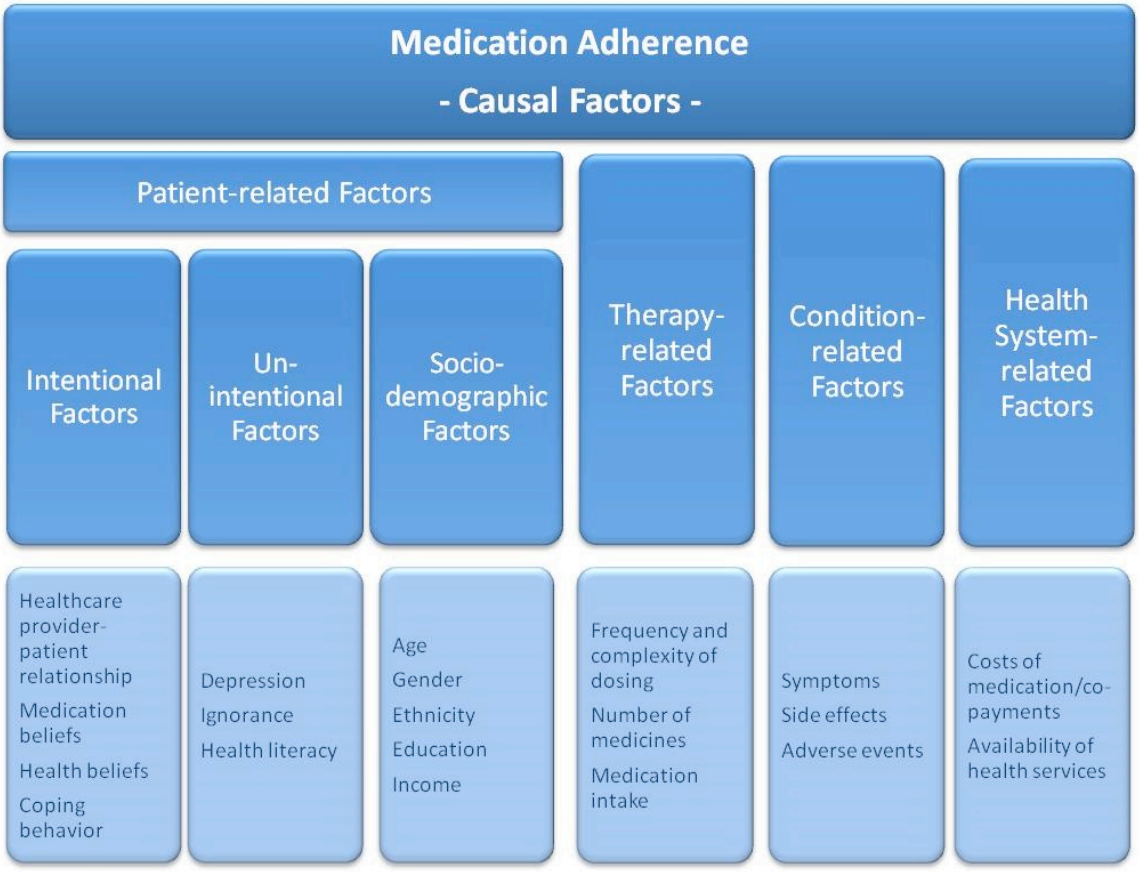


**Figure 4:** Causal factors impacting medication adherence. These factors comprise patient-related, therapy-related, condition-related and health system-related factors.

All six factors described in figure 4 can influence medication adherence. The direct associations between medication adherence and some factors have already been studied in German patients with chronic diseases taking regular medication and with patients taking thromboprophylaxis after orthopedic surgery (Wilke et al., 2011). This study showed that medication non-adherence was lower when people have positive medication beliefs, positive mood and a positive doctor-patient relationship (Wilke et al., 2011).

An ideal measure to assess overall adherence to medication including initiation, persistence, implementation and discontinuation does not exist; therefore a multi-measure approach may be considered where direct and indirect adherence measures are combined (Fairman, 2000).

Direct measures such as drug determination in biological fluids or direct patient observation are often regarded as being the most reliable and accurate approaches. However, individual changes in drug metabolism and multidrug intake affect monitoring of plasma levels, and patient observation is limited to inpatient settings and clinical trials (Fairman, 2000, Nguyen et al., 2014, Lam and Fresco, 2015). Indirect measures comprise medication monitoring (such as pill counting) and self-reported measures; however, medication monitoring is cost intensive and self-reported measures may be less reliable due to patient recall, underreported non-adherence and memory bias issues (Fairman, 2000, Lam and Fresco, 2015, Stirratt et al., 2015). On the other hand, self-reported adherence measures are cost-effective, with a minimum burden to the patient, and easy to administer. Each adherence measure has its advantages and disadvantages and the selection of adherence measures depends on the attributes, research objectives and available resources of each study (Lam and Fresco, 2015).

## 1.4 Tuberculosis

### 1.4.1 Disease characteristics of Tuberculosis

Tuberculosis (TB) caused by the *mycobacterium tuberculosis* is an infectious disease (Bauer et al., 2013, Kittikraisak et al., 2012, WHO, 2016). Transmission of TB between humans is through airborne route by droplet nuclei, usually through coughing, sneezing, talking or singing (NDoH, 2014). TB affects mainly the respiratory system involving the lung parenchyma (pulmonary TB), but can also attack the remaining body known as extrapulmonary TB (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges). Individuals with diagnosed latent TB are not infectious. Suppressed immunity such as in HIV increases the probability to develop active TB (NDoH, 2014). Symptoms of pulmonary TB include a persistent cough of more than two weeks that brings up phlegm, which may be bloody, breathlessness, which is usually mild to begin with and gradually gets worse, lack of appetite and weight loss, a high temperature of 38ºC or above, night sweats, extreme tiredness or fatigue, unexplained pain for more than three weeks (NDoH, 2014).

### 1.4.2 Global disease burden of tuberculosis

TB remains one of the top 10 causes of death worldwide. One third of the world population is infected with *mycobacterium tuberculosis,* having a latent TB, and 10.4 million people felt ill from TB in 2015 (WHO, 2016). About 1.8 million died from TB including 400,000 cases with HIV co-infection, and 60% of the TB cases occur in six countries worldwide: China, India,

Indonesia, Nigeria, Pakistan, and South Africa (WHO, 2016). More than 50% of all HIV co-infections in TB are found in Southern African countries. The rate of new TB cases has slowly remained at 1.5% from the year 2014 to 2015. In the year 2015, about 450,000 cases had a multi-drug resistant TB (MDR-TB). The End TB Strategy of the WHO targets to reduce the prevalence and mortality rate of TB by 50 percent by 2015 and to achieve a prevalence of 1 case in 1 million population per year by 2050 (Mamani et al., 2014, WHO, 2016).

### 1.4.3 Diagnosis of Tuberculosis

Diagnosis of TB relies mainly on self-presentation of individuals with TB symptoms to a health care facility which requires awareness about TB as disease among communities. Diagnostic tests applied include smear microscopy, culture, and polymerase chain reaction (PCR) based assays such as Line Probe Assay and Xpert, as recommended in South Africa (NDoH, 2014). X-rays may be applied in diagnostic testing of TB. However since many diseases mimic TB on x-rays, they are only applied in patients who cannot produce a sputum sample or who may have a negative sputum but are HIV positive (NDoH, 2014) Usually, patients have to provide sputum smear for first diagnosis; sputum smear microscopy determines acid-fast bacilli (AFB), the most common of which is *M. tuberculosis*. This microscopy testing is quick compared to AFB culture which can take days or weeks. A sputum smear positive outcome confirms the existence of AFB, most probably tuberculosis. A smear negative test result can either mean symptoms are not related to mycobateria including *M. tuberculosis* or it may mean mycobacteria were not present in sufficient concentration for detection. Treatment is initiated after sputum smear confirmation.

### 1.4.4 Treatment and monitoring of Tuberculosis

The aim of disease treatment is to improve patient functioning by reducing disease progression and severity (Chassany, 2002). About 87 percent of TB patients can be cured with appropriate and effective treatment (WHO, 2016, Kittikraisak et al., 2012). Without treatment, 70 percent of pulmonary TB cases die within 10 years. Standard treatment of new TB cases is a six-month drug regimen with four antibiotics (rifampicin, isoniazid, ethambutol and pyrazinamide). All four antibiotics are administered orally during the first 8 weeks of treatment (intensive phase), followed by rifampicin and isoniazid for additional four months (continuous phase). Different from standard TB treatment is the treatment of MDR-TB. Patients with MDR-TB who show resistance against rifampicin and isoniazid have to undergo at least 20 months of treatment with expensive and toxic drugs (e.g. amikacin, kanamycin). Mismanagement of individuals receiving MDR-TB treatment may lead to extensively drug-resistant TB (XDR-TB) (NDoH,

2014).

Side effects may develop under standard TB treatment. Side effects may comprise following symptoms: burning, numbness and tingling sensation in the feet, joint pains, anorexia, nausea, abdominal pains, skin rash with/ without itching, changes in the colour of urine, impaired vision, yellowing of eyes, confusion (NDoH, 2014). Monitoring of tuberculosis is essential to observe the treatment response. As no molecular TB tests have been validated for monitoring, pulmonary TB is monitored clinically by body weight control and bacteriological by sputum smear probes. Cure from TB is determined by a negative sputum smear.

## 1.5 HRQOL, medication adherence and tuberculosis

Medication adherence can be associated with a patient´s self-perceived health status (physical and social functioning as well as general health) as shown in patients who underwent percutaneous coronary intervention (Coehlo, 2013). Given a potential relationship between poor HRQOL and non-adherence, a better understanding of HRQOL and how to improve HRQOL of patients with specific diseases may support the improvement of medication adherence (Kruijshaar et al., 2010). There are expectations that a strong medical adherence is associated to a good HRQOL and vice versa (WHO, 2003). The association between HRQOL and medication adherence has been studied rarely. One meta-analysis about qualitative studies examining adherence to TB treatment reported the association between well-being and adherence in TB to be based on two mechanisms (Munro S, 2007). The first mechanism is that TB patients stopped their treatment because they felt better in terms of their health and well-being. The reason behind is that patients perceived the improvement in well-being as a cure of TB. The second mechanism is that patients stopped treatment when they experienced no improvement in their health status and well-being or experienced a worsening in TB. Both mechanisms were based on qualitative studies examining medication adherence in TB patients. Still, only a few published studies assessed adherence to TB treatment in South Africa (Louw et al., 2012, Corless et al., 2009, McInerney et al., 2007, Munro S, 2007) and only one study observed an association between TB treatment adherence and HRQOL outside of South Africa in HIV co-infected people (Deribew A, 2013). It has been recommended to observe the relationship between HRQOL and medication adherence by applying a self-reported PRO measure (Saleem, 2012, WHO, 2003).

## 1.6 Identified research gaps

A literature review about HRQOL and adherence in TB was conducted in order to gain a comprehensive understanding of the current research in the field (Appendix Figure 1).

Including literature until February 2014 research gaps were identified and have led to the formulation of specific research objectives. According to the findings of the literature review, only two studies (Louw et al., 2012, Bauer et al., 2013) evaluated HRQOL in TB patients in South Africa. However, none of these studies included the Western Cape Province, which has the highest TB burden in South Africa. A study evaluating HRQOL during the course of standard TB treatment in the Western Cape Province of South Africa is lacking. The majority of identified studies evaluating HRQOL in TB patients followed a cross-sectional design (Atif et al., 2014a, Bauer et al., 2013); only a few studies followed a prospective longitudinal design to evaluate HRQOL in TB (Atif et al., 2014a, Marra et al., 2008, Kruijshaar et al., 2010, Maguire et al., 2009). However, a prospective study design evaluating HRQOL in active TB patients would allow insights into changes of HRQOL during different treatment phases (Bauer et al., 2013) and might provide valuable information to the South African health setting. Only one study (Dhingra and Rajpal, 2005) worldwide developed a TB-specific HRQOL measure (DR-12) for the Indian health setting. However this TB-specific HRQOL measure has no proven validity and reliability. A validated TB-specific HRQOL instrument is lacking. According to a meta-analysis about HRQOL in TB by Bauer et al (Bauer et al., 2013) qualitative evaluations of HRQOL are not available but would provide valuable information to health care providers about patients' experiences and needs in specific health care settings. Although studies of medication adherence in TB are available, none have evaluated the association with HRQOL aspects.

# 2. Research aims and objectives

Specific research questions were elaborated based on the identified research gaps. The research gaps comprised factors including the need for further research on the patient perspective and patient´s HRQOL, lack of a TB-specific PRO instrument, and the need for quantitative research on medication adherence in TB patients. Furthermore, despite the fact that South Africa is one of the 22 high TB burden countries with one of the highest prevalence and incidence rates in TB worldwide, there is a lack in research about HRQOL and adherence in TB. Based on these factors, following research questions were elaborated:

- How does pulmonary TB affect patients HRQOL in the South African health setting, with focus on the Western Cape Province, which has the highest TB burden in South Africa?
- What outcomes would provide a longitudinal study design of HRQOL evaluation?
- Since no TB-specific HRQOL measure is available, can HRQOL in TB be evaluated with other available generic and disease-specific measures?

- Is there an association between HRQOL and medication adherence in TB?
- Does a combination of different PRO measures applied reflect a potential conceptual framework for pulmonary TB and do they comprise TB relevant psychometric properties?

The research questions based on identified research gaps lead to the following research topic: Health-related Quality of Life and its association to medication adherence in active pulmonary TB patients in South Africa – an integrated patient-centred outcomes approach.

## 2.1 Aim

The overall aim of this PhD research program was to understand the impact of pulmonary TB on HRQOL, considering physical, social and mental health dimensions, and the association between HRQOL and medication adherence in TB in South Africa.

### 2.1.1 Specific research objectives

Thereby the PhD program intended to develop a comprehensive understanding on how changes in HRQOL during TB treatment affect the health status of a patient by following hypotheses and hypothesized relationships:

- To understand the current state of knowledge regarding the impact of TB on HRQOL and medication adherence to TB treatment (Table 1)
- To evaluate HRQOL in active pulmonary TB patients, receiving standard TB treatment, using a combination of generic and disease- and condition-specific HRQOL measures. These HRQOL measures have shown validity and reliability in TB or in a disease with characteristics that are closely related to TB (most preferably chronic obstructive pulmonary disease (COPD)). Hypothesized relationships between HRQOL and socio-demographic data and clinical data (sputum smear results) were planned to be assessed (Table 1).
- To evaluate adherence to anti-TB standard treatment in active pulmonary TB patients, using a patient-reported adherence measure with shown validity and reliability in TB. Hypothesized relationships between medication adherence and clinical data (sputum smear results) were planned to be assessed (Table 1).
- To investigate hypothesized relationships between HRQOL and medication adherence in active pulmonary TB patients receiving standard anti-TB treatment (Table 1).

Table 1 presents the research objectives as research hypothesis.

**Table 1:** Overview of main research objectives. Research objectives are presented as research hypothesis and sub-hypothesis.

| Hypothesis | Sub-hypothesis |
|---|---|
| Patients suffering from pulmonary TB experience a decreased HRQOL in a physical, social and mental health manner which improves as clinical TB data improve due to anti-TB treatment over time. There is a hypothesized relationship between improvement in HRQOL and improvement in clinical TB data over time. | • Patients suffering from pulmonary TB experience a decreased HRQOL in a physical, social and mental health manner.<br>• HRQOL improves as clinical TB improves due to anti-TB treatment over time. |
| Socio-demographic background of the patient with regard to gender, age, education, work status and co-morbidities impacts the HRQOL in TB.<br>There is a hypothesized relationship between HRQOL and socio-demographic characteristics in TB patients. | HRQOL is different in socio-demographic subgroups as following:<br>• Women experience a worse HRQOL than men<br>• Older people tend to have poorer HRQOL in TB than younger people<br>• Patients with higher education experience less impact on HRQOL in TB<br>• Patients working and receiving a financial income have a better HRQOL<br>• Patients suffering from co-morbidities report a worse HRQOL subgroup |
| As medication adherence to TB treatment decreases treatment effectiveness declines with regard to clinical data. Patients with high medication adherence have a better treatment effectiveness which is reflected in improved clinical data. Adherence to anti-TB treatment decreases over time.<br>There is a hypothesized relationship between medication adherence and clinical data in TB patients. | Patients with high medication adherence have a better treatment effectiveness which is reflected in improved clinical data of sputum smear results. Adherence to anti-TB treatment decreases over time. |
| HRQOL and medication adherence affect each other. There is an association between HRQOL and medication adherence in TB patients. | There is an association between HRQOL and medication adherence in TB patients, with two underlying mechanisms:<br>• As HRQOL improves medication adherence decreases<br>• as HRQOL worsens or has no change since treatment start medication adherence decrease<br>Patients with depression and anxiety are hypothesized to have lower medication adherence |

# 3. Country where the research was performed: South Africa

South Africa is one of the largest and most advanced economies on the African continent. It is a middle-income country with a population of 54.96 million people and a GDP of US$ 312.8 billion (TheWorldBank, 2016). The growth of the GDP expected for 2016 is 0.4% (TheWorldBank, 2016). South Africa has one of the highest inequality rates in the world, with a Gini index (dispersion of income or wealth in a country) of 0.66 to 0.7 as reported by the World Bank in 2016 (TheWorldBank, 2016). The country faces a quadruple burden of diseases including perinatal and maternal health disorders, communicable diseases, non-communicable diseases (NCDs), and violence-related injuries (Mayosi et al., 2009). Communicable diseases such as HIV/AIDS, TB and malaria cause the highest burden among the disease burden in South Africa, with TB being a health problem with epidemic proportions (WHO, 2016, Cramm JM, 2010, McInerney et al., 2007). The national mortality rate in TB was 133 per 100,000 population in 2015 (WHO, 2016). The case fatality ratio (estimated mortality / estimated incidence) in TB in South Africa was 0.22 in 2015 (WHO, 2016). In international comparison, the incidence rate is highest in South Africa with 834 new cases per 100,000 population and a total of 454,000 official cases in 2015 (WHO, 2016) (figure 5).

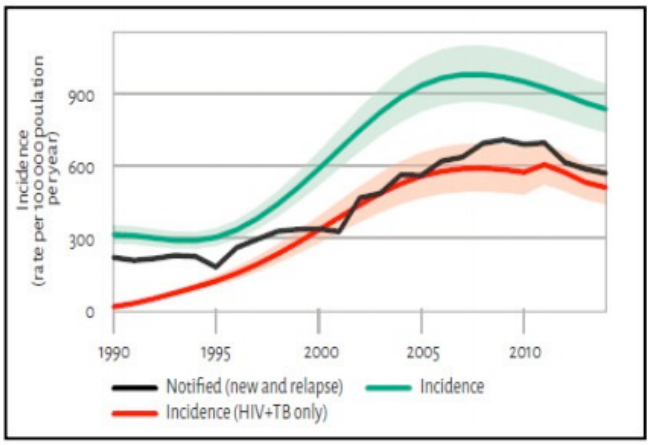


**Figure 5:** Incidence rate of TB in South Africa between 1990 and 2015 (WHO, 2015c).

About 20,000 MDR-TB cases out of 580,000 new MDR-TB cases worldwide were recorded in 2015 in South Africa (WHO, 2016). TB treatment is a challenge since the presence of HIV and related antiretroviral (ARV) treatment exacerbate the risk for TB as a result of immunosuppression (McInerney et al., 2007). Approximately 73% of all TB patients are also

diagnosed HIV positive. South Africa is one of the countries with a relative high rate of missed TB cases; either not diagnosed or diagnosed but not reported. About 90% of all new and relapsed TB cases have a pulmonary TB manifestation (WHO, 2016) Universal health coverage covered treatment of 63% of all TB patients in South Africa.

Based on the latest epidemiological data provided by City Health, City of Cape Town, the highest TB incidence in Cape Town (Western Cape Province) is found in the sub district Khayelitsha.

# 4. Health-related quality of life and its association with medication adherence in active pulmonary tuberculosis– a systematic review of global literature with focus on South Africa

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# Health-related Quality of Life and its Association with Medication Adherence in Active Pulmonary Tuberculosis– A Systematic Review of Global Literature with Focus on South Africa

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## 4.1 Abstract

**Introduction:** Tuberculosis (TB) is a leading cause of morbidity and mortality in South Africa. Clinical parameters are important objective outcomes in TB; however they often are not directly correlated with subjective well-being of the patient, but can be assessed using patient-reported outcome (PRO) measures. Health-related quality of life (HRQOL) is a specific PRO generally multi-dimensional in nature and includes physical, mental and social health domains. The inclusion of HRQOL PROs in trials and clinical practice can provide additional information beyond clinical and microbiological parameters. Furthermore, HRQOL may be associated with medication adherence. This review focuses on patient-reported HRQOL and its association with medication adherence in TB patients in South Africa.

**Methods:** A comprehensive search strategy was developed focusing on the impact of TB on patient-reported HRQOL, the existence of a conceptual framework of TB-specific HRQOL, determinants of medication adherence, and the association of HRQOL with medication adherence. Data were extracted from all identified articles and additional data extraction was performed by two independent reviewers with special focus on longitudinal studies in order to understand changes of HRQOL and adherence over time. Research gaps were identified with regard to patient-reported HRQOL and medication adherence.

**Results:** A total of 66 articles met the eligibility criteria. Ten HRQOL studies and one adherence study used a longitudinal design, none of these in South Africa. A variety of different generic and disease-specific HRQOL measures were identified in the articles. In South Africa four HRQOL and five adherence studies (non-longitudinal) were published. Similar factors (socio-demographic, socio-economic, disease-related, therapy-related, and psycho-social aspects) affect HRQOL and adherence. Although standard TB treatment improved all health domains, psychological well-being and social functioning remained impaired in microbiologically cured patients after treatment.

**Conclusion:** While evidence of TB impact on HRQOL and medication adherence and their association exists, it is very limited for the South African situation. No valid and reliable TB-specific HRQOL measures were identified in this systematic review. An assessment of HRQOL in TB patients in South Africa is required as this may assist with improving current disease management programmes, medication adherence and national treatment guidelines.

## 4.2 Introduction

The global burden of tuberculosis (TB) is still a major public health concern although the United Nation´s Millenium Development Goals (MDGs) target to reverse TB incidence by 2015 has been achieved. Around 9.6 million new TB cases and 1.5 million TB deaths were estimated to occur in 2014 worldwide (WHO, 2015c). Twenty-two high-burden countries defined by the World Health Organization (WHO) account for 80% of all TB cases. Despite the availability and affordability of effective TB medication South Africa has the highest prevalence and incidence rates (696 and 834 cases per 100,000 population) among these countries (WHO, 2015c) TB is South Africa´s leading cause of mortality (134 cases per 100,000 population). TB is known to impact health-related quality of life (HRQOL) (Bauer et al., 2013, Chang B, 2004, Guo et al., 2009). Effective treatment, relapse and the emergence of multi-drug resistant TB (MDR-TB) are closely related to TB treatment adherence and consequent HRQOL (Munro S, 2007). The assessment of an association between both, HRQOL and medication adherence in TB, would provide valuable information on treatment effectiveness, optimal disease management and health policy making.

Patient-reported outcomes (PRO's) provide unique evidence of different aspects of the experience of living with a disease or condition and how important these aspects are to patients. In this sense, they go beyond clinical parameters and respect the integrated nature of health, ideally encompassing physical, mental and social well-being. The measurement of HRQOL using PRO's allows for a multidimensional understanding of health, an evaluation of disease and treatment impact on the health condition and the patients' daily life. It is strongly related to the World Health Organization's (WHO's) definition of health as "*a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity*" (WHO, 1948). A comprehensive knowledge of HRQOL in TB patients can allow for identification of treatment gaps. Addressing these gaps will lead to improvement of health care services and disease prevention strategies, and support health policy making. A number of countries such as the UK, Germany and Australia rely on PRO data about medical interventions for pricing, reimbursement and health policy decision-making about medical interventions. South Africa is becoming increasingly aware of the importance of such outcome evaluations and has released its first guidance on pharmacoeconomic submissions in February 2013 (NDoH, 2013). The aim of this systematic review was to understand HRQOL and medication adherence during TB treatment and how both concepts are associated based on international literature. Longitudinal studies were of particular interest to understand changes in HRQOL and adherence during the course of TB treatment. The focus of this research lies on active pulmonary TB and not on latent TB (LTBI), MDR-TB, XDR-TB, TB in children or TB with HIV co-infection, as these types of TB show different HRQOL outcomes

(Brown et al., 2015). As South Africa suffers from a major TB burden, we put a specific focus on HRQOL and adherence to TB treatment in the South African health setting.

**Keywords**

Health-related quality of life, medication adherence, tuberculosis, patient-reported outcomes, South Africa

## 4.3 Review

### 4.3.1 Methods

#### Search Strategy for identification and selection of relevant studies

A systematic literature search has been performed in PubMed, EMBASE and PsychINFO, with the last search conducted on 22 February 2015. Search terms applied included *tuberculosis, health related quality of life, HRQOL, quality of life, South Africa, patient-reported outcomes, outcome assessment, life quality, well-being, adherence, non-adherence, and compliance*; different combinations were used (Table 1 in the Appendix). Each search term combination resulted in different initial hits which were screened by title and abstract. Articles were excluded if they were not related to the pre-defined search terms or were published in a language other than English. Duplicates were removed. The full texts of all remaining articles were reviewed. References cited by the identified publications were additionally scanned for relevant studies. Data on TB and adherence was additionally taken from the WHO and the Department of Health of the Republic of South Africa. Data from articles with a longitudinal study design were separately extracted and included when psychometric validity and reliability were reported for HRQOL or adherence measures, when changes in HRQOL during TB treatment including at least baseline and end of treatment were reported, and when the study population consisted of new TB cases treated as outpatients.

#### Data Quality and Data Extraction

Data from all identified articles was extracted and structured according to physical, mental and social health aspects of HRQOL; data on medication adherence was summarized. Research on HRQOL and medication adherence in South Africa was described separately. In addition, studies with a longitudinal design were subject to a separate; subsequent data extraction performed by two independent reviewers. This additional extraction covered the PICOS elements (P = population, I = intervention, C = comparator or control, O = outcome, S = study design), with additional items covering major research topic, study objective, study setting,

sample size, PRO measure applied, and measurement time points. Prior to data extraction, all longitudinal studies underwent quality assessment. As longitudinal studies were observational in nature, quality of reporting was evaluated using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Bauer et al., 2013). A STROBE quality checklist with 8 items was applied, with scores ranging from 0 (no quality) to 16 (best quality) (Bauer et al., 2013).

### 4.3.2 Results

Our literature search in PubMed, EMBASE and PsychINFO yielded 988 initial hits. After screening by title and abstract and after removal of duplicates, 61 articles remained. An addition of three WHO reports, two guidelines from the South Africa´s Department of Health and one article identified by hand search of citations resulted in 67 eligible articles for this systematic review. One article was excluded, yielding 66 eligible full-text articles (Figure 6). A detailed description of the literature search is available in the Appendix. The 66 articles comprised 22 cross-sectional studies, 17 longitudinal studies, 7 (systematic) reviews, 8 qualitative studies and 12 articles including editorials, comments and letters. Nine studies were performed in South Africa (four HRQOL and five medication adherence studies; Table 4 in the Appendix). All final 66 articles underwent extraction of information about HRQOL and adherence in TB. The 17 identified longitudinal studies were potentially eligible for separate data extraction; 11 of them actually met the eligibility criteria for separate data extraction, while 6 studies were excluded as eligibility criteria were not met (Table 3 in the Appendix). Application of the STROBE quality of reporting checklist to the 11 longitudinal studies resulted in a median score of 7 for HRQOL studies, with scores ranging from 5 to 11 out of 16 (the greater the score the higher the quality of reporting). The adherence study had a score of 10 (Table 3 in the Appendix).

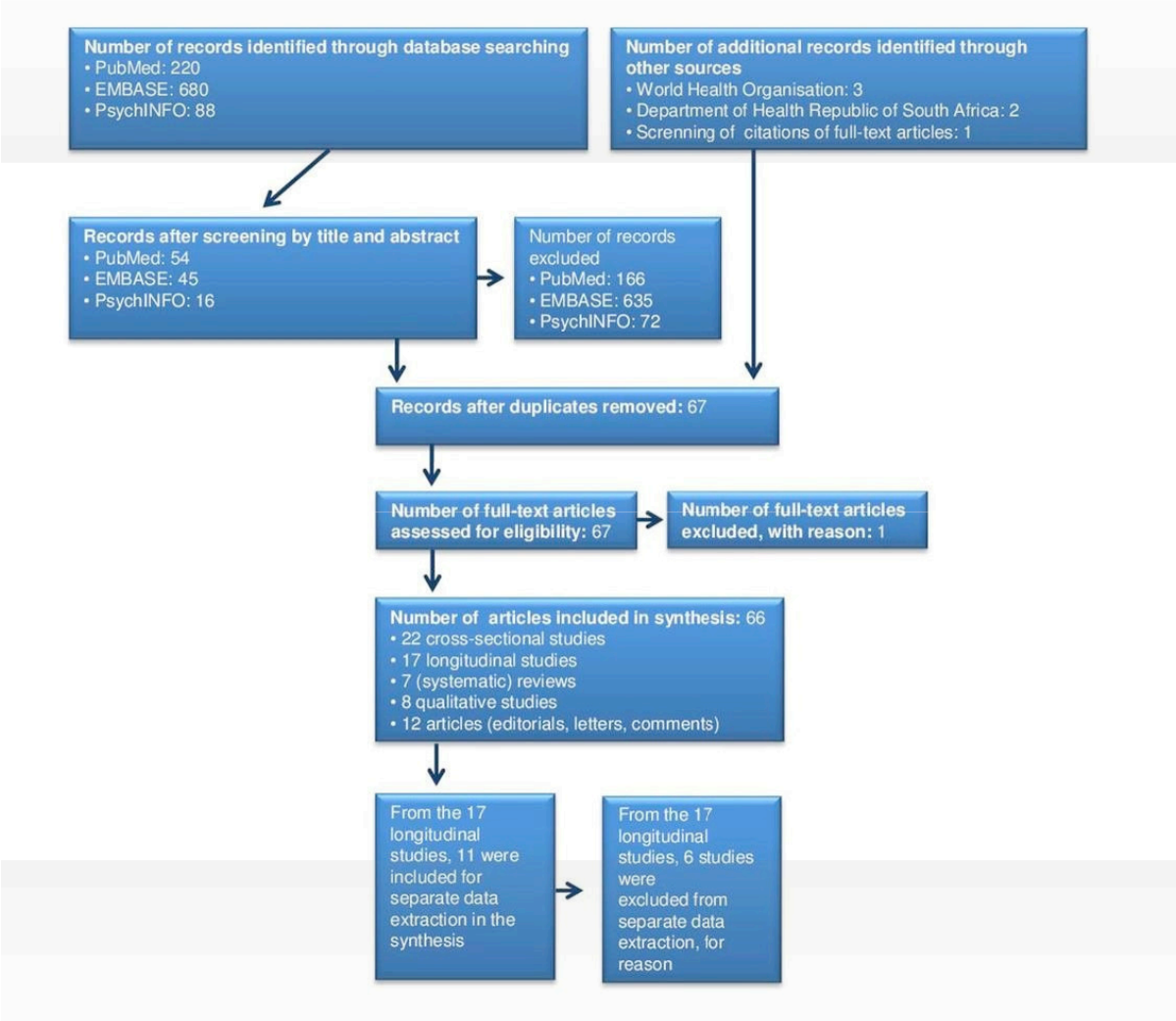


**Figure 6:** Flow diagram of literature search. Literature search process was conducted in the databases PubMed, EMBASE and PsychINFO; additional articles were obtained from World Health Organization and Department of Health Republic of South Africa.

## TB impact on HRQOL

The systematic review found that TB has a negative impact on patients' HRQOL and overall wellbeing (Masumoto et al., 2014, Aggarwal et al., 2013, Babikako et al., 2010, Rajeswari et al., 2005, Chang B, 2004, Hansel NN, 2004). Factors associated with HRQOL in TB included socio-demographic (age, gender) and socio-economic (income, education, housing, social security) factors, disease-related (symptoms) and therapy-related (side effects, adverse events) factors, and psycho-social aspects (isolation and stigmatization, psycho-social burden) (Adeyeye et al., 2014, Masumoto et al., 2014, Aggarwal et al., 2013, Bauer et al., 2013, Deribew A, 2013, Dias et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Chung et al., 2012, Kittikraisak et al., 2012, Louw et al., 2012, Othman, 2011, Aggarwal, 2010, Guo et al., 2010, Dhuria et al., 2009, Guo et al., 2009, Guo N, 2008, Marra et al., 2008, Chamla, 2004, Hansel NN, 2004, Marra et al., 2004). There was some evidence to

suggest that amongst TB patients, psycho-social burden may have a greater impact than clinical symptoms (Chang B, 2004, Hansel NN, 2004). The results of this literature review identified that TB treatment resulted in a significant improvement in HRQOL, especially in physical and psychological dimensions (Aggarwal et al., 2013, Bauer et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Louw et al., 2012, Othman, 2011, Guo et al., 2009, Guo N, 2008, Chamla, 2004). The improvement in HRQOL was greatest during the first 2-3 months (intensive treatment phase) (Bauer et al., 2013, Othman, 2011). The results also revealed that although a patient was defined as microbiologically cured following successful treatment, morbidity still existed due to anatomic and functional changes of the lung at treatment completion (Ralph et al., 2013, Pasipanodya et al., 2007b, Weis and Pasipanodya, 2010, Muniyandi et al., 2007). Specifically, a state of chronic morbidity continued which resulted in health quality loss that differed for developing countries with regard to their socio-demographic and -economic situation (Diel and Lampenius, 2014, Miller et al., 2009, Pasipanodya et al., 2007a). It was also noted that the assessment of HRQOL has currently not been integrated into the WHO guidelines for TB treatment, national guidelines or TB control programmes (Atif et al., 2012a). An important consideration from the results of the review was that patient-reported HRQOL outcomes may differ after the end of treatment depending on the HRQOL measures applied as different measures may measure different concepts (Aggarwal et al., 2013, Chung and Li, 2013, Balgude and Sontakke, 2012, Kruijshaar et al., 2010, Guo et al., 2009, Dion et al., 2004).

### TB impact on Physical Health

TB impacts physical health, resulting in impaired physical functioning, development of fatigue, adverse events of treatment and increased use of health care services. Major physical impairment was reported through somatic symptoms and other TB related physiological outcomes (Awaisu et al., 2012, Guo et al., 2009, Chang B, 2004, Hansel NN, 2004). The impairment in HRQOL was worse in patients with HIV co-infection (Deribew A, 2013). Impaired physical functioning was closely related to the development of fatigue (Chang B, 2004, Hansel NN, 2004). The literature revealed that fatigue was triggered through sleep disturbances, coughing and malnutrition, and TB medication (Hansel NN, 2004). Drug-based treatment of TB impacted HRQOL in two ways. Whilst the TB treatment resulted in a significant improvement in HRQOL (Aggarwal et al., 2013, Bauer et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Louw et al., 2012, Guo et al., 2009, Chamla, 2004), the drugs taken often resulted in adverse drug reactions which negatively affected HRQOL (Hansel NN, 2004). The greatest physical impact on HRQOL was caused by the large quantity of pills and the treatment duration, and a reduction in both was expected to improve HRQOL (Hansel NN, 2004). Health care services may have a negative effect on HRQOL through the relationship between healthcare worker and patient, especially due to a lack of knowledge and

misunderstanding about TB. This relationship was not only important for the degree of compliance with the current TB treatment guidelines, but also comprised emotional support and disease-related information through nurses (Dias et al., 2013, Atif et al., 2012b).

## TB impact on Mental Health

The impact of TB on mental health related to psychological, emotional and spiritual wellbeing, and patients perception of their health. Psychological distress was commonly reported among TB patients (Peltzer K, 2012, Naidoo and Mwaba, 2010), with depression and anxiety being the most frequently reported mental disorders (Peltzer K, 2012, Aamir and Aisha, 2010), especially in TB patients diagnosed with post-traumatic stress disorder (PTSD) (Peltzer et al., 2013). Besides depression and anxiety, feelings of anger were also reported (Hansel NN, 2004). Psychiatric co-morbidity may increase the distress of physical illness, prolong recovery time, and may also lead to poor treatment compliance (Naidoo and Mwaba, 2010). Psychological distress may be caused by social stigmatization followed by social isolation during TB treatment and impacted financial situation (Peltzer K, 2012, Issa BA, 2009, Hansel NN, 2004). Mental disorder in TB patients was associated with socio-demographic and economic factors and in HIV co-infected TB patients also with stigmatization and perceived health status (Peltzer K, 2012, Deribew A, 2013); a misconception about TB including fear of dying, disease transmission, disease symptoms and treatment leads to lower cure and survival rates as the patient may act according to this misconception (Dias et al., 2013, Hansel NN, 2004). Prevalence rates of depression and mental disorders among TB patients in low income countries ranged between 46% to 80% (Peltzer K, 2012, Aamir and Aisha, 2010). About 20% of non-adherent TB patients in Pakistan reported depression and anxiety after treatment completion and developed a multi-drug resistance (Aamir and Aisha, 2010). TB can also have an impact on caregivers. In Malaysia caregivers reported poor mental health and an increased risk of depression (Atif et al., 2013). TB may affect spiritual wellbeing. Patients in the USA experienced TB as a wake-up call which changed their lifestyle in a positive way. These patients stopped drinking alcohol, adopted a healthier lifestyle and became more concerned about their health (Hansel NN, 2004).

## TB impact on Social Health

Diagnosis and treatment of TB can have an impact on social health including reduced social functioning and an increased financial burden as a result of stigmatization (Hansel NN, 2004). Social functioning often comprises roles at the workplace, in the community and within the family (Chang B, 2004, Hansel NN, 2004). The infectious nature of TB can lead to a stigma and disruption of social interaction with others, resulting in social isolation (Dhuria et al., 2009). TB-related stigmatization was often associated with stigma of HIV and AIDS (Naidoo and Mwaba, 2010, Van Rie et al., 2008). Many TB patients were unable to work due to the travel

distance between a health clinic they get the treatment from and workplace, but also due to the disease induced worsening of their physical condition (Dias et al., 2013, Chang B, 2004, Hansel NN, 2004). This may affect the financial and economic situation of TB patients in terms of limited work capacity or inability to work which could lead to a decrease in income or even a total loss of income (Hansel NN, 2004, Dias et al., 2013). Saving travel expenses to reduce the financial burden may lead to medication non-adherence (Chang B, 2004). Some studies indicated that a better financial empowerment could improve TB-related depression, medication adherence and HRQOL (Peltzer K, 2012, Issa BA, 2009). Often family members needed to get involved as caregivers leading to a loss of income by either through reducing their own work (Chang B, 2004) or by providing financial support to the patients (Hansel NN, 2004). TB induced fatigue may impair the sexual function of the patient (Hansel NN, 2004).

### South African studies on HRQOL in TB

In this review four studies which evaluated HRQOL in TB patients in South Africa were identified. All of them applied a cross-sectional design and had a strong focus on psychological distress and mental health (Peltzer et al., 2013, Peltzer K, 2012, Louw et al., 2012, Naidoo and Mwaba, 2010) (Table 3 in the Appendix). The evidence shows that TB impacted physical functioning and mental health domains of HRQOL. Mental disorders and psychological distress were present in TB and TB/HIV co-infected patients (Peltzer K, 2012). Depression was most prevalent (64%), followed by PTSD (30%), feeling of helplessness and a lack of social support (Peltzer et al., 2013, Naidoo and Mwaba, 2010). It was proposed that the integration of screening, treatment and mental health care services for TB patients (Peltzer et al., 2013, Peltzer K, 2012) would improve the quality of health and health outcomes of TB and HIV co-infected patients in South Africa (Louw et al., 2012).

### Adherence to Treatment

Medication adherence is a complex, multi-dimensional, dynamic phenomenon comprising patient behavior with regard to the prescribed interval, dose, and dosing regimen as well as appropriateness of how the medication is taken (Cramer, 2008, Hughes, 2007). In the absence of drug resistance, TB is a curable disease with a six month treatment of antibiotics (Chirwa T, 2013). Medication adherence is a key factor for treatment success (NDoH, 2014), and might have a greater impact on a population´s health than any improvement in specific medical treatments (WHO, 2003). Adherence during the intensive treatment phase (first two months) increases the chance for cure in newly diagnosed patients (Chirwa T, 2013). In contrast, non-adherence leads to spread of free TB bacteria in the community; this may impact the patient by resulting in disability, drug resistance, relapse and risk of death and the community by increased health costs (NDoH, 2014, Chirwa T, 2013, Cramm JM, 2010, Husain MO, 2008). There is no gold standard on how to measure medication adherence. Conventional ways of

adherence control in TB include pill counting and Directly Observed Treatment (DOT); under DOT medication intake is directly observed and thereby it is a surveillance tool to control adherence. A Cochrane systematic review (Volmink and Garner, 2007) compared DOT with self-supervised TB medication treatment. While DOT is an objective mechanism to control adherence, self-supervised treatment depends on the subjective adherence behavior of the patient. The Cochrane review showed no differences in adherence between the two approaches; further clinic based DOT and community based DOT showed no differences. DOT is a key element of DOTS (Directly Observed Therapy, Short course), a TB management programme from WHO that comprises five elements: government control, detection, medication supply, supervised treatment, and monitoring of TB (Naidoo P, 2009, Volmink and Garner, 2007). Although DOTS is commonly practiced, the cure rates in some countries are still low due to poor adherence (Naidoo P, 2009). A number of studies (14, 40, 41, 43, 47, 48, 50, 54-57) identified qualitatively different factors affecting adherence based on behavioral sciences: therapy-related (adverse events), condition-related (TB symptoms, psychological stress and depression), socio-economic and demography-related (gender, age, food access, education, marital status), health system related (inadequate relationship between health care provider and patient, poor health infrastructure), and patient-related (forgetfulness, drug abuse). Adherence may also be influenced by family pressure, insufficient social support, a fear of disclosure, migration within the country or to neighboring countries. Health beliefs of the patient play a major role in adherence (Cramm JM, 2010, Husain MO, 2008) and may impact adherence positively (Dujaili et al., 2015, Aamir and Aisha, 2010, Husain MO, 2008, McInerney et al., 2007, Rowe KA, 2005). or negatively (Cramm JM, 2010, Naidoo P, 2009). Material incentives and enablers promote and assist adherence to TB treatment through higher clinic attendance (Lutge EE, 2012, Rowe KA, 2005). Material incentives include cash or non-cash vouchers and promote adherence in form of a positive reward of the patient´s adherence behavior. Enablers assist adherence by directly acting to overcome financial barriers to treatment such as transport vouchers or food; it is unknown whether incentives and enablers will improve adherence in the long-term (Lutge EE, 2012).

## South African Studies on Adherence

Four studies assessed adherence to TB medication in South Africa: two cross-sectional studies (Lutge E, 2013, Corless et al., 2009) and two qualitative studies (Cramm JM, 2010, Naidoo P, 2009) (table 3 in Appendix). These studies indicated that TB patients were more adherent during the first two months of treatment (intensive phase) when symptoms were more present. Patients believed that they could be cured through effective treatment and through a good health alliance with their health care professional (Cramm JM, 2010, Naidoo P, 2009). A qualitative study by Naidoo et al (Naidoo P, 2009) identified a number of themes in a DOTS environment in South Africa which affect adherence behavior. Non-adherence was related to

poverty, HIV co-infection, stigmatization, an unsupportive social and work environment, and feelings of helplessness and hopelessness (Naidoo P, 2009). Although the psycho-social burden in TB was higher than in HIV patients, adherence to both treatments was comparable and the psycho-social burden did not impact adherence (Corless et al., 2009). Non-adherence was mainly affected by limited food access, a lack of public transport to clinics, the cost of transport, and through social stigmatization (Cramm JM, 2010, Naidoo P, 2009). The two cross-sectional studies observed adherence by economic incentives and by patient reported outcomes. One study revealed that material incentives such as monthly vouchers of US$15 given during treatment did improve treatment completion; 35% of patients receiving no material incentives completed treatment while 43% of patients receiving vouchers did complete the treatment (Lutge E, 2013). However the study was affected by a low fidelity to the delivery of vouchers in public health clinics and further research into this is required. The other study compared medication adherence between TB and HIV patients by applying the patient-reported Morisky Medication Adherence Scale and by counting missed appointments (Corless et al., 2009). On average TB patients missed 1.85 days of treatment and had a good self-reported adherence in this study.

### The Association between HRQOL and Adherence during TB

Our systematic review identified one study which addressed the association between well-being and adherence in TB. This study was a meta-analysis of 44 qualitative studies including 8 studies from South Africa about adherence to TB treatment by Munro et al (Munro S, 2007). The systematic review indicated two underlying mechanisms for the association between well-being and adherence. The first mechanism related to TB patients prematurely stopping their treatment because they felt better. The reason was that patients perceived the improvement in well-being as a cure of TB. On the other hand, the second observed mechanism referred to patients stopping treatment when they experienced no improvement or a worsening in their health status and well-being (Munro S, 2007, WHO, 2003).

### HRQOL and adherence in longitudinal studies

Ten observational studies with a longitudinal design evaluating HRQOL in new smear-positive TB cases receiving TB treatment were eligible for separate data extraction as shown in table 2 (Atif et al., 2014a, Mamani et al., 2014, Aggarwal et al., 2013, Ralph et al., 2013, Balgude and Sontakke, 2012, Kruijshaar et al., 2010, Dhuria et al., 2009, Maguire et al., 2009, Marra et al., 2008, Chamla, 2004). Three studies took place in India (Aggarwal et al., 2013, Balgude and Sontakke, 2012, Dhuria et al., 2009), two in Indonesia (Ralph et al., 2013, Maguire et al., 2009), and one each in Canada, China, Malaysia, the UK and Western Iran (Marra et al., 2008, Chamla, 2004, Atif et al., 2014a, Kruijshaar et al., 2010, Mamani et al., 2014). Studies evaluated HRQOL at diagnosis or before treatment, after 4 weeks of treatment, at switch from

intensive to continuous phase at two months following treatment initiation, after three months and at the end of treatment after six month. Only one study did not include HRQOL data for the end of treatment time point (Kruijshaar et al., 2010). Sample size varied from 30 (Balgude and Sontakke, 2012) to 1034 (Aggarwal et al., 2013) with a mean sample size of 206. Seven different HRQOL measures indentified in this review; three were generic (SF-36, WHOQOL-BREF, EQ-5D), three were dimension-specific measures, either for depression (BDI and Center for Epidemiologic Studies Depression Scale), or for anxiety (State-Trait Anxiety Short Form), and one was respiratory-specific (St. George´s Respiratory Questionnaire (SGRQ)). Independent from HRQOL measure and health setting, all studies reported impaired HRQOL before TB treatment and an improvement in HRQOL due to TB treatment. However, it was noted that residual impairment in HRQOL remained in some patients after successful treatment (Aggarwal et al., 2013, Atif et al., 2014a, Dhuria et al., 2009, Marra et al., 2008). Variables which were shown to predict lower HRQOL prior to treatment initiation included low socio-economic status and depression (Atif et al., 2014a, Kruijshaar et al., 2010). It was also identified from the studies included in the review that HRQOL is most affected in physical and psychological or mental domains (Chamla, 2004, Mamani et al., 2014). The greatest improvement observed in HRQOL due to treatment was in the physical domain (Kruijshaar et al., 2010, Dhuria et al., 2009).

In terms of adherence, there was only one study identified that followed a longitudinal approach (Chirwa T, 2013). This study assessed medication adherence by counting missing days from patient medical record cards. About 35% of patients were non-adherent to TB treatment, with the majority missing less than 15 days of treatment. No longitudinal study addressed the association between HRQOL and adherence in TB.

Table 2: Data Extraction of longitudinal studies evaluating HRQOL and adherence in TB

| Reference | **Study Objective** | **Study Setting/ Sample Size** | **Population** | **Comparator Group** | **HRQOL Measure** | **Application time point of HRQOL Measure** | **Overall Outcome in HRQOL** | **Outcomes in HRQOL Domains** |
|---|---|---|---|---|---|---|---|---|
| Aggarwal et al 2013 (Aggarwal et al., 2013) | To quantify impairment in HRQOL and to evaluate the utility | India<br><br>N=1034 | Newly diagnosed PTB patients | None | WHOQOL-BREF<br><br>Hindi version | 1st time point: within 2 weeks of initiating intensive phase<br>2nd time point: within 2 weeks of switching to continuation phase<br>3rd time point: within 2 weeks of stopping treatment | Impaired HRQOL improves significantly with anti-tuberculosis treatment. Residual impairment is noticed in some patients at the end of treatment | Patients in urban areas and those with higher socioeconomic status (SES) have higher domain scores and better HRQOL. The WHOQOL-BREF physical and psychological domain scores are significantly lower and more affected than other domains. |
| Atif et al 2014 (Atif et al., 2014a) | To evaluate the impact of TB treatment on HRQOL | Malaysia<br><br>n=216 | New smear positive PTB patients; no HIV co-infection | None | SF-36 v2<br><br>Tamil, Malay and Mandarin version | 1st time point: start of treatment<br>2nd time point: end of intensive phase<br>3rd time point: end of treatment | Impaired HRQOL improves significantly with anti-tuberculosis treatment. Scores in the physical and mental health components were still impaired after end of treatment | Health domains improve between baseline and end of the intensive phase, and end of treatment, except for bodily pain and vitality. At the start of treatment, 67.1% of patients are at risk of depression, compared to 35% at end of intensive phase and 23.5% at end of treatment. Patients aged <45 years and/or non-smokers have a better mean physical component summary (PCS) score. Lower and affected mental health is related to smoking, low income and presence of more than three TB symptoms. |

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| Balgude et al 2012 (Balgude and Sontakke, 2012) | To assess the impact of TB and treatment on HRQOL | India<br><br>n= 60, (30 patients and 30 controls) | Newly diagnosed smear positive TB patients | Healthy control from the general population | WHOQOL-BREF plus 2 items examined separately | 1st time point: baseline 2nd time point: after 2 months<br>3rd time point: after 4 months | At baseline, HRQOL is significantly affected with physical and psychological domains most affected. All domains improve after 2 and 4 month treatment. | Mean scores of patients' physical and psychological domains are lower than controls at all 3 time points of assessment. There is significant improvement in the scores at 2 & 4 months of treatment. The mean scores of patients' environmental and social domains are lower than control at baseline, but improve at 4 months of treatment and are comparable to control |
| Chamla 2004 (Chamla, 2004) | To assess impact of TB and treatment on HRQOL | China<br><br>n= 205, (102 patients and 103 controls | TB patients | General population without TB | SF-36<br><br>Chinese version | 1st time point: before treatment<br>2nd time point: after 2 months<br>3rd time point: end of treatment. | HRQOL is impaired at baseline with physical scales most affected and improves due to treatment. | Treatment improves all domains; at end of treatment physical functioning, role-emotional, bodily pain, social functioning, and general health are not different from control. Physical scales are more commonly affected than mental health scales. |
| Dhuria et al 2009 (Dhuria et al., 2009) | To assess impact of TB and treatment on HRQOL | India<br><br>n=180, (n=90 patients and 90 controls) | TB patients | General population matching for age, gender, and socioeconomic status | WHOQOL-BREF<br><br>Hindi version | 1st time point: baseline 2nd time point: 3 months<br>3rd time point: end of treatment. | TB patients have an impaired HRQOL with significant improvement in all domains except social domain after treatment. | The highest improvement is in physical domain, followed by psychological domain. The mean score of overall HRQOL and physical domain at completion of treatment is better in females than males. Males score better in psychological, social and environmental domains. After end of treatment HRQOL is still affected in physical domains compared to healthy controls. |

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| Kruijshaar et al 2010 (Kruijshaar et al., 2010) | To assess the impact of TB and its treatment on patients' health status | UK<br><br>n=61 | TB patients | None | SF-36 v2<br>UK version<br><br>EQ-5D<br>STAI-6<br>CES-D | 1st time point: diagnosis<br>2nd time point: 2 months | Impaired HRQOL improves already after 2 month treatment, but is still below the UK norm score | SF-36 v2 scores improve significantly except for physical functioning, general health perceptions, and physical summary score. Vitality, mental health, and mental health summary scores are comparable to the UK norm. EQ-5D: pain/discomfort and problems with self-care improve while a borderline decrease is seen for mobility, except for self-care. Depression and anxiety improved due to treatment (CES-D and STAI-6 scores). 51% report economic burden due to TB. |
| Maguire et al 2009 (Maguire et al., 2009) | To quantify the impact of TB HRQOL | Indonesia<br><br>n=115 | smear positive PTB patients | None | SGRQ | 1st time point: baseline 2nd time point: 2 months 3rd time point: 6 months | Impaired HRQOL improves with treatment at 2 and 6 months | Although HRQOL improves due to treatment<br>24.6% of patients still have significant lung function impairment after at end of treatment |
| Mamani et al 2014 (Mamani et al., 2014) | To assess the QOL among TB patients | Iran<br><br>n=184 (64 patients and 120 controls) | Pulmonary and extrapulmonary TB patients | Healthy control from general population | SF-36<br><br>Persian version | 1st time point: baseline 2nd time point: 2 months 3rd time point: 6 months | Impaired HRQOL improves due to treatment compared to controls | All domains of SF-36 are significantly impaired and improve after 2 month treatment; improvement between two and six months is not significant. Physical functioning and energy are most affected. |

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| Marra et al 2008 (Marra et al., 2008) | To identify areas of HRQOL affected by latent and active TB; treatment impact on HRQOL | Canada<br><br>n=206 (104 active TB and 102 latent TB) | Active and latent TB patients (LTBI) | LTBI defined as a positive TST result without radiographic or clinical evidence of active TB | SF-36 v2<br><br>BDI | 1st time point: baseline 2nd time point: 3 months 3rd time point: 6 months | At baseline HRQOL is more affected in active than latent TB patients. Treatment improves HRQOL in active but not in latent TB. Patients with active TB have still impaired HRQOL after treatment completion compared to US norms. | All domains of SF-36 improve over treatment in active and latent TB except bodily pain in active and except social functioning and vitality in latent TB. BDI shows no improvement in LTBI participants, but significant improvement for those with active TB. |
| Ralph et al 2013 (Ralph et al., 2013) | To investigate morbidity over TB treatment period | Indonesia<br><br>n=240, (200 patients and 40 controls) | smear positive TB | Healthy control from the general population | SGRQ<br><br>Indonesian version | 1st time point: baseline 2nd time point: 4 weeks 3rd time point: 8 weeks 4th point time: 24 weeks | Impaired HRQOL improved over treatment time. | After treatment 27% of TB patients have moderate to severe pulmonary function impairment. HIV -positive status was significantly associated with worse HRQOL |

| Reference | **Study objective** | **Study Setting** | **Population** | **Comparator Group** | **Adherence Measure** | **Application time point of Adherence Measure** | **Overall Outcome in Adherence** | **Specific Outcome in Adherence** |
|---|---|---|---|---|---|---|---|---|
| Chirwa et al 2013 (Chirwa T, 2013) | To estimate cure rates, and their association with adherence to TB treatment | Malawi<br><br>n=524 | TB patients | None | Retrospective counting of missing days during treatment | Retrospective review of records | Adherence to TB treatment had a significant effect on cure of TB | Overall, 35.1% of patients did not fully adhere to TB treatment. Of these, 86.4% missed < 15 days and 23.4% missed at least 1 day of treatment Overall, 92.7% of patients were cured from TB and 33.7% of these missed at least 1 day of treatment. Patients who missed <15 days and 15 to 29 days of treatment were less likely to be cured compared with those who fully adhered. |

## 4.4 Discussion

This systematic review addressed the issues relevant to understand the impact of TB on HRQOL and medication adherence from a global perspective and specifically for South Africa using an integrative health approach. TB impacts the physical, emotional, psychological, social and economic dimensions of HRQOL, and residual impairment may be still present after treatment. We identified thirty-six studies evaluating HRQOL in TB of which twenty-one studies took place in WHO´s high-burden TB countries. Atif et al (Atif et al., 2014b) reported that most HRQOL studies in TB so far applied a cross-sectional design and our systematic review confirms this finding. Thirteen studies across high-burden countries had a cross-sectional design while only eight studies evaluated longitudinal changes (Table 3). To date, very few studies have followed changes in HRQOL longitudinally over time in TB patient populations. No longitudinal study has been conducted in South Africa even though South Africa has the highest prevalence and incidence among the 22 high-burden TB countries worldwide. Our understanding of the long-term impact of TB on HRQOL, covering the time of treatment and after treatment, is limited. There is a need for further research assessing changes in HRQOL longitudinally, specifically in high-burden countries like South Africa. Most studies on medication adherence during TB treatment employed a qualitative approach observing psychometric aspects of adherence. One systematic review of qualitative studies reported an association between HRQOL and adherence TB (Munro S, 2007). We found that similar factors affect HRQOL and adherence including TB therapy, health condition, socio-economic and demographic factors as well as quality of health care services. Studying the association between HRQOL and medication adherence during TB treatment will allow for a better understanding of how treatment effectiveness can be improved and care for TB patients optimised.

**Table 3:** Eligible Studies included in Data Extraction Representation of eligible studies included in the systematic review and listed according to their WHO high-burden country status.

| WHO high-burden country | Total Number of HRQOL studies | Cross-sectional Design | Longitudinal Design |
|---|---|---|---|
| **China** | 2 (Yin et al., 2012, Chamla, 2004) | 1 | 1 |
| **India** | 6 (Dhingra and Rajpal, 2005, Dhuria et al., 2009, Balgude and Sontakke, 2012, Aggarwal et al., 2013, Muniyandi et al., 2007, Rajeswari et al., 2005) | 1 | 5 |
| **Indonesia** | 2 (Maguire et al., 2009, Ralph et al., 2013) | | 2 |

| | | | |
|---|---|---|---|
| **Nigeria** | 2 (Issa BA, 2009, Adeyeye et al., 2014) | 2 | |
| **Pakistan** | 1 (Husain MO, 2008) | 1 | |
| **Philippines** | 1 (Masumoto et al., 2014) | 1 | |
| **South Africa** | 6 (Louw et al., 2012, Peltzer K, 2012, Peltzer et al., 2013, McInerney et al., 2007, Naidoo and Mwaba, 2010, Corless et al., 2009) | 6 | |
| **Uganda** | 1 (Babikako et al., 2010) | 1 | |
| **Other countries** | **Total Number of HRQOL studies** | **Cross-sectional Design** | **Longitudinal Design** |
| **Canada** | 3 (Dion et al., 2004, Guo N, 2008, Marra et al., 2004) | 2 | 1 |
| **Iraq** | 1 (Dujaili et al., 2015) | | 1 |
| **Malaysia** | 4 (Atif et al., 2013, Atif et al., 2014b, Atif et al., 2014a, Awaisu et al., 2012) | 3 | 1 |
| **Taiwan** | 1 (Chung et al., 2012) | | 1 |
| **Thailand** | 1 (Kittikraisak et al., 2012) | 1 | |
| **UK** | 1 (Kruijshaar et al., 2010) | | 1 |
| **USA** | 2 (Pasipanodya et al., 2007a, Pasipanodya et al., 2007b) | 2 | |
| **Western Iran** | 1 (Mamani et al., 2014) | | 1 |
| **Yemen** | 1 (Othman, 2011) | 1 | |

**Table 3:** Representation of eligible studies included in the systematic review and listed according to their WHO high-burden country status.

The studies included in this systematic review revealed similar HRQOL outcomes with a number of different measures, but a TB-specific measure is lacking. Although two studies

reported developing TB-specific measures, FACIT-TB in Iraq (59) and DR-12 in India (68), neither provides adequate evidence for validity or reliability. Measures applied during longitudinal HRQOL studies were generic (SF-36, WHOQOL-BREF, EQ-5D) and dimension-specific measures, either for depression (BDI and Center for Epidemiologic Studies Depression Scale) or for anxiety (State-Trait Anxiety Short Form), one measure was specific for respiratory diseases (SGRQ). All measures reported similar HRQOL outcomes for TB and confirmed that physical health domains were more affected than mental health domains. All health domains for each measure improved during TB treatment. However, physical impairment was still present after treatment. The measures only capture parts of the health domains relevant to TB or may not be sensitive enough to observe the actual impact of TB on HRQOL. This implies the need for a TB-specific PRO measure which captures all relevant health domains and health aspects of TB including the physical, psychological, and social domains. Such a measure will need to consider socio-demographic and cultural differences between patients with TB, taking into account the stigma of HIV and how the social standing of the patient within his or her community is affected. The development of such a specific measure will also allow a deeper understanding of MDR-TB, TB/HIV co-infection and extrapulmonary TB. Future studies should also include the identification of minimal clinically important difference (MCID), i.e. the smallest difference in a domain which patients perceive as an improvement or a worsening; this is unknown for TB patients and will allow understanding meaningful changes in HRQOL.

Current evidence regarding the association between HRQOL and adherence in TB is lacking globally. Future research about the association between HRQOL and adherence in TB specific will help to optimize existing treatment programs, understand the limitations in TB control and targeted interventions and improving the health status of high-burden TB populations. The WHO´s End TB Strategy targets a TB free world by 2035. One of the three strategic pillars to reach this goal focuses on integrated, patient-centred TB care and prevention. HRQOL assessment allows an integrative understanding of TB from a patient perspective. Resulting knowledge supports an understanding of TB-related physical, mental and social needs and addresses diverse barriers. This patient-centred approach may support quality assessment and rationale use of medicines, which fall under the pillars of the End TB Strategy.

This systematic review had several strength and limitations. It combined qualitative and quantitative research on HRQOL and adherence and this mixed method may be viewed as strength as it ensures capturing all relevant information on the topic. The methodological quality of the eligible studies varied and might have an effect on the reported outcomes. We only applied the STROBE Statement for quality reporting to longitudinal studies; we observed a moderate reporting quality with a median of 7 out of 16 points, indicating that the quality of

the articles included in this review were fairly poor. This might affect the reported information. Most studies applied different PRO measures at differing time points during treatment at different study sites, making any general conclusions regarding the impact of TB on HRQOL difficult. Studies had an observational nature rather than a controlled trial design as mostly applied in systematic reviews; however, observational studies might be more reliable as they observe patients in real life rather than under controlled ideal conditions. Publication bias may be present in this systematic review although our findings were consistent across different settings; we selected peer-reviewed literature from three different databases and included grey literature to control for publication bias. We did not include unpublished information and studies published in a different language than English.

## 4.5 Conclusions

The relevance and importance of HRQOL assessments is growing and HRQOL has become an important tool for the understanding of health outcomes adopting a patient-centred approach to care and treatment. Further research is required in a country-specific context to contribute to efficient decision making with regard to TB related strategies; product approval, pricing and reimbursement as well as health policy making; A number of new anti-TB drugs, vaccines and diagnostics have recently achieved marketing approval or are in late clinical development. Assessment of longitudinal changes in HRQOL and its association to medication adherence in TB in a high TB burden country such as South Africa are not yet available. Such data would support the identification of sustainable health innovations in TB by providing information on benefits and gaps in current treatment strategies tailored for a specific patient population. This will be useful to determine the value of new products and to perform appropriate cost-effectiveness analyses to optimize the allocation of societal resources specifically for South Africa. This is of high relevance as a number of new TB drugs, vaccines and diagnostics have recently achieved marketing approval or are in late clinical development. A longitudinal study assessing HRQOL and medication adherence in active TB in South Africa applying valid and reliable measures that capture all relevant aspects of TB would be necessary to assess the achievement of the WHO´s End TB Strategy pillars.

## 4.6 Declarations

### 4.6.1 Competing interests

The authors declare that they have no competing interests.

### 4.6.2 Authors’ contributions

TKH designed the study. TKH did the systematic review; TKH and AAA extracted the data. TKH analyzed the data. TKH, ES and MS wrote the manuscript. All authors read, contributed to and approved the final manuscript.

### 4.6.3 Authors' information

This systematic review is part of a PhD research project of TKH in joint collaboration between Swiss Tropical and Public Health Institute, University of Basel and University of Cape Town; ES and MS hold the role of joint supervisors and shared senior authorship; BR and BB acted as experts within the PhD team and reviewed the article; AAA acted as second reviewer and performed the data extraction of longitudinal studies.

### 4.6.4 Acknowledgements

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# 5. How to Evaluate Health-Related Quality of Life and its Association with Medication Adherence in Pulmonary Tuberculosis – Designing a Prospective Observational Study in South Africa

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# How to evaluate health-related quality of life and its association with medication adherence in pulmonary tuberculosis – designing a prospective observational study in South Africa

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## 5.1 Abstract

**Introduction:** Health-related quality of life (HRQOL) has become an important measure to identify and shape effective and patient-relevant healthcare interventions innovations through outcomes. Adherence to tuberculosis (TB) treatment is a public health concern. The main objective of this research is to develop a study design for evaluation of HRQOL and its association with medication adherence in TB in South Africa.

**Methodology:** A conceptual framework for HRQOL in TB has been developed to identify patient-reported outcome (PRO) measures for HRQOL and adherence and to generate an endpoint model. Two generic (SF-12 and EQ-5D-5L), one disease-specific (St. George´s Respiratory Questionnaire (SGRQ)) and one condition-specific (Hospital Anxiety and Depression Scale (HADS)) measure for HRQOL and Morisky Medication Adherence Scale (MMAS) for adherence assessment were identified. All measures are applied in a longitudinal multicentre study at five data collection time points during standard TB treatment. Statistical analysis includes multivariable analysis. Change over time in the physical component score (PCS) of SF-12 is defined as primary endpoint. Sample size estimation based thereupon has led to a recruitment target of 96 patients. This study is on-going.

**Discussion:** This is the first longitudinal study in South Africa which evaluates HRQOL and its association with medication adherence in TB in a comprehensive manner. Results will help to improve current treatment programmes and medication adherence and will support the identification of sustainable health innovations in TB, determining the value of new products, and supporting decision making with regard to health policy and pricing.

**Keywords**

Health-related quality of life, adherence, tuberculosis, study design, South Africa

## 5.2 Introduction

According to the World Health Organization (WHO), health has a multi-dimensional nature and comprises physical, mental and social health domains (WHO, 1948). Health-related quality of life (HRQOL) is a patient-reported outcome (PRO) parameter which refers to the multi-dimensional nature of health directly from the patient perspective. Tuberculosis (TB) places a significant burden on the health system of South Africa, which has the highest prevalence and incidence rates of all 22 high-burden TB countries worldwide (WHO, 2015c). Treatment is available in South Africa, however the incidence rate is only slowly decreasing and the relapse rate is high. Both epidemiological parameters may be influenced by HRQOL in TB. They may

also be additionally affected through inadequate treatment adherence although Direct Observed Treatment (DOT) has been introduced for supervised treatment monitoring. To study these associations, further research is required. The study presented here intends to evaluate HRQOL and its association with medication adherence in TB in South Africa. To understand the impact of HRQOL in TB and determinants of medication adherence, we first conducted a systematic review of the available literature (Kastien-Hilka et al., 2016). In brief, active TB impacts HRQOL significantly across different health settings; the impairment affects physical, emotional, psychological and social as well as economical aspects. Although standard TB treatment improves all health domains, psychological well-being and social functioning remained impaired in microbiologically cured patients after treatment (Ralph et al., 2013, Pasipanodya et al., 2007b, Weis and Pasipanodya, 2010, Muniyandi et al., 2007). Most published studies on HRQOL in TB had a cross-sectional design (Atif et al., 2014b), however to fully understand the impairment of HRQOL, TB impact needs to be assessed over the complete treatment period (Brown et al., 2015). In our systematic review we identified only ten studies which have followed a longitudinal approach; none of them in a South African environment (Aggarwal et al., 2013, Atif et al., 2014a, Balgude and Sontakke, 2012, Chamla, 2004, Dhuria et al., 2009, Kruijshaar et al., 2010, Maguire et al., 2009, Mamani et al., 2014, Marra et al., 2008, Ralph et al., 2013). Similar factors as for HRQOL impact medication adherence (Kastien-Hilka et al., 2016, WHO, 2003). Medication adherence "the process by which patients take their medications as prescribed" (Vrijens et al., 2012). It comprises the initiation of the treatment (first dose), implementation of the prescribed dosing regimen, and discontinuation of the therapy (end of therapy), and the persistence (time from initiation until discontinuation) (Vrijens et al., 2012, Lam and Fresco, 2015) Medication adherence is crucial to reach clinical targets and the causes of non-adherence are multi-factorial (Lam and Fresco, 2015, Fairman, 2000). WHO stated that "increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment" (WHO, 2003). Both HRQOL and adherence are related to the patient (Cote, 2003). A change in adherence is followed by a change in HRQOL and a relationship between adherence and HRQOL is existing (Cote, 2003, Kastien-Hilka et al., 2016).

We perform a longitudinal study for evaluating patient-reported HRQOL and its association with medication adherence in TB in South Africa. This study is specific to TB and transferability to other diseases are beyond the scope of this research. The study will provide information on the health status of TB patients and their HRQOL; HRQOL outcomes will allow understanding which health domains are most impacted by TB. Adherence behaviour will be observed from a patient perspective. This will allow us to identify which health aspects of TB are influencing adherence and which health domains are impacted by non-adherence. Since the study is

taking place among patients from South Africa, the cultural and socio-demographic impact on TB are respected. This article describes the study design and rationale.

## 5.3 Materials and stepwise procedures

### 5.3.1 Study aim and outcomes

The main aim of the study is to evaluate HRQOL and medication adherence in active TB patients in South Africa. Specific study outcomes comprise following: to assess TB impact on HRQOL and its longitudinal changes during standard TB treatment; to understand patient-reported medication adherence and its longitudinal changes during standard TB treatment; to evaluate any influence of socio-demographic aspects on HRQOL and adherence with regard to gender, age, education, work status and co-morbidities in sub-group analysis; to assess any association between changes in HRQOL and changes in adherence and sputum smear results; to understand if an association between HRQOL and adherence during standard TB treatment is existing and which health domains are involved.

The following preparatory steps were undertaken during the design phase of the study and are described in detail below: conceptualization of HRQOL in TB; identification of patient-reported measures applied in HRQOL evaluation and in studies of adherence to anti-TB standard treatment; selection of HRQOL and adherence measures capturing all relevant health aspects of TB; definition of data collection points for HRQOL and adherence; identification of a primary endpoint on basis of HRQOL and development of an endpoint model; selection of study setting; definition of study participant inclusion and exclusion criteria; development of a rationale for sample size determination; definition of statistical analysis.

### 5.3.2 Conceptualization of HRQOL in TB

The results of the literature review identified that TB impacts physical, emotional, psychological, social and economic domains of HRQOL, with residual impairment still present in each of these domains even after treatment. Based on these results, a conceptual framework of HRQOL in TB has been developed (figure 7).

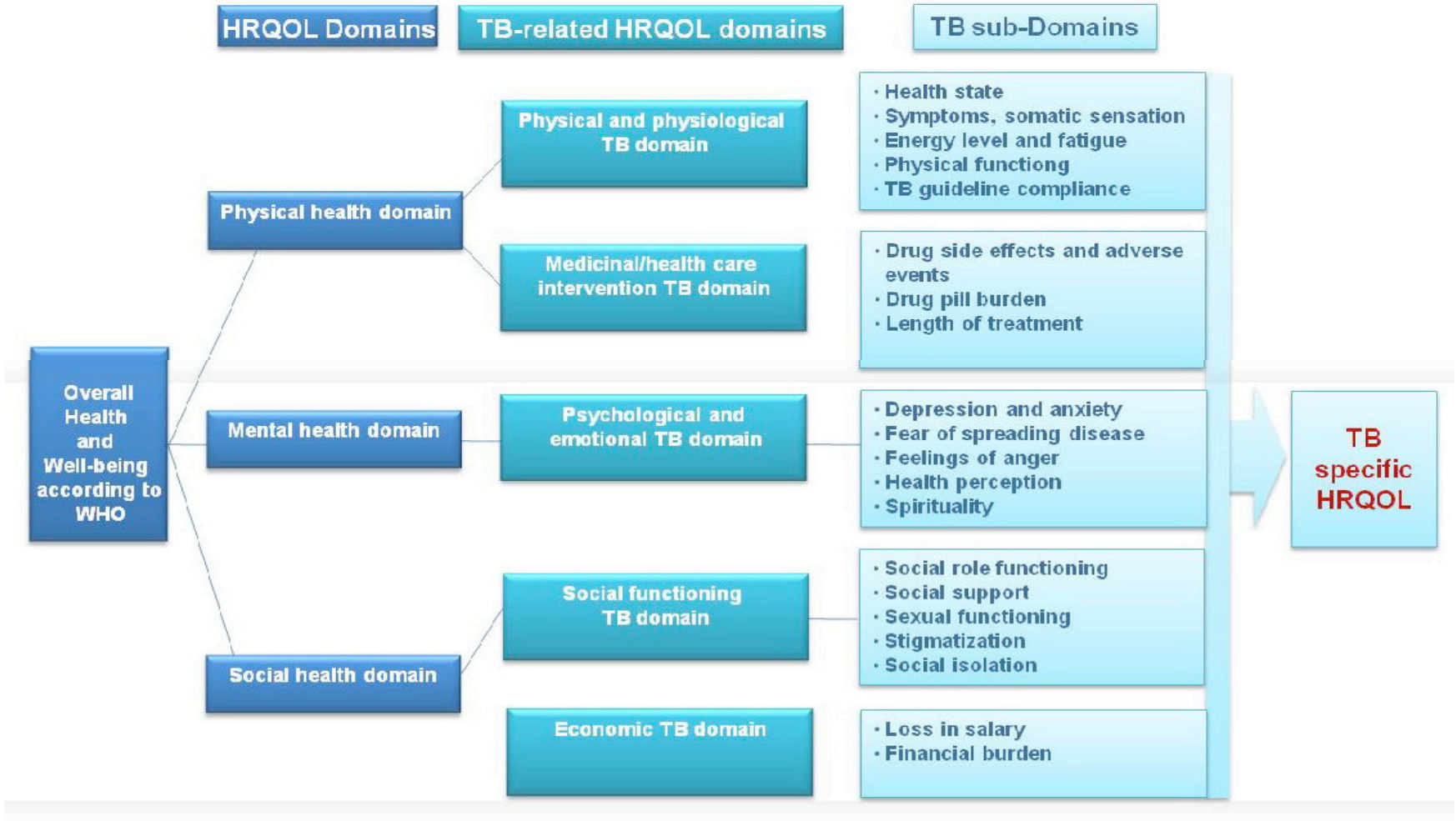


**Figure 7:** Conceptual framework of HRQOL in TB, developed based on systematic review results.

The physical health domain is mainly described by TB-related physical and physiological aspects which comprise disease symptoms, health status, fatigue and physical functioning. There are also influences of TB treatment due to side effects, pill burden and duration of treatment. The mental health domain is mainly impacted by the psychological and emotional aspects related to TB which include depression and anxiety, fear of spreading TB, feelings of anger, health perception of the patient, and patient´s spirituality. The social health domain we defined by the social functioning of the patient and the economic burden related to TB. Social functioning is mainly impacted by social role, social support, sexual functioning, stigmatization and social isolation. The economic burden is influenced by a loss in salary and any financial burden related to being ill.

### 5.3.3 Identification of HRQOL and adherence PRO measures in TB

The systematic review yielded 38 studies which applied patient-reported outcome (PRO) measures in HRQOL and adherence: two systematic reviews, 21 cross-sectional studies, 14 longitudinal studies, and one qualitative study (table 1 in appendix).

Based on the identified studies, 43 HRQOL and three adherence PRO measures were extracted, including 34 reported measures from the systematic reviews of Bauer et al (Bauer et al., 2013) and 17 different HRQOL instruments from Guo et al (Guo et al., 2009) (tables 2 and 3 in appendix). Overall, the most frequently applied HRQOL instrument in TB was the generic Short-Form 36 (SF-36), followed by World Health Organization Quality of Life - BREF (WHOQOL-BREF), EuroQol-5D (EQ-5D) and disease-specific instruments, namely the Beck Depression Inventory (BDI), Kessler-10 (K-10) and St. George´s Respiratory Questionnaire (SGRQ). Our systematic review identified ten studies applying a longitudinal design in HRQOL evaluation in TB (Aggarwal et al., 2013, Atif et al., 2014a, Balgude and Sontakke, 2012, Chamla, 2004, Dhuria et al., 2009, Kruijshaar et al., 2010, Maguire et al., 2009, Mamani et al., 2014, Marra et al., 2008, Ralph et al., 2013). Consistent with the results of the current review, the SF-36 was applied more often than other PROs to observe longitudinal changes. Next in frequency were the WHOQOL-BREF, SGRQ, EQ-5D, BDI, as well as the State-Trait Anxiety Short Form (STAI-6) and Center for Epidemiologic Studies Depression Scale (CES-D). In addition to our literature search, we accessed the database PROQOLID for HRQOL instruments which are applied in pulmonary and psychiatric illnesses and linguistically validated for application in English language in South Africa (PROQOLID). This identified 17 measures (table 4 in appendix).

### 5.3.4 Rationale for selection of HRQOL and adherence PRO measures

A systematic use of generic HRQOL measures in all diseases supports consistent value judgments and transparent reimbursement decision making (eunethta, 2013). Two types of PRO measures are applied in HRQOL evaluations: generic measures and disease- or condition-specific measures. Generic measures have the advantage of allowing comparison of quality of life outcomes across different diseases and can accommodate effects of co-morbid conditions; they are often applied to inform health policy maker about allocation of resources (eunethta, 2013). In contrast to generic measures, disease-specific instruments comprise disease specific health aspects (eunethta, 2013, Doward et al., 2010, Deshpande PR, 2011). Disease- and condition-specific measures may be more sensitive to changes in HRQOL and may better detect important disease-related changes over time. Disease- and condition-specific HRQOL information may be complementary to generic HRQOL measures, specifically when no effect is observed with generic measures. However a recognized and validated TB-specific HRQOL instrument currently does not exist. We therefore followed the approach to select generic and disease- and condition-specific measures which capture all major HRQOL-related aspects of TB based on our conceptual framework.

All 43 measures applied in HRQOL studies and 3 adherence instruments identified by our literature search as well as all 17 instruments from the PROQOLID database search were reviewed. Measures were selected in order to capture physical, mental and social health issues of TB. In addition to consistency with our conceptual framework, selection required that the respective measures had been validated in TB and linguistically validated for English in South Africa. Based on these criteria, we finally selected the St. George´s Respiratory Questionnaire (SGRQ) as a disease-specific measure and the Hospital Anxiety and Depression Scale (HADS) as a condition-specific measure. The SGRQ is recommended as a preferred instrument by the European Medicines Agency (EMA) for evaluating quality of life in COPD patients (EMA, 2012). As a measure specifically for respiratory diseases, it captures important health aspects which can be applied to TB. HADS was selected as it allows evaluation of anxiety and of depression. As a preference-based and a profile measure, we selected the EQ-5D-5L and SF-12. Notably, the SF-12 has previously been used in pulmonary TB patients in South Africa for HRQOL assessment (Louw et al., 2012).

An ideal adherence measure to assess overall adherence to medication including initiation, persistance, implementation and discontinuation does not exist; therefore a multi-measure approach may be considered where direct and indirect adherence measure are combined (Fairman, 2000). Direct measures such as drug determination in biological fluids or direct

patient observation are often regarded as being the most reliable and accurate. However, individual changes in drug metabolism and multidrug intake affect monitoring of plasma levels, and patient observation is limited to inpatient settings and clinical trials (Fairman, 2000, Nguyen et al., 2014, Lam and Fresco, 2015). Indirect measures comprise medication monitoring (such as pill counting) and self-reported measures; however, medication monitoring is cost intensive and self-reported measures may be less reliable due to patient recall, underreported non-adherence and memory bias issues(Fairman, 2000, Lam and Fresco, 2015, Stirratt et al., 2015). Vrijens et al defined adherence measures for the quantitative assessment of initiation, persistance, and implementation (Vrijens et al., 2012). Both, initiation and persistance are time-to-event variables and should be assessed by Kaplan-Meier curves, median persistence or proportion of persistent patients at a given time point. Implementation is assessed by a summary statistic such as the proportion of prescribed drug taken or longitudinally by electronic databases of drug dosing histories. Each adherence measure has its advantages and disadvantages and the selection of adherence measures depends on the attributes, research objectives and available resources of each study (Lam and Fresco, 2015). The present study focuses on the measurement of HRQOL and adherence in a real life middle-income setting in a township of South Africa. The study is purely observational, with no influence on treatment and follows patients during their TB care. The available resources of the study and the study environment do not allow application of direct adherence measures although they would in principle be the best instruments to measure patient´s medication taking behavior (Nguyen et al., 2014); Since DOT is established in South Africa, we decided to apply a self-reported measure as it allows to identify specific reasons for being non-adherent (Nguyen et al., 2014, Lam and Fresco, 2015). Further, a self-reported measure is best applicable to the study environment and study settings as it is cost-effective, with a minimum burden to the patient, easy to administer and flexible in timing and mode of administration. Self-reported adherence measures have additional advantages; they inform about non-adherence before adverse clinical outcomes develop and about adherence determinants such as psychosocial factors (Stirratt et al., 2015). A gold standard for self-reported, questionnaire-based adherence measurement does not exist (Nguyen et al., 2014, Fairman, 2000). The Morisky Medication Adherence Scale (MMAS) is widely used, reliable and valid and has been applied in TB before (Lam and Fresco, 2015, McInerney et al., 2007, Corless et al., 2009, Stirratt et al., 2015). MMAS allows the evaluation of the concept of medication-taking behaviours, barriers to adherence, and beliefs associated with adherence (Lam and Fresco, 2015) including forgetfulness and adverse events (Nguyen et al., 2014). Based on the taxonomy of adherence by Vrijens et al MMAS covers the implementation and discontinuation phase of adherence. The assessment of self-reported scales includes the correlation with an objective adherence measure, and MMAS was correlated with pharmacy records and clinical outcomes (blood

pressure control) as comparison measure of adherence (Nguyen et al., 2014).

All four HRQOL measures and the adherence measures are reliable and validated (PROQOLID, Morisky, 2008b, Lam and Fresco, 2015), and the HRQOL measures were linguistically validated for English in South Africa (St George´s University of London, 2012, Euroqol, PROQOLID). All selected measures are described in detail in the appendix.

### 5.3.5 Rationale for study endpoint model

An endpoint model for the present study was based on measurement concepts as reported by Burke from the US FDA (Burke, 2012). Treatment benefit measurements comprise four different concepts: disease-defining concepts, proximal disease and distal disease impact concepts, and disease impact on general life concepts.

Disease-defining concepts describe clinical signs of a disease. The impact of these disease-specific clinical signs is reflected in proximal disease impact concepts of disease symptoms and somatic sensation. Both disease-defining and proximal disease impact concepts reflect some aspects of the physical health domain of the conceptual psychometric framework of HRQOL. Mental, social and psychosocial domains of HRQOL are represented through the distal disease impact concepts. Distal disease impact concepts include physical, psychological and social functioning, thereby reflecting additional aspects of the physical health domain. The disease impact on general life concept comprises aspects which result from impairment in distal disease impact concepts, such as impairment of social role functioning, economic burden and quality of life in general. Based on the benefit treatment measurement concept of Burke (Burke, 2012) and based on the psychometric concept of TB-specific HRQOL, we developed following endpoint concept for TB (figure 8):

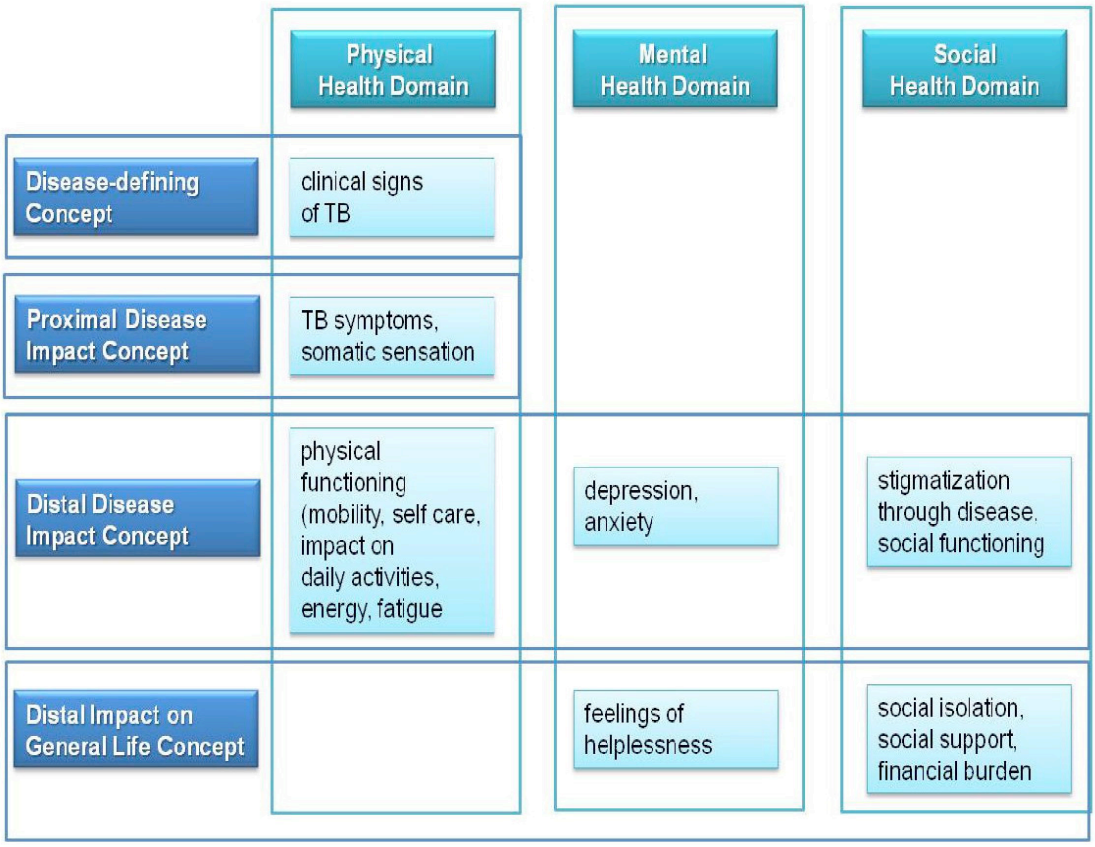


**Figure 8:** Endpoint concept for TB based on major HRQOL health domains and on benefit treatment measurement concepts.

The selected HRQOL and adherence measures were integrated into the endpoint concept. The physical health domain of HRQOL is evaluated by the physical component score of the SF-12 (PCS-12). The change between end of treatment and baseline in the PCS-12 score is defined as the primary study endpoint. The EQ-5D-5L physical domain and SGRQ symptoms domain scores represent secondary endpoints. The mental health domain of HRQOL is assessed by the mental component score of the SF-12 (MCS-12), the EQ-5D-5L mental domain, SGRQ activities domain, and HADS. The (psycho-) social health domain of HRQOL is evaluated by SGRQ impacts on social activities domain. Other endpoints comprise clinical data (sputum smear) for presence of active TB and treatment monitoring as well as medication adherence by application of MMAS-8. Table 4 provides an overview of endpoints selected and related instruments applied. The final endpoint model for evaluation of HRQOL and adherence in TB is presented in figure 9.

| Endpoint (mean difference EOT minus BL) | PRO Measure |
|---|---|
| **Primary endpoint** | SF-12 PCS-12 |
| **Secondary endpoint** | SF-12 MCS-12 |
| | EQ-5D-5L |
| | SGRQ |
| | HADS |
| **Other endpoint** | Clinical data (sputum smear) |
| | MMAS-8 |

**Table 4:** Primary, secondary and other endpoints applied in HRQOL evaluation

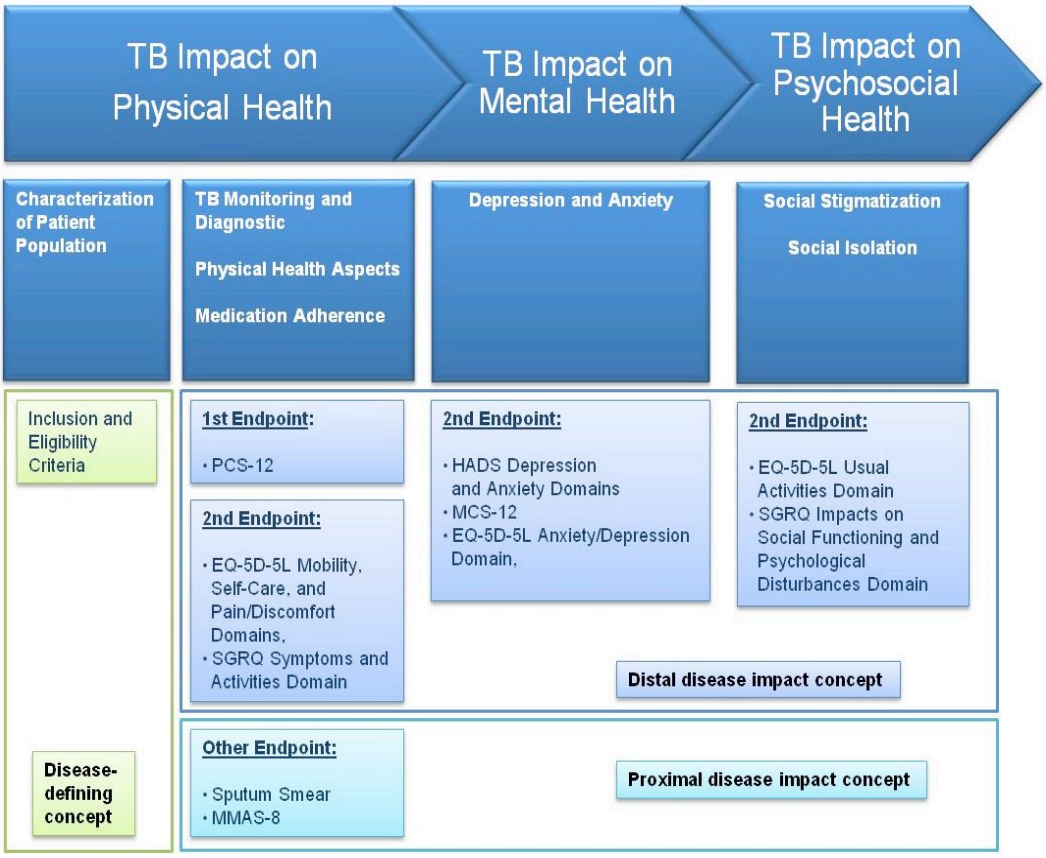


**Figure 9:** The final endpoint model for evaluation of HRQOL and treatment adherence in PTB, respecting HRQOL domains and disease-defining as well as proximal and distalmeasurement concept.

### 5.3.6 Study design and study setting

The study is observational in nature with a longitudinal design including repeated measures of HRQOL and adherence per study participant. Multiple health facilities are included and the study has thereby a multi-centre design. The highest TB burden in Cape Town is recorded in the Khayelitsha sub-district. Six health facilities with the highest TB caseloads per month were selected. Each health facility has an outpatient TB department. The caseloads of TB cases for each selected health facility were provided through the Western Cape Province.

### 5.3.7 Patient population and participant recruitment

The patient population comprises patients diagnosed with active pulmonary TB. TB patients are eligible if their age is 18 years or older and if they have not received standard TB treatment prior to this study. Patients are excluded if they are diagnosed with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), and/or with HIV co-infection. The eligibility status of each patient is subject to verification by the responsible TB nurse of each health facility. Based on a patient information document, eligible patients are informed about nature, purpose, potential risks and benefits of the study. Patients have the opportunity to decline their participation or to withdraw from the study at any time point. If an eligible patient agrees to participate in the study, a written informed consent is obtained before study start. The sample population is reached by pooling eligible patients from all study sites.

### 5.3.8 Study procedure

Eligible participants receive a six month standard TB treatment with rifampicin, isoniazid, ethambutol and pyrazinamide at each health clinic or health centre. The drug treatment is local standard care according to the national TB guideline and DOT is applied (NDoH, 2014). The treatment is not influenced by this non-interventional research study. The study evaluates HRQOL and adherence based on questionnaires completed by patients, who are treated and managed in the health facility independently from this study. Most studies evaluating HRQOL longitudinally included data collection before treatment or at treatment start, at the switch from the intensive to continuous treatment phase and at end of treatment. (Aggarwal et al., 2013, Atif et al., 2014a, Balgude and Sontakke, 2012, Chamla, 2004, Dhuria et al., 2009, Kruijshaar et al., 2010, Maguire et al., 2009, Mamani et al., 2014, Marra et al., 2008, Ralph et al., 2013). We decided on a tighter data collection regimen to monitor changes in HRQOL more closely and included five different time points over the 6 month treatment period: beginning of treatment (baseline) and follow-up visits 1-4 after 1, 2, 4 month and 6 month (end of treatment).

Data collection starts when TB treatment is initiated; the four HRQOL measures and a socio-demographic questionnaire are applied at baseline (treatment start). The four HRQOL measures are repeatedly applied at all follow up visits 1-4 together with the MMAS. Data are collected based on combined completion of paper questionnaires and face-to-face interviews through trained field workers. Training of field workers is based on a Standard Operating Procedure (SOP) specifically written for this study. Questionnaires are scanned by the field worker for any missing responses. The patient is asked to provide an answer for the missing response unless the question was intentionally left unanswered. TB-related clinical data (sputum smear results) are collected from TB nurses when available during the treatment period for each patient.

### 5.3.9 Data management

All paper-based documents including the questionnaires and informed consent forms are stored at the University of Cape Town for a period of ten years. The HRQOL, adherence and socio-demographic measures, and sputum smear results data are transferred to an electronic database independently by two research team members. Every third questionnaire is entered into a second database. Both databases are reconciled to minimize errors related to data entry. All questionnaire responses are scored according to each questionnaire´s manual instructions. Scored data are prepared for statistical analysis applying SPSS software.

### 5.3.10 Rationale for sample size determination

The primary endpoint is the Physical Component Score (PCS) of SF-12. Walter (Walters, 2004) compared four different methods for sample size estimation using SF-36 as primary endpoint. Since SF-12 has shown comparable results with SF-36, both measures are seen as similar and comparable and the methods discussed applicable to SF-12. We decided to select a method for sample size determination which is based on the mean difference. The estimation of mean difference in PCS-12 scores is defined as average mean difference score between end of treatment (EOT) and baseline (BL). We therefore performed a literature search for studies applying SF-12 or SF-36 as an outcome measure during TB treatment, and found 10 studies presenting SF-12 and SF-36 scores (Babikako et al., 2010, Dion et al., 2004, Guo N, 2008, Kruijshaar et al., 2010, Marra et al., 2008, Atif et al., 2014a, Louw et al., 2012, Bauer et al., 2013). Only two studies reported PCS-36 scores over the 6 month long TB treatment, and observed a change in mean score over time (baseline to end of treatment) with a mean difference of 4.0 (Babikako et al., 2010) and of 4.1 (Atif et al., 2014a). The minimal important difference (MID) for SF-36 and SF-12 is reported with > 3 points by the questionnaire manual

(Maruish ME, 2009). We therefore assumed a mean difference of 4.0 for our study. A standard deviation (SD) for PCS-12 was defined with the value 7 at end of treatment for PCS-36 (Atif et al., 2014a). Final sample size was calculated based on a mean difference of 4.0 and a SD of 7 for mean PCS-12, resulting in a standardized effect size of 0.57. Using the standardized effect size with a two-sided 5% level of significance and a 95% power yielded in an estimated sample size n = 80 subjects. We estimated an attrition rate of 20% leading to a final sample size n = 96 patients.

### 5.3.11 Anticipated results

Based on published HRQOL studies in TB, we expect an improvement in HRQOL during the course of treatment; especially physical health aspects are expected to improve. However, some residual physical impairment has previously been reported after treatment end, although patients' were microbiologically cured. Reported mental and psychosocial health aspects included depression and anxiety, and social isolation and stigmatization. We expect to find these aspects of health impairment reflected in HRQOL outcomes at the beginning of treatment. As TB treatment requires a long-term dosing regimen, we expect a decreasing adherence behaviour over the treatment course, although DOT is established and a requirement in South Africa. Potential pitfalls of our study are mainly driven by the infrastructure of the health setting in the township Khayelitsha, which, however, reflects South African reality. Patients have no regular access to mobile phones and interview dates for HRQOL and adherence interviews are difficult to organize; follow up with the patients is also difficult for the health facilities. We expect a number of missing interviews and interviews taken not at the required time points, albeit around the target interview dates. Our HRQOL and adherence measures are self-reported measures and reflect a subjective patient view. Related bias including over- and under-reporting of both concepts can be expected. This will be consistent with the individual patient's TB condition. Experienced pitfalls for future studies will be discussed as lessons learned from our study.

### 5.3.12 Statistical analysis

All statistical analyses are conducted using IBM SPSS Version 22®. Descriptive statistics are calculated for socio-demographic descriptors of the patient population and all study outcomes. Study outcomes comprise the means of all HRQOL domain and total scores, adherence scores and sputum smear results, and related changes over time. Categorical variables are described by frequencies, proportions (%) and number of missing values. Continuous variables (HRQOL, adherence) are described by the mean and median as measures of central tendency, first and

third quartiles, standard deviation (SD), minimum (Min) and maximum value (Max), and number of missing values. Continuous variables are checked for non-normality with q-q plots and histograms. Outliners are observed via boxplots; if applicable 5% trimmed means may be calculated. Ordinal variables representing responses to questionnaire items are described in the same way as categorical and/or continuous variables, depending on their properties. For example, responses to an item with 3 answer levels would be described in the same way as a categorical variable whereas responses to an 11 step (0-10) rating scale would be described in the same way as a continuous variable.

Change of each HRQOL measure and of the adherence measure between baseline and each follow up visit is calculated based on mean scores. Changes in mean scores between baseline and end of treatment are presented as boxplots. Differences between baseline and each follow up are examined based on significance testing; choice of tests considers the distribution of the variables involved. For distributions with no or only limited deviations from normality, the paired t-test is used, otherwise the Mann-Whitney U test. The level of statistical significance is set at 5%, two-sided for both the paired t-test and Mann-Whitney U test. Change in HRQOL mean scores over time (BL, visit 1-4) is further examined by two-way repeated measure analysis of variance (ANOVA), for all HRQOL instruments.

Responsiveness of HRQOL measures refers to their ability to detect important change over time in the concept measured, even if this change is small. Each change in mean score for each measure is compared with its reported MID. When the change in mean score is equal or above the MID, the change is interpreted as meaningful. Further, the effect size is calculated by dividing the change in mean score through the standard deviation at baseline (0.2, 0.5 and 0.8 represent small, medium and large effect size) (Cohen, 1988, Aggarwal et al., 2013). It is further observed which health domains improve, worsen, or remain unchanged over time based on change in mean scores. Hypothesis testing is applied to HRQOL, adherence and sputum smear outcomes. The hypotheses testing comprises following assumptions: HRQOL improves, adherence declines, and sputum smear results improve over time from baseline to end of treatment. Hypothesis testing is performed by repeated measures ANOVA if data are normally distributed or with the Kruskal-Wallis test for non-normally distributed data. Sub-group analyses are performed additionally, by gender, age, ethnicity, marital status, educational and work status, and co-morbidities.

Additional relationships are assessed for HRQOL, adherence, and sputum smear results, including sub-groups analyses according to socio-demographic data. First, the correlations between all health domains of all HRQOL measures at baseline are assessed by applying Pearson´s correlation coefficient or Spearman´s rho coefficient. A correlation matrix is presented. Second, it is examined how changes in HRQOL and changes in adherence are

associated with changes in sputum smear results over time. Correlation coefficients are calculated and linear mixed regression models are estimated. Third, it is examined how changes in both HRQOL and adherence are linked with the socio-demographic variables by applying linear mixed regression models. A final analysis assesses how HRQOL and adherence are associated with each other, from baseline to end of treatment, by applying linear mixed regression models. Adjustments for multiple testing will be made where sensible. Related issues will be discussed.

## 5.4 Discussion

The impact of TB on patients' HRQOL has been reported in international studies including some conducted in high-burden TB countries but its longitudinal changes have not been assessed in South African TB patients. South Africa is the country with the highest prevalence and incidence rate in TB among all 22 high-burden countries (WHO, 2015c). Limited knowledge about adherence behaviour during TB treatment is available, most from qualitative studies. Both outcomes, HRQOL and adherence, are assumed to impact each other but this association has not been studied longitudinally so far. The objective of this research is to perform a study evaluating HRQOL and its association with medication adherence in patients with active pulmonary tuberculosis in South Africa. We developed a conceptual framework for HRQOL in TB capturing all TB related physical, mental and psycho-social health aspects; based on a systematic literature search we found a total of 43 different HRQOL and three adherence measures which were applied in TB. Based on these findings we selected HRQOL and adherence measures which capture all HRQOL constructs in TB according to our conceptual framework. The rationale of PRO measure selection respected the use of generic HRQOL measures which allow comparison between different diseases and thus support consistent value judgment and transparency e.g. in reimbursement decision making (eunethta, 2013). Further, we included disease- and condition-specific instruments which are more sensitive to change than generic instruments. This ultimately led to the selection of two generic measures (EQ-5D-5L and SF-12), one disease-specific (St George Respiratory Questionnaire) and one condition-specific measure (Hospital Anxiety and Depression Scale). As a patient-reported adherence instrument, we selected the Morisky Medication Adherence Scale (MMAS). Validity and reliability of these selected PRO measures, including their linguistic validation for English for South Africa, is given. MID was identified from literature for each HRQOL measure to understand meaningful changes over time. Based on the conceptual framework and selection of PRO measures, an endpoint model with the change between end of treatment and baseline in the physical component score (PCS) of SF-12 defined as primary endpoint was developed. PCS score of SF-12 is selected as primary endpoint since TB has a

major impact on the physical health. Based on the primary endpoint, the required sample size was determined to be 96 participants. The described protocol is specific to TB, however the rationale for selection of HRQOL and adherence measures may be transferred to other studies applying PRO measures and might be useful for the development of a general approach for future studies. Patient-reported HRQOL reflects the patient perspective, and is an information source for health service quality and treatment effectiveness which could support the decision making during reimbursement, access to medicines and health policy process (McKenna, 2011, Calvert, 2014). A number of clinical trials include PRO measures for assessing efficacy as endpoint to generate an added value and to support biochemical endpoints (Doward et al., 2010). Post-marketing studies apply PRO measures for evaluation of effectiveness to inform treatment guidelines (Acquadro C, 2003a). To ensure data quality and evidence reporting, the study design and methodology of PRO trials are of importance. PRO-specific rationale and objectives, PRO endpoint specification, timing of PRO assessment, sample size determination for HRQOL studies, PRO data collection, and statistical analysis are key aspects of study design and methodology (Calvert, 2014). We developed our study design according to these aspects. It is hoped that this study will provide important information about physical, mental and psycho-social health aspects of TB in the South African socio-demographic context. This additional knowledge about TB, which goes beyond well-known physiological and clinical parameter, should inform current treatment guidelines for South Africa. Currently, a number of new TB drugs and diagnostic devices are under development or in a clinical phase. An integrative knowledge about HRQOL should assist with evaluating the added value of newly developed TB drug products and treatment procedures in comparative effectiveness research (CER) studies. Outcomes from CER will support resource allocation, reimbursement decisions, access to medicines and health policy making in TB in the context of the implementation of National Health Insurance for South Africa. The evaluation of HRQOL and its association with adherence in TB using the selected PRO measures could support future research and development of a TB-specific measure by reviewing the different health domains and their items for TB-relevant aspects. Such TB-specific measure may be integrated into standard care to monitor TB treatment with an integrative patient-centred approach.

## 5.5 Declarations

### 5.5.1 Ethics approval and consent to participate

The study respects the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, the Declaration of Helsinki in its current version and South African Good Clinical Practice (GCP). The study was approved by the institutional review commission of the Swiss Tropical and Public Health Institute. Ethical approval and clearance have been obtained from four different institutions: the ethical commission of North-West and Central Switzerland (EKNZ), the ethical committees of the University of Cape Town, City Health City of Cape Town, and the Western Cape Government.

### 5.5.2 Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### 5.5.3 Authors' contributions

TK designed the study with support of MS and ES. TK, MS and ES wrote the manuscript. All authors read, contributed to and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# 6. Health-related quality of life in South African patients with pulmonary tuberculosis

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# Health-related quality of life in South African patients with pulmonary tuberculosis

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## 6.1 Abstract

**Background:** The evaluation of patient-reported health-related quality of life (HRQOL) in pulmonary tuberculosis (TB) contributes to a comprehensive understanding of the burden associated with this disease. The aim of this study was to assess the overall impact of TB on the health status and on single health domains identified in the WHO definition of health, including physical, mental and social health aspects.

**Methods:** Four instruments for HRQOL evaluation were applied in a longitudinal multicentre study during six-month standard TB treatment in South Africa. These included the generic SF-12 and EQ-5D-5L, the disease-specific St. George´s Respiratory Questionnaire (SGRQ) and the condition-specific Hospital Anxiety and Depression Scale (HADS). Statistical analysis included significance testing, univariable and multivariable analysis, and repeated measures ANOVA. Change over time in the physical component score (PCS) of SF-12 was defined as primary endpoint. A target sample size of 96 patients was estimated.

**Results:** HRQOL of the study participants was impaired in all physical, mental and psycho-social health domains at treatment start. HRQOL improved significantly and in a clinically meaningful manner during the course of standard TB treatment, over the period of the study. The greatest improvement (95%) was observed in mental health. Younger patients with higher education and who were employed had a better HRQOL.

**Discussion:** This study demonstrates the need for an integrative understanding of TB with HRQOL as core element to inform gaps in current TB management. Improvements in the management of TB following an integrative patient-centred approach will contribute towards meeting the United Nations Sustainable Development Goal 3 (SDG3) target and will support the End TB strategy of the WHO.

## 6.2 Introduction

At the beginning of 2016, the United Nations (UN) introduced the Sustainable Development Goals (SDGs) to replace the Millennium Development Goals (MDGs) established in 2000 (WHO, 2015b). The third goal of the SDGs (SGD3) aims to ensure healthy lives and promote well-being at all ages (WHO, 2015b). One target of SGD3 focuses on universal health coverage, including access to safe, effective, high quality and affordable essential medicines (WHO, 2015d). Access to medicines requires sponsors to demonstrate that the medicine is safe, effective and affordable. The evidence of the real benefit of a treatment is usually evaluated based on clinical trials and real world data evidence. Only after this evidence has been provided, can medicines be made accessible through healthcare organizations. The World Health Organization (WHO) claims that patient involvement in their healthcare is a social, economic and technical necessity (Doward et al., 2010). The evaluation of a patient-reported perspective of a disease and treatment contributes to a comprehensive understanding of the benefit and risk associated with that disease. This is important as some concepts cannot be measured objectively. One specific patient-reported outcome (PRO) is health-related quality of life (HRQOL). HRQOL is a PRO which refers to the multi-dimensional nature of health, and usually includes physical, mental and social health domains (WHO, 1948).

A further target of the UN SDG 3 includes an end to the epidemic of tuberculosis by 2030 (WHO, 2015a). Tuberculosis (TB) places a significant burden on the health system of South Africa, which has the highest prevalence and incidence rates of all 22 countries with a high burden of TB worldwide (WHO, 2015c).

The impact of TB on HRQOL has been reported in a systematic literature review (Kastien-Hilka et al 2016). This systematic review found that TB had a negative impact on patients' HRQOL and overall wellbeing. The review further identified several factors associated with HRQOL in TB which included socio-demographic (age, gender) and socio-economic (income, education, housing, social security) characteristics, disease-related (symptoms) and therapy-related (side

effects, adverse events) factors, and psycho-social aspects (isolation and stigmatization, psycho-social burden) (Adeyeye et al., 2014, Masumoto et al., 2014, Aggarwal et al., 2013, Bauer et al., 2013, Deribew A, 2013, Dias et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Chung et al., 2012, Kittikraisak et al., 2012, Louw et al., 2012, Othman, 2011, Aggarwal, 2010, Guo et al., 2010, Dhuria et al., 2009, Guo et al., 2009, Guo N, 2008, Marra et al., 2008, Chamla, 2004, Hansel NN, 2004, Marra et al., 2004). Significant physical impairment caused by somatic symptoms and consequences of TB has also been reported (Awaisu et al., 2012, Guo et al., 2009, Chang B, 2004, Hansel NN, 2004).

Although TB treatment results in a significant improvement in HRQOL, especially in physical and psychological dimensions (Aggarwal et al., 2013, Bauer et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Louw et al., 2012, Othman, 2011, Guo et al., 2009, Guo N, 2008, Chamla, 2004) the treatment regimen can be difficult for patients due to adverse drug reactions, the quantity of pills and treatment duration. This may have a significant impact on levels of adherence in this patient population. There is also some published evidence to suggest that amongst TB patients, psycho-social burden may have a greater impact than clinical symptoms. Specifically, anxiety and depression are the most frequently reported mental disorders reported in TB patients (Peltzer K, 2012, Aamir and Aisha, 2010). It is believed that psychological distress may be caused by social stigmatization because of public misconception that a TB patient suffers from HIV co-infection (Naidoo and Mwaba, 2010, Van Rie et al., 2008). This association with HIV/AIDS may lead to a perception of social isolation during TB treatment and further impacted by the poor financial situation of many patients (Peltzer K, 2012, Issa BA, 2009, Hansel NN, 2004).

The impact of TB on HRQOL in South African populations was assessed in two studies only, (Louw et al., 2012, Westaway, 2001). As most other published studies addressing HRQOL in TB patients, both studies followed a cross-sectional study design. Longitudinal changes in HRQOL assessed in South African TB patients were not available when our study was initiated. Since information on HRQOL contributes to efficient decision making, product approval, pricing

and reimbursement as well as health policy making, HRQOL data will support the identification of sustainable health innovations in TB. A recognized reliable and validated TB-specific HRQOL measure has not been available, however all relevant HRQOL aspects of TB need to be captured to assess the achievement of the WHO´s End TB Strategy pillars.

The aim of this research was to evaluate patient-reported HRQOL in pulmonary TB in South Africa. The study sought to understand the overall impact of TB on the health status and on single health domains identified in the WHO definition of health, including physical mental and social health aspects. The study addressed the impairment in HRQOL associated with TB, prior to treatment and longitudinal changes in HRQOL over the course of a six-month standard TB treatment.

## 6.3 Methods

A detailed description of the study design and methodology has been published previously (Kastien-Hilka et al 2016). Briefly, the study followed an observational longitudinal design including prospective, repeated measures of HRQOL per study participant.

### 6.3.1 Patient population and participant recruitment

Study participants were recruited between November 2014 and May 2015 at six selected primary health care clinics with the highest TB caseloads per month in Cape Town. Four of these facilities are run by the local government, and two by the provincial government, and are located in the Khayelitsha sub-district of the Cape Town Metro district. The sub-district has the highest TB burden in Cape Town, based on latest available case loads from 2012 provided through the Western Cape Province. The study population comprised of patients diagnosed with active pulmonary TB. TB patients who were 18 years or older and were not diagnosed with TB before were eligible. Patients were excluded if they were diagnosed with multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), and/or had HIV co-infection. The eligibility status of each patient was subject to verification by the nurse dedicated

to TB patients of each health facility. Based on a patient information document, eligible patients were informed about the nature, purpose, potential risks and benefits of the study. Patients had the opportunity to decline their participation or to withdraw from the study at any time point. Patients who agreed to participate in the study signed a written informed consent.

Recruitment of new TB cases without HIV co-infection was difficult as a high proportion of TB patients are also HIV co-infected in South Africa. In order to meet the sample size in the pre-determined time frame, one additional clinic in a neighboring district was included in the study.

### 6.3.2 Study procedures

Eligible participants received a six month standard TB treatment with rifampicin, isoniazid, ethambutol and pyrazinamide. This standard treatment was not influenced by the study design. HRQOL was evaluated during the treatment course. The data collection regimen to monitor changes in HRQOL included five different time points over the six-month treatment period: beginning of treatment (baseline) and at follow-up visits after 4, 8, 16 weeks and after six-month treatment. Data collection started when TB patients visited the study sites for treatment initiation; four HRQOL measures and one socio-demographic questionnaire were applied at baseline (treatment start). These four HRQOL measures were re-applied at all follow up visits. Data were collected based on completion of paper questionnaires during face-to-face interviews conducted by trained field workers. Questionnaires were scanned by the field worker for any missing responses during the interviews.

### 6.3.3 Study Materials

The rationale for the selection of HRQOL measures has been described previously (Kastien-Hilka et al 2016). Two generic (European Quality of Life 5 Dimensions 5 levels (EQ-5D-5L) and Short-Form 12 items (SF-12)), one disease-specific (St. George´s Respiratory Questionnaire (SGRQ)) and one condition-specific (Hospital Anxiety and Depression Scale (HADS)) HRQOL measures were used.

### EQ-5D-5L

EQ-5D-5L (Euroqol) is widely used as a utility index for estimating QALYs in cost-effectiveness studies (Euroqol, PROQOLID). It comprises five items/domains (5D) (Mobility, Self Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) with each domain having five levels (5L): no problems, slight problems, moderate problems, severe problems, and extreme problems; The EQ-5D-5L includes further one vertical visual analogue scale (VAS 20 cm). Index-based values (utilities) are calculated from EQ-5D-5L by applying country-specific valuation algorithms. No South African specific valuation algorithms were available. Therefore, algorithms developed for the UK and for Zimbabwe, the only African country with an available algorithm, were used in this study. The EQ-5D-5L utilities range from 0 to 1, with higher scores indicating better health. A minimally important difference (MID) is only known for the 3 level version of EQ-5D, with a MID of 0.074 (range -0.011 - 0.140) and a MID of 7 for VAS scores (Walters, 2005). EQ-5D-5L has an improved sensitivity compared to the 3 level version and its MID is also assumed for the 5 level version.

### SF-12

Short-Form 12 (SF-12) is an abbreviated version of SF-36 containing 12 items representing eight domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health) (Ware, PROQOLID). Domains are aggregated into composite summary scores, Physical Component Score (PCS-12) and Mental Component Sore (MCS-12). Scoring ranges from 0 to 100 with greater scores representing better HRQOL. A score between 47 and 53 reflects normal scores for both PCS and MCS based on US population norms (Maruish, 2009, Atif et al., 2014a). No population norms for South Africa or other African countries are available. A MID of at least 3 points has been suggested for the SF-36 (Maruish, 2009) and can also be used for SF-12v2 (Maruish ME, 2009).

### St. George´s Respiratory Questionnaire

St. George´s Respiratory Questionnaire (SGRQ) is a disease-specific instrument designed to assess patients with respiratory tract and immune system diseases, especially asthma,

pulmonary diseases, and chronic obstructive disease (Jones, 2009, PROQOLID). SGRQ comprises 50 items in three domains (Symptoms, Activity, and Impacts on daily life). Scores are scaled from 0 to 100, with higher scores indicating worse HRQOL. A MID for SGRQ is defined as an improvement of 4 points in the domain scores and the total score (Jones, 2005).

### Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS) is a condition-specific instrument applied in psychology and psychiatry to detect states of anxiety and depression (El Achhab et al., 2008). HADS comprises 14 items in two domains, Anxiety domain and Depression domain. The scores of each subscale range from 0-21 (8-10 mild, 11-14 moderate, 15-21 severe). A MID for HADS is not available from the developer. A MID of 1.5 points has been estimated for chronic obstructive pulmonary disease (COPD), corresponding to a change from baseline of 20% and informed by both anchor- and distribution-based methods (Puhan et al., 2008).

## 6.3.4 Sample Size

The primary endpoint was defined as change in mean score of PCS-12 between baseline and six-month treatment. As SF-12 and SF-36 are comparable measures, sample size determination was based on the change in mean score of PCS-36 as reported by Walter (Walters, 2004). We assumed a 4.0 point change in PCS-12 mean score (higher than the MID of 3 points) between baseline and visit 4 (six-months treatment) (Babikako et al., 2010) (Atif et al., 2014a), and a corresponding standard deviation (SD) of 7.0 for the mean score after six-months treatment (Atif et al., 2014a), resulting in a standardized effect size of 0.57. Using the standardized effect size with a two-sided 5% level of significance and a 95% power yielded in an estimated sample size of n = 80 participants. We estimated an attrition rate of 20% resulting in a final sample size of n = 96 participants.

### 6.3.5 Ethics

The study adhered to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, the Declaration of Helsinki and South African Good Clinical Practice (GCP). The study was approved by the institutional review commission of the Swiss Tropical and Public Health Institute in Basel, Switzerland. Ethical approval was obtained from the ethical commission of North-West and Central Switzerland (EKNZ) and the ethics committee of the University of Cape Town. City Health of the City of Cape Town and the Western Cape Government of South Africa gave institutional approval of the study.

### 6.3.6 Statistical analysis

Missing interviews were recorded as the absence of the study participant at the appointed interview time frame. Missing data were recorded when the interviewed participant did not complete HRQOL measures, or only insufficiently, hindering calculation of a domain or total score. Significance testing (paired-samples t-test), multivariable analysis and repeated measures ANOVA were based on observations that contained all data points required for a specific analysis.

All HRQOL responses were transferred to an excel-based database and all measures were scored according to each measure´s instructions.

EQ-5D-5L utility scores were calculation based on valuation algorithms for the UK and Zimbabwe, applying the EQ-5D calculator (Euroqol). SF-12 component scores PCS-12 and MCS-12 as well as SGRQ domain and total score were calculated applying specific scoring software provided through the measure´s developer. HADS was scored based on an excel worksheet according to manual instructions.

Interpretation of EQ-5D-5L domain scores and HADS Anxiety and Depression domains were both based on categories: EQ-5D-5L on its five levels (no problems, slight problems, moderate

problems, severe problems, and extreme problems) and both HADS domains on three levels (mild, moderate, severe). The SF-12 component scores and EQ-5D VAS were both interpreted based on a range from 0 (worst health) to 100 (best health), the EQ-5D-5L utility index on a range from 0 (worst health) to 1 (best health). The SGRQ domains and total score were interpreted based on a range between 0 (best health) to 100 (worst health) and compared to scores derived from a population with no history of respiratory disease (Jones, 2009).

Descriptive statistics were applied to socio-demographic data; further to all HRQOL data at baseline and at all follow-up visits to understand the HRQOL impairment of TB patients. Descriptive statistics were conducted including frequencies (N, N missing, %), central tendency (mean, median), and confidence interval (set at 95%). Distribution of data was examined by standard deviation (SD), minimum and maximum values, and frequency plots.

Overall changes in HRQOL between baseline and six-month treatment (visit 4) were calculated as frequencies (%). Longitudinal changes were determined by the change in mean scores between all follow-up visits and baseline. The change in mean scores was examined by paired-samples t-test with a statistical significance (2-tailed) set a priori at $P < 0.05$. Changes in mean scores in the intensive treatment phase (baseline to visit 2) were compared to changes in the continuous treatment phase (visit 2 to visit 4) based on paired-samples t-test with a statistical significance (2-tailed) set a priori at $P < 0.05$. The change in mean scores at each time point from baseline was also compared to the reported minimally important difference (MID) for each measure to understand if the longitudinal changes in HRQOL were clinically meaningful. Paired-samples t-test was applied to examine the difference between changes in mean scores and MID at a significance level of $P< 0.05$.

Differences in HRQOL mean scores among all HRQOL measures over time (baseline and follow-up visit 1-4) were examined by repeated measures ANOVA. Bonferroni correction was applied to repeated measures ANOVA for multiplicity of tests.

Responsiveness over time for each HRQOL was measured as an effect size partial eta

squared providing information of the effect of time on changes in HRQOL aspects. The time effects were based on tests of within-subjects effects. When Mauchly´s test of sphericity was not met (significance < 0.05), both partial eta squared and observed power were derived from the Greenhouse-Geisser correction.

The impact of socio-demographic factors including age, gender, educational status and work status were elaborated. At baseline univariable analysis was applied to understand which factors might be associated with HRQOL, by using a cut off of P = 0.2. Resulting candidate factors were further assessed in multivariable models to understand the impact of socio-demographic factors over time (change from baseline to six month treatment (visit 4)). The univariable and multivariable analysis included a general linear model and an analysis of variance (ANOVA). The time effect of socio-demographic factors based on an effect size partial eta squared was further included by applying repeated measures ANOVA. Threshold values for the effect size were derived from Cohen (Cohen, 1988): 0.1 was interpreted as small, 0.3 as medium, 0.5 as large and 0.8 as very large.

Robustness of the findings was assessed by sensitivity analyses by excluding HRQOL data from visit 3. Further, the assessment of longitudinal changes of HRQOL over time including baseline and all follow-up data as described above was repeated by excluding data from visit 3, which was affected by a very low number of available observations. Results were checked for consistency.

## 6.4 Results

In total, 131 eligible patients were recruited and agreed to participate in the study. Overall, 444 interviews were conducted over the duration of the study with questionnaires completed for data analysis.

From 131 participants who had baseline interviews conducted, 84 (64%) participated in the follow-up interview at visit 1, 85 (64%) participated at visit 2, 48 (36%) participated at visit 3 and 96 (70%) participated at visit 4. Only 20% of participants completed all HRQOL

questionnaires at all time points during treatment as per protocol (Table 5).

**Table 5:** Overview of interviews taken at each data collection time point per study site.

| Data Collection Point | Total Number Interviews | Number of interviews | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Study site 1 | Study site 2 | Study site 3 | Study site 4 | Study site 5 | Study site 6 | Study site 7 |
| Baseline (treatment start) | **131** | **54** | **9** | **18** | **9** | **8** | **13** | **20** |
| Visit 1 (4 weeks post treatment start) | **84** | **31** | **8** | **17** | **5** | **6** | **3** | **14** |
| Visit 2 (8 weeks post treatment start) | **85** | **34** | **8** | **18** | **2** | **5** | **9** | **9** |
| Visit 3 (16 weeks post treatment start) | **48** | **7** | **10** | **17** | **1** | **1** | **7** | **5** |
| Visit 4 (24 weeks post treatment start) | **96** | **41** | **9** | **17** | **3** | **2** | **9** | **15** |
| Total | **444** | | | | | | | |

During the course of treatment a total of 47, 46, 83, and 35 patients did not participate in follow- up interviews 1 to 4, respectively. In the majority of cases the reason for absence of participants was unknown. Of those participants who attended an appointment during the study period, none refused to participate in the interview. However, four patients were unable to participate at follow-up interviews as they had been transferred to a different hospital not included in this study and one patient received a custodial sentence. The lowest attendance rate to interviews was observed after 16 weeks of treatment (visit 3). The reasons why participants did not attend their clinic appointments, and hence the low response rate, was unknown.

In total, nine questionnaires were not completed by patients during the fieldwork. Whilst completing the sections on HRQOL measures, two patients did not answer the

socio-demographic questionnaire, but all HRQOL measures; these two patients were still included in the data analysis. One of each measure was not answered during the data collection: SF- 12 at baseline and at visit 1; EQ-5-D-5L at baseline and at visit 4; SGRQ at baseline, and HADS visit 1 and visit 2.

### 6.4.1 Description of the study population

Table 6 describes the study population. Of 131 study participants, two participants did not provide information on socio-demographic data; 129 participants were included in the description of the study population. Study participants who provided socio-demographic data (n=129) comprised 64% (n=82) men and 36% (n=47) women, age ranged from 18 years to 80 years, with the majority of participants being between 20 and 40 years and with a mean age of 36 years. The majority of participants were black (90%), living alone (i.e. not married nor co-habitation; 82%), and high school education attainment (68%). The majority of the study participants (73%) were unemployed, students or pensioners. Only 21% of the study participants were aware about existing co-morbidities impacting their health, most of them reporting to be diagnosed with other respiratory diseases or diabetes.

The characteristics of the full study population were similar to the characteristics of those patients who provided information at the last visit, after six months of treatment.

**Table 6:** Socio-demographic description of study population.

| Socio-demographic Factors | Study population | | |
|---|---|---|---|
| | N | % | *N missing |
| Gender | 129 | | 2 |
| Male | 82 | 63.6 | |
| Female | 47 | 36.4 | |
| Age | 129 | | 2 |
| Mean age | 35.8 | | |
| Median age | 31 | | |
| Min | 18 | | |
| Max | 80 | | |

| | | | | |
|---|---|---|---|---|
| Age Groups | | 129 | | 2 |
| | 18-30 | 60 | 46.5 | |
| | 31-50 | 46 | 35.7 | |
| | >51 | 23 | 17.8 | |
| Ethnicity | | 129 | | 2 |
| | black | 116 | 89.9 | |
| | other | 13 | 10.1 | |
| Marital status | Total | 129 | | 2 |
| | single/ never married /divorced/separated/widowed | 103 | 81.7 | |
| | married/co-habitation | 23 | 18.3 | |
| Education | | 129 | | 2 |
| | Primary school | 30 | 23.8 | |
| | High school | 86 | 68.3 | |
| | College or university | 10 | 7.9 | |
| Employment status | | 128 | | 3 |
| | Employed/Self-employed/own business | 34 | 26.6 | |
| | Unemployed/Student/Pensioner | 94 | 73.4 | |
| Co-morbidities | | 27 | | 104 |
| | Other respiratory diseases | 13 | 48.1 | |
| | Diabetes | 13 | 48.1 | |
| | Cancer | | | |
| | Cardio-vascular diseases | 1 | 3.7 | |
| | Unknown co-morbidities | | | |

### 6.4.2 HRQOL impairment of TB patients at treatment start

Based on each measure´s score interpretation the HRQOL of the study participants was impaired in all physical, mental and psycho-social health domains at treatment start (baseline) (Table 7).

**Table 7:** Baseline impairment of HRQOL in TB patients at treatment start.

| HRQOL measure | HRQOL domain | N (%) | Mean score (SD) | 95% Confidence Interval | Median | Range | | N miss |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Min | Max | |
| **SF12** | **PCS-12** | 129 | 35.930 (8.321) | 34.477 – 37.376 | 33.990 | 16.100 | 57.090 | 2 |
| | **MCS-12** | 129 | 36.011 (11.487) | 34.013 – 38.015 | 35.840 | 11.690 | 68.900 | 2 |
| **EQ-5D** | **Mobility** | 129 | 2.442 (1.117) | 2.247 – 2.637 | 3.000 | 1.000 | 5.000 | 2 |
| | **Self Care** | 129 | 2.434 (1.131) | 2.237 – 2.631 | 3.000 | 1.000 | 5.000 | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **Usual Activities** | 129 | 2.558 (1.224) | 2.345 – 2.771 | 3.000 | 1.000 | 5.000 | 2 |
| | **Pain&Discomfort** | 129 | 2.496 (1.098) | 2.305 – 2.687 | 3.000 | 1.000 | 5.000 | 2 |
| | **Anxiety&Depressi on** | 129 | 2.566 (1.224) | 2.353 – 2.779 | 2.000 | 1.000 | 5.000 | 2 |
| | **utility Index (UK)** | 129 | 0.505 (0.328) | 0.448 – 0.562 | 0.546 | -0.594 | 1.000 | 2 |
| | **utility Index (Zim)** | 129 | 0.620 (0.203) | 0.584 – 0.655 | 0.621 | -0.145 | 0.900 | 2 |
| | **VAS score** | 129 | 54.512 (18.066) | 51.364 – 57.659 | 50.000 | 10.000 | 100.000 | 2 |
| **SGRQ** | **Symptoms** | 126 | 41.333 (33.803) | 35.349 – 47.317 | 45.419 | 0.000 | 100.000 | 5 |
| | **Activities** | 126 | 70.087 (30.868) | 64.622 – 75.522 | 79.671 | 0.000 | 100.00 | 5 |
| | **Impact** | 126 | 61.542 (25.638) | 57.003 – 66.081 | 66.798 | 0.000 | 100.00 | 5 |
| | **Total score** | 126 | 61.134 (23.045) | 57.055 – 65.214 | 66.366 | 0.000 | 92.643 | 5 |
| **HADS** | **Anxiety** | 131 | 11.504 (5.772) | 10.506 – 12.502 | 12.000 | 0.000 | 21.000 | 0 |
| | **Depression** | 131 | 12.092 (6.237) | 11.014 – 13.170 | 13.000 | 0.000 | 21.000 | 0 |

SF-12: 0 to 100 (= best HRQOL); EQ-5D domains: 1 = no problems, 2 = slight problems, 3 = moderate problems, 4 = severe problems, 5 = extreme problems. EQ-5D total index 0 to 1 (best HRQOL); EQ-5D VAS: 0 = worst health to 100 (= best health); SGRQ 0 to 100 (= worst health); HADS: normal (0-7) mild (8-10) moderate (11-14) severe (15-21)

### 6.4.3 Development of HRQOL during TB treatment

All scores of HRQOL domains improved during the course of standard TB treatment, and over the period of the study (Figure 10). These changes were statistically significant. The largest improvement was observed in domains relating to mental health (increase in mean score between baseline and six month treatment of 59% - 95%), with the highest change observed in the HADS Anxiety and Depression domains, followed by improvements in the physical health domains and the social health domains . The primary endpoint defined as change in mean score of PCS-12 between baseline and six months from treatment initiation (visit 4) showed a change of 20 points (from 35.93 to 55.21) which was statistically significant (P <0.005) (Figure 11). The change in mean score was also greater than the published MID threshold to be considered clinically meaningful.

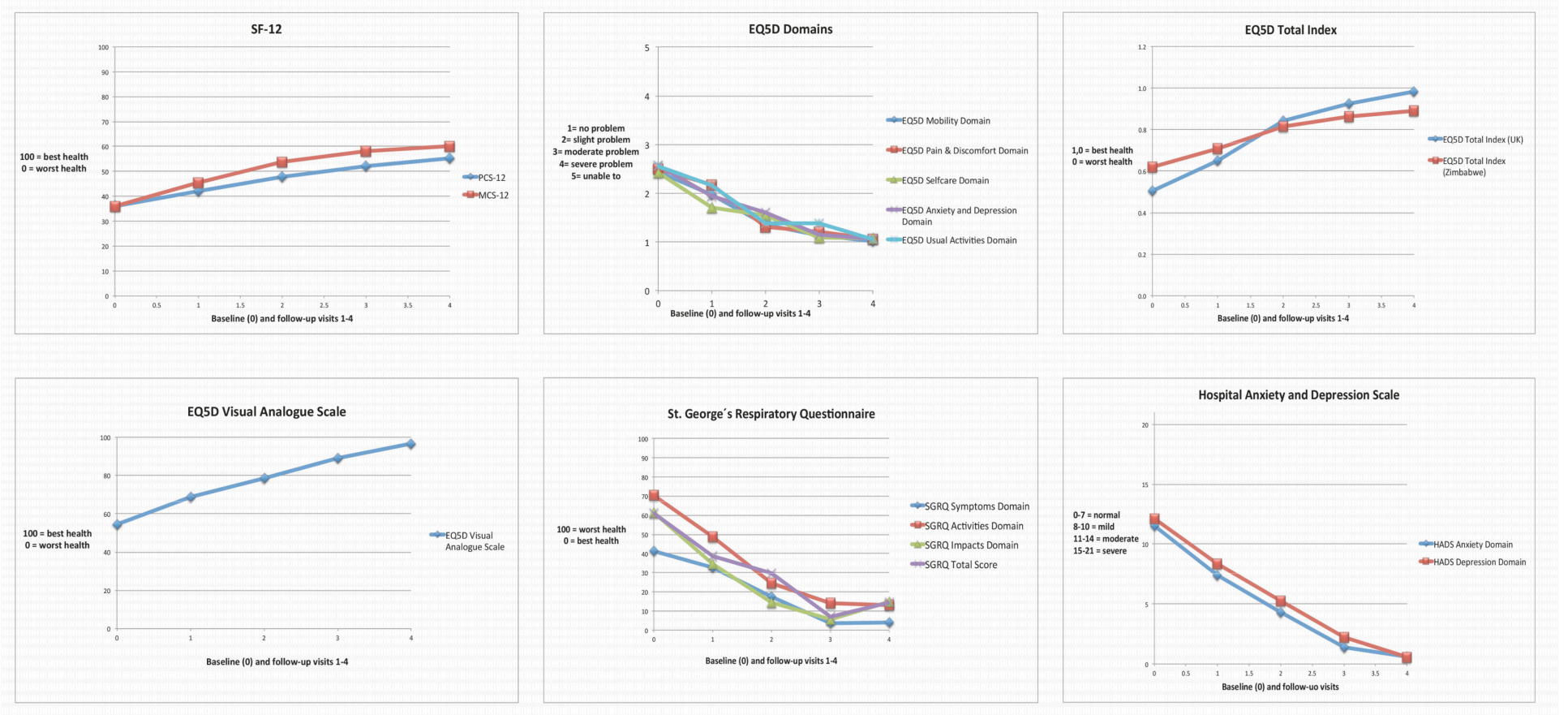


**Figure 10:** The development of HRQOL over six-month treatment, presented for each HRQOL measure and its health domains.

**Figure 11: Histograms of PCS-12 at baseline and after six-month treatment**

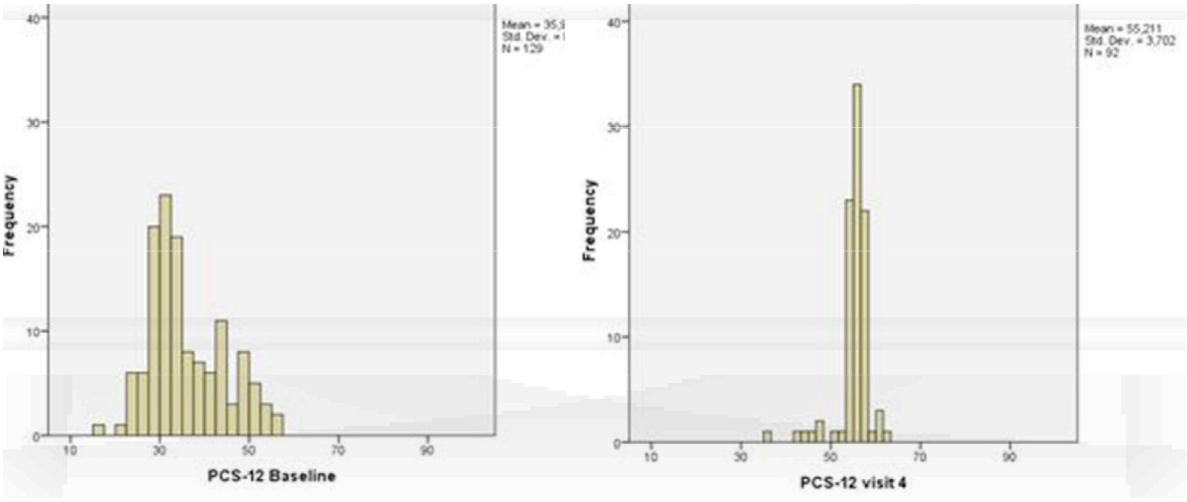


**Figure 11:** Histograms of PCS-12 at baseline and after six-month treatment.

The change in HRQOL over time was statistically significant based on average mean scores. The change was greater than published MID thresholds for each HRQOL measure and thereby clinically meaningful. The MCS-12 mean score showed a greater relative improvement by

+67% over six month treatment than the PCS-12 (+54%). Both component scores changed to a value of 55 points for PCS-12 and 60 points for MCS-12 and these values were above U.S. population norms (47 points for PCS-12 and 53 points for MCS-12) (Atif et al., 2014a, Maruish, 2009). All EQ-5D-5L average domain scores changed from an average state of "moderate health problems" to a state reporting "no problems" (+57-59%). The total index of EQ-5D reflected the same change as was observed on domain level. The total index calculated using the UK valuation algorithm changed by +94%. However, the total index value based on the Zimbabwe valuation algorithm changed by only +44%. The health status of the TB patients measured with the EQ-5D VAS changed by +78%.

The three SGRQ domains showed the greatest change in the physical symptoms domain with +90% improvement. Both domains of HADS (anxiety and depression) changed by +95% from a state of "moderate problems" to a state of reporting "no problems".

The changes in mean scores during the intensive treatment phase were significant and

(baseline to visit 2) higher than during the continuous treatment phase (visit 2 to visit 4). The changes in mean scores of the SGRQ Activities and Impact domains as well as in the SGRQ total score were non-significant during the continuous phase (S1 Table).

Changes in mean scores increased constantly until six month treatment for SF-12, EQ-5D VAS and HADS. The change in EQ-5D and SGRQ mean scores also increased significantly but with a peak after 16 weeks of treatment (visit 3) and changes in mean scores decreased until six month of treatment. Repeated measures ANOVA confirmed that the overall improvement in all HRQOL measures was associated with a statistically significant time effect ranging between 58% and 85%, with the highest effect observed on the health status (EQ-5D VAS) (S2 Table). Sensitivity analysis applied to repeated measure by leaving out data from visit 3 confirmed the robustness of the findings

### 6.4.4 The Influence of socio-demographic factors on baseline HRQOL and longitudinal changes in HRQOL

Significant results from the univariable analysis including the socio-demographic factors gender, age, educational level and work status were further assessed in a multivariable model.

The univariable analysis showed that HRQOL at baseline was more impacted in older patients with low educational background and without work. Age and education were significant factors in mental health domains, with younger patients with higher education reporting better HRQOL; work status played no major role in the mental health. With exception of MCS-12, gender played no role in HRQOL. Only in MCS-12 women reported a lower HRQOL than men. The multivariable model confirmed that younger patients (SGRQ Impacts domain, SGRQ total score, HADS Anxiety and Depression domains) with higher education (EQ-5D total index, HADS Anxiety and Depression domains) and with work (EQ-5D total index, SGRQ Symptoms domain) had a better HRQOL at baseline. These effects were only seen at baseline for all HRQOL measures (Table 8) and not after six months of treatment. PCS-12 mean scores at six months were not significantly different for gender, age, educational

background and employment status.

**Table 8:** Associations between HRQOL and socio-demographic factors at baseline by applying a multivariable model.

| | EQ-5D utility index UK | EQ-5D utility index Zim | SGRQ Symptoms | SGRQ Impacts | SGRQ total | HADS Anxiety | HADS Depression |
|---|---|---|---|---|---|---|---|
| Age | | | | | | | |
| P* value | - | 0.047 | - | 0.046 | 0.020 | 0.017 | 0.029 |
| 18-30 years | - | 0.655 | - | 56.959 | 55.998 | 11.462 | 11.179 |
| 31-50 years | - | 0.615 | - | 63.373 | 63.381 | 11.297 | 12.703 |
| >51 years | - | 0.501 | - | 75.168 | 74.813 | 15.588 | 15.824 |
| Education | | | | | | | |
| P* value | 0.015 | 0.015 | - | - | - | 0.010 | 0.044 |
| Primary school | 0.340 | 0.516 | - | - | - | 14.526 | 15.158 |
| High school | 0.528 | 0.629 | - | - | - | 11.862 | 12.154 |
| College or University | 0.745 | 0.766 | - | - | - | 7.286 | 9.000 |
| Work Status | | | | | | | |
| P* value | 0.008 | 0.010 | 0.020 | - | - | - | - |
| Employed, self-employed, own business | 0.669 | 0.713 | 26.917 | - | - | - | - |
| Unemployed, student, pensioner | 0.444 | 0.578 | 46.399 | - | - | - | - |

Results from the repeated measures ANOVA showed no statistically significant effect of gender and age on the overall HRQOL improvement. However, education and work status showed significant effects. Patients with higher education and with work reported better HRQOL. Education (df = 1.000, F = 6.632, P = 0.012, eta = 0.074) and work status (df = 1.000, F = 7.789, P = 0.007, eta = 0.086) had a statistically significant but small effect on the HRQOL improvement with regard to PCS-12 (physical health). Similar effects were observed for the EQ5D utility indices (UK valuation algorithm: education df = 1.000, F = 7.071, P = 0.009, eta = 0.078; work status df = 1.000, F = 7.799, P = 0.006, eta = 0.085); Zimbabwe valuation algorithm: education df = 1.000, F = 6.821, P = 0.011, eta = 0.075; work status df = 1.000, F = 7.438, P = 0.008, eta = 0.081). Further, work status

showed a statistically significant (df 1.000, F = 7.654, P = 0.007, eta = 0.081) but small effect on the overall improvement of the HRQOL domain SGRQ Symptoms (physical health) (S3 Table).

## 6.5 Discussion

The increasing prevalence of non-communicable diseases (NCDs) and communicable diseases such as TB in South Africa leads to an increased pressure on healthcare resources. More importantly, from the patient perspective it also has an impact on the general well-being and HRQOL of patients.

This study was designed to evaluate changes in HRQOL in South African patients recently diagnosed with TB (without HIV co-infection) during the course of standard TB treatment over a six-month period. Two generic HRQOL measures (SF-12 and EQ-5D), a disease-specific measure (SGRQ) for respiratory diseases and a condition-specific measure for anxiety and depression, the HADS were used to assess HRQOL (Kastien-Hilka, 2016). These four HRQOL measure captured relevant health aspects of TB in the physical, mental and psychosocial domains. The study population was recruited from the Cape Town district Khayelitsha, a socio- economically disadvantaged area. The majority of TB patients were in the productive years of their lives. However, more than 70% were not in employment. At the start of treatment, HRQOL domains and total scores on all measures indicated significant impairment in HRQOL. The results demonstrate that HRQOL improved significantly over treatment time, with the greatest improvement observed during the intensive phase of treatment and with greatest improvement in mental health domains.

Socio-demographic predictors for HRQOL at baseline included age, educational background and work status. Younger TB patients with a higher education, and who were in employment reported better HRQOL at baseline. A significant effect of educational background and work status has been reported before (Kastien-Hilka et al., 2016, Darvishpoor Kakhki and Masjedi, 2015). It can be assumed that a better education increases

the chances for work and financial security which might have a positive effect on HRQOL by improved self-care, improved social interactions, less psycho-social distress and less financial burden. Gender differences showed no significant effect on most HRQOL domains at baseline; only in the MCS-12 women reported a lower HRQOL than men. These effects of age, education and work status were not found after six months of treatment.

Gender and age were no predictors for positive changes in HRQOL over the treatment course. A recent study from Louw et al 2016 confirmed our findings of a non-effect of gender and age on HRQOL in TB patients after six month treatment in other Provinces in South Africa (Louw et al., 2016). However, the same study reported that higher education was significantly associated with an improvement in mental health (MCS-12) after six month of treatment. Our study confirmed the effect of education on mental health aspects (anxiety and depression) only at baseline.

All changes over treatment time were statistically significant and were also clinically meaningful. The greatest improvements in physical health were measured with the respiratory-specific measure SGRQ. The primary endpoint defined as overall change in PCS-12 did not reflect the greatest improvements. It can be assumed that the Symptoms domain of SGRQ captures physical impairment due to TB in more detail and thereby being more sensitive to any changes in HRQOL than generic measures such as SF-12 and EQ-5D.

The study results revealed that the greatest improvement in all HRQOL domains was seen in the mental health of TB patients. The condition-specific HADS measure showed a similar impact on mental health at treatment start as reported from a study in Pakistan (Husain MO, 2008). These results confirm previous findings suggesting that mental health is an important aspect in the treatment of TB. About 46-80% of TB patients in South Africa report common mental disorders (Westaway, 2001, Naidoo and Mwaba, 2010). This psychological distress is associated with physiological TB symptoms, perceived health status, adverse events through anti-TB treatment and treatment outcome (Peltzer K, 2012). Furthermore, psychological distress may be caused by social stigmatization (HIV co-

infection) followed by social isolation during TB treatment and impacted financial situation including fear of dying and disease transmission (Peltzer K, 2012, Issa BA, 2009, Hansel NN, 2004, Naidoo and Mwaba, 2010, Aamir and Aisha, 2010). Special focus on reduction of stigmatization should be given in the management of TB to reduce the psychological distress (Cremers et al., 2015). This may suggest that patients perceive a positive outlook suffering less from the depression and anxiety associated with TB in South Africa. This again, is something that should be considered in the light of non-adherence. Inclusion of psychological support and treatment of mental disorders in the management of TB should be considered as well as interventions to reduce the stigmatization related to TB to improve the overall treatment outcome.

The physical and mental impairment seen in the South African patient population in this study is confirmed by studies in other countries applying the same HRQOL measures. The generic SF-12 measure indicated at treatment start a similar impairment in both the PCS-12 and MCS- 12 with a score of 36, presenting defective physical functioning and a high risk for depression. A similar HRQOL impairment was reported in a study with TB affected immigrants in the UK (Kruijshaar et al., 2010) and from a study in Yemen (Jaber et al., 2016). Other studies which measured HRQOL by SF-36 or SF-12 in TB patients reported higher scores between 40 and 61 and thereby a better HRQOL at treatment start in Canada, Uganda, and Malaysia (Babikako et al., 2010, Dion et al., 2004, Guo N, 2008, Marra et al., 2008, Atif et al., 2014a, Bauer et al., 2015). Measuring the HRQOL in TB with the generic measure EQ-5D, our TB patients in South Africa reported a more impaired HRQOL and health status than in other countries (Malaysia, the UK, Canada) (Dion et al., 2004, Kruijshaar et al., 2010, Awaisu et al., 2012). The same effect was found with the respiratory-specific measure SGRQ showing that our study population had a more impacted HRQOL than TB patients from Indonesia (Maguire et al., 2009). The SGRQ total score still showed some impairment with a score of 14 compared to a value of 5-7 reported by people from Spain with no respiratory history (Jones, 2009).

The phenomenon of an initial worsening in HRQOL after treatment start reported previously could not be confirmed by our observations (Chung and Li, 2013). Our study confirmed that the greatest improvement in HRQOL was seen during the intensive phase and this observation was reported before (Aggarwal et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Othman, 2011, Chamla, 2004). It is expected that monitoring of adherence during this treatment phase should be implemented to ensure that patients continue with their medication regime as many may perceive this improvement in their HRQOL as a sign of 'cure' and therefore no need to continue with their medication.

Comparing the results from the EQ-5D VAS and EQ-5D utility index based on value sets from UK with value sets from Zimbabwe clearly showed some cultural differences in HRQOL changes over time and its interpretation, and highlight the need for specific population norms for South Africa. The EQ-5D VAS reached a higher value of 97 than that of the general population in the UK of 82.5 and in Zimbabwe of 79.8 (Jelsma, 2003). At baseline the utility index derived from the UK value set was by 0.115 points lower than the utility index derived from the Zimbabwean value set and this difference was greater than the MID for EQ-5D-5L. This is critically important in the context of the increasing request for cost-effectiveness analysis (CEA) from health systems in the allocation of resources. The EQ-5D is the preferred instrument to estimate population-based utilities for the calculation of quality-adjusted life years (QALYs) to provide a cost per QALY outcome in CEA. In 2013, the South African Department of Health published the Guidelines for Pharmacoeconomic Submissions which requests the use of QALYs for CEA (NDoH, 2013). The development towards pharmacoeconomic evaluations in South Africa for efficient decision making would require data acquisition to establish South African population norms for the EQ-5D.

## 6.6 Limitations

This study had several limitations. Our sample size was difficult to reach in one restricted

district due to the low number of TB patients without HIV co-infection, as well as due to time and resource limitations in this study. In South Africa the high majority of TB patients are HIV co-infected; this study did exclude HIV co-infection to understand the isolated TB impact on HRQOL. Further, this study did not include a comparison or control group from the general population, for time and resource limitations. Our study did not apply a mixed method approach and was limited to a quantitative approach; patient perspectives about TB in a South African cultural background were not qualitatively assessed. Such data might have enriched the quantitative findings for HRQOL in this study. HRQOL was only assessed in a specific district of the Western Cape Province with a specific socio-demographic and –economic situation. Results from this study may not be generalizable to the rest of the South African population which is very diverse. Receiving treatment for their condition may have put an increased economic pressure on these participants as they may have been unable to take on work or consider their working options due to the travel distance between a health clinic they get the treatment from and workplace, but also due to the disease induced worsening of their physical condition (Dias et al., 2013, Chang B, 2004, Hansel NN, 2004).

Additionally, there is an increased risk of tuberculosis when diagnosed with diabetes (Ottermann, 2013), therefore we expected diabetes as a major co-morbidity in our TB patients. We included questions about NCDs in our study, however it was apparent that only a small portion of TB patients were aware of any co-morbidity they may have, including diabetes. We assume that other health issues are unknown to a majority of TB patients have. These unknown co-morbidities are assumed to have an additional impact on the HRQOL in TB patients at baseline which we could not distinguish.

## 6.7 Conclusions

TB negatively impacts the HRQOL of patients, with specific impairment reported in physical, mental and psycho-social health aspects, however with treatment HRQOL improves significantly. Different aspects of health (HRQOL domains) are impacted differently and it

would appear that the rate of improvement in each domain may also be different. HRQOL reveals different outcomes depending on the type of measure applied and depending on the cultural background and the study setting, making comparison of HRQOL outcomes difficult. Generic HRQOL PROs may not adequately capture all relevant aspects of TB, and thus a disease-specific HRQOL measure is required. This study also demonstrates the need for an integrative understanding of TB with HRQOL as core element to inform gaps in current TB management. Improvements in the management of TB following an integrative patient-centred approach will contribute towards meeting the UN SDG3 target and will support the End TB strategy of the WHO.

## 6.8 Acknowledgments

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## 6.9 Supporting Information

S1 Table. Changes in HRQOL in the intensive and continuous treatment phase.

S2 Table. Overall treatment time effect on HRQOL (test of within-subjects effects).

S3 Table. Effects of socio-demographic factors on overall HRQOL improvement.

# 7. The association between health-related quality of life and medication adherence in pulmonary tuberculosis in South Africa

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# The association between health-related quality of life and medication adherence in pulmonary tuberculosis in South Africa

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## 7.1 Abstract

**Background:** Health-related quality of life (HRQOL) and adherence to treatment have implications for patient management and care. Tuberculosis (TB) and its treatment present a major public health concern in the South African health care system. This study aimed to evaluate the association between HRQOL and adherence in TB patients in South Africa.

**Methods:** Four self-reported HRQOL and one self-reported adherence measures were used in an observational longitudinal multicentre study during six-month standard TB treatment. The relationship between both concepts was examined in 131 patients using Spearman´s rho correlations and linear regression models.

**Results:** HRQOL improved over six-month TB treatment, whereas adherence mean scores stayed constant with participants attaining a medium average level. Associations between HRQOL and adherence were mainly weak and included a positive relationship with improvements in anxiety and depression, pain and discomfort, and psycho-social health aspects.

**Conclusion:** This study has clearly demonstrated that management of TB patients must address their specific mental and psycho-social needs, besides adequate drug treatment. An integrative patient-centred approach will contribute towards supporting the Sustainability Development Goal 3 target and the End TB strategy.

## 7.2 Introduction

According to the World Health Organization (WHO), health is a multi-dimensional construct and comprises physical, mental and social health domains (WHO, 1948). Health-related quality of life (HRQOL) can be measured using patient-reported outcome (PRO) measures, which take into account these different domains of health. Non-adherence to treatment has a negative impact on HRQOL and other measures of health care and outcomes including clinical effectiveness, morbidity, medical and psycho-social complications and health care costs (direct and indirect costs) (Cramer, 2008, WHO, 2003). The WHO has defined inadequate adherence to medication as a major problem in the management of chronic diseases (WHO, 2003). According to WHO, increased medication adherence could have a greater impact on the health of a population than any improvement in specific medical treatments (WHO, 2003). Both adherence and HRQOL are important indicators for the effectiveness and treatment success of therapeutic interventions (Cote, 2003). However, the association between HRQOL and adherence to treatment has rarely been studied in some chronic conditions including tuberculosis (TB).

TB places a significant burden on the health systems of countries where this condition is not controlled. South Africa, which has the highest prevalence and incidence rates of all 22 high-burden TB countries worldwide (WHO, 2015c), has committed a significant portion of its health budget to expand early detection and treatment of TB (Christian, 2016). Aside from the financial burden on the South African health budget, TB also places a considerable burden on the patient, significantly impacting the physical, emotional, psycho-social as well as economical domains of health (Kastien-Hilka et al., 2016). These same domains are known to impact medication adherence (WHO, 2003). Standard TB treatment is available in South Africa, including supervised monitoring and adherence checks by the introduction of Direct Observed Treatment (DOT).

Cote et al and Saleem et al propose a model whereby HRQOL is an *ultimate outcome* while adherence is seen as an *intermediate outcome* (process variable). This model follows that any impact of a therapeutic intervention is revealed by a change in adherence first, followed by a change in HRQOL (Cote, 2003, Saleem, 2012). However, the relationship between these two concepts is complicated by the fact that HRQOL may also directly influence adherence (Agh, 2015). A systematic review by Munro et al identified two underlying mechanisms for the association between well-being and adherence, specific to TB treatment (Munro S, 2007). In this alternative model, the first mechanism relates to TB patients prematurely stopping their treatment because they fell better, with patients perceiving the improvement in well-being as a cure of TB. On the other hand, the second observed mechanism refers to

patients stopping treatment when they experience no improvement or a worsening in their health status and well- being, i.e. the medication was not working (Munro S, 2007, WHO, 2003). This alternative model would imply that a change in HRQOL appears first, and is followed by a change in adherence behaviour.

The aim of this research was to evaluate the relationship between patient-reported HRQOL and adherence in pulmonary TB in South Africa using a longitudinal study design. The study provides information on the longitudinal changes in HRQOL and adherence during six-month treatment. The evaluation of both concepts over time allows identifying which health aspects of TB have an influence on adherence and which health domains are affected by non-adherence.

## 7.3 Methods

A detailed description of the study design and methodology has previously been published (Kastien-Hilka, 2016). Briefly, the study used an observational longitudinal design including repeated measures of HRQOL.

### 7.3.1 Patient population and participant recruitment

Study participants were recruited between November 2014 and May 2015 at six selected primary health care clinics with the highest TB caseloads per month in Cape Town. Four of these facilities are run by the local government, and two by the provincial government; all are located in the Khayelitsha sub-district of the Cape Town Metro district. This sub-district has the highest TB burden in Cape Town, based on latest 2012 survey data provided by the Western Cape Province. Recruitment of new TB cases without HIV co-infection was difficult, as a high proportion of TB patients are HIV co-infected in South Africa. In order to meet the sample size in the pre-determined time frame, one additional clinic in the neighboring district Delft was included in the study.

The study population comprised of patients newly diagnosed with active pulmonary TB who were 18 years of age or older. Patients were excluded if they were diagnosed with multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and/or had HIV co-infection. The eligibility status of each patient was subject to verification by the nurse dedicated to TB patients at each health facility.

### 7.3.2 Study procedures

Eligible participants received their regular six-month standard of care TB treatment with rifampicin, isoniazid, ethambutol and pyrazinamide. Self-reported HRQOL and adherence were documented at the following time points during the six-month treatment period: at beginning of treatment (baseline, HRQOL only) and at follow-up visits (4, 8, 16 weeks and after six-month treatment). At the same time points sputum smear results were collected in order to monitor treatment success. Data collection started when TB patients visited the study sites for treatment initiation; four HRQOL measures and one socio-demographic questionnaire were applied at baseline (treatment start). These four HRQOL measures were re-applied together with a self-reported adherence measure at all follow up visits. Data were collected using paper questionnaires during face-to-face interviews conducted by trained field workers. Questionnaires were scanned by the field worker for any missing responses during

the interviews. Sputum smear results for each participating patient were provided through the study sites nurses.

### 7.3.3 Study material

The rationale for the selection of HRQOL measures and adherence measure has been described previously (Kastien-Hilka, 2016). Two generic (EQ5D-5L and SF-12), one disease- specific (SGRQ) and one condition-specific (HADS) HRQOL measures were chosen. A detailed description of each HRQOL measure is available in the supplement material. As self- reported adherence measure the Morisky Medication Adherence Scale 8 items (MMAS-8) was selected (Krousel-Wood, 2009, Morisky and DiMatteo, 2011, Morisky, 2008a). The scale is a generic measure assessing long-term chronic and infectious medical regimens is reliable and valid and has been applied in TB before (Lam and Fresco, 2015, McInerney et al., 2007, Corless et al., 2009, Stirratt et al., 2015). The MMAS has shown to be sensitive to identify low adherence and is a simple scale to identify and monitor adherence (Morisky, 2008b). The MMAS-8 scale ranges from 0 to 8.0; total scores are interpreted in the following way: low adherence <6.0, medium adherence 6.0 – 8.0, and high adherence =8.0.

### 7.3.4 Statistical analysis

All statistical analyses were conducted using IBM SPSS Version 23®. Statistical analysis of the HRQOL measures and changes over treatment time has been described elsewhere. Descriptive analyses were applied to socio-demographic data and sputum smear results; and all adherence data at all follow-up visits 1-4 to understand the longitudinal development of adherence during six month treatment. Descriptive analyses included frequencies (N, N missing, %), central tendency (mean, median), and confidence interval (set at 95%). Distribution of data was examined by standard deviation (SD), minimum and maximum values, and frequency plots.

Longitudinal changes in adherence were examined by the change in mean scores between follow-up visit 1 and follow-up visits 2, 3, and 4. The change in mean scores was assessed by paired-samples t-test with a statistical significance (2-tailed) set a priori at $P < 0.05$. Differences in adherence mean scores over time were also examined by repeated measures ANOVA. Bonferroni correction was applied .to account for multiple testing. The effect size partial eta squared provides information of the effect of time on changes in adherence. The time effects were based on tests of within-subjects effects. When Mauchly´s test of sphericity was not met

(significance < 0.05), both partial eta squared and observed power were derived from the Greenhouse-Geisser correction. The impact of socio-demographic factors including gender, age, educational background and work status were assessed by applying multivariate analysis with adherence at visit 1 and visit 4 as dependent variable.

Associations between mean scores of HRQOL and adherence were examined using a step-wise method. First, descriptive, HRQOL and adherence measures were scrutinized for a possible relationship. Second, Spearman´s rho correlation coefficients were calculated between HRQOL domains and total mean scores on the one hand and adherences mean scores, on the other hand at all time points. In addition, correlations were applied to HRQOL and adherence and sputum smear results. Further, Spearman´s rho correlation coefficients were examined between changes in HRQOL mean scores (between baseline and visit 2; between baseline and visit 4) and adherence mean scores at visit 4. The strength of correlations was categorised as follows: 0-0.1 = no correlation, 0.1-0.3 = weak correlation, 0.3-
0.5 = moderate correlation and 0.5-1.0 = strong correlation (Cohen, 1988). In a third step, a linear regression model (univariate analysis, multivariate analysis and repeated measures ANOVA) was used to examine the associations over time and to examine which domain-based associations from the correlation analysis are confirmed by the regression model. Multivariate analysis was performed for changes in mean scores of HRQOL between baseline and visit 2 and adherence mean score at visit 2; and for changes in mean scores of HRQOL between baseline and visit 4 and adherence mean scores at visit 4. Changes in HRQOL were treated as dependent variable and adherence scores visit 2 and visit 4 were explanatory, fixed factors in the multivariate model. Differences in HRQOL mean scores between baseline and visit 4 and differences in mean adherence scores between visit 1 and visit 4 were examined by a two factorial repeated measures ANOVA, treating both HRQOL and adherence as dependent variables. Bonferroni correction was applied. A repeated measures ANOVA was conducted with HRQOL as dependent variable and adherence was inserted as fixed factor to examine the effect of time on HRQOL changes by categorizing adherence as good, medium or low adherence. Furthermore, univariate analysis was applied changes in HRQOL mean scores during the intensive treatment phase (Baseline to visit 2) and during the continuous treatment phase (visit 2 to visit 4) with adherence as a categorical variable (good, medium, low) and a fixed factor at the end of each treatment phase (visit 2 and visit 4). Partial eta squared ($\eta^2$) was applied as effect size to observe the effect of adherence on changes in HRQOL mean scores.

## 7.4 Results

### 7.4.1 Development of HRQOL over treatment time

Baseline scores indicated significant impairment in overall HRQOL and domains. Socio-demographic determinants associated with baseline HRQOL were age, education and work status, where older, less educated and unemployed (or not working) patients report poorer HRQOL. Gender showed no significant effect on HRQOL.

All HRQOL domains and total scores improved over six-month of TB treatment, with highest improvement during the intensive treatment phase (first 8 weeks of treatment). These changes were statistically significant, and based on the thresholds set by minimal important difference (MID) for each measure, were also clinically meaningful. The greatest improvement in HRQOL was observed in mental health domain, such as anxiety and depression.

### 7.4.2 Development of adherence over treatment time

Table 9 and figure 12 present self-reported adherence from 4 weeks (visit 1) to six months (visit 4) of standard TB treatment. The mean scores of adherence were in the range of medium adherence for the complete treatment time. Mean score for adherence at 4 weeks (visit 1) and 6 months (visit 4) were identical. Paired samples t-test confirmed that changes between visit 1 and visit 2, 3 and visit 4 were not statistically significant (2-tailed). Repeated measures ANOVA confirmed these findings, and treatment time had no significant effect on the adherence behaviour (P= 0.116, partial eta squared = 0.084).

Based on the adherence grading of MMAS-8, the majority of TB patients reported a good adherence at all time points during treatment (74% - 89%). This good level of adherence remained unchanged in most patients (79%) throughout the study period. However, approximately 21% of patients classified as a good adherer at visit 1 changed their adherence behaviour to medium and low adherence after six months. In the group of patients with medium and low adherence, 46% improved their adherence to good adherence behaviour after six month of treatment.

**Table 9:** Development of adherence over treatment time based on average mean scores in adherence at each data collection point over six month TB treatment.

| Time | Mean (SD), N | CI95%<br>Range | Good adherence mean score<br>% | Medium adherence mean score<br>% | Low adherence mean score<br>% |
|---|---|---|---|---|---|
| **Visit 1** | 7.400 (1.474)<br>84 | (7.076-7.716)<br>8 | 8.000<br>73.8 | 6.734<br>19.0 | 2.917<br>7.1 |
| **Visit 2** | 7.622 (1.053)<br>84 | (7.394-7,851)<br>8 | 8.000<br>78.6 | 6.800<br>17.9 | 3.417<br>3.6 |
| **Visit 3** | 7.800 (0.671)<br>47 | (7.601-7.995)<br>3.5 | 8.000<br>89.4 | 6.833<br>6.4 | 5.000<br>4.3 |
| **Visit 4** | 7.400 (1.503)<br>95 | (7.089-7.701)<br>7 | 8.000<br>76.8 | 6.789<br>13.7 | 3.361<br>9.5 |
| **Good adherence = 8, medium adherence = 6-8, low adherence < 6** | | | | | |

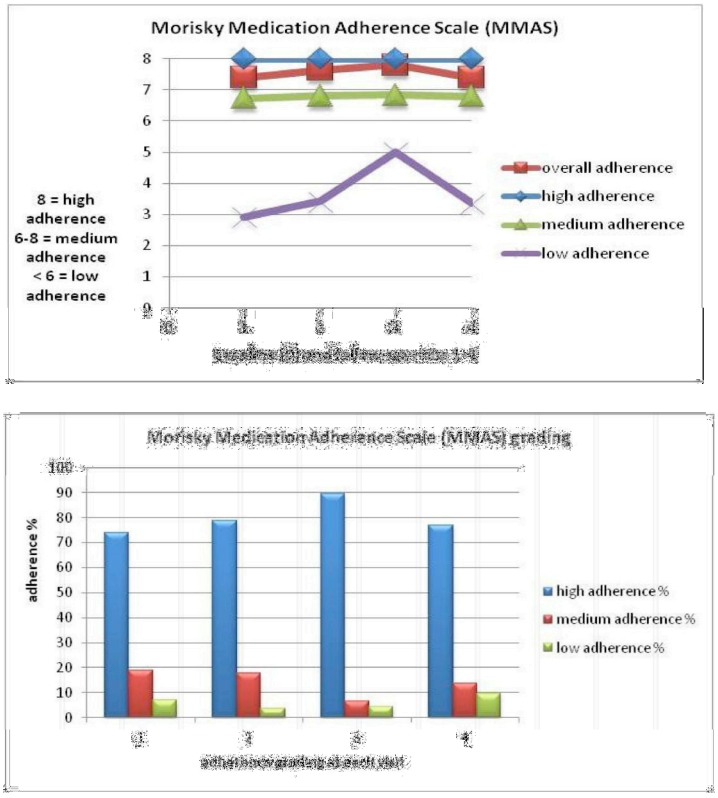


**Figure 12:** Development of adherence over six month TB treatment, based on average mean scores.

Age, gender and work status showed no impact on the adherence at visit 1 and visit 4. Only education had a statistically significant influence on the adherence at visit 4 ($\eta^2$= 0.129 P= 0.016). At six-month treatment a lower educational background led to better adherence scores than a higher education.

Associations between HRQOL and sputum smear results and between adherence to medication and sputum smear results were not examined since routinely collection of sputum smear results for each participating patient was only possible in few cases. Only one of the seven study sites applied sputum smear testing during the course of treatment, but only in single cases and not regularly when patients came to the clinics on a monthly basis.

### 7.4.3 Association between HRQOL and adherence over treatment time

HRQOL improved significantly over the treatment time, while mean adherence scores remained constant at a medium adherence level. The most pronounced correlation indicated a moderate and positive association between adherence in the first 4 weeks and EQ-5D Anxiety/Depression at six-month treatment (r = -0.430 p< 0.001). The same positive but weak relationship was observed between adherence in the first 4 weeks and EQ-5D utility index (both UK and Zim based) at six-month treatment (r = 0.364, p= 0.003). At six-month treatment a weak but positive relationship between Symptoms and Activities domains (SGRQ) and adherence was observed (r = -0.297 p= 0.004; r = -0.317 p= 0.002).

Spearman´s rho correlation was also calculated for overall changes in HRQOL mean scores (baseline to visit 4) and adherence at six-month of treatment. Statistically significant, weak correlations were observed between the overall improvement of the HADS Anxiety (r= 0.226 P= 0.026), EQ-5D Pain/Discomfort (r= 0.232 P= 0.026), SGRQ Impacts (r= 0.291 P= 0.005)
and SGRQ total scores (r= 0.226 P= 0.014) and adherence at six-month treatment. All relationships showed that an improvement in HRQOL between baseline and visit 4 was positively associated with adherence.

The multivariate model confirmed some of these findings. It showed positive, statistically significant but weak associations between overall improvements in the EQ-5D Pain/Discomfort domain ($\eta^2$ = 0.098 P= 0.041), SGRQ Activities domain ($\eta^2$= 0.110 P= 0.026), SGRQ Impacts domain ($\eta^2$= 0.131 P= 0.011) and SGRQ total score ($\eta^2$= 0.135 P= 0.013) and adherence at visit 4. The association between HRQOL domains and adherence was responsible for 10% -

14% of the variance in the HRQOL domains. In addition, an association between improvement of SGRQ total score ($\eta^2$= 0.102 P= 0.039) in the first 8 weeks of treatment and adherence at visit 4 was found, which accounted for 11% of the variance of HRQOL improvement. Patients with good adherence had a greater change in HRQOL than patients with medium and low adherence. For the SGRQ Activities and Impacts domains as well as for the SGRQ total score, a worsening was observed for medium adherers.

The positive associations between overall improvements in the EQ-5D Pain/Discomfort domain ($\eta^2$= 0.071 P= 0.038), SGRQ Impacts domain ($\eta^2$= 0.088 P= 0.015) and SGRQ total score ($\eta^2$= 0.077 P= 0.031) and adherence at six-month treatment from the multivariate model were further confirmed by statistically significant results from repeated measures ANOVA.

The association between HRQOL improvements and different levels of adherence was assessed by comparing the intensive and the continuous treatment phases. No significant relationships between HRQOL and adherence levels were found during the intensive treatment phase. The associations found from Spearman´s rho correlation, multivariate model and repeated measures ANOVA were confirmed for the continuous treatment phase. During the continuous treatment phase there were significant and positive associations between HRQOL and adherence, with an effect size of 10% to 15% related to the EQ-5D Pain/Discomfort domain ($\eta^2$= 0.103, P= 0.032), EQ-5D VAS ($\eta^2$ = 0.156 P= 0.004), SGRQ Activities ($\eta^2$= 0.123, P= 0.015) and Impact domains ($\eta^2$= 0.124 P= 0.014). Good adherers reported a greater change in HRQOL than low adherers. Medium adherers showed a worsening in HRQOL during the continuous treatment phase in the domains SGRQ Impacts and Activities (Table 10).

**Table 10:** Associations between HRQOL and adherence during the intensive and continuous treatment phases based on linear regression models for three HRQOL domains.

| HRQOL | Spearman´s rho correlation at 6 month treatment<br>r (Sig) | Spearman´s rho correlation (changes in HRQOL)<br>r (Sig) | Univariate Model<br>$\eta^2$(Sig) | Multivariate Model<br>$\eta^2$(Sig) | Repeated measures ANOVA<br>$\eta^2$(Sig) |
|---|---|---|---|---|---|
| EQ-5D Pain/Discomfort | | 0.232<br>(P= 0.026 | 0.103<br>(P= 0.032) | 0.098<br>(P= 0.041) | 0.071<br>(P= 0.038) |
| SGRQ Activities | -0.317<br>(P= 0.002) | | 0.123<br>(P= 0.015) | 0.110<br>(P= 0.026) | |
| SGRQ Impacts | | 0.291<br>(P= 0.005) | 0.124<br>(P= 0.014) | 0.131<br>(P= 0.011) | 0.088<br>(P= 0.015) |

*Significance level <0.05; HRQOL: health-related quality of life; effect size partial eta squared ($\eta^2$); EQ-5D: EuroQol Questionnaire; SGRQ: St. George´s Respiratory Questionnaire

## 7.5 Discussion

HRQOL and adherence to medication are two distinct concepts that are thought to be interrelated and require consideration, in the interest of optimal management of the patient. Both concepts are impacted by a number of factors including disease-related, mental health, psycho-social-related, socio-demographic and socio-economic factors (Kastien-Hilka et al., 2016). TB has a negative impact on many domains of HRQOL including the physical, mental, psycho-social and economic domains. Adherence to TB treatment is essential for successful treatment and cure of the patient; and adherence may be impacted by the patients' perception of their HRQOL. Adherence is still a major health issue in South Africa, even though direct observed treatment (DOT) for ensuring adherence has been implemented.

The present study sought to evaluate the association between HRQOL and adherence in TB patients in South Africa. There are several key findings. First, while HRQOL improved in all domains, adherence behavior was constant, with adherence of most patients being classified as medium during the course of six-month standard treatment. About 76% were good adherers and 24% were non-adherers. Another study reported a similar finding with 26% TB patients in Southern Africa being non-adherent (Theron et al., 2015). Second, gender, age and work status had no effect on the adherence over treatment time. Only education showed a significant effect on adherence at six-month treatment, with patients with lower education reporting better adherence. Patients with higher education had a lower adherence at six month of treatment.

Third, this study showed statistically significant, but mainly weak associations between HRQOL and adherence. Generally, there were positive associations between adherence during the first four weeks of treatment and good HRQOL in terms of lower levels of anxiety and depression and overall HRQOL (utility) at six-month treatment. This would suggest that higher levels of adherence may positively influence the improvements in psychological distress. Our study did not find associations between HRQOL at treatment start and adherence over treatment time. However, other studies reported that an impaired HRQOL in at treatment start negatively impacts adherence in patients with chronic obstructive pulmonary disease (COPD) (Agh, 2015).

Psychological distress, including anxiety and depression are reported to be prevalent in TB

patients (Theron et al., 2015). While good adherence to treatment improved anxiety and depression, depression at treatment start may be a trigger for non- adherence although our study did not find this reciprocal relationship between HRQOL and adherence. Theron et al assessed psychological distress in TB patients in Southern Africa and observed a significant relationship between higher levels of TB-related psychological distress and non-adherence (Theron et al., 2015).

The results of the present study revealed an effect of treatment time on the overall improvement in HRQOL, specifically significant positive associations between lower levels of pain, discomfort and psycho-social factors related to TB and higher overall adherence during the continuous treatment phase. Our study findings about the associations between HRQOL and adherence were confirmed to be present only during eight to 24 weeks of treatment rather than during the first eight weeks of treatment (intensive phase).

Very few studies have assessed the association between HRQOL and adherence in other diseases so far. Similar to the present study, only a weak to negligible association between HRQOL and adherence could be demonstrated. Various HRQOL PRO measures have been applied, mainly generic instruments such as RAND-12, SF-12, HUI2 and HUI 3 (Cote, 2003) and EQ-5D (Saleem, 2012, Agh, 2015), but also the respiratory-specific SGRQ (Agh, 2015) and psychological measure Kessler-10 (Theron et al., 2015). The methods for adherence monitoring included self-reported measures such as MMAS (Cote, 2003, Agh, 2015) and The Drug Attitude Inventory (DAI-10) (Saleem, 2012), electronic monitoring and DOTS clinic cards for TB adherence monitoring (Theron et al., 2015). Our study applied a similar concept of generic, disease- and condition-specific HRQOL measures and a self-reported adherence tool and confirmed the weak associations reported in other studies by our findings. Our study combined generic with disease- and condition specific HRQOL measures to ensure that all possible relevant HRQOL domains were captured. These different types of PRO measures capture different aspects of health and this might influence the association with adherence. Generic measures such as SF-12 and EQ-5D might not be sensitive enough to examine associations to adherence. We only found weak associations between the single item of the generic EQ-5D measuring pain and discomfort and adherence. The respiratory-specific HRQOL measure SGRQ showed significant association with adherence, specifically in the psycho-social domains of health measured in this PRO.

## 7.6 Limitations

Our study has several limitations. We used a self-reported measure of adherence. This may have impacted the reliability of the observed relationship between HRQOL and adherence. An ideal adherence measure would assess overall adherence to medication including initiation, persistence, implementation and discontinuation. However, such a measure does not exist; therefore a multi-measure approach should be considered where direct and indirect adherence measures are combined (Fairman, 2000). Direct measures such as drug determination in biological fluids or direct patient observation are often regarded as being the most reliable and accurate. However, individual changes in drug metabolism and multidrug intake affect monitoring of plasma levels, and patient observation is limited to inpatient settings and clinical trials (Fairman, 2000, Nguyen et al., 2014, Lam and Fresco, 2015). Indirect measures comprise medication monitoring (such as pill counting) and self-reported measures; however, medication monitoring is cost intensive and self-reported measures may be less reliable due to patient recall, underreported non-adherence and memory bias issues (Fairman, 2000, Lam and Fresco, 2015, Stirratt et al., 2015). Each adherence measure has its advantages and disadvantages (Lam and Fresco, 2015). Direct Observed Treatment (DOT) has been introduced for supervised treatment monitoring in South Africa to ensure adherence to treatment. A self-reported measure is best applicable to the study environment and study settings as it is cost-effective, with a minimum burden to the patient, easy to administer and flexible in timing and mode of administration. Self-reported adherence measures have additional advantages; they inform about non-adherence before adverse clinical outcomes develop and about adherence determinants such as psychosocial factors (Stirratt et al., 2015). Our study was limited by missing clinical data for treatment monitoring. Sputum smear results were not tested on a regular basis in the clinics during the course of treatment and a clinical parameter for monitoring the effectiveness of TB treatment was not available to draw associations between clinical parameter in TB and HRQOL and adherence development.

## 7.7 Conclusion

Very few studies have evaluated the association between different HRQOL aspects and adherence to treatment before. Adherence to medication is a major public health concern and is a crucial step toward improving health outcomes and lowering health care costs. Non- adherence impacts HRQOL and both concepts are interrelated. In

South Africa DOT is established to ensure adherence to TB treatment, however this only works when patients attend the clinic for their treatment. Even though DOT has been established in South Africa, TB prevalence and incidence rates are still high in South Africa. Our study showed that a reciprocal relationship exists between adherence and HRQOL in TB in a South African setting. However, this relationship was very weak and limited to pain, discomfort and psycho-social aspects related to TB. HRQOL is affected by a number of different factors and not limited to medication adherence; this might explain the weak associations found. This study has clearly demonstrated that management of TB patients must address their specific mental and psycho- social needs, besides adequate drug treatment. Such integrative patient-centred approach should result in an improvement in the quality of life of these patients and will contribute towards supporting the UN SDG3 target and the End TB strategy of the WHO.

## 7.8 Declarations

### 7.8.1 Ethics

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and adhered to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, the Declaration of Helsinki and South African Good Clinical Practice (GCP). The study was approved by the institutional review commission of the Swiss Tropical and Public Health Institute in Basel, Switzerland. Ethical approval was obtained from the ethical commission of North-West and Central Switzerland (EKNZ) and the ethics committee of the University of Cape Town. City Health of the City of Cape Town and the Western Cape Government of South Africa gave institutional approval of the study. Based on a patient information document, eligible patients were informed about the nature, purpose, potential risks and benefits of the study. Informed consent was obtained from all individual participants included in the study.

### 7.8.2 Conflict of interest

The authors declare to have no conflict of interest.

### 7.8.3 Acknowledgements

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# 8. Discussion

## 8.1 Tuberculosis in South Africa

Although tuberculosis (TB) has existed for thousands of years and effective treatment is available, it is still a major public health concern worldwide. One third of the world population is infected with *mycobacterium tuberculosis,* having a latent TB infection, and 10.4 million people fell ill from TB in 2015 (WHO, 2016). About 1.8 million persons died from TB, including 400,000 cases with HIV co-infection. In international comparison, the incidence rate is one of the highest in South Africa, with 834 new cases per 100,000 population and a total of 454,000 official cases in 2015 (WHO, 2016). More than 1% of the South African population are affected by TB in their lives and 80% are estimated to have a latent TB which carries considerable risk of progression to active TB (TBfacts.org). The TB-specific mortality rate was 133 per 100,000 population in South Africa in 2015 (WHO, 2016). With a significant burden of diseases (infectious diseases, non-communicable diseases, perinatal and maternal disorders, and injury-related disorders), the South African society experiences increased pressure on its scarce healthcare resources (Mayosi et al., 2009). At the patient level, TB has a significant negative impact on the health-related quality of life and general well-being (Kastien-Hilka et al., 2016).

The work presented here is well embedded in the United Nations (UN) third Sustainable Development Goal (SDG) which aims to ensure healthy lives and promote well-being at all ages, including the end to the epidemic of TB (WHO, 2015b). The World Health Organization (WHO) has claimed that patient involvement in their healthcare is a social, economic and technical necessity (Doward et al., 2010). Examining the patient perspective on disease applying patient-reported outcomes (PROs) allows for a better understanding of the burden of TB and the impact of TB treatment in an integrative manner, and provides information beyond biomedical and clinical parameters (Deshpande, 2011, Doward et al., 2010, Acquadro C, 2003b). Health-related quality of life (HRQOL) is a PRO-specific concept which includes physical, mental and social health domains. Given that the treatment of TB involves a lengthy process of medication over time, it is surprising that to date very few studies have followed changes in HRQOL longitudinally over time in TB patient populations. More importantly, no longitudinal study has assessed HRQOL over time in South Africa.

HRQOL is associated with medication adherence (Agh, 2015, Chung and Li, 2013, Cote, 2003, Saleem, 2012, Theron et al., 2015). Both concepts may influence each other in a reciprocal

relationship (Cote, 2003, Saleem, 2012, Munro S, 2007). While research about the association between HRQOL and adherence in TB is lacking, such information may help to optimize treatment programs, understand the limitations in TB control, aid the development of targeted interventions and improving the health status of high-burden TB populations.

## 8.2 Summary of study methodology

The overall aim of this doctorate thesis research program was to understand the impact of TB on South African patients with a patient-centred approach. This approach focused on HRQOL and adherence to standard TB treatment. A systematic review was conducted to generate an evidence base for the development and performance of a longitudinal study evaluating HRQOL, medication adherence, and the association of both in new TB cases (older than 18 years) without HIV co-infection in South Africa. The study was conducted in seven health clinics with dedicated TB units in Khayelitsha and Delft, two sub-districts in Cape Town. Two generic (SF-12 and EQ-5D-5L), one respiratory-specific (SGRQ) and one condition-specific (HADS) PROs for HRQOL evaluation were applied over a treatment period of six months. The study thereby followed the recommendation to combine generic and disease-specific measures to capture all relevant health aspects in TB and to deliver complementary information (eunethta, 2013). All HRQOL measures have been validated in TB populations: SF-12 , EQ-5D-5L (Dion et al., 2004), SGRQ (Pasipanodya et al., 2007a), and HADS (Duko, 2015). According to the respective manuals, all four measures have been validated linguistically for English for South Africa. Adherence was measured with the indirect self-reported measure Morisky Medication Adherence Scale (MMAS-8). MMAS-8 has been validated in a number of different study populations, diseases and languages, including pulmonary TB patients (Mkopi, 2014). Linguistic validation of MMAS-8 has been performed for English for South Africa (De Klerk, 2003). All study sites confirmed prior to the start of the study that TB patients of the clinics are fluent in English. Therefore, no other translations were performed. PRO outcomes are often requested by regulatory bodies and these regulatory authorities require validation of applied instruments in a population similar to the study population. The present study followed this approach to the extent possible and applied PRO instruments which had previously been validated in TB populations and in the South African population.

The data collection process, role and responsibilities as well as the training of interviewers is described in a Standard Operating Procedure (SOP) (see Appendix supplementary material chapter 5). Interviewers recruited participants, performed the interviews, reviewed each questionnaire for missing items, and followed up each participant.

## 8.3 Summary of findings

To briefly summarize the findings of this doctorate research program, our systematic review showed that TB impacts HRQOL negatively and that similar factors also impact medication adherence. However only a small number of studies assessed HRQOL in TB over the course of treatment and no longitudinal study has been conducted in South Africa. Information on the impact of TB on the patient from a patient perspective is very limited for the South African situation. The present longitudinal study enrolled 131 participants in total. The majority were in their productive age between 20 and 40 years (mean age 36 years), of black ethnicity, received high school education and were without a job engagement. Our study outcomes showed an overall negative impact of TB on patients' HRQOL Younger patients with higher education and being in a work engagement reported a better HRQOL. Education and work status were identified as socio-demographic predictors showing a significant association with HRQOL at the beginning of TB treatment while age was a predictor on only a single mental health domain.

We observed greater impairment in the psychological and psycho-social aspects of health than in physical health, at treatment start. The greatest impairment and greatest improvement over time among all health aspects in TB were seen for mental health, particular depression and anxiety. Overall, HRQOL improved significantly and with meaningful changes over the course of six-month treatment. The biggest improvements in HRQOL were seen during the first eight weeks of treatment (intensive phase).

While HRQOL improved over the course of treatment, the average mean score in adherence was constantly on a medium adherer level for six months. About 76% of the study TB patients reported a good adherence while 24% reported to be non-adherent (medium and low adherer). Education was the only socio-demographic predictor for adherence in our study, showing TB patients with a lower education reporting a better adherence in South Africa.

The association between HRQOL and medication adherence was examined based on HRQOL and adherence data which were collected at the same time points (4, 8, 16 weeks and six months post-treatment start). A positive weak association between overall improvements (changes in mean scores between treatment start and six months of treatment) in HRQOL and adherence at treatment start was observed. Good adherence at treatment start had a positive impact on the overall improvement in mental health and psycho-social health aspects after six months of treatment. These associations were only confirmed for the continuous treatment

phase (remaining 16 weeks of treatment with isoniazid and rifampicin). No associations between HRQOL and adherence were found during the intensive treatment phase (first 8 weeks of treatment with all four oral antibiotic drugs).

## 8.4 Comparison with published literature and related considerations

Several of our findings were also reported by other authors. Our observations support and confirm that gender and age as socio-demographic factors have no impact on HRQOL in TB patients, as was just recently reported for a different South African population (Louw et al., 2016). A greater impairment in psychological and psycho-social health aspects compared to physical health was also found by others (Aggarwal et al., 2013, Bauer et al., 2013, Ralph et al., 2013, Awaisu et al., 2012, Balgude and Sontakke, 2012, Louw et al., 2012, Othman, 2011, Guo et al., 2009, Guo N, 2008, Chamla, 2004). The improvements in HRQOL were greater during the intensive phase than during the continuous phase of TB treatment as confirmed by others (Bauer et al., 2013, Othman, 2011). As we did not follow-up patients beyond 6 months and beyond treatment completion, if morbidity still existed due to TB after treatment completion could not be verified. Morbidity after treatment completion may exist due to anatomic and functional changes of the lung at treatment completion although the person was microbiologically cured and this was found by others (Ralph et al., 2013, Pasipanodya et al., 2007b, Weis and Pasipanodya, 2010, Muniyandi et al., 2007). As reported elsewhere previously (Awaisu et al., 2012, Guo et al., 2009, Chang B, 2004, Hansel NN, 2004), TB also has a negative impact on physical health. The respiratory measure SGRQ measured the greatest improvements in physical health (Symptoms domain) and seemed to capture these health aspects with higher sensitivity compared to the two generic measures SF-12 and EQ-5D-5L. It is most likely that the impaired physical functioning was closely related to the development of fatigue, adverse drug events, and quantity of drug pills and treatment duration (Chang B, 2004, Hansel NN, 2004).

An additional analysis of the mental health domains of the HRQOL measures was conducted but not included in the manuscripts forming the main part of this thesis. It has been included here to support the interpretation of our findings. This analysis comprised the visual presentation of improvements in mental health domains (MCS-12, EQ-5D-5L Anxiety/Depression, HADS Anxiety, and HADS Depression) over the course of six months treatment based on single patient scores rather than on mean scores. The mean scores might mask the variability and subjectivity reported by the single patient. This additional analysis showed that the impairment in mental health was very variable within the study population at the beginning of treatment, while the mental health status reported after six-month of treatment

showed substantially less variation (figure 13).

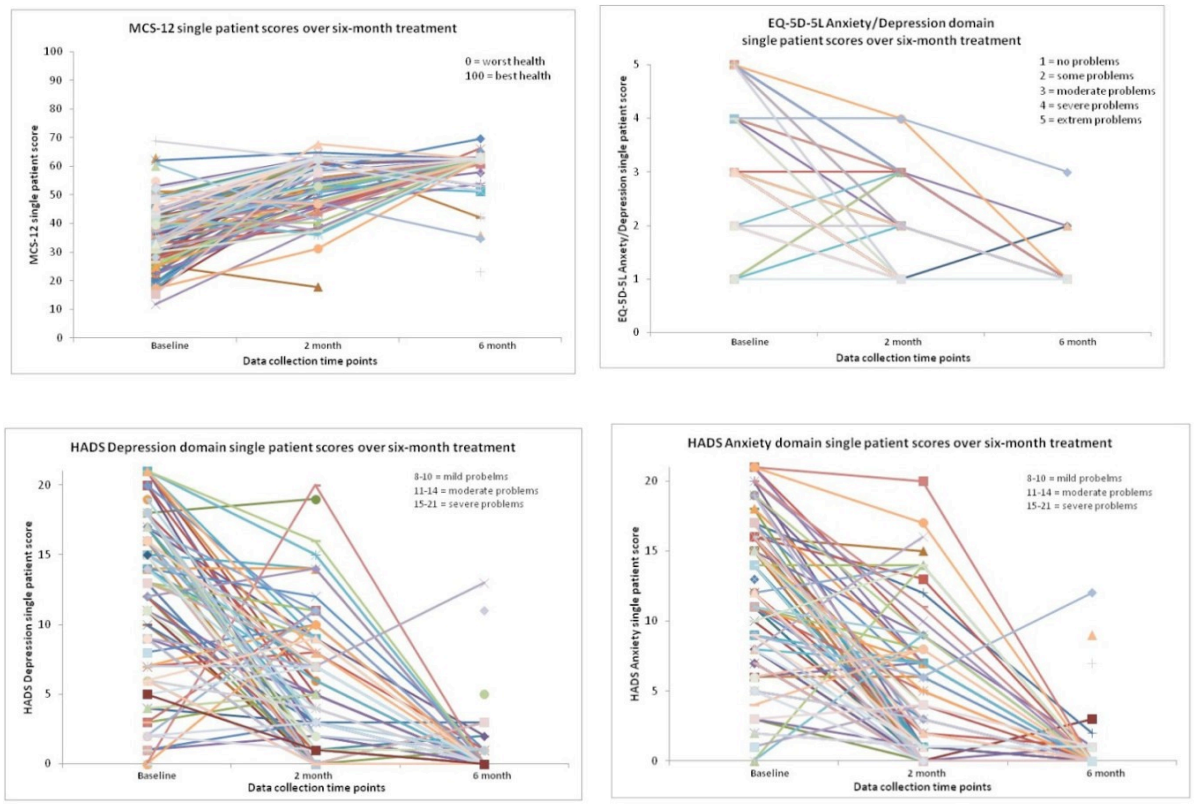


**Figure 13:** Improvements in mental health measured by SF-12, EQ-5D-5L and HADS over six-month TB treatment, presented as change in single patient scores

Our findings about impaired mental health in TB patients are in line with other reports stating that about 46-80% of TB patients in South Africa have mental disorders (Westaway, 2001, Naidoo and Mwaba, 2010), with depression and anxiety being the most frequently reported ones. Such psychiatric co-morbidity may be linked to psycho-social aspects related to TB, most commonly stigmatization and social isolation, which all may increase the distress of physical illness and may also impact the adherence to medication. There may be a connotation of TB with HIV/AIDS, particularly in South Africa, where more than 70% of all HIV/AIDS cases suffer also from TB. This may lead to stigma and disruption of social interaction with others, resulting in social isolation (Dhuria et al., 2009, Naidoo and Mwaba, 2010, Van Rie et al., 2008). Such stigmatization and social isolation might also apply to our TB patients. Inability to work due to TB symptoms and its infectious nature may lead to a decrease in income or even a total loss of income (Hansel NN, 2004, Dias et al., 2013) and increases the psychological pressure on the patient. Financial constraints due to the socio-economic situation of most TB patients in South Africa but also the severity of TB often lead to the situation that patients are unable to travel to the next clinic to seek TB treatment. TB patients from this study reported

frequently being too sick to come to the clinic or being too sick to take their medication according to treatment instructions. The overall improvements in mental health over six-month treatment may be related to the overall improvement in physical and psycho-social aspects related to TB. Although rarely mentioned in the literature it should be mentioned here that a psycho- stimulating effect was observed under isoniazid TB treatment during clinical trials in 1953 in the U.S. (Healy, 1996). Until today this effect has not been confirmed and our study did not investigate in this effect further.

The study intended to collect sputum smear results for all participating patients during the treatment course in order to understand how changes in sputum smear results may be associated with changes in HRQOL and adherence. However, only in a minority of TB cases (19 patients, 14.5% of the study population) the clinics collected data on sputum smears. This was a common practice in all clinics. Some clinics applied X-rays to some patients for diagnostic testing. Sputum smear results are expressed as number of bacilli and range from 0 (no bacterial found) to +3. For the 19 patients with sputum smear data collected, overall HRQOL improved while sputum smear results showed an unchanged value of +3 confirming the presence of bacilli. As the number of patients with sputum results was very small and the values for sputum remained unchanged over the treatment period, we decided not to use the clinical data for investigation of any associations between sputum, HRQOL and adherence.

Medication adherence is a key factor for treatment success (NDoH, 2014). TB patients being non-adherent to TB treatment expose other non-infected people to the risk of spreading free TB bacteria and this may result in physical disability, drug resistance, relapse and risk of death in the community and in increased healthcare costs (NDoH, 2014, Chirwa T, 2013, Cramm JM, 2010, Husain MO, 2008). Our expectations were to observe a good adherence at the beginning of the treatment and a deterioration of adherence alongside improvements in HRQOL. However, the mean score of adherence was constantly on a medium adherer level for six months, with patients reporting a lower education showing better adherence. In South Africa non-adherence to TB treatment is reported to be related to poverty, HIV co-infection, stigmatization, an unsupportive social and work environment, and feelings of helplessness and hopelessness, limited transport to the clinics, and limited food access (Naidoo P, 2009). That good adherence may be associated with both lower and higher levels of education was reported in different diseases (Jin, 2008). A higher education might support a better understanding of the disease and its treatment and might therefore lead to a better adherence. However, it might also apply that a less educated patient might trust the advice of the physician more and thereby may have a better adherence (Jin, 2008).

A systematic review on adherence to TB treatment (Munro S, 2007) reported two underlying

patterns: TB patients become non-adherent when they either experienced an improved well-being and perceived this as cure from TB or when they experienced no improvement or even a worsening in well-being. The positive weak associations found between HRQOL and adherence in our study might be because generic PRO measures such as SF-12 and EQ-5D-5L are not sensitive enough to capture all changes in HRQOL in TB and thereby the association to adherence may be observed as weak; or other factors not captured in this study such as other socio-demographic or psycho-social aspects influence the association between HRQOL and adherence. Or the association between HRQOL and adherence might be indeed as weak as observed in our study. The positive associations were only found during the continuous treatment phase, and not during the intensive treatment phase. This finding suggests that it is particularly important to identify and understand drivers of adherence to TB treatment and how adherence can be supported during the continuous treatment phase. Based on different statistical methods applied (correlations and linear regression models considering the temporal sequence of observations) to investigate the association between HRQOL and adherence the study confirmed an, albeit weak, positive relationship between aspects of pain and discomfort measured by EQ-5D-5L and psycho-social health aspects measured by SGRQ, and adherence, with HRQOL being the driver for adherence. These findings may indicate that TB management should also focus on any impairment in mental and psycho-social health in TB patients and that the association between HRQOL and adherence should be considered as essential part of the TB management. However, based on the weak associations found and considering limited sample size and missing data, we cannot exclude the possibility that the associations found were merely due to chance.

## 8.5 Generalizability of study findings

Our study showed in which way and to which extent TB impacts patients in South Africa, from a patient perspective including physical, mental and psycho-social health aspects. These findings support the bio-psycho-social health model which was introduced by George Engel in the 1970s. George Engel highlighted that a patient´s suffering can only be understood when a disease is observed in its biological, psychological and social dimensions (Borrell-Carrio et al., 2004). Contrary to the biomedical health model which regards the patient as an object by separating the body and mind in a dualistic way (Hatala, 2012, Borrell-Carrio et al., 2004), the bio-psycho-social health model follows a humanistic and integrative approach. Biological, psychological and social factors are implicated in different stages of a pathogenesis and health aetiology (Hatala, 2012). In addition, our study outcomes indicated how the different

dimensions of health included in the bio-psycho-social health model are interlinked with the medication adherence, particularly with mental and psycho-social aspects (Adwok, 2012). The impairment found in HRQOL at treatment start and the improvement in HRQOL during the course of TB treatment was reported by a number of other studies in different countries as reported in our systematic review (Kastien-Hilka et al., 2016). However, the selection of different HRQOL measures and mode of application might lead to different HRQOL scores. The socio-demographic background might also impact the HRQOL outcomes. Thereby, our HRQOL data may not be generalizable to other study populations. The same may apply to outcomes generated with the self-reported adherence measure. The positive weak associations found in our study between HRQOL and adherence may not be generalizable to other populations. The number of available literature on associations between HRQOL and adherence to medication is very little and reported results are contradictory.

Our study methodology may be generalizable to other studies following a patient-centred approach by applying PRO measures in other TB studies and even in other diseases. The methodology for PRO selection and thereupon the rationale for endpoint model and sample size determination are applicable to other outcomes research studies.

## 8.6 Future research agenda

This study identified a need for further research and recommendations for a future research agenda are briefly discussed here. Our dataset may allow further statistical analysis by exploring underlying patterns for adherence and non-adherence in TB. Such exploratory statistical analysis may provide a deeper understanding of adherence patterns in TB and of the association between HRQOL and adherence. It may inform TB management programs to improve the healthcare service.

Furthermore, our dataset allows for the calculation of QALYs based on utilities calculated from EQ-5D. Combined with the identification of costs, these QALYs can be applied in comparative studies to allow cost-effectiveness analysis (CEA). In 2013, the South African Department of Health published the Guidelines for Pharmacoeconomic Submissions which requests the use of QALYs for CEA (NDoH, 2013). However, preference-based utilities need to be estimated on basis of valuation algorithms (value sets) derived from general population studies. Such value sets are available for some countries but not for South Africa. Our study estimated the utilities for patients on TB standard treatment using the UK and on the Zimbabwean value sets. The resulting utilities differed and showed that based on the UK value set, the HRQOL of our patients during TB treatment improved by 94%, while based on

the Zimbabwean value set the improvement was only 44%. This difference may have an impact on the calculation of QALYs and on CEA outcomes. This in turn may impact the allocation of resources when making decisions within the National Health Insurance in South Africa. The National Department of Health South Africa (NDoH) requests in their National Pharmacoeconomic Guideline the calculation of QALYs when performing a CEA. If the NDoH decides for EQ-5D as preferred utility measure, then a study research on generating a value set for South Africa would be needed. Our study outcomes were presented and discussed with the NDoH during a joint workshop in October 2016 (Fundisa, 2016). The need for HRQOL instruments specific for South Africa related to TB as well as other common diseases (e.g., diabetes) will be a matter of further discussion with the NDoH.

Our dataset may support the development of a TB-specific HRQOL measure which is still lacking. A detailed analysis of the dataset on an item-by-item basis might evaluate which items reflect the patient´s perspective in TB more than others. It might be that some items were answered more often than others or some items were only answered very little or not at all, as they might not reflect the relevance for the patient with regard to TB. Such analysis would require to be supported by in-depth interviews of TB patients in order to select relevant elements for a TB-specific measure.

In addition to TB, South Africa is facing the double burden of TB with HIV co-infection and of MDR-TB. Therefore, a study combining generic and disease- or condition-specific HRQOL measures evaluating HRQOL in TB patients with HIV co-infection and in patients with MDR- TB will complete the understanding of the impact of TB on patients living in South Africa. A similar approach should be applied to understand the impact of TB on children, although PRO studies in children are a specific challenge and child-friendly PROs are required. In this context, it will be advisable to consider the development and validation of a TB-specific HRQOL measure for South Africa which can be applied in other countries after its validation.

Furthermore, the evaluation of HRQOL allows the identification of added benefits of new TB treatment options planning to access the South African market. If a new healthcare product in TB may show a greater improvement in HRQOL compared to standard TB care, this extra gain in HRQOL may be defined as an added benefit. This added benefit may enable the healthcare system to recognize relevant innovations and to distinguish against any me-too healthcare products. As a number of new TB drugs, vaccines and diagnostic tools are in late clinical stage development and will enter the market soon, South Africa needs to make decisions which products are best for the patient and most cost-effective for the healthcare system. Our study methodology may advice on how a comparative study with new technologies might be

designed and which issues might develop. Information on HRQOL should support the identification of sustainable products.

TB impacts a person beyond their microbiological infection and related disease symptoms. TB affects several dimensions in the health-related life of a person and can have societal consequences due to its psycho-social impact. Future research may investigate if the implementation of psychological support throughout the course of treatment might not only ensure an integrative approach to treatment but also assist with an improvement in the adherence to treatment and thereby treatment success. Such study should consider the socio- demographic environment of the patients when optimizing the TB management in community and public health programmes for South Africa. Outcomes from such research may further discuss if and how psycho-social support should be considered to be included in the National TB guideline. Further, the study outcome may inform health policy makers with regard to initiatives to improve medication adherence to TB treatment in the South African public health system. Further research would then be required to discuss how the knowledge about psycho- social health issues related to TB may be included in the training of healthcare providers in South Africa. And integration of screening for mental and psychological disorders in TB patients might help to improve adherence to TB treatment.

## 8.7 Limitations

This PhD research has several limitations. The preparatory systematic review on HRQOL and adherence applied mixed methods by combining literature from qualitative and quantitative studies and did not include solely randomized controlled trials for quantitative analysis. This may be viewed as a limitation. However, the mixed-methods approach ensured capturing all relevant information on the topic. Publication bias may be present in the systematic review but we selected peer-reviewed literature from three different databases and included grey literature to minimise publication bias. We did not include unpublished information and studies published in a different language than English.

The longitudinal study also faced several limitations. Time and resource constraints as well as the fact that a high number of TB patients are HIV co-infected did impact the recruitment process. Based on HIV tests applied during the TB diagnostic procedure before treatment start, this study did exclude HIV co-infection to understand the isolated TB impact on HRQOL. Whether the participating TB patients developed HIV during the treatment was not tested. HIV co-infection impacts HRQOL further and unknown HIV co-infection during treatment might have influenced our outcomes.

Further, we could not include a comparison or control group from the general population, due to limited time and resources. Single group studies are often claimed to be non-informative without a comparator group. However, longitudinal studies as ours can be a source of relevant information by making before-after comparisons and observing change over time.

Our longitudinal study was limited to a quantitative approach; patient perspectives about TB in a South African cultural background were not qualitatively assessed. Such data might have enriched the quantitative findings on HRQOL in this study. HRQOL was only assessed in a specific district of the Western Cape Province with a specific socio-demographic and – economic situation.

Additionally, there is an increased risk of tuberculosis in patients with co-morbidities, however only a small portion of TB patients were aware of any co-morbidity they may have had, such as e.g. diabetes. In a majority of cases the study participants were unable to provide information on co-morbidities and we assume that other health issues were unknown to the majority of them. These unknown co-morbidities might have had an additional impact on the HRQOL in TB patients at baseline which we could not distinguish.

Although all applied HRQOL measures and the MMAS-8 had been previously validated in TB populations and linguistically validated for English for South Africa, study populations may differ by their socio-demographic and socio-economic background. The populations of the validation studies may not have been similar to our study population in all socio-demographic and socio-economic aspects. This may be reflected in our study outcomes.

The use of a self-reported measure of adherence may have impacted the reliability of the observed relationship between HRQOL and adherence. A self-reported measure may be less reliable due to patient recall, underreported non-adherence and memory bias issue. An ideal adherence measure would assess overall adherence to medication including initiation, persistence, implementation and discontinuation, but such a measure does not exist. Optimally, a multi-measure approach should be considered where direct and indirect adherence measures are combined (Fairman, 2000). Since Direct Observed Treatment (DOT) has been introduced for supervised treatment monitoring in South Africa to ensure adherence to treatment, we applied a self-reported measure to DOT as it was cost-effective and best applicable to the study environment and study settings, with a minimum burden to the patient, easy to administer and flexible in timing and mode of administration. Adverse events are known to impact medication adherence negatively. One item of the MMAS-8 asks: “Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it?”While the MMAS-8 does not measure adverse events, this item may allude to possible adverse events. The

same item might theoretically bias the association between HRQOL and medication adherence examined in the present study due to a limited degree of overlap between concepts. MMAS-8 includes two items with a short recall period (“Thinking over the past two weeks, were there any days when you did not take your TB medicine?” and “Did you take your TB medicine yesterday?”). However, the recall period of the two items is different and the overall recall period of the MMAS-8 is not clearly defined.

PRO measures reflect the subjective perspective of the patient. However, there might be a temptation to 'please the doctor' when answering questions. Social desirability is always a concern in any study using subjective outcomes. It might also have had an impact on the outcomes of this study. In addition, although interviewers were not allowed to interpret the applied PRO measures as per the SOP, a certain degree of interpretation may have occurred and impacted or biased our study results. Our study was limited by missing sputum smear results for treatment monitoring. Sputum smear results were not tested on a regular basis in the clinics during the course of treatment and a clinical parameter for monitoring the effectiveness of TB treatment was not available to draw associations between clinical parameters in TB and the development of HRQOL and adherence.

# 9. Conclusions

The relevance and importance of HRQOL assessments is growing and HRQOL has become an important tool for the understanding of health outcomes adopting a patient-centered approach to care and treatment. This work demonstrates the need for an integrative understanding of TB with HRQOL as core element to understand gaps in current TB management. This study has demonstrated that management of TB patients should address their specific mental and psycho-social needs, besides adequate drug treatment and that these specific needs may be associated with adherence to medication, although weak. The adoption of the bio-psycho-social health model into the health system of South Africa may help to reduce the burden of TB and of other communicable and non-communicable diseases. Considering the application of PROs and their results in the decision-making process in the healthcare system of South Africa, with a particular focus on HRQOL, may support an integrative understanding of the burden of disease for the South African population from the perspective of patient, the end-client and end-consumer within the system. Such integrative patient-centred approach should result in an improvement in the health-related quality of life of these patients and will contribute towards supporting the UN SDG3 target and the End TB strategy of the WHO. Furthermore, information on PROs is

introduced to the South African healthcare system now and there is a need for validated local PRO data for pharmacoeconomic assessments to inform the healthcare system efficiently. HRQOL allows identification of the value for money principle which will be the driver for future healthcare spending in the public sector. Lastly, both the private and public sector view pharmacoeconomics as an important part of rational use and decision-making process in the South African healthcare system to ensure availability and accessibility of affordable essential medicines.

# 10. References


AAMIR, S. & AISHA 2010. Co-Morbid Anxiety and Depression Among Pulmonary Tuberculosis Patients. Journal of the College of Physicians and Surgeons Pakistan 20, 703-704

ACQUADRO C, B. R., DUBOIS D, KLINE LEIDY N, MARQUIS P, REVICKI D, ROTHMAN M, FOR THE PRO HARMONIZATION GROUP 2003a. Incorporating the Patient´s Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration February 16, 2001. *Value in Health,* 6**,** 522-531.

ACQUADRO C, B. R., DUBOIS D, KLINE LEIDY N, MARQUIS P, REVICKI D, ROTHMAN M, FOR THE PRO HARMONIZATION GROUP 2003b. Incorporating the Patient's Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. *Value in Health,* 6**,** 522-531.

ADEYEYE, O. O., OGUNLEYE, O. O., COKER, A., KUYINU, Y., BAMISILE, R. T., EKRIKPO, U. & ONADEKO, B. 2014. Factors influencing quality of life and predictors of low quality of life scores in patients on treatment for pulmonary tuberculosis: a cross sectional study. *Journal of Public Health in Africa,* 5.

ADWOK, J., WOLSKEE, P. 2012. Health psychology and health care interventions in sub-Saharan African countries. *South Sudan Medical Journal,* 5**,** 62-65.

AGGARWAL, A. N. 2010. Health-related quality of life: A neglected aspect of pulmonary tuberculosis. *Lung India,* 27**,** 1-3.

AGGARWAL, A. N., GUPTA, D., JANMEJA, A. K. & JINDAL, S. K. 2013. Assessment of health-related quality of life in patients with pulmonary tuberculosis under programme conditions. *Int J Tuberc Lung Dis,* 17**,** 947-53.

AGH, T., DÖMÖTÖR, P., BARTFAI, Z., INOTAI, A., FUJSZ, E., MESZAROS, A. 2015. Relationship Between Mediaction Adherence and Health-Related Quality of Life in Subjects with COPD: A Systematic Review. *Respiratory Care,* 60.

APALONE, G., DE CARLI, G., BRUNETTI, M., GARATTINI, S. 2001. Health-Related Quality of Life (HR-QOL) and Regulatroy Issues - An assessment of the European Agency for the Evaluation of Medicinal Products (EMEA) Recommendations on the use of HR- QOL measures in drug approval. *Pharmacoeconomics,* 19**,** 187-195.

APPLEBY, J., DEVLIN, N. 2005. Mesuring NHS Success - Can patients' views on health outcomes help to manage performance? *King´s Fund Publications*.

ATIF, M., SULAIMAN, S. A., SHAFIE, A. A., ALI, I., HASSALI, M. A. & SALEEM, F. 2012a. WHO guidelines for treatment of tuberculosis: the missing links. *Int J Clin Pharm,* 34**,** 506-9.

ATIF, M., SULAIMAN, S. A., SHAFIE, A. A., ASIF, M. & AHMAD, N. 2013. SF-36v2 norms and its' discriminative properties among healthy households of tuberculosis patients in Malaysia. *Qual Life Res,* 22**,** 1955-64.

ATIF, M., SULAIMAN, S. A., SHAFIE, A. A., ASIF, M., SARFRAZ, M. K., LOW, H. C. & BABAR, Z. U. 2014a. Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study. *Health Qual Life Outcomes,* 12**,** 19.

ATIF, M., SULAIMAN, S. A. S., SHAFIE, A. A., MUTTALIF, A. R., HASSALI, M. A. & SALEEM, F. 2012b. Health-Related Quality of Life (HRQoL) in Co-Morbid Tuberculosis Relapse Patient: A Case Report from Malaysia. *Tropical Journal of Pharmaceutical Research,* 11.

ATIF, M., TOGHRAYEE, Z., SULAIMAN, S. A. S., SHAFIE, A. A., LOW, H. C. & BABAR, Z.-

U.-D. 2014b. Missing Data Analysis in Longitudinal Studies: Findings from a Quality of Life Study in Malaysian Tuberculosis Patients. *Applied Research in Quality of Life,* 10**,** 95-105.

AWAISU, A., HANIKI NIK MOHAMED, M., NOORDIN, N. M., MUTTALIF, A. R., AZIZ, N. A., SYED SULAIMAN, S. A. & MAHAYIDDIN, A. A. 2012. Impact of connecting tuberculosis directly observed therapy short-course with smoking cessation on health- related quality of life. *Tob Induc Dis,* 10**,** 2.

BABIKAKO, H. M., NEUHAUSER, D., KATAMBA, A. & MUPERE, E. 2010. Feasibility, reliability and validity of health-related quality of life questionnaire among adult pulmonary tuberculosis patients in urban Uganda: cross-sectional study. *Health Qual Life Outcomes,* 8**,** 93.

BALGUDE, A. & SONTAKKE, S. 2012. Study of impact of antitubercular therapy on quality of life. *Indian J Med Sci,* 66**,** 71-7.

BAUER, M., AHMED, S., BENEDETTI, A., GREENAWAY, C., LALLI, M., LEAVENS, A., MENZIES, D., VADEBONCOEUR, C., VISSANDJEE, B., WYNNE, A. & SCHWARTZMAN, K. 2015. Health-related quality of life and tuberculosis: a longitudinal cohort study. *Health Qual Life Outcomes,* 13**,** 65.

BAUER, M., LEAVENS, A. & SCHWARTZMAN, K. 2013. A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. *Qual Life Res,* 22**,** 2213-35.

BORRELL-CARRIO, F., SUCHMAN, A. L. & EPSTEIN, R. M. 2004. The biopsychosocial model 25 years later: principles, practice, and scientific inquiry. *Ann Fam Med,* 2**,** 576-82.

BOTTOMLEY, A., JONES, D. & CLAASSENS, L. 2009. Patient-reported outcomes: assessment and current perspectives of the guidelines of the Food and Drug Administration and the reflection paper of the European Medicines Agency. *Eur J Cancer,* 45**,** 347-53.

BRESNAHAN, B. W. & RUNDELL, S. D. 2014. Including patient-reported outcomes and patient-reported resource-use questionnaires in studies. *Acad Radiol,* 21**,** 1129-37.

BROWN, J., CAPOCCI, S., SMITH, C., MORRIS, S., ABUBAKAR, I. & LIPMAN, M. 2015. Health status and quality of life in tuberculosis. *Int J Infect Dis,* 32**,** 68-75.

BURKE, L. 2012. An FDA Perspective on Clinical Trial Endpoint Measurements. ACTTION- II.

BURKE, L. B., KENNEDY, D.L., MISKALA, P.H., PAPADOPOULOS, E.J., TRENTACOSTI, A.M. 2008. The Use of Patient-Reported Outcome Measures in the Evaluation of Medical Products for Regulatory Approval. *Clinical pharmacology & Therapeutics,* 84**,** 281-283.

CALVERT, M., KYTE, D., DUFFY, H., GHEORGHE, A., MERCIECA-BEBBER, R., IVES, J., DRAPER, H., BRUNDAGE, M., BLAZEBY, J., KING, M. 2014. Patient-Reported Outcome (PRO) Assessment in Clinical Trials: A Systematic Review of Guidance for Trial Protocol Writers. *PLoS One,* 9.

CENTERS FOR DISEASE CONTROL AND PREVENTION. 2016. *Policy and Practical Implications of HRQOL Surveillance* [Online]. Available: https://www.cdc.gov/hrqol/policy.htm [Accessed 07 November 2016 2016].

CHAMLA, D. 2004. The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China. *Int J Tuberc Lung Dis,* 8**,** 1100-6.

CHANG B, W. A., HANSEL NN, DIETTE GB 2004. Quality of life in tuberculosis: A review of the English literature. *Quality of Life Research* 13**,** 1633-1642.

CHASSANY, O., SAGNIER, P. 2002. PATIENT-REPORTED OUTCOMES: THE EXAMPLE OF HEALTH-RELATED QUALITY OF LIFE—A EUROPEAN GUIDANCE DOCUMENT FOR THE IMPROVED INTEGRATION OF HEALTH-RELATED QUALITY OF LIFE ASSESSMENT IN THE DRUG REGULATORY PROCESS. *Drug Information Journal,* 36**,** 209-238.

CHIRWA T, N. P., CHIRWA E, KETLOGETSWE A, BELLO G, DAMBE I, NDALAMA D,

JOSHUA M 2013. Levels of tuberculosis treatment adherence among sputum smear positive pulmonary tuberculosis patients attending care at Zomba Central hospital, southern Malaw. *PLoS One,* 28**,** 1-6.

CHRISTIAN, C. S. 2016. *South African health budget takes a back seat but gets the basics* [Online]. Available: http://theconversation.com/south-african-health-budget-takes-a- back-seat-but-gets-the-basics-55342 [Accessed 08 October 2016].

CHUNG, W. & LI, C. 2013. Can DOTS improve quality of life among patients with pulmonary tuberculosis? . *Int J Tuberc Lung Dis,* 17**,** 425-426.

CHUNG, W. S., LAN, Y. L. & YANG, M. C. 2012. Psychometric testing of the short version of the world health organization quality of life (WHOQOL-BREF) questionnaire among pulmonary tuberculosis patients in Taiwan. *BMC Public Health,* 12**,** 630.

COEHLO, M., COSTA, E., RICHTER, V., DESSOTTE, C., SCHMIDT, M., DATAS, R., ROSSI, L., FURUYA, R. 2013. PERCEIVED HEALTH STATUS AND PHARMACOLOGICAL ADHERENCE OF PATIENTS WHO UNDERWENT PERCUTANEOUS CORONARY INTERVENTION. *Rev Gaúcha Enferm,* 34**,** 86-94.

COHEN, J. 1988. *Statistical power analysis for the behavioral sciences.,* Hillsdale, NJ, USA, Lawrence Earlbaum Associates.

CORLESS, I. B., WANTLAND, D., BHENGU, B., MCINERNEY, P., NCAMA, B., NICHOLAS, P. K., MCGIBBON, C., WONG, E. & DAVIS, S. M. 2009. HIV and tuberculosis in Durban, South Africa: adherence to two medication regimens. *AIDS Care,* 21**,** 1106-13.

COTE, I., FARRIS, K., FEENY, D. 2003. Is adherence to drug treatment correlated with health-related quality of life? *Qual Life Res,* 12**,** 621-633.

CRAMER, A. J., ROY, A., BURRELL, A., FAIRCHILD, J.C., FULDEORE, M.J., OLLENDORF, D.A., WONG, K.P. 2008. Medication Compliance and Persistence: Terminology and Definitions. *Value in Health,* 11**,** 44-47.

CRAMM JM, V. E. J., MOLLER V, FINKENFLÜGEL H 2010. Patient Views on Determinants of Compliance with Tuberculosis Treatment in the Eastern Cape, South Africa. An Application of Q-Methodology. *Patient,* 3**,** 159-172.

CREMERS, A. L., DE LAAT, M. M., KAPATA, N., GERRETS, R., KLIPSTEIN-GROBUSCH, K. & GROBUSCH, M. P. 2015. Assessing the consequences of stigma for tuberculosis patients in urban Zambia. *PLoS One,* 10**,** e0119861.

DARVISHPOOR KAKHKI, A. & MASJEDI, M. R. 2015. Factors Associated with Health-Related Quality of Life in Tuberculosis Patients Referred to the National Research Institute of Tuberculosis and Lung Disease in Tehran. *Tuberc Respir Dis (Seoul),* 78**,** 309-14.

DE KLERK, H., DE VILLIERS, P.J.T., ISAACS, S., 2003. Prevalence and characteristics of erectile dysfunction in black and mixed race primary care populations of the Cape Flats and Helderberg Basin area of the Western Cape, South Africa. *SA Fam Prac,* 45**,** 10-16.

DERIBEW A, D. K., REDA AA, TESFAYE M, HAILMICHAEL Y, MAJA T, COLEBUNDERS R 2013. Change in quality of life: a follow up study among patients with HIV infection with and without TB in Ethiopia. *BMC Public Health* 13**,** 1-6.

DESHPANDE PR, R. S., SUDEEPTHI BL, NAZIR CPA 2011. Patient-reported outcomes: A new era in clinical research. *Perspectives in Clinical Research,* 2**,** 137-144.

DESHPANDE, R., RAJAN, S., SUDEEPHI, L.B., NAZIR, C.P.A. 2011. Patient-reported outcomes: a new era in clinical research. *Perspectives in Clinical Research,* 2**,** 137-144.

DHINGRA, V. K. & RAJPAL, S. 2005. Health related quality of life (HRQL) scoring (DR-12 score) in tuberculosis--additional evaluative tool under DOTS. *J Commun Dis,* 37**,** 261-8.

DHURIA, M., SHARMA, N., NARENDER PAL, S., RAM CHANDER, J., SAHA, R. & GOPAL KRISHAN, I. 2009. A study of the impact of tuberculosis on the quality of life and the

effect after treatment with DOTS. *Asia Pac J Public Health,* 21**,** 312-20.
DIAS, A. A., DE OLIVEIRA, D. M., TURATO, E. R. & DE FIGUEIREDO, R. M. 2013. Life experiences of patients who have completed tuberculosis treatment: a qualitative investigation in southeast Brazil. *BMC Public Health,* 13**,** 595.
DIEL, R. & LAMPENIUS, N. 2014. Cost-effectiveness analysis of interventions for tuberculosis control: DALYs versus QALYs. *Pharmacoeconomics,* 32**,** 617-26.
DION, M. J., TOUSIGNANT, P., BOURBEAU, J., MENZIES, D. & SCHWARTZMAN, K. 2004. Feasibility and reliability of health-related quality of life measurements among tuberculosis patients. *Qual Life Res,* 13**,** 653-65.
DOWARD, L. C., GNANASAKTHY, A. & BAKER, M. G. 2010. Patient reported outcomes: looking beyond the label claim. *Health Qual Life Outcomes,* 8**,** 89.
DUJAILI, J. A., SULAIMAN, S. A., HASSALI, M. A., AWAISU, A., BLEBIL, A. Q. & BREDLE, J. M. 2015. Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq. *Int J Infect Dis,* 31**,** 4-8.
DUKO, B., GEBEYEHU, A., AYANO, G. 2015. Prevalence and correlates of depression and anxiety among patients with tuberculosis at WolaitaSodo University Hospital and Sodo Health Center, WolaitaSodo, South Ethiopia, Cross sectional study. *BMC Psychiatry,* 15.
EL ACHHAB, Y., NEJJARI, C., CHIKRI, M. & LYOUSSI, B. 2008. Disease-specific health-related quality of life instruments among adults diabetic: A systematic review. *Diabetes Res Clin Pract,* 80**,** 171-84.
EUROPEAN MEDICINES AGENCY (EMA). 2012. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). *In:* CHMP (ed.).
EUNETHTA, E. N. F. H. T. A. 2013. Guideline: endpoints used for relative effectiveness assessment of pharmaceuticals health-related quality of life and utility measures.
EUROPEAN MEDICINES AGENCY (EMA). 2005. REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTHRELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS. London, UK.
EUROQOL. *EQ-5D-5L* [Online]. Available: http://www.euroqol.org/eq-5d-products/eq-5d-5l.html [Accessed 16 December 2015].
FAIRMAN, K., MOTHERAL, B. 2000. Evaluating Medication Adherence: Which measure is right for your program? *Journal of Managed Care Pharmacy,* 6**,** 499-506.
FOOD AND DRUG ADMINISTRATION (FDA, U. S.). 2009. Guidance for Industry - Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. *In:* ADMINISTRATION, U. S. D. O. H. A. H. S. F. A. D. (ed.).
FUNDISA. 2016. *Pharmacoeconomics in South Africa: Now and the Future - Value-Based Patient-Centred Healthcare in South Africa* [Online]. Available: http://www.fundisa- academy.com/?controller=pages&view=load&id=home [Accessed 28 December 2016].
GNANASAKTHY, A., LEWIS, S., CLARK, M., MORDIN, M., DEMURO, C. 2013. Potential of patient-reported outcomes as nonprimary endpoints in clinical trials. *Health Qual Life Outcomes,* 11**,** 1-7.
GUO, N., MARRA, C. A. & MARRA, F. 2010. Responses to comments of Weis. *Health Qual Life Outcomes,* 8**,** 6.
GUO, N., MARRA, F. & MARRA, C. A. 2009. Measuring health-related quality of life in tuberculosis: a systematic review. *Health Qual Life Outcomes,* 7**,** 14.
GUO N, M. C., MARRA F, MOADEBI S, ELWOOD RK, FITZGERALD JM 2008. Health state
utilities in latent and active tuberculosis. *Value in Health* 11**,** 1154-1161.
HANSEL NN, W. A., CHANG B, DIETTE GB 2004. Quality of life in tuberculosis: patient and provider perspectives. *Quality of Life Research* 13**,** 639-652.

HATALA, A. R. 2012. The Status of the “Biopsychosocial” Model in Health Psychology: Towards an Integrated Approach and a Critique of Cultural Conceptions. *Open Journal of Medical Psychology,* 01**,** 51-62.

HEALY, D. 1996. The psychopharmacologists: interviews.: Chapman and Hall. .

HUGHES, D., COWELL, W., KONCZ, T., CRAMER, J. 2007. Methods for Integrating Medication Compliance and Persistence in Pharmacoeconomic Evaluations. *Value in Health,* 10**,** 498-509.

HUSAIN MO, D. S., CHAUDHRY IB, RIZVI N, WAHEED W 2008. The relationship between anxiety, depression and illness perception in tuberculosis patients in Pakistan. *Clinical Practice and Epidemiology in Mental Health,* 4**,** 1-5.

ISSA BA, Y. A., KURANGA SI 2009. Depression comorbidity among patients with tuberculosis in a university teaching hospital outpatient clinic in Nigeria. *Mental Health in Family Medicine* 6**,** 133-138.

JABER, A. A., KHAN, A. H., SYED SULAIMAN, S. A., AHMAD, N. & ANAAM, M. S. 2016. Evaluation of Health-Related Quality of Life among Tuberculosis Patients in Two Cities in Yemen. *PLoS One,* 11**,** e0156258.

JELSMA, J., HANSEN, K., DE WEEDRT, W., DE COCK, P., KIND, P. 2003. How do Zimbabweans value health states? *Population Health Metrics,* 1**,** 10.

JIN, J., SKLAR, G.E., OH, V.M.S., LI, S.C. 2008. Factors affecting therapeutic compliance: A review from the patient’s perspective. *Therapeutics and Clinical Risk Management,* 4**,** 269–286.

JONES, P. W. 2005. St. George´s Respiratory Questionnaire: MCID. *Journal of Chronic Obstructive Pulmonary,* 2**,** 75-79.

JONES, P. W. 2009. ST GEORGE’S RESPIRATORY QUESTIONNAIRE MANUAL. *In:* ST GEORGE´S UNIVERSITY OF LONDON, L. (ed.).

KASTIEN-HILKA, T., ABULFATHI, A., ROSENKRANZ, B., BENNETT, B., SCHWENKGLENKS, M. & SINANOVIC, E. 2016. Health-related quality of life and its association with medication adherence in active pulmonary tuberculosis- a systematic review of global literature with focus on South Africa. *Health Qual Life Outcomes,* 14**,** 42.

KASTIEN-HILKA, T., ROSENKRANZ, B., BENNETT, B., SINANOVIC, E., SCHWENKGLENKS, M. 2016. How to evaluate health-related quality of life and its association with medication adherence in pulmonary tuberculosis – designing a prospective observational study in South Africa. . *Frontiers in Pharmacology: Pharmaceutical Medicine and Outcomes Research*.

KITTIKRAISAK, W., KINGKAEW, P., TEERAWATTANANON, Y., YOTHASAMUT, J., NATESUWAN, S., MANOSUTHI, W., CHONGSUVIVATWONG, V. & WHITEHEAD, S. J. 2012. Health related quality of life among patients with tuberculosis and HIV in Thailand. *PLoS One,* 7**,** e29775.

KROUSEL-WOOD, M., ISLAM, T., WEBBER, L.S., RE, R.N., MORISKY, D.E., MUNTNER, P. 2009. New Medication Adherence Scale Versus Pharmacy Fill Rates in Seniors with Hypertension. *THE AMERICAN JOURNAL OF MANAGED CARE,* 15.

KRUIJSHAAR, M. E., LIPMAN, M., ESSINK-BOT, M. L., LOZEWICZ, S., CREER, D., DART, S., MAGUIRE, H. & ABUBAKAR, I. 2010. Health status of UK patients with active tuberculosis. *Int J Tuberc Lung Dis,* 14**,** 296-302.

LAM, W. Y. & FRESCO, P. 2015. Medication Adherence Measures: An Overview. *Biomed Res Int,* 2015**,** 217047.

LOUW, J., PELTZER, K., NAIDOO, P., MATSEKE, G., MCHUNU, G. & TUTSHANA, B. 2012. Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. *Health Qual Life Outcomes,* 10**,** 77.

LOUW, J. S., MABASO, M. & PELTZER, K. 2016. Change in Health-Related Quality of Life among Pulmonary Tuberculosis Patients at Primary Health Care Settings in South Africa: A Prospective Cohort Study. *PLoS One,* 11**,** e0151892.

LUTGE E, L. S., VOLMINK J, FRIEDMAN I, LOMBARD C 2013. Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. *Trials,* 14**,** 1-13.
LUTGE EE, W. C., KNIGHT SE, VOLMINK J 2012. Material Incentives and Enablers in the Management of Tuberculosis. *Cochrane Database Syst Rev,* 18.
MAGUIRE, G. P., ANSTEY, N. M., ARDIAN, M., WARAMORI, G., TJITRA, E., KENANGALEM, E., HANDOJO, T. & KELLY, P. M. 2009. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. *Int J Tuberc Lung Dis,* 13**,** 1500-6.
MAMANI, M., MAJZOOBI, M. M., GHAHFAROKHI, S. M., ESNA-ASHARI, F. & KERAMAT, F. 2014. Assessment of Health-related Quality of Life among Patients with Tuberculosis in Hamadan, Western Iran. *Oman Med J,* 29**,** 102-5.
MARRA, C. A., MARRA, F., COLLEY, L., MOADEBI, S., ELWOOD, R. K. & FITZGERALD, J. M. 2008. Health-related quality of life trajectories among adults with tuberculosis: differences between latent and active infection. *Chest,* 133**,** 396-403.
MARRA, C. A., MARRA, F., COX, V. C., PALEPU, A. & FITZGERALD, J. M. 2004. Factors influencing quality of life in patients with active tuberculosis. *Health Qual Life Outcomes,* 2**,** 58.
MARUISH, M. E., AND KOSINSKI, M. 2009. A Guide to the Development of Certified Short Form Survey Interpretation and Reporting Capabilities. Quality Metrics Incorporated.
MARUISH ME, K. M. 2009. A guide to the development of certified short form survey interpretation and reporting capabilities *In:* INCORPORATED, Q. (ed.).
MASUMOTO, S., YAMAMOTO, T., OHKADO, A., YOSHIMATSU, S., QUERRI, A. G. & KAMIYA, Y. 2014. Factors associated with health-related quality of life among pulmonary tuberculosis patients in Manila, the Philippines. *Qual Life Res,* 23**,** 1523-33.
MAYOSI, B. M., FLISHER, A. J., LALLOO, U. G., SITAS, F., TOLLMAN, S. M. & BRADSHAW, D. 2009. The burden of non-communicable diseases in South Africa. *The Lancet,* 374**,** 934-947.
MCINERNEY, P. A., NICHOLAS, P. K., WANTLAND, D., CORLESS, I. B., NCAMA, B., BHENGU, B., MCGIBBON, C. A., DAVIS, S. M. & GALLAGHER, D. M. 2007. Characteristics of anti-tuberculosis medication adherence in South Africa. *Appl Nurs Res,* 20**,** 164-70.
MCKENNA, S. P. 2011. Measuring patient-reported outcomes: moving eyond misplaced common sense to hard science. *BMC Medicine,* 9.
MILLER, T. L., MCNABB, S. J., HILSENRATH, P., PASIPANODYA, J. & WEIS, S. E. 2009. Personal and societal health quality lost to tuberculosis. *PLoS One,* 4**,** e5080.
MKOPI, A., RANGE, N., LWILLA, F., EGWAGA, S., SCHULZE, A., GEUBBELS, E., VAN LETH, F. 2014. Validation of indirect tuberculosis treatment adherence measures in a resource-constrained setting. *International Journal of Tuberculosis and Lung Diseases,* 18**,** 804-809.
MORISKY, D. E., ANG, A., KROUSEL-WOOD, M., WARD, H.J. 2008a. Predictive Validation of a Medication Adherence Measure in an Outpatient Setting. *The Journal of Clinical Hypertension,* 10**,** 348-354.
MORISKY, D. E., ANG, A., KROUSEL-WOOD, M., WARD, H.J. 2008b. Predictive Validity of a Medication Adherence Measure in an Outpatient Setting. *The Journal of Clinical Hypertension,* 10**,** 348-354.
MORISKY, D. E. & DIMATTEO, M. R. 2011. Improving the measurement of self-reported medication nonadherence: Final response. *Journal of Clinical Epidemiology,* 64**,** 262-263.
MUNIYANDI, M., RAJESWARI, R., BALASUBRAMANIAN, R., NIRUPA, C., GOPI, P. G., JAGGARAJAMMA, K., SHEELA, F. & NARAYANAN, P. R. 2007. Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients. *Int J*

*Tuberc Lung Dis,* 11**,** 887-92.
MUNRO S, L. S., SMITH H, ENGEL M, FREIHEIM A, VOLMINK J 2007. Patient Adherence to Tuberculosis Treatment: A Systematic Review of Qualitative Research. *PLOS Medicine* 4**,** 1230-1245.
NAIDOO P, D. J., COOPER D 2009. Exploring tuberculosis patients' adherence to treatment regimens and prevention programs at a public health site. *Qualitative Health Research* 19**,** 55-70.
NAIDOO, P. & MWABA, K. 2010. Helplessness, Depression, and Social Support Among People Being Treated for Tuberculosis in South Africa. *Social Behavior and Personality: an international journal,* 38**,** 1323-1333.
NATIONAL DEPARTMENT OF HEALTH SOUTH AFRICA (NDoH). 2013. Guidelines for Pharmacoeconomic Submissions 2012. *In:* AFRICA, D. O. H. S. (ed.) *Government Gazette*
NATIONAL DEPARTMENT OF HEALTH SOUTH AFRICA (NDoH). 2014. National Tuberculosis Management Guidelines 2014.
NGUYEN, T. M., LA CAZE, A. & COTTRELL, N. 2014. What are validated self-report adherence scales really measuring?: a systematic review. *Br J Clin Pharmacol,* 77**,** 427-45.
OTHMAN, Q. 2011. Health related quality of life of pulmonary and extrapulmonary tuberculosis patients in Yemen. *African Journal of Pharmacy and Pharmacology,* 5**,** 547-553.
OTTERMANN, B. 2013. *Prevalence of diabetes in South Africa* [Online]. Available: http://www.health24.com/Medical/Diabetes/About-diabetes/Diabetes-tsunami-hits- South-Africa-20130210 [Accessed 03 May 2016].
PASIPANODYA, J. G., MILLER, T. L., VECINO, M., MUNGUIA, G., BAE, S., DREWYER, G.
& WEIS, S. E. 2007a. Using the St. George respiratory questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. *Chest,* 132**,** 1591-8.
PASIPANODYA, J. G., MILLER, T. L., VECINO, M., MUNGUIA, G., GARMON, R., BAE, S., DREWYER, G. & WEIS, S. E. 2007b. Pulmonary impairment after tuberculosis. *Chest,* 131**,** 1817-24.
PATRICK, D., BURKE, L. 2013. Focusing on the Patient in Drug Development and Research. *Value in Health,* 19**,** 5-8.
PATRICK, D. L., BURKE, L., POWERS, J.H., SCOTT, J.A., ROCK, E.P., DAWISHA, S., O´NEILL, R., KENNEDY, D.L. 2007. Patient-Reported Outcomes to Support Medical Product Labeling Claims: FDA Perspective. *Value in Health,* 10**,** S125-S137.
PELTZER, K., NAIDOO, P., MATSEKE, G., LOUW, J., MCHUNU, G. & TUTSHANA, B. 2013. Prevalence of post-traumatic stress symptoms and associated factors in tuberculosis (TB), TB retreatment and/or TB–HIV co-infected primary public health- care patients in three districts in South Africa. *Psychology, Health & Medicine,* 18**,** 387-397.
PELTZER K, N. P., MATSEKE G, LOUW J, MCHUNU G, TUTSHANA B 2012. Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. *BMC Psychiatry* 12**,** 1-10.
PATIENT-REPORTED OUTCOME AND QUALITY OF LIFE DATABASE (PROQOLID). 2001 ed. France: Mapi Research Institute.
PUHAN, M. A., FREY, M., BUCHI, S. & SCHUNEMANN, H. J. 2008. The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes,* 6**,** 46.
RAJESWARI, R., MUNIYANDI, M., BALASUBRAMANIAN, R. & NARAYANAN, P. R. 2005. Perceptions of tuberculosis patients about their physical, mental and social well-being: a field report from south India. *Soc Sci Med,* 60**,** 1845-53.
RALPH, A. P., KENANGALEM, E., WARAMORI, G., PONTORORING, G. J., SANDJAJA, TJITRA, E., MAGUIRE, G. P., KELLY, P. M. & ANSTEY, N. M. 2013. High morbidity

during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. *PLoS One,* 8**,** e80302.
REASNER, D., BAL, V., HALLING, K., DANIELS, S., SHIELDS, A., TURPIN, R., 2015. Patient-reported endpoints and the relevance to payers and regulators: is there agreement? *Patient-reported outcome consortium workshop.*
ROTHMAN, M., BURKE, L., ERICKSON, P., KLINE LEIDY, N., PATRICK, D.L., PETRIE, C.D. 2009. Use of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification:The ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PROTask Force Report. *Value in Health,* 12**,** 1075-1083.
ROWE KA, M. B., HARGREAVES JR, PORTER JD, HAUSLER HP, PRONYK PM 2005. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? *International Journal of Tuberculosis and Lung Diseases* 9**,** 263-269.
RUOF, J., SCHWARTZ, F. W., SCHULENBURG, J. M. & DINTSIOS, C. M. 2014. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. *Eur J Health Econ,* 15**,** 577-89.
SCIENTIFIC ADVISORY COMMITTEE OF THE MEDICAL OUTCOMES TRUST (SACMOT). 2002. Assessing health status and quality-of-life instruments: Attributes and review criteria. *Quality of Life Research,* 11**,** 193-205.
SALEEM, F., HASSALI, M.A., SHAFIE, A.A., AWAD, G.A., ATIF, M., UL HAQ, N., ALJADHEY, H., FAROOQUI, M. 2012. Does treatment adherence correlates with health related quality of life? findings from a cross sectional study. *BMC Public Health,* 12.
ST GEORGE´S UNIVERSITY OF LONDON, L. 2012. LIST OF SGRQ TRANSLATIONS AVAILABLE FROM SGUL.
STIRRATT, M. J., DUNBAR-JACOB, J., CRANE, H. M., SIMONI, J. M., CZAJKOWSKI, S., HILLIARD, M. E., AIKENS, J. E., HUNTER, C. M., VELLIGAN, D. I., HUNTLEY, K., OGEDEGBE, G., RAND, C. S., SCHRON, E. & NILSEN, W. J. 2015. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med,* 5**,** 470-82.
TBFACTS.ORG. *Information about tuberculosis* [Online]. Available: http://www.tbfacts.org/ [Accessed 23 October 2016].
THERON, G., PETER, J., ZIJENAH, L., CHANDA, D., MANGU, C., CLOWES, P., RACHOW, A., LESOSKY, M., HOELSCHER, M., PYM, A., MWABA, P., MASON, P., NAIDOO, P., POORAN, A., SOHN, H., PAI, M., STEIN, D. J. & DHEDA, K. 2015. Psychological distress and its relationship with non-adherence to TB treatment: a multicentre study. *BMC Infect Dis,* 15**,** 253.
THE WORLD BANK. 2016. *South Africa* [Online]. Available: http://www.worldbank.org/en/country/southafrica/overview [Accessed 07 November 2016 2016].
VAN RIE, A., SENGUPTA, S., PUNGRASSAMI, P., BALTHIP, Q., CHOONUAN, S., KASETJAROEN, Y., STRAUSS, R. P. & CHONGSUVIVATWONG, V. 2008. Measuring stigma associated with tuberculosis and HIV/AIDS in southern Thailand: exploratory and confirmatory factor analyses of two new scales. *Trop Med Int Health,* 13**,** 21-30.
VOLMINK, J. & GARNER, P. 2007. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst Rev,* 17.
VRIJENS, B., DE GEEST, S., HUGHES, D. A., PRZEMYSLAW, K., DEMONCEAU, J., RUPPAR, T., DOBBELS, F., FARGHER, E., MORRISON, V., LEWEK, P., MATYJASZCZYK, M., MSHELIA, C., CLYNE, W., ARONSON, J. K., URQUHART, J. & TEAM, A. B. C. P. 2012. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol,* 73**,** 691-705.

WALTERS, S. J. 2004. Sample size and power estimation for studies with health related quality of life outcomes: a comparison of four methods using the SF-36. *Health and Quality of Life Outcomes,* 2.
WALTERS, S. J., BRAZIER, J.E. 2005. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of Life Research,* 14**,** 1523-1532.
WARE, J. E. *SF-12v2* [Online]. Available: https://campaign.optum.com/optum-outcomes/what-we-do/health-surveys/sf-12v2-health-survey.html [Accessed 23
September 2014 2014].
WEIS, S. E. & PASIPANODYA, J. G. 2010. Measuring health-related quality of life in tuberculosis: a systemic review--response. *Health Qual Life Outcomes,* 8**,** 7; author reply 6.
WESTAWAY, M. S., RHEEDER, P., GUMEDE, T. 2001. The effect of type 2 Diabetes Mellitus on health-related quality of life (HRQOL). *Curationis*.
WORLD HEALTH ORGANIZATION (WHO). 1948. Available: http://www.who.int/about/definition/en/print.htm [Accessed 04 April 2016].
WORLD HEALTH ORGANIZATION (WHO). 2003. Adherence To Long-Term Therapies – Evidence for Action.
WORLD HEALTH ORGANIZATION (WHO). 2015a. The End TB Strategy.
WORLD HEALTH ORGANIZATION (WHO). 2015b. *From MDGs to SDGs, WHO launches new report* [Online]. Available: http://www.who.int/mediacentre/news/releases/2015/mdg-sdg-report/en/ [Accessed 14 May 2016 2016].
WORLD HEALTH ORGANIZATION (WHO). 2015c. Global Tuberculosis Report 2015.
WORLD HEALTH ORGANIZATION (WHO). 2015d. Health in 2015: from MDGs, Millennium Development Goals to SDGs, Sustainable Development Goals. Switzerland.
WORLD HEALTH ORGANIZATION (WHO). 2016. Global Tuberculosis Report.
WILKE, T., MULLER, S. & MORISKY, D. E. 2011. Toward identifying the causes and combinations of causes increasing the risks of nonadherence to medical regimens: combined results of two German self-report surveys. *Value Health,* 14**,** 1092-100.
YIN, X., TU, X., TONG, Y., YANG, R., WANG, Y., CAO, S., FAN, H., WANG, F., GONG, Y., YIN, P. & LU, Z. 2012. Development and validation of a tuberculosis medication adherence scale. *PLoS One,* 7**,** e50328.

# Appendix

## Supplementary material to Chapter 2.1

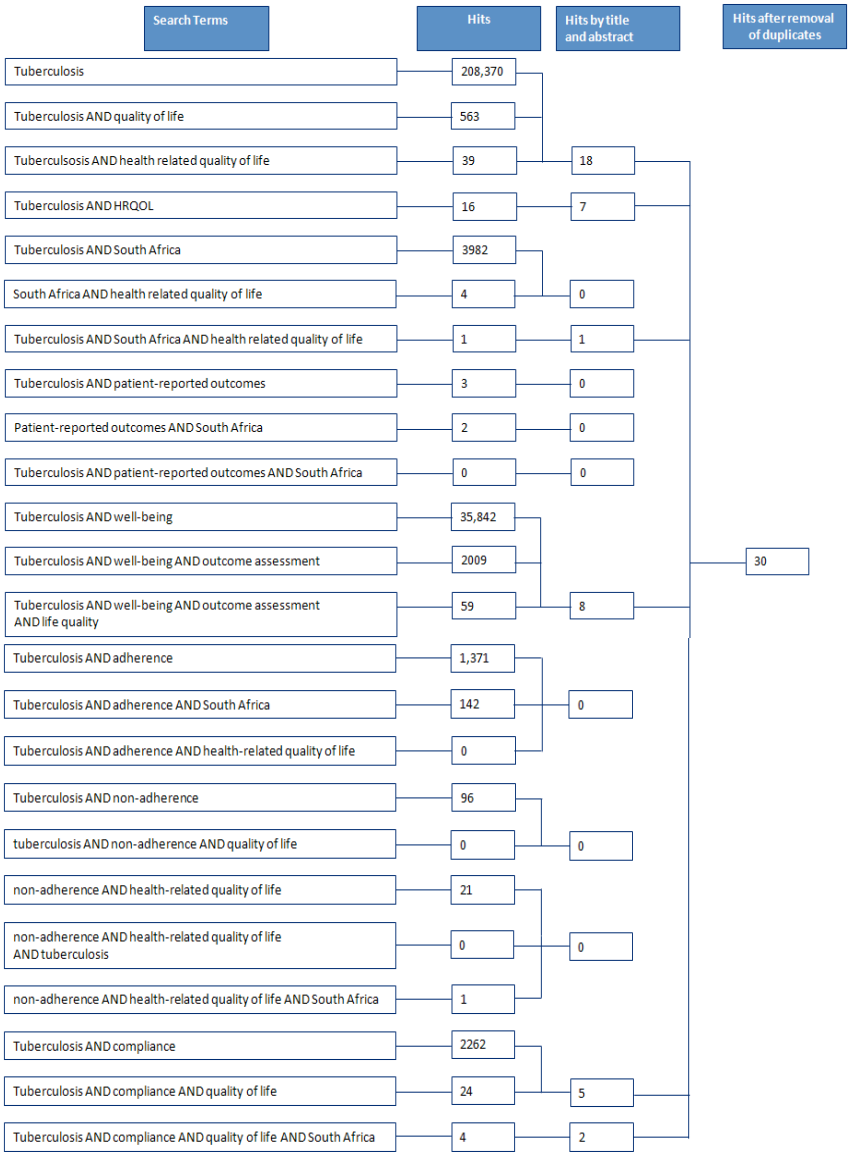


**Figure 1**: Literature search strategy conducted in Pubmed to formulate research objectives.

## Supplementary material to Chapter 4

### Search strategy for identification and selection of relevant studies

A systematic and comprehensive literature search was performed in PubMed, EMBASE and PsychINFO, with the last search conducted on 22 February 2015. Search terms applied included *tuberculosis, health related quality of life, HRQOL, quality of life, South Africa, patient-reported outcomes, outcome assessment, life quality, well-being, adherence, non-adherence, and compliance.* All search terms were combined differently and applied to each database, as shown in table 1:

**Table 1:** Combination of search terms. Search terms were combined differently 16 times and applied to the databases PubMed, EMBASE and PsychINFO.

| Search Term combinations applied to Pubmed, EMBASE and PsychINFO |
|---|
| Tuberculosis AND health related quality of life |
| Tuberculosis AND HRQOL |
| South Africa AND health related quality of life |
| Tuberculosis AND South Africa AND health related quality of life |
| Tuberculosis AND patient-reported outcomes |
| Patient-reported outcomes AND South Africa |
| Tuberculosis AND patient-reported outcomes AND South Africa |
| Tuberculosis AND well-being AND outcome assessment AND life quality |
| Pulmonary Tuberculosis AND adherence AND South Africa |
| Tuberculosis AND adherence AND health-related quality of life |
| Tuberculosis AND non-adherence AND quality of life |
| Non-adherence AND health-related quality of life |
| Non-adherence AND health-related quality of life AND tuberculosis |
| Non-adherence AND health-related quality of life AND South Africa |
| Tuberculosis AND compliance AND quality of life |
| Tuberculosis AND compliance AND quality of life AND South Africa |

Each search term combination was applied to the database separately and resulted in “initial hits”. Initial hits were then screened by title and abstract with regard to search terms and selected articles resulted in “Hits by abstract and title”. Articles were excluded if they were not related to the pre-defined search terms or were published in a language other than English. From the selected articles, duplicates were removed and resulted in “Hits after removal of duplicates”.

The following figures 1-3 present each search term combination with its related initial hits and number of articles after review by title and abstract and removal of duplicates, for each database.

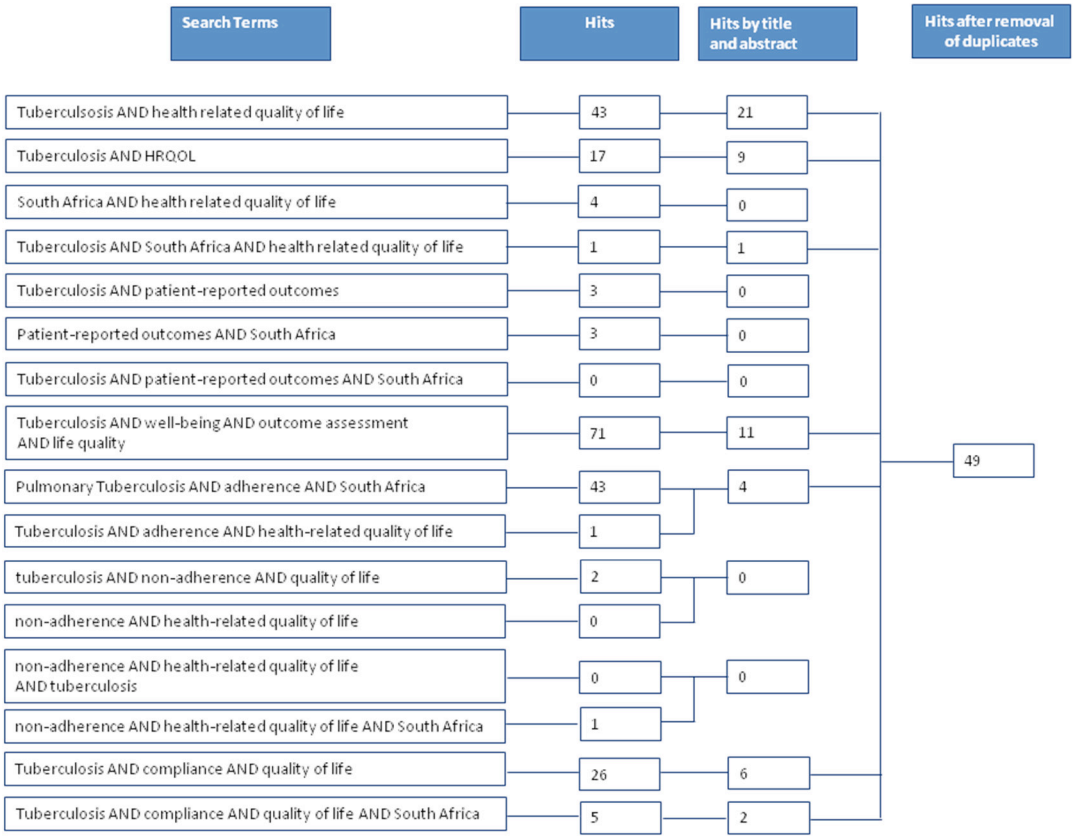


**Figure 1:** Search strategy in Pubmed.

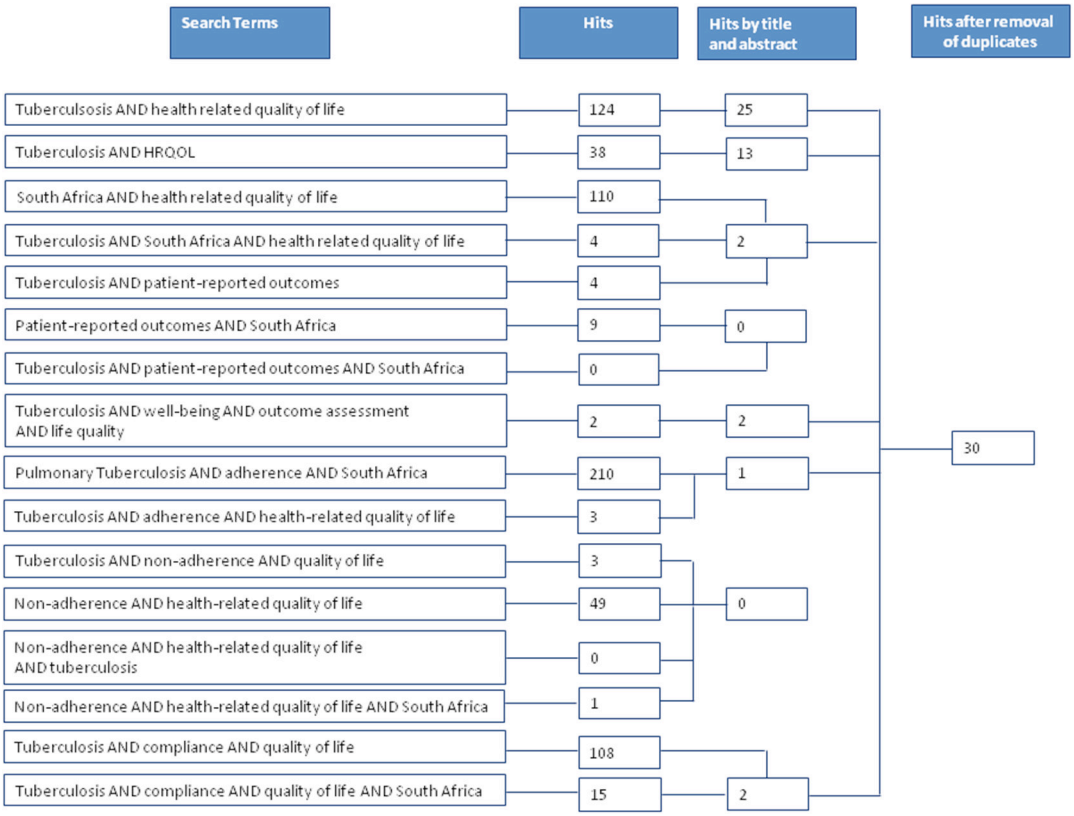


**Figure 2:** Search Strategy in EMBASE.

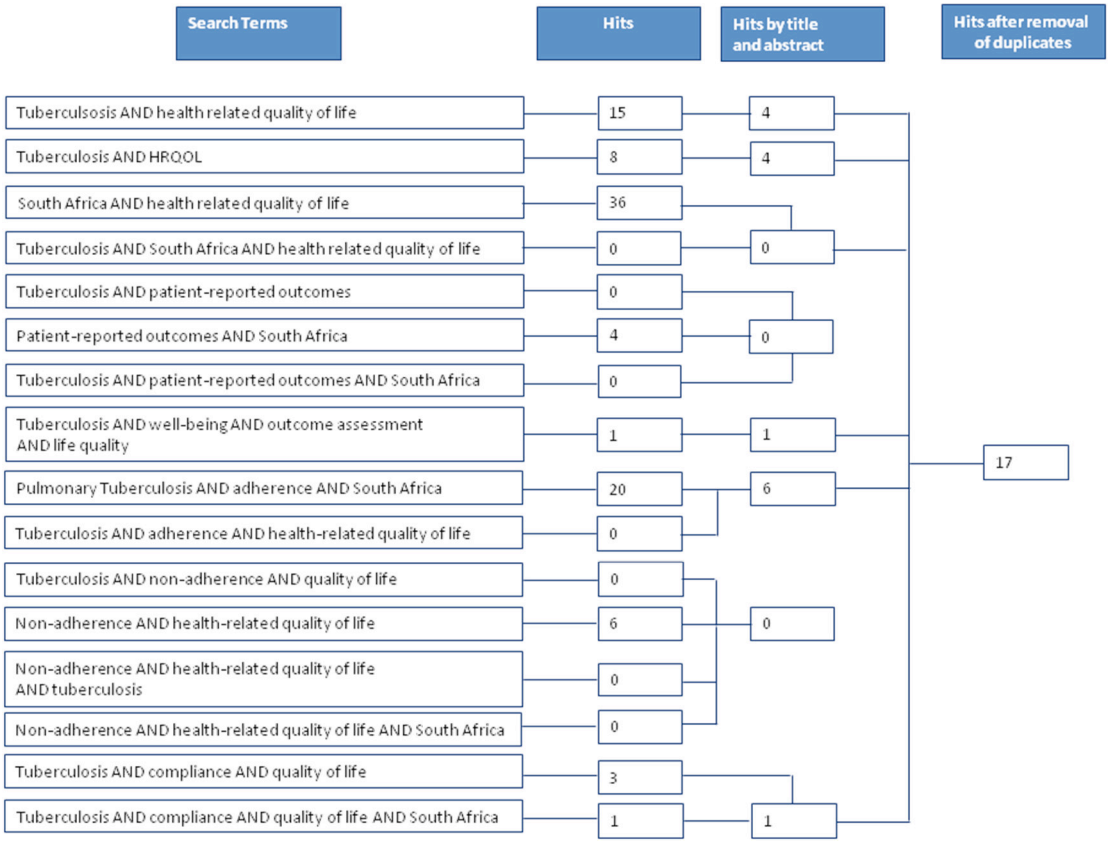


**Figure 3:** Search Strategy in PsychINFO.

Our literature search in PubMed, EMBASE and PsychINFO yielded 988 initial hits; after screening by title and abstract and after removal of duplicates, 61 articles remained. Addition of three WHO reports, two guidelines from Department of Health South Africa and one article identified by hand search of citations resulted in 67 eligible articles for this systematic review. One article was excluded, yielding 66 eligible full-text articles (Figure 4). A detailed description of the literature search is available in the Appendix. The 66 articles comprised 22 cross-sectional studies, 17 longitudinal studies, 7 (systematic) reviews, 8 qualitative studies and 12 articles including editorials, comments and letters. Nine studies were performed in South Africa (four HRQOL and five medication adherence studies; Table 4). All final 66 articles underwent extraction of information about HRQOL and adherence in TB. The 17 identified longitudinal studies were potentially eligible for separate data extraction; 11 of them actually met the eligibility criteria for separate data extraction, while 6 studies were excluded as eligibility criteria were not met (Table 3). Application of the STROBE quality of reporting checklist to the 11 longitudinal studies resulted in a median score of 7 for HRQOL studies, with scores ranging from 5 to 11 out of 16 (the greater the score the higher the quality of reporting). The adherence study had a score of 10 (Table 3).

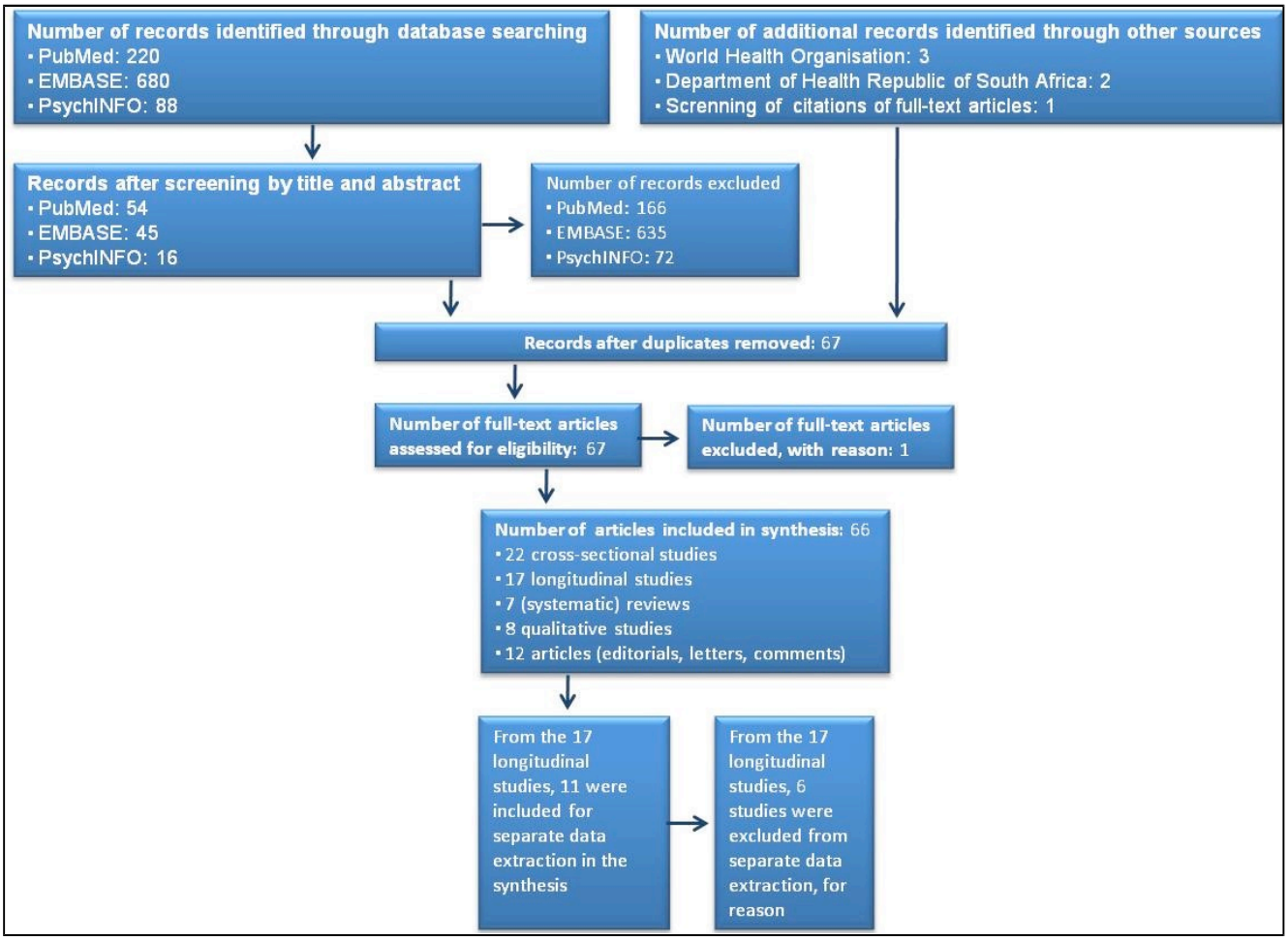


**Figure 4:** Literature search process in the databases PubMed, EMBASE and PsychINFO; additional articles were obtained from World Health Organization and Department of Health Republic of South Africa.

All final 66 articles were uploaded to EndNote X7 version 3.1. Table 2 presents all 66 identified articles included in this systematic review.

## Table 2: Articles finally included in the systematic review

| Reference | Study Design | Comment |
|---|---|---|
| Adeyeye et al 2014: Factors influencing quality of life and predictors of low quality of life scores in patients on treatment for pulmonary tuberculosis: a cross sectional study. | cross-sectional | |
| Aggarwal et al 2013: Assessment of health-related quality of life in patients with pulmonary tuberculosis under programme conditions. | longitudinal | |
| Aggarwal et al 2010: Health-related quality of life: A neglected aspect of pulmonary tuberculosis. | editorial | |
| Aamir and Aisha 2010: Co-morbid anxiety and depression among pulmonary tuberculosis patients. | review | |
| Atif et al 2012: WHO guidelines for treatment of tuberculosis: the missing links. | research support | |
| Atif et al 2014: Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study | longitudinal | |
| Atif 2013: SF-36v2 norms and its' discriminative properties among healthy households of tuberculosis patients in Malaysia | cross-sectional | |
| Atif et al (2015) Missing Data Analysis in Longitudinal Studies: Findings from a Quality of Life Study in Malaysian Tuberculosis Patients | cross-sectional | |
| Atif et al 2012: Health-Related Quality of Life (HRQoL) in co-morbid tuberculosis relapse patient: A case report from Malaysia. | commentary | |
| Awaisu et al 2012: Impact of connecting tuberculosis directly observed therapy short-course with smoking cessation on health-related quality of life. | cross-sectional | |
| Babikako et al 2010: Feasibility, reliability and validity of health-related quality of life questionnaire among adult pulmonary tuberculosis patients in urban Uganda: cross-sectional study. | cross-sectional | |
| Balgude et al 2012: Study of impact of antitubercular therapy on quality of life. | longitudinal | |
| Bauer et al 2013: A systematic review and meta-analysis of the impact of tuberculosis on health-related quality of life. | systematic review | |
| Chamla 2004: The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China | longitudinal | |
| Chang et al (2004) Quality of life in tuberculosis: A review of the English language literature | Reviews | |
| Chirwa et al 2013: Levels of tuberculosis treatment adherence among sputum smear positive pulmonary tuberculosis patients attending care at Zomba Central hospital, southern Malawi, 2007-2008. | longitudinal | |
| Chung et al 2013: Can DOTS improve quality of life among patients with pulmonary tuberculosis? | letter | |
| Chung et al 2012:Psychometric testing of the short version of the world health organization quality of life (WHOQOL-BREF) questionnaire among pulmonary tuberculosis patients in Taiwan. | longitudinal, instrument validation | |
| Cramm et al 2010: Patient views on determinants of compliance with tuberculosis treatment in the eastern cape, South Africa: an application of q-methodology. | qualitative study | |
| Corless et al 2009: HIV and tuberculosis in Durban, South Africa: adherence to two medication regimens. | cross-sectional | |
| Department of Health Republic of South Africa (2013) Guidelines for Pharmacoeconomic Submissions 2012. Government Gazette No. 36118. | | accessed from DoH |
| Department of Health Republic of South Africa (2014) National Tuberculosis Management Guidelines 2014. ISBN: 978-1-920031-82-4 | | accessed from DoH |
| Deribew et al 2013: Change in quality of life: a follow up study among patients with HIV infection with and without TB in Ethiopia. | longitudinal | |
| Dhingra and Rajpal 2005: Health related quality of life (HRQL) scoring (DR-12 score) in tuberculosis--additional evaluative tool under DOTS | longitudinal, instrument development and validation | |
| Dhuria et al 2009: A Study of the Impact of Tuberculosis on the Quality of Life and the Effect After Treatment With DOTS | longitudinal | |
| Dias et al 2013: Life experiences of patients who have completed tuberculosis treatment: a qualitative investigation in southeast Brazil. | qualitative | |
| Diel and Lampenius 2014: Cost-effectiveness analysis of interventions for tuberculosis control: DALYs versus QALYs. | cost-effectiveness study | |
| Dion et al 2004: Feasibility and reliability of health-related quality of life measurements among tuberculosis patients | cross-sectional | |
| Dujaili et al 2015: Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq | longitudinal | |
| Guo et al 2009: Measuring health-related quality of life in tuberculosis: a systematic review. | systematic review | |
| Guo et al 2010: Impact of adverse drug reaction and predictivity of quality of life status in tuberculosis. | editor reply | |
| Guo et al 2008: Health state utilities in latent and active tuberculosis. | cross-sectional | |
| Hansel et al 2004: Quality of life in tuberculosis: patient and provider perspectives | qualitative study | |

## Articles finally included in the systematic review (cont.)

| Reference | Study Design | Comment |
|---|---|---|
| Husain et al2008: The relationship between anxiety, depression and illness perception in tuberculosis patients in Pakistan | cross-sectional | |
| Issa et al 2009: Depression comorbidity among patients with tuberculosis in a university teaching hospital outpatient clinic in Nigeria. | cross-sectional | |
| Kittikraisak et al 2012: Health related quality of life among patients with tuberculosis and HIV in Thailand. | cross-sectional | |
| Kruijshaar et al 2010: Health status of UK patients with active tuberculosis | longitudinal | |
| Louw et al 2012: Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. | cross-sectional | |
| Lutge et al 2013: Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. | longitudinal | |
| Lutge et al 2012: Material incentives and enablers in the management of tuberculosis. Cochrane Database Syst Rev. 18;1:CD007952 | Cochrane systematic review | |
| Maguire et al 2009: Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. | longitudinal | |
| Mamani et al 2014: Assessment of Health-related Quality of Life among Patients with Tuberculosis in Hamadan, Western Iran | longitudinal | |
| Marra et al 2004: Factors influencing quality of life in patients with active tuberculosis. | qualitative study | |
| Marra et al 2008: Health-related quality of life trajectories among adults with tuberculosis: differences between latent and active infection. | longitudinal | |
| Masumoto et al 2014: Factors associated with health-related quality of life among pulmonary tuberculosis patients in Manila, the Philippines. | corss-sectional | |
| Mclnerney et al 2007: Characteristics of anti-tuberculosis medication adherence in South Africa. | cross-sectional | |
| Miller et al 2009: Personal and societal health quality lost to tuberculosis.PLoS One. 2009;4(4):e5080 | cost-effectiveness study | |
| Muniyandi et al 2007: Evaluation of post-treatment health-related quality of life (HRQoL) among tuberculosis patients | cross-sectional | |
| Munro et al 2007: Patient Adherence to Tuberculosis Treatment: A Systematic Review of Qualitative Research | systematic review of qualitative research | |
| Naidoo and Mwaba 2010: Helplessness, depression, and social support among people being treated for tuberculosis in South Africa. | qualitative study | |
| Naidoo et al 2009: Exploring tuberculosis patients' adherence to treatment regimens and prevention programs at a public health site. | qualitative study | |
| Othman et al 2011: Health related quality of life of pulmonary and extrapulmonary tuberculosis patients in Yemen. 5:4(547-553) | cross-sectional, instrument validation | |
| Pasipanodya et al 2007: Using the St. George Respiratory Questionnaire to ascertain health quality in persons with treated pulmonary tuberculosis. | cross-sectional, instrument validation | |
| Pasipanodya et al (2007) Pulmonary Impairment after Tuberculosis. Chest 131;6:1817-1824. | cross-sectional | |
| Peltzer et al 2013: Prevalence of post-traumatic stress symptoms and associated factors in tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health-care patients in three districts in South Africa. | cross-sectional | |
| Peltzer et al 2012: Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. | cross-sectional | |
| Rajeswari et al 2005: Perceptions of tuberculosis patients about their physical, mental and social well-being: A field report from south India. | longitudinal | |
| Ralph et al 2013: High Morbidity during Treatment and Residual Pulmonary Disability in Pulmonary Tuberculosis: Under-Recognised Phenomena | longitudinal | |
| Rowe et al 2005: Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? | qualitative study | taken from Mclnerny et al 2007 |
| Van Rie et al 2008: Measuring stigma associated with tuberculosis and HIV/AIDS in southern Thailand: exploratory and confirmatory factor analyses of two new scales. | cross-sectional | |
| Volmink and Garner 2007: Directly observed therapy for treating tuberculosis. | Cochrane systematic review | |
| Weis and Pasipanodya 2010: Measuring health-related quality of life in tuberculosis: a systemic review--response. | response | |
| WHO (World Health Organization) 2013: Global Tuberculosis Report 2013. | WHO report | accessed from WHO website |
| WHO (World Health Organization) 2012: South Africa Tuberculosis Profile. | WHO country profile | accessed from WHO website |
| WHO (World Health Organization) 2003: Adherence To Long-Term Therapies – Evidence for Action. | WHO report | accessed from WHO website |
| Yin et al 2012: Development and validation of a Tuberculosis Mediaction Adherence Scale | cross-sectional, instrument development and validation | |

# Quality of reporting check list for longitudinal studies

**Table 3:** Quality of reporting of longitudinal studies in HRQOL and medication adherence in PTB according to STROBE Statement and Bauer et al (2013).

| Reference | Study type | Study applicable for systematic review according to inclusion criteria | Quality Item 1 Description of study population | Quality Item 2 Description of sampling mechanism | Quality Item 3 Accounting to losses of follow up | Quality Item 4 Quality check of HRQOL responses performed during data collection | Quality Item 5 Description of HRQOL instrument used in data collection | Quality Item 6 Data entry check before analysis | Quality Item 7 Interviewer training (before and throughout data collection process) | Quality Item 8 Discussion of strength and limitations of study | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Aggarwal AN, Gupta D, Janmeja AK, Jindal SK (2013) Assessment of health-related quality of life in patients with pulmonary tuberculosis under programme conditions. INT J TUBERC LUNG DIS 17(7):947–953 | longitudinal | applicable | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 2 | 6 |
| Atif M, Sulaiman SA, Shafie AA, Asif M, Sarfraz MK, Low HC, Babar ZU (2014) Impact of tuberculosis treatment on health-related quality of life of pulmonary tuberculosis patients: a follow-up study.Health Qual Life Outcomes 14;12:19 | longitudinal | applicable | 2 | 2 | 2 | 0 | 2 | 0 | 1 | 2 | 11 |
| Balgude A and Sontakke S (2012) Study of impact of antitubercular therapy on quality of life. Indian Journal of Medical Sciences 66(3-4):71-7. | longitudinal | applicable | 2 | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 5 |
| Chamla D (2004) The assessment of patients' health-related quality of life during tuberculosis treatment in Wuhan, China. International Journal of Tuberculosis and Lung Diseases 8(9):1100-1106. | longitudinal | applicable | 2 | 2 |  | 0 | 2 | 0 | 0 | 0 | 6 |
| Dhuria M, Sharma N, Singh NP, Jiloha RC, Saha R, Ingle GK (2009) A Study of the Impact of Tuberculosis on the Quality of Life and the Effect After Treatment With DOTS. Asia-Pacific Journal of Public Health 21(3):312-320. | longitudinal | applicable | 2 | 1 | 1 | 0 | 2 | 0 | 0 | 0 | 6 |
| Kruijshaar ME, Lipman M, Essink-Bot ML, Lozewicz S, Creer D, Dart S, Maguire H, Abubakar I. (2010) Health status of UK patients with active tuberculosis. International Journal of Tuberculosis and Lung Diseases 14(3):296-302. | longitudinal | applicable | 2 | 2 | 0 | 0 | 2 | 0 | 1 | 2 | 9 |
| Maguire GP, Anstey NM, Ardian M, Waramori G, Tjitra E, Kenangalem E, Handojo T, Kelly PM (2009) Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. International Journal of Tuberculosis and Lung Diseases 13(12):1500-1506. | longitudinal | applicable | 2 | 1 | 2 | 0 | 1 | 0 | 0 | 1 | 7 |
| Mamani M, Majzoobi MM, Ghahfarokhi SM, Esna-Ashari F, Keramat F (2014) Assessment of Health-related Quality of Life among Patients with Tuberculosis in Hamadan, Western Iran. Oman Medical Journal 29 (2):102-105. | longitudinal | applicable | 1 | 2 | 0 | 0 | 2 | 0 | 1 | 1 | 7 |
| Marra CA, Marra F, Colley L, Moadebi S, Elwood RK, Fitzgerald JM. (2008) Health-related quality of life trajectories among adults with tuberculosis: differences between latent and active infection. Chest 133(2):396-403. | longitudinal | applicable | 2 | 2 | 1 | 0 | 2 | 0 | 1 | 2 | 9 |
| Ralph AP, Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, Maguire GP, Kelly PM, Anstey NM. (2013) High Morbidity during Treatment and Residual Pulmonary Disability in Pulmonary Tuberculosis: Under-Recognised Phenomena. Quality of Life Research 22:2213-2235 | longitudinal | applicable | 2 | 2 | 2 | 0 | 1 | 1 | 0 | 1 | 9 |
| Chung WS, Lan YL, Yang MC. (2012) Psychometric testing of the short version of the world health organization quality of life (WHOQOL-BREF) questionnaire among pulmonary tuberculosis patients in Taiwan. BMC Public Health 12:630:1-10. | longitudinal | psychometric instrument validation study |  |  |  |  |  |  |  |  |  |
| Dhingra VK and Rajpal S (2005) Health related quality of life (HRQL) scoring (DR-12 score) in tuberculosis--additional evaluative tool under DOTS. Journal of Communicable Diseases 37(4):261-8. | longitudinal | not applicable since new unvalidated instrument underwent validation study |  |  |  |  |  |  |  |  |  |
| Deribew A, Deribe K, Reda AA, Tesfaye M, Hailmichael Y, Maja T, Colebunders R (2013) Change in quality of life: a follow up study among patients with HIV infection with and without TB in Ethiopia. BMC Public Health 13:408:1-6 | longitudinal | not applicable since only TB/HIV co-infection included |  |  |  |  |  |  |  |  |  |
| Dujaili JA, Sulaiman SA, Hassali MA, Awaisu A, Blebil AQ, Bredle JM (2015) Health-related quality of life as a predictor of tuberculosis treatment outcomes in Iraq.Int J Infect Dis 31:4-8 | longitudinal | not applicable since validation study of new developed instrument |  |  |  |  |  |  |  |  |  |
| Rajeswari R, Muniyandi M, Balasubramanian R, Narayanan PR (2005) Perceptions of tuberculosis patients about their physical, mental and social well-being: A field report from South India. Social Science and Medicine 60(8), 1845–1853. | longitudinal | not applicable since a modified but unvalidated version of SF-36 was applied |  |  |  |  |  |  |  |  |  |

| Reference | Study type | Study applicable for systematic review according to inclusion criteria | Quality Item 1 Description of study population | Quality Item 2 Description of sampling mechanism | Quality Item 3 Accounting to losses of follow up | Quality Item 4 Quality check of adherence responses performed during data collection | Quality Item 5 Description of adherence instrument used in data collection | Quality Item 6 Data entry check before analysis | Quality Item 7 Interviewer training (before and throughout data collection process) | Quality Item 8 Discussion of strength and limitations of study | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chirwa T1, Nyasulu P, Chirwa E, Ketlogetswe A, Bello G, Dambe I, Ndalama D, Joshua M.(2013) Levels of tuberculosis treatment adherence among sputum smear positive pulmonary tuberculosis patients attending care at Zomba Central hospital, southern Malawi, 2007-2008. PLoS One. 28;8(5) | longitudinal | applicable | 1 | 2 | 2 | 1 | 2 | 0 | 1 | 1 | 10 |
| Lutge et al 2013: Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. | longitudinal | not applicable since adherence was measured by monetary incentives provided to patients; high chance for bias through monetary incetive |  |  |  |  |  |  |  |  |  |

**Table 4:** Studies on HRQOL and medication adherence performed in South Africa. From all eligible articles included in the systematic review nine articles reported research performed on HRQOL and adherence in South Africa.

| Reference | Study Design | Study Topic |
|---|---|---|
| Louw J, Peltzer K, Naidoo P, Matseke G, Mchunu G, Tutshana B. (2012) Quality of life among tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health care patients in three districts in South Africa. Health and Quality of Life Outcomes 10:77:1-8. | cross-sectional | HRQOL |
| Naidoo P and Mwaba K (2010) Helplessness, depression, and social support among people being treated for tuberculosis in South Africa. Social Behavior and Personality, Vol 38(10):1323-1334. | qualitative study | HRQOL |
| Peltzer K, Naidoo P, Matseke G, Louw J, McHunu G, Tutshana B. (2013) Prevalence of post-traumatic stress symptoms and associated factors in tuberculosis (TB), TB retreatment and/or TB-HIV co-infected primary public health-care patients in three districts in South Africa. Psychol Health Med. 18(4):387-97 | cross-sectional | HRQOL |
| Peltzer K, Naidoo P, Matseke G, Louw J, McHunu G, Tutshana B. (2012) Prevalence of psychological distress and associated factors in tuberculosis patients in public primary care clinics in South Africa. BMC Psychiatry. 2012 Jul 27;12:89. | cross-sectional | HRQOL |
| McInerney PA, Nicholas PK, Wantland D, Corless IB, Ncama B, Bhengu B, McGibbon CA, Davis SM, Gallagher DM (2007) Characteristics of anti-tuberculosis medication adherence in South Africa. Applied Nursing Research 20(4):164-70. | cross-sectional | adherence and HRQOL |
| Corless IB, Wantland D, Bhengu B, McInerney P, Ncama B, Nicholas PK, McGibbon C, Wong E, Davis SM (2009) HIV and tuberculosis in Durban, South Africa: adherence to two medication regimens. AIDS Care 21(9):1106-1113. | cross-sectional | adherence |
| Lutge E, Lewin S, Volmink J, Friedman I, Lombard C. (2013) Economic support to improve tuberculosis treatment outcomes in South Africa: a pragmatic cluster-randomized controlled trial. Trials. 14:154 | cross-sectional | adherence |
| Cramm JM, van Exel J, Møller V, Finkenflügel H. (2010) Patient views on determinants of compliance with tuberculosis treatment in the eastern cape, South Africa: an application of q-methodology. Patient 3(3):159-72. | qualitative study | adherence |
| Naidoo P, Dick J, Cooper D. (2009) Exploring tuberculosis patients' adherence to treatment regimens and prevention programs at a public health site.Qual Health Res. 19(1):55-70 | qualitative study | adherence |

# Supplementary material chapter 5

**Table 1:** Studies included in the development of study design.

| Studies applying PRO instruments in TB | Study Type | Country |
|---|---|---|
| Adeyeye et al 2014 (Adeyeye et al., 2014) | cross-sectional | Nigeria |
| Aggarwal et al 2013 (Aggarwal et al., 2013) | longitudinal | India |
| Atif et al 2014 (Atif et al., 2014b) | cross-sectional | Malaysia |
| Atif et al 2014 (Atif et al., 2014a) | longitudinal | Malaysia |
| Atif et al 2013 (Atif et al., 2013) | cross-sectional | Malaysia |
| Awaisu et al 2012 (Awaisu et al., 2012) | cross-sectional | Malaysia |
| Babikako et al 2010 (Babikako et al., 2010) | cross-sectional | Uganda |
| Balgude et al 2012 (Balgude and Sontakke, 2012) | longitudinal | India |
| Bauer et al 2013 (Bauer et al., 2013) | systematic review | NA |
| Chamla 2004 (Chamla, 2004) | longitudinal | China |
| Chung et al 2012 (Chung et al., 2012) | longitudinal | Taiwan |
| Corless et al 2009 (Corless et al., 2009) | cross-sectional | South Africa |
| Dhingra and Rajpal 2005 (Dhingra and Rajpal, 2005) | longitudinal | India |
| Dhuria et al 2009 (Dhuria et al., 2009) | longitudinal | India |
| Dion et al 2004 (Dion et al., 2004) | cross-sectional | Canada |
| Dujaili et al 2015 (Dujaili et al., 2015) | longitudinal | Iraq |
| Guo et al 2009 (Guo et al., 2009) | systematic review | NA |
| Guo et al 2008 (Guo N, 2008) | cross-sectional | Canada |

| | | |
|---|---|---|
| Husain et al 2008 (Husain MO, 2008) | cross-sectional | Pakistan |
| Issa et al 2009 (Bauer et al., 2013) | cross-sectional | Nigeria |
| Kittikraisak et al 2012 (Kittikraisak et al., 2012) | cross-sectional | Thailand |
| Kruijshaar et al 2010 (Kruijshaar et al., 2010) | longitudinal | UK |
| Louw et al 2012 (Louw et al., 2012) | cross-sectional | South Africa |
| Maguire et al 2009 (Maguire et al., 2009) | longitudinal | Indonesia |
| Mamani et al 2014 (Mamani et al., 2014) | longitudinal | Western Iran |
| Marra et al 2008 (Marra et al., 2008) | longitudinal | Canada |
| Masumoto et al 2014 (Masumoto et al., 2014) | cross-sectional | Philippines |
| McInerney et al 2007 (McInerney et al., 2007) | cross-sectional | South Africa |
| Muniyandi et al 2007 (Muniyandi et al., 2007) | cross-sectional | India |
| Naidoo and Mwaba 2010 (Naidoo and Mwaba, 2010) | qualitative | South Africa |
| Othman et al 2011 (Othman, 2011) | cross-sectional | Yemen |
| Pasipanodya et al 2007 (Pasipanodya et al., 2007a) | cross-sectional | USA |
| Pasipanodya et al 2007 B (Pasipanodya et al., 2007b) | cross-sectional | USA |
| Peltzer et al 2013 (Peltzer et al., 2013) | cross-sectional | South Africa |
| Peltzer et al 2012 (Peltzer K, 2012) | cross-sectional | South Africa |
| Rajeswari et al 2005 (Rajeswari et al., 2005) | longitudinal | India |
| Ralph et al 2013 (Ralph et al., 2013) | longitudinal | Indonesia |
| Yin et al 2012 (Yin et al., 2012) | cross-sectional | China |

**Table 2:** HRQOL measures identified and extracted from studies included.

| PRO measures applied in assessment of HRQOL | Number of single studies identified | Countries |
|---|---|---|
| **Short-Form-36 (SF-36)** | 18 | Uganda, Canada, China, South Africa, UK, India, Western Iran, Malaysia, USA, India |
| **World Health Organization´s Quality of Life - BREF (WHOQOL-BREF)** | 5 | India, Taiwan, Nigeria |
| **EuroQoL (EQ-5D)** | 4 | Canada, UK, Thailand, Malaysia |
| **Beck Depression Inventory (BDI)** | 4 | South Africa, Turkey, Canada |
| **Kessler-10** | 4 | South Africa, Ethiopia |
| **St. George´s Respiratory Questionnaire (SGRQ)** | 4 | USA, Indonesia |
| **Standard Gamble (SG)** | 3 | Canada, UK, Turkey |
| **Visual Analogue Scale (VAS)** | 3 | Canada, Thailand |
| **General Health Questionnaire 12 (GHQ-12)** | 2 | Turkey, Nigeria |
| **Mood Adjective Check List Short Form (MACL** | 2 | Sweden |
| **Severe Respiratory Insufficiency Questionnaire (SRI)** | 2 | Spain, Germany |
| **SF-6D utility score** | 2 | Canada |
| **Sickness Impact Profile (SIP)** | 2 | Sweden |
| **State-Trait Anxiety Inventory Short Form (STAI-6)** | 2 | UK, Turkey |
| **Center for Epidemiologic Studies Depression Scale (CES-D)** | 2 | UK, USA |
| **Duke Health Profile (DUKE)** | 2 | Colombia, Philippines |
| **DR-12** | 2 | India, Yemen |
| **Hospital Anxiety and Depression Scale (HADS)** | 1 | Pakistan |
| **Short-Form 12 (SF-12)** | 1 | South Africa |
| **Beck Depression Inventory (BDI) Short Form** | 1 | South Africa |
| **Brief Disability Questionnaire (BDQ)** | 1 | Turkey |
| **Dysfunctional Analysis Questionnaire (DAQ)** | 1 | India |
| **Health Utilities Index 2 (HUI 2)** | 1 | Canada |
| **Health Utilities Index 3 (HUI 3)** | 1 | Canada |
| **Life Satisfaction Index Z** | 1 | China |
| **Mental Health Index (MHI-5)** | 1 | USA |
| **Modified Version of SF-36** | 1 | India |
| **Modified St. Georges Respiratory Questionnaire** | 1 | Indonesia |
| **Present State Examination (PSE)** | 1 | Nigeria |
| **Rosenberg Self-Esteem Scale (RSE)** | 1 | South Africa |

| | | |
|---|---|---|
| **Self-Rating Anxiety Scale (SAS)** | 1 | China |
| **Sheehan Disability Scale (SDS)** | 1 | China |
| **Social Support Rating Scale (SSRS)** | 1 | China |
| **Symptoms Check List (SCL-90)** | 1 | China |
| **Voice Handicap Index-10 (VHI-10)** | 1 | Turkey |
| **Quality of Life Questionnaire (QLQ)** | 1 | Turkey |
| **Short-Form 8 (SF-8)** | 1 | Philippines |
| **Medical Research Council (MRC) dyspnea scale** | 1 | Philippines |
| **Primary Care PTSD screen** | 1 | South Africa |
| **World Health Organization´s Quality of Life - HIV (WHOQOL-HIV)** | 1 | Ethiopia |
| **The Functional Assessment of Chronic Illness Therapy-Tuberculosis (FACIT-TB)** | 1 | Iraq |
| **Illness Perception Questionnaire (IPQ)** | 1 | Pakistan |
| **Patient Health Questionnaire (PHQ-9)** | 1 | Nigeria |

**Table 3:** Adherence measures identified and extracted from published studies included

| PRO measures applied in adherence assessment | Number of studies | Country |
|---|---|---|
| **Morisky Medication Adherence Scale (MMAS)** | 2 | South Africa |
| **Perceived Nonadherence Scale (ACTG)** | 1 | South Africa |
| **TB medication adherence scale (TBMAS)** | 1 | China |

**Table 4:** presents 17 instruments for HRQOL assessment in the indications pulmonary, respiratory and psychological diseases and linguistically validated for English in South Africa, accessed from PROQOLID database.

| PRO HRQOL measures | Pathology/Disease |
|---|---|
| Baseline and Transition Dyspnea Indexes (BDI-TDI) | Pulmonary Disease, Chronic Obstructive ,Respiratory Tract Diseases |
| Clinical COPD Questionnaire (CCQ) | Pulmonary Disease, Chronic Obstructive ,Respiratory Tract Diseases |
| Chronic Respiratory Disease Questionnaire Self-Administered Standardized (CRQ-SAS) | Pulmonary Disease, Chronic Obstructive ,Respiratory Tract Diseases |
| Inhaled Corticosteroid Questionnaire (ICQ) | Pulmonary Disease, Chronic Obstructive ,Respiratory Tract Diseases |

| | |
|---|---|
| St George's Respiratory Questionnaire (SGRQ) | Pulmonary Disease, Chronic Obstructive ,Respiratory Tract Diseases |
| Asthma Control Diary (ACD) | Respiratory Tract Diseases |
| Asthma Control Questionnaire (ACQ) | Respiratory Tract Diseases |
| Asthma Control Test (ACT) | Respiratory Tract Diseases |
| Asthma Quality of Life Questionnaire (AQLQ) | Respiratory Tract Diseases |
| Community-Acquired Pneumonia Symptom questionnaire (CAP-Sym) | Respiratory Tract Diseases |
| EORTC Quality of Life Questionnaire - Lung Cancer Module (EORTC-QLQ LC13) | Respiratory Tract Diseases |
| Geriatric Depression Scale (GDS) | Psychiatry/Psychology |
| Hospital Anxiety and Depression scale (HADS) | Psychiatry/Psychology |
| Inventory of Depressive Symptomatology (IDS-SR and IDS-C) | Psychiatry/Psychology |
| Montgomery-Asberg Depression Rating Scale (MADRS) | Psychiatry/Psychology |
| Quick Inventory of Depressive Symptomatology (QIDS-SR and QIDS-C) | Psychiatry/Psychology |
| Quality of Life in Depression Scale (QLDS) | Psychiatry/Psychology |

## Description of Selected HRQOL and Adherence PROMs

The following section provides a description of the PROMs applied to evaluate HRQOL and medication adherence in TB. Information was derived from PROQOLID database (PROQOLID) for EQ-5D, SF-12v2, SGRQ and HADS and from the developer of MMAS Prof Morisky for the MMAS instrument.

### EQ-5D-5L (provided through EuroQol)

EQ-5D (Euroqol) assesses health outcomes and is widely used as a utility index for estimating QALYs in cost-effectiveness studies. EQ-5D comprises 5 domains/items

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression

and one vertical visual analogue scale (VAS 20 cm). Each item allows five levels of severity of response ranging from 'no problems' to´ extreme problems'. Higher scores indicate better HRQOL. The VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. This information is used as quantitative measure of health as

judged by the individual respondents. Index-based values (utilities) are calculated from EQ-5D-5L by deriving values from country-specific value sets. Such value-sets for EQ-5D-5L are currently under development. A crosswalk between the 5L and 3L of EQ-5D is available for 10 countries, including Zimbabwe as only African country. Value sets for South Africa are not available for any version of EQ-5D. The completion time for EQ-5D takes a few minutes. Reliability, validity and ability to detect change are approved (PROQOLID) A minimal important difference (MID) for EQ-5D-3L is approved with Mean MID = 0.074 (range -0.011 - 0.140) and MID = 7 for VAS scores (Walters, 2005).

### Short-Form 12 (SF-12) (Author Ware John E, provided through Quality Metrics)

SF-12 is an abbreviated version of SF-36 containing 12 items over 8 domains:

- Physical functioning (PF) with 2 items
- Role physical (RP) with 2 items
- Bodily pain (BP) with 1 item
- General health (GH) with 1 item
- Vitality (VT) with 1 item
- Social functioning (SF) with 1 item
- Role emotional (RE) with 2 items
- Mental health (MH) with 2 items

Domains can be aggregated into composite summary scores for physical and mental state, referred to as Physical Component Score (PCS-12) and Mental Component Sore (MCS-12). PCS-12 includes PF, RP, BP, and GH domains, MCS-12 include VT, SF, RE and MH domains. Scoring ranges from 0 to 100; greater scores represent better HRQOL. The completion time for SF-12v2 is 2 minutes. Reliability, validity and ability to detect change are approved (PROQOLID). A minimal important difference for SF-12v2 is not defined; however a minimum meaningful difference for SF-36 is mentioned as > 3 point change (Maruish, 2009). SF-36 and SF-12v2 are comparable in their outcomes and a minimum meaningful difference of > 3 points can be considered for SF-12v2 (Maruish ME, 2009).

### St. George´s Respiratory Questionnaire (SGRQ) (Author Jones Paul W, provided through The St. George's University of London Medical School)

A disease-specific instrument designed to assess patients with respiratory tract diseases and immune system diseases, especially asthma, pulmonary diseases, and chronic obstructive disease. SGRQ comprises 50 items over 3 domains (symptoms, activity, and impacts on daily

life) over two parts. Part I covers symptoms (several scales) and Part II covers activity and impacts on daily life (dichotomous true/false) except the last question (4-point Likert scale). The Symptom Component Score is calculated from questions 1-8, the Activity Component Score is calculated from questions 11 and 15, and the Impacts Component Score is calculated from questions 9-10, 12-14, and 16-17. Scores are scaled from 0 to 100, with higher scores indicating worse HRQOL. The completion time for SGRQ is 10 minutes. Reliability, validity and ability to detect change are approved (PROQOLID). A minimal important difference (MID) for SGRQ is defined as improvement of 4 points on the separate domains and the total score (Jones, 2005).

### Hospital Anxiety and Depression Scale (HADS) (Authors Snaith RP and Zigmond AS, provided through GL Assessment)

HADS is an instrument applied in psychology/psychiatry to detect states of anxiety and depression. HADS comprises 14 items over 2 dimensions

- Anxiety with 7 items
- Depression with 7 items

Scores for each item range from 0 to 3, with higher scores indicating worse HRQOL (i.e. more anxiety and depression). The anxiety subscale scoring ranges from 0-21 (8-10 mild anxiety, 11-14 moderate anxiety, 15-21 severe anxiety). The completion time for HADS is 2-5 minutes. Reliability, validity and ability to detect change are approved (PROQOLID). A minimal important difference (MID) for HADS has not been evaluated. A MID was observed for COPD with a value of 1.5 points corresponding to a change from baseline of 20% and informed by both anchor- and distribution-based methods (Puhan et al., 2008).

### Morisky Medication Adherence Scale (MMAS-8) (Author Morisky DE)

MMAS-8 is being used in the assessment of self-reported medication taking behaviour (Krousel-Wood, 2009, Morisky and DiMatteo, 2011, Morisky, 2008a). The scale is a generic measure assessing long-term chronic and infectious medical regimens, such as high blood pressure, diabetes, tuberculosis, HIV, elevated serum lipids, osteoporosis, immuno-suppressant medication. It is a reliable and valid indicator to assess self-reported medication-taking behaviour, including several levels of criterion related validity (blood pressure control, HgA1c) discriminant validity (social desirability) and persistence using pharmacy fills as a criterion. MMAS has a high sensitivity of 93% to identify low adherence and is a simple scale

to identify and monitor adherence (Morisky, 2008b). The MMAS-8 scale ranges from 0 to 8.0; total scores are interpreted in the following way:

- Low adherence <6.0
- Medium adherence 6.0 – 8.0
- High adherence =8.0

# Standard Operating Procedure (SOP) for application of questionnaires evaluating the health-related quality of life and medication adherence in pulmonary tuberculosis

## 1. Purpose and Scope

- The present SOP provides an overview of the procedures that take place during application of questionnaires evaluating the health-related quality of life (HRQOL) and medication adherence in patients newly diagnosed with pulmonary tuberculosis. The SOP refers to the research study entitled *health-related quality of life and its association to medication adherence in pulmonary tuberculosis in South Africa – an integrated patient-centred outcomes approach* (protocol version 1.4/25.08.2014).
- The applied questionnaires are objective means of collecting information about TB patient´s HRQOL and medication adherence behavior. In the present research study they are used as independent research instruments.
- There are no strict reporting criteria for questionnaire-based research projects, when compared with the conduct of randomized trials. In order, therefore, to prevent methodological errors and to promote the collection of high quality data a process should be followed to ensure that questionnaire-based research and data collection is well-designed, well-managed, non-discriminatory and reduces potential bias, with a view to contributing to a generalizable evidence base.
- This SOP is relevant for all research team members involved in the data collection process and application of questionnaires evaluating HRQOL and medication adherence in pulmonary TB patients. It is important that all study personnel fully understand and comply with this SOP.

## 2. Definitions

This section provides a short explanation of terminology used in this SOP.

| Terminology | Explanation |
|---|---|
| **Face-to-face administration** | In-person administration of a questionnaire by a trained interviewer |
| **Health-related quality of life** | The value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by |

| | |
|---|---|
| | disease, injury, treatment, or policy. Measurement of health-related quality of life addresses the various dimensions of health and well-being |
| **Measure** | Questionnaires designed for use with a particular patient group |
| **Medication adherence** | Patient behaviour with regard to the prescribed interval, dose, and dosing regimen as well as quality of how medication is taken and is expressed as percentage of total number of doses taken or therapy days available |
| **Patient-reported outcome** | Any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else |
| **Self-administered** | Respondents read and answer the questions by themselves, without assistance. The respondent completes the questionnaire herself or himself according to written or oral instructions |

## 3. Abbreviations

HRQOL Health-related quality of life
PRO patient-reported outcome
TB Tuberculosis

## 4. Roles and Responsibilities

- This SOP applies to research team members of the present research study, who are involved in the data collection process including the application of questionnaires evaluating HRQOL and medication adherence
- Research team members directly involved in the data collection process comprise:
    - Main researcher
    - Principal investigators (research supervisors)
    - Research assistant
    - Assisting field worker

## 5. Data Protection and Confidentiality

- The collection and processing of personal or sensitive data is governed by local law of South Africa
- In the majority of cases where sensitive personal data are being collected, explicit consent is necessary. For consent to be explicit, individuals must have a full understanding of what their data will be used for and they must 'opt□in.' A patient information and informed consent document is handed out to the patient and the informed consent has to be signed after agreement to participate. The patientinformation remains with the patient; the signed informed consent is collected and remains with the research team
- Personally sensitive data include, but are not limited to, socio-demographic data, physical and mental health, social behaviour, and clinical data in the context to

anti-TB drug treatment monitoring

- Personally sensitive data are protected by anonymization of each patient participating. A unique identifier code is assigned by the investigator to each study participant. This subject identification (SID) code protects the subject's identity and confidentiality in the research file. SID is used in lieu of the subject's name on all research documents that go to the sponsor or outside of the institution where the patient is treated
- The subject identification (SID) code is additionally collected on a subject identification code list. The SID code list exists for each study site facility and comprises the SID code for each patient enrolled into the study at the specific study site and links the patient SID code to the medical record number of the patient at the clinic. Since one research team member is dedicated to one health facility, the SID code list per clinic remains with the respective research team member during the time of recruitment. After recruitment the SID code list is handed over to the main researcher. During recruitment the field worker has to show the SID code list to the main researcher or to the research assistant on a weekly basis.

## 6. Questionnaires and Study Material

The questionnaires applied in the present research study comprise

- Four different HRQOL measures:
  - Short Form 12 (SF-12)
  - EuroQol 5 Dimensions (EQ-5D-5L)
  - St. George´s Respiratory Questionnaire (SGRQ)
  - Hospital Anxiety and Depression Scale (HADS)
- One adherence medication measure:
  - Morisky Medication Adherence Scale 8 items (MMAS-8)
- One questionnaire for assessing socio-demographic characteristics

All questionnaires are PRO measures which are paper-based and self-administered, thereby providing subjective information from the patient directly. All questionnaires are closed which means each item is answered by ticking the most applicable predetermined answer.

Further study material comprises

- Patient Information and Informed Consent
- Subject Identification Code List
- Monitoring Sheet

The patient information is a document that explains the study research in a more common language. This document is designed for the patient to take it home for his or her reference. The informed consent is a one-pager available in English and Xhosa and has to be signed by the patient if he or she confirms to participate in the study. The informed consent has to be collected and handed over to the main researcher or principal investigator. The monitoring sheet is a one-pager assigned for each participating patient. This sheet is a constant part of the patient research folder and is used for every visit you interact with the patient. The monitoring sheet contains information about facility name and study site log number, patient code (SID code), patient study group, treatment start, expected follow-up visits (based on treatment start), and sputum smear results at all visits where questionnaires are applied.

## 7. Procedures

### 7.1 Eligible participants

- The purpose of application of questionnaires is to evaluate the HRQOL and medication adherence of pulmonary TB patients during anti-TB treatment comprising four different antibiotic drugs over 6 month.
- Patients eligible for the research study are older than 18 years, are newly diagnosed with pulmonary TB and will start standard drug treatment for their first time; and who have no HIV co-infection and no multi-drug resistant (MDR) TB.
- Eligible patients belong either to a group of patients receiving complete treatment under supervision in the health clinic – thereafter called" clinic group"; or eligible patients belong to a group of patients receiving their treatment in their community and visiting the health clinic on predefined visits for diagnostic monitoring and drug collection – thereafter called "community group"
- All eligible patients participating (clinic group and community group) fill out four different HRQOL questionnaires and one socio-demographic questionnaire at baseline (visit 0)
- All eligible patients participating (clinic group and community group) fill out four different HRQOL questionnaires and one medication adherence questionnaire at visit 1 (after 4 weeks of treatment), visit 2 (after 8 weeks of treatment and changing from intensive to continuous phase), visit 3 (after 16 weeks of treatment), and visit 4 (after 24 weeks treatment and end of treatment).

## 7.2 Data collection process

- Data collection comprises a time frame of 6 month of anti-TB drug treatment comprising four different antibiotics for each eligible participant, starting with treatment start, thereafter called baseline, and finalizing with end of treatment
- Data are collected at five different time points (baseline, visits 1,2,3,4) for eligible participants from the clinic group and at a minimum of three different time points (baseline, visit 2, visit 4) from eligible participants from the community group
- The five data collection points are defined as in the following table:

| Data Collection Time Point | Description |
|---|---|
| **Visit 0** | begin of treatment which is start of the intensive phase and baseline (BL) |
| **Visit 1** | after 1 month of treatment and middle of the intensive phase |
| **Visit 2** | after 2 month of treatment and switch from intensive to continuation phase |
| **Visit 3** | after 4 month of treatment which is in the middle of the continuation phase |
| **Visit 4** | after 6 month of treatment which is end of treatment (EOT) |

- At baseline socio-demographic characteristics are collected
- At baseline and at visits 1, 2, 3, and 4 HRQOL data are collected
- At visit 2 (change from intensive to continuous phase) and visit 4 (end of treatment) medication adherence data are collected
- The administration of all questionnaires for data collection is assigned to pre- determined research team members

Data collection at baseline has a time window of three days, meaning data can be collected within first three days of treatment start. All follow-up visits have a time window of one week.

## 7.3 Data Collection and Questionnaire Administration

### Step-wise process at Baseline:

Step 1: A nurse informs you via SMS or by calling that the clinic has identified an eligible patient; the nurse provides you with the date the respective patient is visiting the clinic. You have to be at the clinic at the same date.

Step 2: A nurse refers you to the eligible patient. Before you talk to the patient, ask

the nurse to hand out a safety mask for you. You have to wear a safety mask all the time you talk to patients for your own health safety.

Step 3: Introduce the study to the eligible patient by using the patient information document; mention that participants are receiving a token in form of a voucher from us after completion of each visit. After he or she has confirmed to participate in the study, hand out the patient information to the patient for their reference.

Step 4: Get the informed consent form signed by the patient and collect the informed consent for our reference.

Step 5: Use the SID code list (a separate document) and write down a patient unique SID code; the SID coding for patients is linked to the study site log number. Study site log numbers are the following:

| Study Site Log Number | Study Site Name |
|---|---|
| **1-HRQOLTB** | Khayelitsha Site B |
| **2-HRQOLTB** | Michael Mapongwana Hospital |
| **3-HRQOLTB** | Town 2 Clinic |
| **4-HRQOLTB** | Kuyasa Clinic |
| **5-HRQOLTB** | Matthew Goniwe Clinic |
| **6-HRQOLTB** | Nolungile Clinic |

The unique patient SID code is composed of the study site log number plus a consecutive numbering; the following is an example of a consecutive numbering for Khayelitsha site B:

1-HRQOLTB_001
1-HRQOLTB_002
1-HRQOLTB_003

Step 6: Use the SID code list to write down the medical record number of the patient which the study site has assigned to the patient in the TB registry book.

Step 7: Use the monitoring sheet (a separate document) to write down

- Facility name and study site log number
- Patient code (SID code)

- Patient study group (clinic group or community group)
- Date of treatment start
- Confirm if participant has received a voucher after questionnaire completion or not with YES or NO
- Sputum smear result at baseline/treatment start

Ask the nurse to provide you with the date of treatment start which is written down in the TB registry book and with the sputum smear result before treatment.

Step 8: Start with the baseline interviews by applying the document "Questionnaires at baseline". Apply the questionnaires to the patient while he or she is waiting for seeing the doctor and /or waiting for treatment/diagnostic results.

The questionnaires are originally designed for self-administration and the patient should complete the questionnaires without the help of others (e.g. site staff, family, friends, etc.). If the patient is not illiterate the patient should has the choice of completing the questionnaires by their own.

The *only* exception: if the patient is blind or illiterate the questionnaires may be read to the patient verbatim, but the reader must not aid in the interpretation of questions or in the selection of answers.

All questionnaires should be completed before any other site activities, i.e. before seeing the physician, any tests or treatment, receive results of tests, etc.

Step 9: Explain shortly the significance and relevance of the questionnaires to the participant; remind participants that we are asking them to complete these questionnaires because we are interested in hearing directly from them how they are doing; this will help motivate participants to comply with data collection.

Step 10: If the patient self-completes the questionnaires make sure the patient understands how to fill out the questionnaires and make sure they can be completed in privacy. Inform the patient that the information is confidential.

Step 11: The person responsible for questionnaires (assigned research team members) should retrieve the completed forms. Check that all questions have been answered and that only one answer is recorded for each question.

If a participant has questions or is unable to complete the questionnaires by himself/ herself:

- Remind him/her there are no right or wrong answers
- Remind him/her to choose the answer that most reflects what is true for them
- Do NOT reword, interpret or paraphrase questions or response options
- Do NOT suggest answers or help a patient select an answer under any circumstances

### Step-wise process for follow-up visits:

Step 1: Use the monitoring sheet (a separate document) to write down:

- Visit date according to clinic or community group
- Confirm if participant has received a voucher after questionnaire completion or not with YES or NO
- Sputum smear result according to the visit date

Step 2: Apply the questionnaires to the patient while he or she is waiting for seeing the doctor and /or waiting for treatment/diagnostic results.

The questionnaires are originally designed for self-administration and the patient should complete the questionnaires without the help of others (e.g. site staff, family, friends, etc.). If the patient is not illiterate the patient should has the choice of completing the questionnaires by their own.

The *only* exception: if the patient is blind or illiterate the questionnaires may be read to the patient verbatim, but the reader must not aid in the interpretation of questions or in the selection of answers.

All questionnaires should be completed before any other site activities, i.e. before seeing the physician, any tests or treatment, receive results of tests, etc.

Step 3: Explain shortly the significance and relevance of the questionnaires to the participant; remind participants that we are asking them to complete these questionnaires because we are interested in hearing directly from them how they are doing; this will help motivate participants to comply with data collection.

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and that only one answer is recorded for each question.

If a participant has questions or is unable to complete the questionnaires by himself/ herself:

- Remind him/her there are no right or wrong answers
- Remind him/her to choose the answer that most reflects what is true for them
- Do NOT reword, interpret or paraphrase questions or response options
- Do NOT suggest answers or help a patient select an answer under any circumstances

## 7.4 Missing Data

- Quickly review the completed questionnaires to look for missing or multiple responses to a question
- Patients should be approached as quickly as possible if any responses are missing or are marked incorrectly and asked to complete all questions and/or clarify responses where more than one response has been given
- PRO data cannot be queried at a later date
- Missing questionnaires and missing questions should be minimized as much as possible
- If there is much missing data we will not be able to meaningfully interpret the PRO data

## 8. Related Documents

- PhD proposal version 1.4/25.08.2014
- Questionnaires version 1.2/15.08.2014
- Patient Information and Informed Consent version 1.2/11.08.2014
- Monitoring Sheet version 1.0/15.10.2014
- Subject Identification Code List version 1.0/15.10.2014

## Supplementary material to chapters 5, 6, and 7

### Patient-reported outcome (PRO)

### measures SF-12

**This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.** ***Thank you for completing this survey!***

**For each of the following questions, please mark an ☒ in the one box that best describes your answer.**

1. **In general, would you say your health is:**

| Excellent | Very good | Good | Fair | Poor |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

2. **The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?**

| | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---|---|---|
| a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐ 1 | ☐ 2 | ☐ 3 |
| b. Climbing several flights of stairs | ☐ 1 | ☐ 2 | ☐ 3 |

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b. Were limited in the kind of work or other activities | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Accomplished less than you would like | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b. Did work or other activities less carefully than usual | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

| Not at all | A little bit | Moderately | Quite a bit | Extremely |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

| | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|---|
| a. Have you felt calm and peaceful? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| b. Have you had a lot of energy? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |
| c. Have you felt downhearted and depressed? | ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

| All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|---|---|---|---|---|
| ☐ 1 | ☐ 2 | ☐ 3 | ☐ 4 | ☐ 5 |

*Thank you for completing these questions!*

## EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

I have no problems in walking about

I have slight problems in walking about

I have moderate problems in walking about

I have severe problems in walking about

I am unable to walk about

**SELF-CARE**

I have no problems washing or dressing myself

I have slight problems washing or dressing myself

I have moderate problems washing or dressing myself

I have severe problems washing or dressing myself

I am unable to wash or dress myself

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities

I have slight problems doing my usual activities

I have moderate problems doing my usual activities

I have severe problems doing my usual activities

I am unable to do my usual activities

**PAIN / DISCOMFORT**

I have no pain or discomfort

I have slight pain or discomfort

I have moderate pain or discomfort

I have severe pain or discomfort

I have extreme pain or discomfort

**ANXIETY / DEPRESSION**

I am not anxious or depressed

I am slightly anxious or depressed

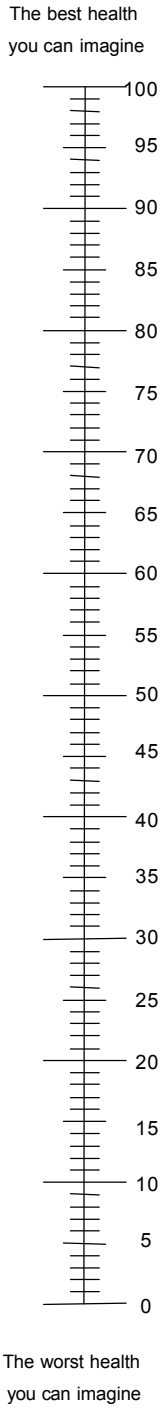
I am moderately anxious or depressed

I am severely anxious or depressed

I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



# St. George´s Respiratory Questionnaire (SGRQ)

## ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)
## ENGLISH FOR SOUTH AFRICA

*This questionnaire is designed to help us learn more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.*

*Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.*

*Before completing the rest of the questionnaire:*

*Please tick (✓) one box to show how you describe your current health:*

| Very good | Good | Fair | Poor | Very poor |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |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# St. George's Respiratory Questionnaire
## PART 1

***Questions about how much chest trouble you have had during the past 3 months.***

Please tick (✓) *one box for each question*:

| | | most days a week | several days a week | a few days a month | only with chest infections | not at all |
|---|---|---|---|---|---|---|
| 1. | During the past 3 months, I have coughed: | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | During the past 3 months, I have coughed up phlegm (sputum): | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | During the past 3 months, I have had shortness of breath: | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | During the past 3 months, I have had attacks of wheezing: | ☐ | ☐ | ☐ | ☐ | ☐ |

5. During the past 3 months, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
*(Go to question 7 if you had no severe attacks)*

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. During the past 3 months, in an average week, how many good days, (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse when you get up in the morning?

Please tick (✓) *one*:

- No ☐
- Yes ☐

# St. George's Respiratory Questionnaire
## PART 2

**Section 1**

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment:

Please tick (✓) *one*:

- My chest trouble made me stop work completely ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

**Section 2**

***Questions about what activities usually make you feel breathless <u>these days</u>.***

| Please tick (✓) ***each box*** that applies to you ***these days***: | True | False |
|---|---|---|
| Sitting or lying still | ☐ | ☐ |
| Getting washed or dressed | ☐ | ☐ |
| Walking around the home | ☐ | ☐ |
| Walking outside on level ground | ☐ | ☐ |
| Walking up a flight of stairs | ☐ | ☐ |
| Walking up hills | ☐ | ☐ |
| Playing sports | ☐ | ☐ |

## St. George's Respiratory Questionnaire
### PART 2

**Section 3**

***Some more questions about your cough and breathlessness <u>these days</u>.***

| | Please tick (✓) ***each box*** that applies to you ***these days***: True | False |
|---|---|---|
| My cough hurts | ☐ | ☐ |
| My cough makes me tired | ☐ | ☐ |
| I am breathless when I talk | ☐ | ☐ |
| I am breathless when I bend over | ☐ | ☐ |
| My cough or breathing disturbs my sleep | ☐ | ☐ |
| I get exhausted easily | ☐ | ☐ |

**Section 4**

***Questions about other effects that your chest trouble may have on you <u>these days</u>.***

| | Please tick (✓) ***each box*** that applies to you ***these days***: True | False |
|---|---|---|
| My cough or breathing is embarrassing in public | ☐ | ☐ |
| My chest trouble is a nuisance to my family, friends or neighbours | ☐ | ☐ |
| I get afraid or panic when I cannot get my breath | ☐ | ☐ |
| I feel that I am not in control of my chest problem | ☐ | ☐ |
| I do not expect my chest to get any better | ☐ | ☐ |
| I have become frail or an invalid because of my chest | ☐ | ☐ |
| Exercise is not safe for me | ☐ | ☐ |
| Everything seems too much of an effort | ☐ | ☐ |

**Section 5**

***Questions about your medication:***
***If you are receiving no medication go straight to section 6.***

| | Please tick (✓) ***each box*** that applies to you ***these days***: True | False |
|---|---|---|
| My medication does not help me very much | ☐ | ☐ |
| I get embarrassed using my medication in public | ☐ | ☐ |
| I have unpleasant side effects from my medication | ☐ | ☐ |
| My medication interferes with my life a lot | ☐ | ☐ |

# St. George's Respiratory Questionnaire
## PART 2

**Section 6**

***These are questions about how your activities might be affected by your breathing.***

Please tick (✓) ***each box*** that applies to you ***because of your breathing***:

| | True | False |
|---|---|---|
| I take a long time to get washed or dressed | ☐ | ☐ |
| I cannot take a bath or shower, or I take a long time | ☐ | ☐ |
| I walk slower than other people, or I stop for rests | ☐ | ☐ |
| Jobs such as housework take a long time, or I have to stop for rests | ☐ | ☐ |
| If I walk up one flight of stairs, I have to go slowly or stop | ☐ | ☐ |
| If I hurry or walk fast, I have to stop or slow down | ☐ | ☐ |
| My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, play bowls or play golf | ☐ | ☐ |
| My breathing makes it difficult to do things such as carry heavy loads, dig in the garden, jog or walk (8 km/hour), play tennis or swim | ☐ | ☐ |
| My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports | ☐ | ☐ |

**Section 7**

***We would like to know how your chest <u>usually</u> affects your daily life.***

Please tick (✓) ***each box*** that applies to you ***because of your chest trouble***:

| | True | False |
|---|---|---|
| I cannot play sports or games | ☐ | ☐ |
| I cannot go out for entertainment or recreation | ☐ | ☐ |
| I cannot go out of the house to do the shopping | ☐ | ☐ |
| I cannot do housework | ☐ | ☐ |
| I cannot move far from my bed or chair | ☐ | ☐ |

# St. George's Respiratory Questionnaire

*Here i.s a list of other ac6vities that your chest trouble may prevent you doing. (You do not have to* tick (V) *these, they areju.st toremind you of ways in which your breathlessness may affect you):*

Goingfor v1Slks or wsl}(ingthe dog

Doing things at home or inthe garden

Sexual infercoorse

Going out to ctiurch.pub,club or place of entertainment

Going outin bad weather or WIto smoky rooms

Vsiting family or fiends or playing with chtdren

Please write down any otherimportant acti'vities that yow chesttrouble may stop you doing:

Please tick {"') only one box which you think best describes how your chest affects you:

| | |
|---|---|
| t does not stop *me* doing anything I would like to do | D |
| It stops m-e doing one or two things I would like to do | D |
| f stops *me* doing most of the things I YOuld ke to do | D tt |
| stops me doing everything I YOuld ke to do | D |

Thank *you for completing this questionnaire. Before you* finish *VtOUld you please check to see that you have answered all the* ques6cns.

## Hospital Anxiety and Depression Scale (HADS)

A D

**I feel tense or 'wound up'**
- [3] Most of the time
- [2] A lot of the time
- [1] From time to time, occasionally
- [0] Not at all

**I still enjoy the things I used to enjoy**
- [0] Definitely as much
- [1] Not quite so much
- [2] Only a little
- [3] Hardly at all

**I get a sort of frightened feeling as if something awful is about to happen**
- [3] Very definitely and quite badly
- [2] Yes, but not too badly
- [1] A little, but it doesn't worry me
- [0] Not at all

**I can laugh and see the funny side of things**
- [0] As much as I always could
- [1] Not quite so much now
- [2] Definitely not so much now
- [3] Not at all

**Worrying thoughts go through my mind**
- [3] A great deal of the time
- [2] A lot of the time
- [1] Not too often
- [0] Very little

**I feel cheerful**
- [3] Never
- [2] Not often
- [1] Sometimes
- [0] Most of the time

**I can sit at ease and feel relaxed**
- [0] Definitely
- [1] Usually
- [2] Not often
- [3] Not at all

**I feel as if I am slowed down**
- [3] Nearly all the time
- [2] Very often
- [1] Sometimes
- [0] Not at all

**I get a sort of frightened feeling like 'butterflies' in the stomach**
- [0] Not at all
- [1] Occasionally
- [2] Quite often
- [3] Very often

**I have lost interest in my appearance**
- [3] Definitely
- [2] I don't take as much care as I should
- [1] I may not take quite as much care
- [0] I take just as much care as ever

**I feel restless as if I have to be on the move**
- [3] Very much indeed
- [2] Quite a lot
- [1] Not very much
- [0] Not at all

**I look forward with enjoyment to things**
- [0] As much as I ever did
- [1] Rather less than I used to
- [2] Definitely less than I used to
- [3] Hardly at all

**I get sudden feelings of panic**
- [3] Very often indeed
- [2] Quite often
- [1] Not very often
- [0] Not at all

**I can enjoy a good book or radio or television programme**
- [0] Often
- [1] Sometimes
- [2] Not often
- [3] Very seldom

**Now check that you have answered all the questions**

A D

**This form is printed in green. Any other colour is an unauthorized photocopy.** TOTAL


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## Morisky Medication Adherence Scale (MMAS-8)

| **You indicated that you are taking medication for your (identify health concern, such as "high blood pressure"). Individuals have identified several issues regarding their medication-taking behavior and we are interested in your experiences. There is no right or wrong answer. Please answer each question based on your personal experience with your [health concern] medication.** | | |
|---|---|---|
| **(Please check your response below)** | | |
| | **No=1** | **Yes=0** |
| 1. Do you sometimes forget to take your tuberculosis pills? | | |
| 2. People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past two weeks, were there any days when you did not take your tuberculosis medicine? | | |
| 3. Have you ever cut back or stopped taking your medication without telling your doctor, because you felt worse when you took it? | | |
| 4. When you travel or leave home, do you sometimes forget to bring along your tuberculosis medication? | | |
| 5. Did you take your tuberculosis medicine yesterday? | | |
| 6. When you feel like your tuberculosis is under control, do you sometimes stop taking your medicine? | | |
| 7. Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your tuberculosis treatment plan? | | |

8. How often do you have difficulty remembering to take all your medications?

(**Please circle your response below)**

Never/Rarely…… **... 4**

Once in a

while……**3**

Sometimes…… **... 2**

Usually……**1**

All the

time……..**0**

### Coding Instructions for the ©Morisky Medication Adherence Scale (8-Item)

You will need to reverse the code response in a positive direction for item number 5 and standardize the code for item 8 (0-4), resulting in a scale from low adherence to high adherence. Item 8 is divided by 4 when calculating a summated score. This procedure standardizes the 5-point Likert scale. The total scale has a range of 0 to 8.0. The

eight-item compliance scale had an alpha reliability of 0.83 (n= 1367) among patients diagnosed with essential hypertension attending an outpatient clinic of a large teaching hospital. We have used a 75% completion criterion for establishing eligibility. The median value of all missing items would be substituted for the missing item for individuals meeting the eligibility criterion.

**Re-codes:**

**If Item5 = 0 Item5r = 1 (high adherence)**

**If Item8=4 Item8r = 1 (highest adherence)**

**If Item8=3 Item8r = .75 (high adherence)**

**If Item8=2 Item8r = .50 (moderate adherence)**

**If Item8=1 Item8r = .25 (low adherence)**

**If Item8=0 Item8r = 0 (lowest adherence)**

| **Adherence Level** | **Percent** |
|---|---|
| Low Adherence (< 6) | 32.1 |
| Medium Adherence (6 to <8) | 52.0 |
| High Adherence (= 8) | 15.9 |

# Supplementary material chapter 6

**S1 Table.** Changes in HRQOL in the intensive and continuous treatment phase**.**

| HRQOL | Treatment Phase | N (pairwise) | Change in mean | P value |
|---|---|---|---|---|
| **PCS-12** | Intensive phase | 83 | 11.785 | < 0.05 |
| | Continuous phase | 65 | 7.991 | < 0.05 |
| **MCS-12** | Intensive phase | 83 | 17.708 | < 0.05 |
| | Continuous phase | 67 | 6.644 | < 0.05 |
| **EQ-5D total index UK** | Intensive phase | 84 | 0.365 | < 0.05 |
| | Continuous phase | 67 | 0.152 | < 0.05 |
| **EQ-5D total index Zimbabwe** | Intensive phase | 84 | 0.213 | < 0.05 |
| | Continuous phase | 67 | 0.083 | < 0.05 |
| **EQ-5D VAS** | Intensive phase | 85 | 24.482 | < 0.05 |
| | Continuous phase | 69 | 18.681 | < 0.05 |
| **SGRQ Symptoms** | Intensive phase | 80 | 26.602 | < 0.05 |
| | Continuous phase | 68 | 11.505 | 0.002 |
| **SGRQ Activities** | Intensive phase | 84 | 46.481 | < 0.05 |
| | Continuous phase | 69 | 9.442 | 0.527 |
| **SGRQ Impacts** | Intensive phase | 84 | 46.953 | < 0.05 |
| | Continuous phase | 70 | 4.246 | 0.767 |
| **SGRQ total score** | Intensive phase | 81 | 32.070 | < 0.05 |
| | Continuous phase | 68 | 14.546 | 0.487 |
| **HADS Anxiety** | Intensive phase | 85 | 7.600 | < 0.05 |
| | Continuous phase | 68 | 3.82 | < 0.05 |
| **HADS Depression** | Intensive phase | 85 | 7.071 | < 0.05 |
| | Continuous phase | 68 | 4.779 | < 0.05 |

**S2 Table.** Overall treatment time effect on HRQOL (test of within-subjects effects).

| | | | | | Sensitivity Analysis baseline, 8 weeks and 24 weeks treatment | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **HRQOL** | **N** | **P < 0.05** | **Partial eta squared** | **Observed power** | **HRQOL** | **N** | **P < 0.05** | **Partial eta squared** | **Observed power** |
| **PCS-12** | 26 | <0.05 | 0.686 | 1.000 | PCS-12 | 65 | < 0.05 | 0.748 | 1.000 |
| **MCS-12** | 27 | <0.05 | 0.698 | 1.000 | MCS-12 | 67 | < 0.05 | 0.691 | 1.000 |
| **EQ5D total index UK** | 27 | <0.05 | 0.619 | 1.000 | EQ5D total index UK | 66 | < 0.05 | 0.621 | 1.000 |
| **EQ5D total index Zimbabwe** | 27 | <0.05 | 0.596 | 1.000 | EQ5D total index Zimbabwe | 66 | < 0.05 | 0.588 | 1.000 |
| **EQ5D VAS** | 28 | <0.05 | 0.845 | 1.000 | EQ5D VAS | 69 | < 0.05 | 0.808 | 1.000 |
| **SGRQ Symptoms** | 23 | <0.05 | 0.582 | 1.000 | SGRQ Symptoms | 65 | < 0.05 | 0.425 | 1.000 |
| **SGRQ Activities** | 28 | 0.286 | 0.043 | 0.192 | SGRQ Activities | 68 | 0.001 | 0.143 | 0.933 |
| **SGRQ Impacts** | 28 | 0.231 | 0.053 | 0.226 | SGRQ Impacts | 69 | 0.002 | 0.126 | 0.887 |
| **SGRQ total score** | 24 | 0.494 | 0.030 | 0.157 | SGRQ total score | 65 | 0.057 | 0.047 | 0.538 |
| **HADS Anxiety** | 27 | <0.05 | 0.653 | 1.000 | HADS Anxiety | 68 | <0.05 | 0.664 | 1.000 |
| **HADS Depression** | 27 | <0.05 | 0.604 | 1.000 | HADS Depression | 68 | <0.05 | 0.642 | 1.000 |
| Greenhouse-Geisser Test was applied as sphericity was not assumed (p < 0.05) | | | | | | | | | |

**S3 Table.** Effects of socio-demographic factors on overall HRQOL improvement.

| HRQOL | Source | Df | F | P value (*Sig < 0.05) | Partial eta squared |
|---|---|---|---|---|---|
| PCS-12 | PCS-12 x gender | 1.000 | 1.047 | 0.309 | 0.012 |
| | PCS-12 x Age Groups | 1.000 | 0.082 | 0.775 | 0.001 |
| | PCS-12 x Education | 1.000 | 6.632 | 0.012* | 0.074 |
| | PCS-12 x Work Status | 1.000 | 7.789 | 0.007* | 0.086 |
| MCS-12 | MCS-12 x gender | 1.000 | 1.949 | 0.166 | 0.022 |
| | MCS-12 x Age Groups | 1.000 | 0.000 | 0.999 | 0.000 |
| | MCS-12 x Education | 1.000 | 0.880 | 0.351 | 0.010 |
| | MCS-12 x Work Status | 1.000 | 1.341 | 0.250 | 0.015 |
| EQ5D total index UK | EQ5DindexUK x gender | 1.000 | 0.484 | 0.488 | 0.006 |
| | EQ5DindexUK x Age Grou ps | 1.000 | 1.537 | 0.219 | 0.018 |
| | EQ5DindexUK x Education | 1.000 | 7.071 | 0.009* | 0.078 |
| | EQ5DindexUK x Work Stat us | 1.000 | 7.799 | 0.006* | 0.085 |
| EQ5D total index Zimbabwe | EQ5DindexZim x gender | 1.000 | 0.263 | 0.609 | 0.003 |
| | EQ5DindexZim x Age Groups | 1.000 | 1.696 | 0.196 | 0.020 |
| | EQ5DindexZim x Educatior | 1.000 | 6.821 | 0.011* | 0.075 |
| | EQ5DindexZim x Work Sta tus | 1.000 | 7.438 | 0.008* | 0.081 |
| EQ5D VAS | EQ5D VAS x gender | 1.000 | 0.190 | 0.664 | 0.002 |
| | EQ5D VAS x Age Groups | 1.000 | 1.467 | 0.229 | 0.017 |
| | EQ5D VAS x Education | 1.000 | 3.098 | 0.082 | 0.034 |
| | EQ5D VAS x Work Status | 1.000 | 1.878 | 0.174 | 0.021 |
| SGRQ Symptoms | SGRQ Symptoms x gende r | 1.000 | 0.217 | 0.642 | 0.003 |
| | SGRQ Symptoms x Age G roups | 1.000 | 3.325 | 0.072 | 0.038 |
| | SGRQ Symptoms x Educa tion | 1.000 | 0.004 | 0.950 | 0.000 |
| | SGRQ Symptoms x Work Status | 1.000 | 7.654 | 0.007* | 0.083 |
| SGRQ Activities | SGRQ Activities x gender | 1.000 | 0.435 | 0.511 | 0.005 |
| | SGRQ Activities x Age Gro ups | 1.000 | 0.364 | 0.548 | 0.004 |
| | SGRQ Activities x Education | 1.000 | 1.929 | 0.169 | 0.022 |
| | SGRQ Activities x Work St atus | 1.000 | 0.202 | 0.655 | 0.002 |
| SGRQ Impacts | SGRQ Impacts x gender | 1.000 | 0.702 | 0.404 | 0.008 |
| | SGRQ Impacts x Age Grou ps | 1.000 | 0.462 | 0.498 | 0.005 |
| | SGRQ Impacts x Education | 1.000 | 1.889 | 0.173 | 0.021 |
| | SGRQ Impacts x Work Sta tus | 1.000 | 0.638 | 0.427 | 0.007 |
| SGRQ total score | SGRQ total score x gender | 1.000 | 0.669 | 0.416 | 0.008 |
| | SGRQ total score x Age Gr oups | 1.000 | 0.461 | 0.499 | 0.006 |
| | SGRQ total score x Educat ion | 1.000 | 2.271 | 0.136 | 0.027 |

| | | | | | |
|---|---|---|---|---|---|
| | SGRQ total score x Work Status | 1.000 | 0.280 | 0.598 | 0.003 |
| HADS Anxiety | HADS Anxiety x gender | 1.000 | 0.470 | 0.495 | 0.006 |
| | HADS Anxiety x Age Groups | 1.000 | 1.396 | 0.241 | 0.016 |
| | HADS Anxiety x Education | 1.000 | 3.881 | 0.052 | 0.044 |
| | HADS Anxiety x Work Status | 1.000 | 0.794 | 0.375 | 0.009 |
| HADS Depression | HADS Depression x gender | 1.000 | 0.302 | 0.584 | 0.004 |
| | HADS Depression x Age Groups | 1.000 | 3.499 | 0.065 | 0.040 |
| | HADS Depression x Education | 1.000 | 2.377 | 0.127 | 0.027 |
| | HADS Depression x Work Status | 1.000 | 0.321 | 0.572 | 0.004 |

# Curriculum Vitae

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## Personal Dates

Date of Birth: 1 February

1978 Nationality: German

## Profile

- Effective and positive team player and team coordinator with excellent professional knowledge of pharmaceutical industry-related and healthcare issues, characterized by trustworthiness and absolute reliability
- Successful attendee at training seminars on regular basis to maximise potential and increase already superb know-how
- Successful solution-finder through ability for precise analyses and quick comprehension, with consistent implementation
- Inter-disciplinary and conceptual worker with precise power of judgement
- Thoughtful, responsible, target-orientated and conscientiously actor and producer of high-quality work under pressure

## Key Competencies

- International Pharmacoeconomics, Health Economics & Outcomes Research
- Sales Management / Project Management / Business Development pharmaceutical industry
- Deep industry knowledge and broad experience of the international pharmaceutical industry
- Budget responsibility and Contract negotiations
- Competencies in qualitative & quantitative research methodologies
- Strong presentation and communication skills, in both industry and academia
- Advanced computer skills
- Language skills: German (native speaker), English (completely fluent, TOEFL 2000), Spanish (basic), Acient Greek (Graecum/qualification in acient Greek), Latin (Latinum/qualification in Latin)

## Work Experience

Since 01/2016 **Lecturer in the postgraduate programme International Pharmacoeconomics, Health Economics and Market Strategies for Healthcare Products (M.Sc.)**

Fresenius University of Applied Sciences, Idstein (Germany)

- Lecturer for the topics pharmacoeconomics and outcomes research

08/2014 – 12/2016 **PhD candidate Epidemiology and Public Health,**

Swiss Tropical and Public Health Institute, Basel (Switzerland)

- PhD research in collaboration with Swiss Tropical and Public Health Institute, European Center of Pharmaceutical Medicine University of Basel and Health Economics Unit at University of Cape Town
- Full-time PhD based on a three-years research grant
- Research project: Health-related Quality of Life and its Association with Medication Adherence in Pulmonary Tuberculosis in South Africa – an integrated Patient-Centred Outcomes Approach

*Motivation for change: professional continuation in International Pharmacoeconomics and Health Economics with focus on outcomes research in African Countries*

Since 11/2011 **Independent Consultant Healthcare**

Cape Town (South Africa) and Wiesbaden (Germany)

- Member of the organizing committee of the 3-day workshop "Pharmacoeconomics in South Africa: Now and the Future Value-Based Patient-Centred Healthcare in South Africa", Fundisa African Academy for Medicinal Development (Cape Town, South Africa)
- Development, structuring and professional writing of an African country report with health system focus for BroadReach Healthcare (Cape Town, South Africa) (2013)
- Supported Endeva UG (Berlin, Germany) in healthcare and pharmaceutical industry related questions, reviewer of the report and facilitator of the workshop "Bringing Medicines to low-income Markets" in cooperation with GIZ and BMZ (2011 and 2012)

04/2012 – 12/2013 **Manager Health Economics & Outcome Research (HEOR)**

Intendis / Bayer Healthcare, Berlin (Germany)

- Development of HEOR related strategy for all Bayer Dermatology projects (global development projects and life-cycle management projects)
- Planning, tracking and adjustment of health economic activities and study programs
- Preparation of global product value dossiers based on relevant clinical and economical evidence, literature research and relevant comparative benchmarks
- Steering of optimal global health economic planning and support of product launch sequence

*Motivation for change: professional continuation in International Pharmacoeconomics and Health Economics in an industry position*

09/2010 – 02/2011 **Independent Consultant Pharmaceutical Industry**

Cape Town (South Africa)

- Successful preparation of Fine Chemicals Corporation (Cape Town) for EU customer cGMP audits in cooperation with Midas Pharma (Ingelheim)

*Motivation for change: professional re-orientation, 1 year maternity and parental time*

10/2009 – 12/2010 **Lecturer in the postgraduate program "Bio- and Pharmaceutical Analysis" (M.Sc.)**

Fresenius University of Applied Sciences, Idstein (Germany)

- Creation and implementation of the Module "The Pharmaceutical Industry"

11/2008 – 08/2010 **Project Manager Formulation Development and Dossier Development**

Midas Pharma GmbH,Ingelheim (Germany)

- Creating new solutions for drug formulation and life cycle management questions on behalf of clients
- Successful acquisition of platform technology partners and new clients
- Sole responsibility for management of contract development and contract manufacturing projects of finished products including contract negotiations, technology transfer and budget responsibility
- Supervision and coordination of vertical integrated projects for innovative drug products starting from the API until the finished product (custom synthesis, business development, formulation development, contract manufacture)
- Co-Auditor cGMP and client visits worldwide

*Motivation of change: internal change from the operational to the strategic business unit within Midas Pharma to broaden and deepen experiences within the pharmaceutical value chain*

02/2006 – 11/2008 **Sales Manager New Chemical Entities (NCE)**

Midas Pharma GmbH, Ingelheim (Germany): independent marketing and distribution company, supports clients and manufacturing partners in all questions concerning Active Pharmaceutical Ingredients, Biosimilars, Custom Synthesis, Contract Manufacture, International Licensing, Pharmaceutical Dossiers, Regulatory Affairs and Self-Medication/OTC.

- Successful processing of customer- and supplier-related commercially and/or technical requests
- Principal Management
- Budget and sales responsibility
- Customer and supplier visits worldwide

*Motivation for change: attractive job offer through Midas Pharma which represented my professional objectives and future perspectives*

08/2005 – 11/2005 **Project Leader Diagnostic Development**

Diasys Diagnostic Systems, Holzheim (Germany): leading specialist in development and manufacturing of diagnostic system solutions of high quality combined with ease of use and reduced environmental burden

- Development of a diagnostic kit for calcium determination in human serum

*Motivation for change: research project-related work at Fresenius University of Applied Sciences was time limited as part of a*

*Professor sponsorship through STADA*

11/2004 – 07/2005 **Scientific Associate Department of Health Economics**

Fresenius University of Applied Sciences, Idstein (Germany): one of the largest and most renowned private educational institutions in Germany, with over 160 years of scientific experience in the educational sector.

- Organized and performed a scientific review (published) and presentation in collaboration with an international pharmaceutical company "Clinical efficacy and health economic aspects of Erythropoietin in the treatment of tumoranemia"

*Motivation for change: vectron therapeutics AG was closed down in June 2004 due to financial sponsorship*

10/2002 - 06/2004 **Scientist Liposomal Research & Development**

vectron therapeutics AG, Marburg (Germany): biopharmaceutical company developing chemotherapeutics and vaccines for cancer treatment using their patented drug delivery technology to enhance pharmacokinetics.

- Investigation and development of a new and innovative lipid-based drug delivery systems (biophysical and biochemical studies, in vitro and in vivo studies, pharmacokinetic and pharmacodynamic studies)

02/2002 - 06/2002 **Diplom thesis Department of Formulations**

Celator Technologies Inc, Vancouver/BC (Canada)

07/2001 - 09/2001 **Internship Product Management**

Aventis Pharma Deutschland GmbH, Bad Soden (Germany)

08/2000 - 01/2001 **Internship/Industry Placement Semester Analytical Chemistry**

Boehringer-Ingelheim (Canada) Ltd, Laval/QC, (Canada)

## Education & Qualifications

08/2014 – 12/2016 **Doctoral studies (PhD) in Epidemiology and Public Health**

Registered PhD candidate at University of Basel (Switzerland) and University of Cape Town (South Africa)

PhD research: "Health-related Quality of Life and its Association with Medication Adherence in Pulmonary Tuberculosis in South Africa – an integrated Patient-Centred Outcomes Approach". Expected graduation on 14 December 2016

09/2007 - 07/2010 **Master of Science (MSc) in International Pharmacoeconomics & Health Economics**

Cardiff University, Welsh School of Pharmacy, (Wales/UK)

Master Thesis: "Cost-effectiveness of Erythropoietin in the Treatment of Cancer-related Anaemia - A Question of Evidence" in cooperation with the Federal Statistical Office of Germany, Wiesbaden (Germany)

09/1998 - 06/2002 **Diplom (Dipl. Ing.) (Bachelor of Honours) in International Chemical Engineering/Applied Chemistry**

Private European University of Applied Sciences Fresenius, Idstein (Germany)

Diplom Thesis "Pharmaceutical Drug Development: A Novel Approach for Liposomal Entrapment of Anticancer Chemotherapeutic Agents", at Celator Technologies Inc., Vancouver/BC (Canada)

01/2001 – 06/2001 **Scholarship-Exchange Student**

California State University Long Beach, Long Beach/CA (USA)

Courses: Biochemistry, Chemical Engineering Lab II, Chemical Industry with Lab, Fundamentals in Economics

08/1988 - 06/1997 **General Qualification for University Entrance: Abitur**

Dilthey-Gymnasium, Wiesbaden (Germany)

## Professional Training

08/2014 – 12/2016 Three year PhD training program in Public Health, Swiss School of Public Health (SSPH+), (Switzerland)

03/2015 Certificate Clinical Investigator Course Level 1 and 2 (CLIC), Fundisa African Academy of Medicines Development, Cape Town (South Africa)

07/2008 Certificate in Basic Lead Auditor Training (cGMP) Midas Pharma GmbH, Ingelheim (Germany)

07/2007 – 09/2007 Certificate in Innovation Management

Long distance course, Managementcircle GmbH (Germany)

03/2002 Certificate in Radionuclide Safety and Methodology University of British Columbia, Vancouver/BC (Canada)

03/2000 - 01/2002 Qualifications in Economics, Marketing and Distribution Management

Private European University of Applied Sciences Fresenius,Idstein (Germany)

## Awards

09/2007 – 09/2009 Scholarship from Hochschule Fresenius for MSc studies in "International Master of Science in Pharmacoeconomics and Health Economics" with Cardiff University/Wales, UK

02/2002 - 06/2002 Scholarship of the German Academic Exchange Service (DAAD)

01/2001 - 05/2001 Fulltime Study Scholarship of the German Academic Exchange Service

(DAAD)

## Patents and Publications

- Kastien-Hilka, T., Rosenkranz, B., Bennett, B., Sinanovic, E., Schwenkglenks, M. (2016) How to evaluate health-related quality of life and its association with medication adherence in pulmonary tuberculosis – designing a prospective observational study in South Africa. Frontiers in Pharmacology: Pharmaceutical Medicine and Outcomes Research. doi: 10.3389/fphar.2016.00125.
- Poster presentation at Geneva Health Forum, Geneva (Switzerland), April 2016 Tanja Kastien- Hilka, Bernd Rosenkranz, Bryan Bennett, Edina Sinanovic, Matthias Schwenkglenks How to evaluate health-related quality of life and its association with medication adherence in pulmonary tuberculosis – designing a prospective observational study in South Africa.
- Kastien-Hilka, T., Abulfathi, A., Rosenkranz, B., Bennett, B., Schwenkglenks, M., and Sinanovic, E. (2016). Health-related quality of life and its association with medication adherence in active pulmonary tuberculosis- a systematic review of global literature with focus on South Africa. Health Qual Life Outcomes 14, 42. doi: 10.1186/s12955-016-0442-6.
- Poster publication with oral presentation at Provincial Health Research Day, Cape Town (South Africa), November 2015 Tanja Kastien-Hilka, Edina Sinanovic, Matthias Schwenkglenks, Bryan Bennett, Bernd Rosenkranz. Health-related Quality of Life and its Association with Medication Adherence in Pulmonary Tuberculosis in South Africa (SA) – A Systematic Review of qualitative and quantitative literature.
- Poster publication at European Congress on Tropical Medicine and International Health, Basel (Switzerland), September 2015: Tanja Kastien-Hilka, Edina Sinanovic, Matthias Schwenkglenks, Bryan Bennett, Bernd Rosenkranz. Health-related Quality of Life and its Association with Medication Adherence in Pulmonary Tuberculosis in South Africa (SA) – A Systematic Review of qualitative and quantitative literature.
- Hilka T. and Neises G. 2006. Ein Hormon im Wandel – Der richtungweisende Zukunftstrend: Einsatz von Erythropoietin zur Behandlung der Tumoranämie. Schulz-Kirchner Verlag ISBN 978-3-8248-0388-0
- Müller R, Müller-Brüsselbach S, Hilka T, Nahde T, Graser A, Hölig P (Inventors) Vectron Therapeutics AG (applicant). Drug Delivery Vehicles and uses thereof. European Patent Office 03027944-2-2114, 2003.
- Poster publication at School of Pharmacy, University of London (London/UK), 2003: Hilka T, Nahde T, Graser A, Müller-brüsselbach S, Kontermann R, Müller R. 2003. Vectron´s Novel Liposomal Drug Delivery System: Curasomes.