ASSESSMENT OF LUNG FUNCTION ABNORMALITIES IN ADULT PATIENTS WITH TUBERCULOSIS IN A HIGH HIV-PREVALENT SETTING AND THE IMPACT OF A PULMONARY REHABILITATION INTERVENTION TO IMPROVE LUNG FUNCTION, FUNCTIONAL CAPACITY, AND QUALITY OF LIFE.

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DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to and quotation in this dissertation from the work or works of other people has been attributed and has been cited and referenced.

Signature: Signed by candidate **Date:** 4 March 2022

Shamila Manie

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Shamila Manie
PhD Survivor

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AACVPR	American Association of Cardiovascular and Pulmonary Rehabilitation
ACCP	American College of Chest Physicians
ACSM	American College of Sport Medicine
AIDS	Acquired Immune-Deficiency Syndrome
A-LFT	Acceptable lung function test
BMI	Body mass index
CG	Control Group
COAD	Chronic obstructive airways disease
COPD	Chronic obstructive pulmonary disease
CXR	Chest x-ray
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
HAP	Household air pollution
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
HRQoL	Health-related quality of life
IG	Intervention group
LTFU	Loss to follow-up
MDR-TB	Multi-drug resistant tuberculosis
MIR	Medical International Research
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	Pulmonary rehabilitation programme
PTLD	Post-tuberculosis lung disease
QoL	Quality of life
RCT	Randomised controlled trial
SDG	Sustainable Development Goals
SGRQ	St George's Respiratory Questionnaire
TB	Tuberculosis (in this thesis TB refers to pulmonary tuberculosis only)
U-LFT	Unacceptable lung function test
WHO	World Health Organisation
3MST	Three-minute step test
6MWD	Six-minute walk distance
6MWT	Six-minute walk test

GLOSSARY OF TERMS

TERM	DEFINITION
EXERCISE INTENSITY: Calculated using one's maximal heart rate (MHR) which is calculated by subtracting one's age from 220 e.g. 220-35=185 (Lato & Polar, 2020)	
Low intensity	40-50% of maximal heart rate (MHR)
Medium intensity	50-70% of submaximal heart rate
High intensity	70-85% of submaximal heart rate
LUNG FUNCTION CLASSIFICATIONS: In this study participants were first classified into three categories based on their spirometry results and these are listed below with the lung function parameters	
Normal	FVC and FEV_1 are within 80% of the predicted value. FEV_1/FVC ratio is ≥70% of predicted values
Restrictive	FVC <80% of predicted values
Obstructive	FEV_1/FVC ratio <70% of predicted values
Mixed	FVC <80% and FEV_1/FVC ratio is <70% of predicted values
LUNG HEALTH: For the purpose of this thesis, lung health is described as the ability of the lungs to function optimally in individuals in order for them to engage in meaningful activities of daily living despite the presence of respiratory illness.	
Severity of lung function classification for restriction and obstruction:	
OBSTRUCTION	Spirometric values: FEV_1 % predicted is ≥ 80%
Stage 1 (mild)	Clinical criteria: At this stage, the patient may not be aware that their lung function is abnormal
Stage 2 (moderate)	Spirometric values: FEV_1/FVC < 0.7 and 50% ≤ FEV_1 < 80% predicted Clinical criteria: Symptoms usually progress at this stage, with shortness of breath typically developing on exertion.
Stage 3 (severe)	Spirometric values: FEV_1/FVC < 0.7 and 30% ≤ FEV_1 < 50% predicted Clinical criteria: Shortness of breath typically worsens at this stage and often limits patients' daily activities. Exacerbations typically begin at this stage
Stage 4 (very severe)	Spirometric values: FEV_1/FVC < 0.7 and FEV_1< 30% predicted or FEV_1< 50% predicted plus chronic respiratory failure Clinical criteria: At this stage, quality of life is very appreciably impaired, and exacerbations may be life-threatening
RESTRICTION*	FVC % predicted ≥ 80%
No restriction	FEV1/FVC ≥70%
Mild restriction	FVC % predicted is ≥65% but <80%
Moderate restriction	FVC % predicted is ≥50% but < 65%
Severe Restriction	FVC % predicted is <50%

Glossary of Terms continued.

TERM	DEFINITION
Spirometry	Method of assessing lung function by measuring the volume of air that the patient can expel from the lungs after a maximal inspiration. It has become the most accurate and reliable way of supporting a diagnosis of chronic obstructive pulmonary disease (COPD) (Miller *et al.*, 2005; Koegelenberg, Swart and Irusen, 2013).
METHODS FOR ASCERTAINING TB DIAGNOSIS	
Sputum smear	Positive pulmonary TB case is based on the presence of at least 1+ acid fast bacilli (AFB+) in at least one sputum sample in countries with a well-functioning external quality assurance (EQA) system (revised definition by WHO 2007)
TB culture	A test to see if the TB bacteria *Mycobacterium tuberculosis* is present. The substances are either solid substances on culture plates or bottles of liquid known as culture broths. The substances are chosen to make it easy as possible for the bacteria to grow.
Xpert MTB/Rif assay	The Xpert MTB/Rif test is a cartridge-based fully automated nucleic acid amplification test (NAAT) for TB case detection and rifampicin resistance testing. It is suitable for use in disease-endemic countries such as South Africa. It purifies, concentrates, amplifies (by rapid, real-time PCR) and identifies targeted nucleic acid sequences in the TB genome, and provides results from unprocessed sputum samples in less than 2 hours, with minimal hands-on technical time (WHO Xpert MTB/RIF implementation manual, 2014)
TB EPIDEMIOLOGICAL INDICATORS	
TB Prevalence	The number of cases of a disease present in a particular population at a given time.
TB Incidence	The number of NEW cases that develop in a given period in time

*** *Restriction:*** *For the purpose of this study, we acknowledge that spirometry restriction does not equate to plethysmography restriction. However, we do not have plethysmography data available.*

ABSTRACT

Background: Globally, tuberculosis (TB) continues to be a major health problem. In the most recent World Health Organisation (WHO) Global Tuberculosis Report of 2019, TB was ranked as the leading cause of death from an infectious disease ahead of the human immunodeficiency virus (HIV) and acquired immune-deficiency syndrome (AIDS). In the 2019 WHO Global Report on TB, there is little information relating to TB post-cure effects and management. Although there is evidence that successful completion of TB treatment does not equate to normal lung function, there is growing need for research, both during and after TB treatment, on the extent of lung function abnormalities and how these impact on the individual's quality of life (QoL). Pulmonary rehabilitation programmes may provide a continuum of care for individuals with TB to address both lung function abnormalities as well as positively impacting on QoL.

Objectives: The present PhD thesis aimed to provide insight into the extent of pulmonary disease in individuals with pulmonary TB during and near completion of TB treatment as well as to establish whether provision of a pulmonary rehabilitation programme (PRP) could address the research gap. To achieve this, three linked studies were undertaken in the form of observational (prevalence) study (Study 1), a systematic review (Study 2), and a randomised control trial (Study 3).

Study One: Observational Study

Objectives: The overall aim of the present observational study was to ascertain the prevalence of lung function abnormalities in first time, drug sensitive individuals living with TB, with or without HIV co-infection, at near completion (at least four months) of TB treatment. The specific objectives were to determine: i) baseline clinical and socio-economic profile, ii) baseline information pertaining to the QoL outcome measures of EQ-5D-3L and the St George's Respiratory Questionnaire (SGRQ), iii) measure lung function parameters, iv) establish the proportion of participants with normal or abnormal (obstructive, restrictive, or mixed) lung function and the severity of these, v) whether a correlation of lung function abnormalities with chest x-ray (CXR) abnormalities exist, vi) establish whether a relationship exists between lung function and QoL measures, and vii) identify the predictors of lung function abnormality in individuals being treated for active TB.

Methods: A cross-sectional prevalence study using a sample of convenience was conducted. Inclusion criteria included all adult male and females between the age of 18-80 years with confirmed (smear positive or by CXR) drug-susceptible TB who were receiving treatment, with or without HIV co-infection, for at least four months (16 weeks).

Participants were excluded from Study 1 if they were adult patients who had had previous TB episodes, recent severe chest trauma (within the previous three months), a recent history of pneumonia, known atopic asthma, chronic bronchitis, emphysema, bronchiectasis prior to TB diagnosis, cardiac failure, or any other unrelated respiratory disease as reported in their medical folder. Participants completed two QoL questionnaires (EQ-5D-3L and SGRQ), a self-designed clinical research form to collect descriptive data, a six-minute walk test (6MWT), CXR, and spirometry once off.

Results: The sample of 305 participants were predominantly male (n=168: 55,1%), had a median age of 36 years (IQR:28-43), and had median time of 19 weeks (IQR:18-22) on TB treatment. Overall, 32% of the sample presented with abnormal lung function (obstructive=11%, restrictive=15%, and mixed=6%). Only 2.2% of the total sample had two or more co-morbidities. There was no statistically significant difference (p=0.29) in distance covered by participants who had obstructive compared to restrictive lung function abnormality. After logistic regression analysis of clinical and socio-demographic variables (multi-variate), only being older (56–65 years old) and being obese were statistically significant (p=0.02 and p=0.04 respectively). When considering QoL, only the domain of mobility for the EQ-5D-3L questionnaire was statistically associated with abnormal lung function (p=0.02). Linear regression modelling for continuous variables of lung function (FEV_1, FVC, FEV_1/FVC and percentage predicted of FEV_1, FVC, and FEV_1/FVC) with SGRQ, 6MWD, and CXR scores yielded no predictor.

Conclusion: Overall, 32% of participants presented with abnormal lung function, which is lower than comparator studies investigating lung function in TB populations. Quality of life measures for most participants was considered good at the time of assessment. Limitations to Study 1 related to the absence of normative data for a healthy population relating to lung function and 6MWD to compare the findings in this TB population. Recommendations for future research would be to establish normative data for these outcome measures. Regarding lung function testing, it is recommended that training of correct execution of the spirometry techniques is performed prior to assessment as the technique may be unfamiliar compared to the routine tests done at clinic visits for individuals receiving TB treatment.

Study Two: Systematic Narrative Review

A systematic review was conducted to establish the evidence of the impact of non-pharmacological intervention programmes (pulmonary rehabilitation) in the rehabilitation of individuals living with TB on lung function outcomes.

Methods: MEDLINE via Pubmed, CENTRAL, CINAHL, PEDro, Web of Science, Scopus, Science Direct, and African Index Medicus, including Google Scholar were searched (from January 1995 to December 2016 with an updated search in November 2018) for randomised control trials, quasi-experimental and pre-post-test studies on PRPs for adult individuals with TB specifically with lung function measures as primary outcome.

Results: In total, 1 705 studies were obtained from the search. Once duplicate studies were removed, 1 220 studies remained. The titles and abstracts of these studies were screened resulting in 1 210 studies being excluded. Therefore, 10 studies were potentially eligible. Once the full-text articles were assessed, four studies met the inclusion criteria. Of the included studies, only one was a randomised control trial, two studies were single arm before and after studies, and one study was a prospective non-randomised open trial (two arms). In total, there were 178 participants in these studies, with sample sizes ranging from 10 to 67 participants. All four selected studies had both male and female participants; however, overall, male participants were the majority with 69% versus 21% females. The mean age across the studies was 70 years. No statistically significant difference ($p>0.05$) was found regarding lung function parameters and the PRPs. No meta-analysis could be performed as data could not be pooled due to the differences in study characteristics and outcome measures.

Conclusion: This review was unable to support or negate the use of pulmonary rehabilitation for individuals with TB primarily due to the lack of well-designed and executed randomised control trials. The studies showed that no effect on FEV_1 was demonstrated. The researchers recommended that future research investigates the extent of pulmonary sequelae in patients after completion of TB chemotherapy in large-scale studies. Long-term follow-up in those who have had TB without surgical intervention should be prioritised to see the extent of lung function disorders in this population, particularly in countries on the high-burden list for the disease. A further recommendation is that well executed randomised control trials that control for biases to investigate pulmonary rehabilitation in populations of individuals with TB should be prioritised as there is a need to develop an evidence-based continuum of care.

Study Three: Randomised Controlled Trial

Objectives: The overall objective of study three was to determine what the impact of a contextually relevant PRP would have on individuals living with TB, with or without HIV co-infection, on outcomes related to lung function, functional capacity, and QoL.

Methods: A pilot randomised, single blinded, pre-test-post-test design was used. Inclusion criteria were all adult males and females between 18-65 years with TB confirmed by Gene Xpert, irrespective of number of TB episodes, HIV status, or having chronic obstructive pulmonary disease. Participants had to be within their first week of TB treatment. Participants with only extra-pulmonary TB, recent severe chest trauma (within the last three months), a recent history of pneumonia (within one month), known atopic asthma, cardiac failure, or any other unrelated respiratory disease as reported in their medical folders or who had defaulted on their treatment were excluded. In addition to this, if participants failed the pre-participation health screening and were non-ambulate due to paralysis or amputation, they were also excluded. Fifty-eight participants were randomised into a control group (CG) receiving only pharmacological therapy and the intervention group (IG) who received pulmonary rehabilitation in addition to pharmacological therapy. The PRP was held for 12 weeks and consisted of two weekly sessions with a duration of 45 minutes each, which was delivered at a community centre. Participants completed two QoL questionnaires (EQ-5D-3L and SGRQ), a self-designed clinical research form to collect descriptive data, a three-minute step test, and spirometry at three time points (enrolment, at six weeks, and at 12 weeks). T-tests were conducted to determine the difference between means of the CG and IG for lung function parameters, functional capacity, and QoL outcomes.

Results: There were 29 participants in each group. Regarding sex, age, and number of co-morbidities the two groups were well matched. Regarding HIV status, the CG had more participants that were HIV positive (n=22) and on anti-retroviral therapy (n=11) than their IG counterparts (n=13 and n=5 respectively). Nearly half of the participants had a first time TB diagnosis, with the participants in the IG having reported more recurring TB incidences overall (n=16 vs. n=13). A t-test for difference between means showed no statistical significance for the CG and IG regarding $FEV_{1,}$ FVC, and FEV_1/FVC ratio for absolute or percentage predicted values. Forty-three percent of participants in the total sample had normal lung function at baseline, with the remaining participants being classified as having either obstructive (26%), restrictive (21%), or mixed (10%) lung function. At baseline, 48% of participants in the CG had abnormal lung function compared to 67% in the IG. At six weeks there was no change in the CG regarding lung abnormalities. However, the IG only had 33% abnormal lung function at the same time point.

Although there was no statistical significance for any of the lung function categories, there was a 42% improvement in normal lung function at six weeks in the IG compared to the CG at baseline. The median baseline number of steps taken by the CG was 79 steps (IQR:42-134) compared to 117 steps by the IG (IQR:84-154). A t-test conducted to test the difference between means for the CG and IG was statistically significant for the step test ($p=0.002$) at six weeks for the IG, but not at 12 weeks ($p=0.13$). No correlation was found between the SGRQ (QoL parameter) and any lung function parameter ($p>0.05$) at 12 weeks.

Conclusion: Although the changes in lung function, functional capacity, and QoL did not reach statistical significance at completion of the PRP for the IG, the continued improvement in all the outcomes for the IG from 0 weeks to 12 weeks holds potential clinical significance.

CHAPTER ONE: INTRODUCTION

1.1 Background to the Thesis

Globally, tuberculosis (TB) continues to be a major health problem (Alemayehu et al., 2017; Vishwanath, Babar, Naik, & Kamble, 2019). In the most recent World Health Organisation (WHO) Global TB Report of 2019, TB was ranked as the leading cause of death from an infectious disease ahead of the human immunodeficiency virus (HIV) and acquired immune-deficiency syndrome (AIDS) (World Health Organisation, 2019). Robert Koch first discovered the *Mycobacterium tuberculosis* bacillus in 1882 (Nobel Prize Outreach AB, 2014), which has continued to have a significant impact on mortality and morbidity rates worldwide (World Health Organisation, 2019). In 2018, the WHO reported that an estimated 10 million new cases of TB occurred globally, with 1.5 million people worldwide succumbing to the disease (World Health Organisation, 2019). Despite these alarming numbers, the WHO has made progress in reducing the mortality rates and number of new cases since it declared TB a global public health threat in 1993. Worldwide, mortality rates in HIV-negative individuals with TB are estimated to have fallen by 29% since 2000 and by 5% since 2015. In the WHO European regions, the TB incidence rate has declined the fastest between 2013–2017 at a rate of 5% per year. South Africa, which is included on the list of the 30 most high burden countries, also made impressive strides in reducing TB incidence (4–8%) over the same five-year period (World Health Organisation, 2019). These gains can be attributed to improved case detection, better monitoring systems, improved and expanded TB and HIV prevention care, and new diagnostic tools such as GeneXpert that has reduced time to diagnosis.

Improved cure rates over the previous decade have led to a shift in primary focus for international research from mortality to a focus on morbidity despite TB treatment. Research describing the lingering effects of TB on lung function has revealed a reduction in lung function parameters which often persists after successful completion of TB treatment and contributes to the emergence of chronic obstructive airways disease (COAD) (Akkara et al., 2013; Allwood, Myer, & Bateman, 2013; Baig, Saeed, & Khalil, 2010; Cruz et al., 2008; Ehrlich, Adams, Baatjies, & Jeebhay, 2011; Maguire et al., 2009). The impact of these pulmonary sequelae also has long-term negative effects on the quality of life (QoL) of people previously treated for TB (Guo, Marra, & Marra, 2009). Other long-term negative effects include adverse side effects such as ototoxicity in multi-drug resistant TB (MDR-TB) due to chemotherapy drugs (Petersen & Rogers, 2015), social stigmatisation, and anxiety and depression due to lack of knowledge of the disease (Chang, Wu, Hansel, & Diette, 2004; Deribew et al., 2009; Guo et

al., 2009; Hansel, Wu, Chang, & Diette, 2004; Maguire et al., 2009; Marra, Marra, Cox, Palepu, & Fitzgerald, 2004).

In the 2019 WHO Global TB Report, there is little information relating to TB post-cure effects and management. Although there is evidence that the successful completion of TB treatment does not equate to normal lung function, there is a growing need for research, both during and after TB treatment, on the extent of lung function abnormalities and how this impacts on the individual's QoL (Fiogbe et al., 2019; Manji et al., 2016; Ralph et al., 2013; Van Kampen et al., 2018; Van Zyl Smit et al., 2010; Visca et al., 2019).

In South Africa, which is listed as one of the eight countries accounting for two-thirds of new TB cases globally (World Health Organisation, 2019), scant research is available on the prevalence of abnormal lung function in the general population or in those treated for TB, as well as on the need for continuums of care for patients with TB despite growing evidence regarding the need for this (Daniels, Irusen, Pharaoh, & Hanekom, 2019; De Grass, Manie, & Amosun, 2014; Hnizdo, Singh, & Churchyard, 2000). From the researcher's personal experience, the scope of practice for physiotherapists regarding TB care has been obtaining ample sputum samples to confirm diagnosis and no more. Although it is limited, local research over the past 10 years has identified abnormal lung functions in patients with TB post-cure in selected populations (Allwood et al., 2013; Daniels et al., 2019; De Grass et al., 2014; Ehrlich et al., 2011). An earlier study conducted by physiotherapists investigated exercise capacity and lung function in patients who had been receiving TB treatment for two weeks (Hall & De Charmoy, 2002). The authors concluded that exercise capacity was markedly reduced in patients with TB after two weeks of treatment although it did not seem to have an impact on their functional capacity. The authors were uncertain as to the benefit of a pulmonary rehabilitation programme (PRP) and therefore suggested that education alone would be sufficient.

However, a preliminary home-based PRP in patients with TB (n=67) conducted in Cape Town, South Africa in 2014 by De Grass et al. (2014) concluded that the change within the intervention group (IG) from baseline to the completion of the programme at six weeks was statistically significant (FVC: p=0.004, 95% CI: -0.36 to -0.07; FEV_1 p=0.001, 95% CI: -0.33 to -0.08). Similarly, the difference between the IG and control group (CG) in the exercise tolerance outcome was statistically significant at the end of the sixth week (p=0.007; 95% CI: 15.37 to 92.7). The authors concluded that these differences provided an impetus for considering and implementing a PRP during TB treatment to limit the pulmonary sequalae experienced after microbiological cure (De Grass et al., 2014).

These findings are supported by a recent non-systematic review by Muñoz-Torrico et al. (2016), who questioned whether a rationale for PRPs following successful completion of TB treatment existed and stated, "the evidence found suggests that TB is definitively responsible for functional sequelae, primarily causing an obstructive pattern on spirometry (but also restrictive and mixed patterns), and that there is a rationale for pulmonary rehabilitation" (Muñoz-Torrico et al., 2016). From the improved cure rates observed with the management of TB globally, the need to focus on the post-cure phase becomes important.

In a recent South African publication by Daniels et al. (2019), the authors investigated the health-related QoL (HRQoL), lung function, and functional capacity of individuals residing in the Brede Valley district after TB cure and reported that all had been compromised. Therefore, understanding the prevalence of lung function abnormalities in individuals being treated for active TB in a community setting, with or without HIV co-infection, could help to understand the need for expanded treatment strategies for these patients. This forms the overall theme of the studies reported in this thesis. The outcome has the potential to contribute to the WHO global strategies to address TB, which to date have no recommended guidelines for the care of people with TB in the post-cure phase (Van Kampen et al., 2018).

1.2 General Aims and Research Questions of the Thesis

This thesis comprises three studies aimed at providing insight into the extent of pulmonary disease in individuals with TB during and nearing the completion of their TB treatment. The specific research questions and objectives addressed in each of these studies are outlined below.

Study 1: ***What is the prevalence of lung function abnormalities in people being treated for active TB in a community setting in South Africa, with or without co-infection with HIV?***

The aim of this observational study was to ascertain the prevalence of lung function abnormalities in patients with first time, drug sensitive TB, with or without HIV co-infection at near completion (at least four months) of their TB treatment. The specific objectives were to:

- determine the baseline socio-economic profile (age, sex, level of education, amenities, employment, and exposure to biomass) and clinical profile (comorbidities, HIV status, TB treatment, smoking history, body mass index [BMI], lung function, exercise tolerance, and QoL) of participants;

- measure lung function parameters of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio as well as the percentage of predicted FEV_1 and FVC after at least four months on TB treatment;
- establish the proportion of participants with normal or abnormal (obstructive, restrictive, or mixed) lung function;
- ascertain the severity of lung function abnormalities;
- determine the association between lung function abnormalities and chest x-ray (CXR), lung function, and QoL variables; and
- identify the predictors (HIV, age, sex, and smoking status) of lung function abnormality in people being treated for active TB.

Study 2: ***What is the evidence of the impact of non-pharmacological intervention programmes in the rehabilitation of people living with TB?***

A systematic narrative review was carried out to determine the effectiveness of interventions for improving lung function and functional capacity for people with TB. In addition, this review aimed to inform decisions regarding the components of the proposed intervention for study three.

The specific objectives for the systematic review were to:

- ascertain whether exercise-based interventions for patients with TB are effective in the management of pulmonary disease; and
- determine the most suitable components of a PRP in the context of a resource-limited primary care public sector setting.

Study 3: ***What is the impact of a contextually relevant PRP on people living with TB, with or without HIV co-infection, on outcomes related to lung function, functional capacity, and QoL?***

This study, a pilot randomised control trial (RCT), assessed the effectiveness of a PRP on outcomes related to lung function, functional capacity, and QoL.

The specific objectives were to:

- measure baseline parameters pertaining to lung function, functional capacity, and QoL at enrolment into a RCT at 0 months (time of TB diagnosis);
- measure lung function, functional capacity, and QoL at six weeks into the intervention, at completion (at 12 weeks) as well as three-, six-, and 12-months post intervention; and
- compare the baseline parameters of lung function, functional capacity, and QoL at the mid-intervention point (six weeks) and at completion of the intervention (12 weeks).

The above measurements were also taken for the CG. Figure 1 below describes the links between the three studies.

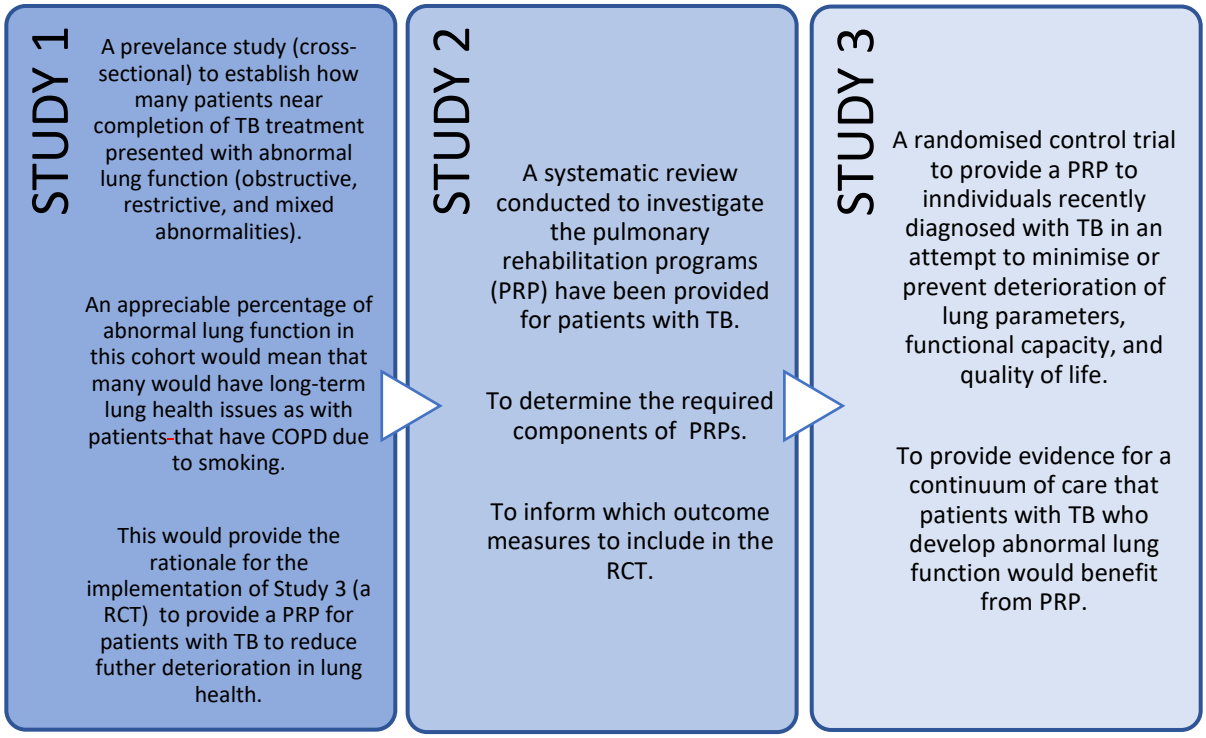


Figure 1. The Links Between the Three Studies included in this Thesis.

1.3 Significance of the study

1.3.1 Why is this study important?

In considering South Africa's high prevalence of TB, the present study will provide new knowledge and improved understanding of the extent of lung function abnormality in those who are still receiving TB therapy, as most studies have been conducted in individuals who have completed TB treatment (Harries et al., 2016).

1.3.2 How will it add to physiotherapy knowledge in relation to TB?

Physiotherapists are well positioned to provide pulmonary rehabilitation which not only focuses on physical improvement and functional capacity but can also impact and address several social determinants that effect people with TB and positively impact their QoL within their communities. Identifying patients with TB who are at risk of developing significant lung function abnormality may aid physiotherapists in providing early intervention and a continuum of care post completion of TB treatment, which is currently non-existent.

1.3.3 How will it help?

Data collected in this study will facilitate the development of guidelines for managing patients with TB, both during and post TB cure, and position physiotherapists to aid in the continuum of rehabilitative care for those living with TB.

1.3.4 Research setting and motivation to conduct the study

The study was conducted in Khayelitsha from 3 February 2016 to 31 March 2017 (prevalence study) and from 5 February to 31 November 2018 (intervention study). The area was selected as it had one of the highest incidences of TB and HIV infection in the Cape Metropole (Statistics South Africa, 2012). In sub-Saharan Africa, the TB epidemic is also driven by the co-infection of HIV (Mahtab & Coetzee, 2017). Khayelitsha is an informal settlement spanning 38.71km^2 (Statistics South Africa, 2012) established during the Apartheid era to house 200 000 black South Africans (Figure 2). However, this figure has long been surpassed, with the previous census (conducted in 2011) reporting a population of 391 749 (Statistics South Africa, 2012).

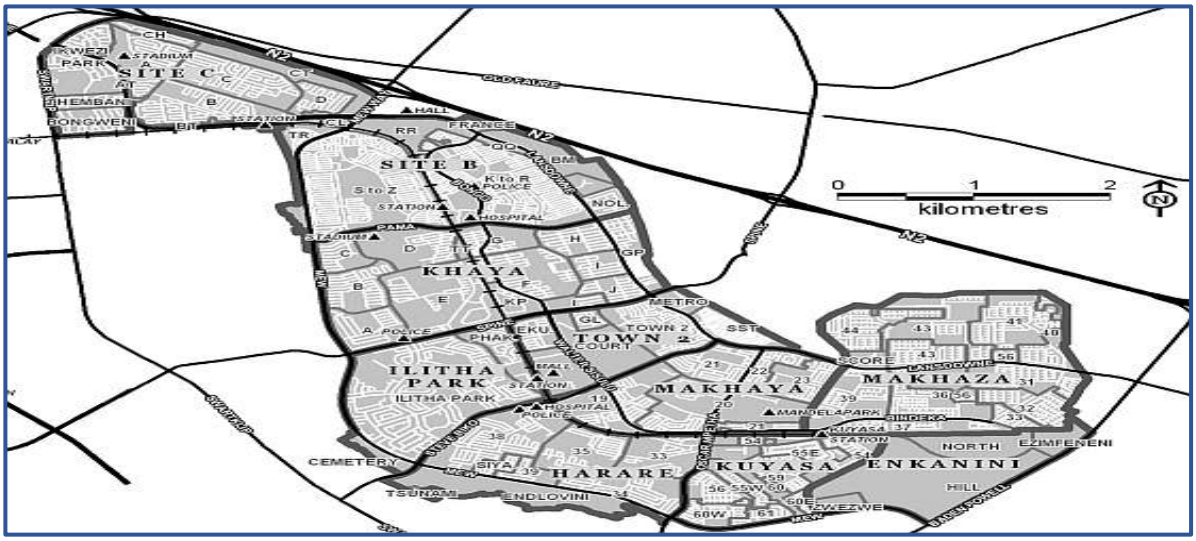


Figure 2. Map of Khayelitsha.

Khayelitsha is primarily low-lying, situated approximately 28km from the city centre. This leads to annual flooding during the Cape winter months, particularly between June and August each year. Depicted in Figure 3 below, housing is primarily in the form of shack dwellings in very close proximity, often less than 1m apart (Housing Development Agency, 2013). Infrastructure for services such as sewerage, roads, and running water within informal settlements is limited, which contributes and further impacts on the spread of disease.

Figure 3. Shack Dwelling and Flooding.

Not only is the physical space challenging, but the socio-economic issues of poverty, poor nutrition, illiteracy, crime, and unemployment are additional challenges that people living in Khayelitsha face daily. Although anyone may be infected with TB, it is widely acknowledged that it is an infectious disease of poverty (Pedrazzoli et al., 2017). Findings from the 2011 census reported that 74% of these households had a monthly income of less than R3 100 (Approximately US$212 or €180.41). Within the Khayelitsha/Mitchells Plain area, approximately 63% of households fall within the low-income bracket, of which 16.5% have no income (Western Cape Government, 2016). Poverty, safety, and unequal access to adequate health care have been identified by the End TB Strategy Campaign as important social and structural determinants that effect eradication of the disease.

In the most recent crime statistics provide by the South African Police Service, Khayelitsha is ranked third for incidences of murder and violent crime within the Western Cape Province (Crime Stats SA, 2019). In addition to the above, the stigma of TB is still prevalent (Abebe et al., 2010; Cramm & Nieboer, 2011) despite continued government programmes to educate at the primary health care level and through media platforms. These are but a few of the factors that contribute to the high incidence of TB amongst individuals living in Khayelitsha and a key determinant for conducting the present research in this setting. In Study 1, a prevalence study, two sites (Ubuntu Site B clinic and Michael Mapongwana Community Health Centre) were used to recruit participants. However, 90% of participants were recruited from Ubuntu Site B Clinic and, therefore, the only site used for recruitment during Study 3.

1.4 Thesis Structure

Chapter 1 includes an introduction and provides background to the study. This is followed by the general aims and objectives for each study. The significance of the study, the research setting, and the thesis layout are also described.

In **Chapter 2**, the literature regarding the extent of TB both locally and globally is reviewed, with a focus on what has been accomplished to date regarding treatment for individuals living with TB to reach the Sustainable Development Goals (SDGs) as set out by the United Nations (Appendix A). Following, the development of pulmonary impairment after tuberculosis is discussed, how it effects QoL, and its association with chronic disease. The social and structural determinants of TB are explored, followed by a review of pulmonary rehabilitation in chronic obstructive pulmonary disease (COPD).

Chapter 3 introduces the cross-sectional study (Study 1 - prevalence study) and reports on the methodology utilised, analysis of results, and concludes with a discussion thereof.

Chapter 4 presents a narrative systematic review (Study 2) of pulmonary rehabilitation of individuals who have been infected with TB. The effectiveness of a PRP on lung function and functional capacity is specifically reviewed. Unfortunately, a meta-analysis could not be performed due to heterogeneity amongst studies, with only one quasi-RCT meeting the primary outcome measure of lung function criteria.

Chapter 5 reports on the pilot RCT (Study 3) and presents its methodology, analysis of results, as well as a discussion of the results.

Chapter 6 presents the overall discussion of the thesis in relation to the results of each of the three studies. Reference is made to the literature and a critical evaluation of the results of the intervention study is provided. Finally, the limitations are discussed, recommendations for clinical practice and future research are provided, and an overall conclusion is presented.

CHAPTER TWO: LITERATURE REVIEW

2.1 Global Burden of TB

According to the most recent Global TB Report by the WHO, TB continues to be the leading cause of death from a single infectious agent, surpassing HIV (World Health Organisation, 2019). Globally, 10 million people fell ill with TB during 2018, with 1.5 million deaths reported (which included individuals with HIV). Although this number has been relatively stable over the previous few years, the burden of disease varies amongst countries. The distribution of TB cases by WHO region identifies the South-East Asia region with the highest proportion at 44%, followed by Africa (24%), and the Western Pacific (18%). There were, however, WHO regions with much smaller percentages, including the Eastern Mediterranean (8%), Europe (3%), and the Americas (3%)(World Health Organisation, 2019).

Of the 30 high-burden TB countries listed by the WHO, eight developing countries account for two-thirds of the global TB burden: India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%), and South Africa (3%) (World Health Organisation, 2019). These eight countries, along with the other 22 high burden countries, account for 87% of global TB cases. The number of drug resistant TB cases also continues to increase. In the 2019 Global TB Report (World Health Organisation, 2019), drug resistant TB continues to be a problem at a country, region, and global level, with approximately half a million individuals reported as Rifampicin resistant in 2018, of whom 78% had MDR-TB. Worldwide, the aggregated reduction in the TB incidence rate was 6.3% for the period 2015−2018 and 11% for TB deaths over the same period. Both the reduction in incidence and death rate for TB fall short of the End TB Strategy targets of reducing these indicators by 20% and 35% by 2020 respectively (World Health Organisation, 2019).

Despite these figures, there have been gains in the fight against TB in the area of improved diagnostics, early detection and notification, improved access to health care, and vaccine development (World Health Organisation, 2019). Regarding diagnostic and detection of drug resistance, in 2010 the WHO recommended the use of automated DNA testing for TB (Xpert MTB/RIF assay) as the initial diagnostic test for individuals suspected of MDR-TB or with HIV. This has resulted in improved detection and identification of Rifampicin resistance (World Health Organisation, 2015b). In a recent breakthrough in vaccine development amongst adults infected with *mycobacterium tuberculosis*, vaccination with M72/AS01$_E$ provided a sustained level of protection against active TB for at least three years (Tait et al., 2019).

This is a significant result as it is the first new vaccine for preventing TB since the development of the BCG vaccine in 1921, which does not provide consistent protection in adults residing in high-burden TB countries (Tait et al., 2019).

Since 1993, the WHO has driven various campaigns to address the burden of disease related to TB and to improve case detection and notification. In the current TB report, it was noted that their first milestone had been reached – the target of 7 million people receiving TB care in 2018. These campaigns focused on eradicating the disease globally as well as addressing the related social determinants. Most notably as a result these campaigns, the first high-level meeting on TB was held in 2017 to discuss the status of the TB epidemic with heads of state. This meeting led to a political agreement by United Nation member states to recommit to the SDGs and the WHO's End TB strategy. The 17 SDGs followed on from the Millennium Development Goals which concluded in 2015, and served as the framework to address issues related to the health and well-being of all. These goals recognise that "ending poverty and other deprivations must go hand-in-hand with strategies that improve health and education, reduce inequality and spur economic growth" (World Health Organisation, 2000). Sustainable Development Goal Three specifically speaks to good health and well-being and aims to ensure healthy lives and the promotion well-being for all ages. Regarding TB specifically, the SDG target aims to reduce TB incidence by 80% and TB deaths by 90%, and further aims to eradicate the devastating cost implications for households affected by the disease by 2030 (World Health Organisation, 2015a). The End TB strategy, which aims to end global TB between 2015 and 2035, has interim milestones which includes a 2020 milestone, which is that no TB household should incur catastrophic costs while treating the disease (World Health Organisation, 2019).

2.2 Social Determinants of TB

Although anyone may be susceptible to TB infection, it is widely known to be a disease related to poverty, resulting in the burden of disease falling on the poorest and most vulnerable in society. Despite diagnosis and treatment for TB being theoretically universally free, the treatment package, which consists of several clinic visits for directly observed therapy, still incurs a substantial cost to patients and their families (Steffen et al., 2010). In the WHO End TB Strategy for 2015–2035, implementation of comprehensive strategies to ensure universal health coverage and interventions to address the underlying social determinants of TB are foregrounded as critical elements. Emphasis on prevention and care of TB by paying attention to policies that may alleviate poverty and social protection programmes is essential to reduce the incidence of TB (Siroka, Ponce, & Lönnroth, 2016).

Social protection is defined by the International Labour Organisation as: “nationally defined sets of basic social security guarantees which ensure protection aimed at preventing or alleviating poverty, vulnerability, and social exclusion” (Siroka et al., 2016)(p. 473).

Despite emphasis being placed on addressing the social determinants of health related to TB, limited studies have explored the association between social protection and TB burden, specifically in developing countries where the burden of the disease is highest. In a recent study by Pedrazzoli et al. (2017), the authors reviewed mathematical models of TB to evaluate the impact of the structural determinants of TB. Their systematic search produced eight studies published between 2008 and 2015, seven of which focused on proximal social determinants (nutritional status, wealth, air pollution and overcrowding, and comorbidities such as HIV/AIDS and diabetes) and one that focused on macro-economic determinants of TB and hence the impact of distal determinants (government expenditure on public health services and gross domestic product). In a related study, the authors considered 21 European Union countries and reported an inverse association between social protection spending and TB incidence (r=-0.65; p=0.0003) and mortality (r=-0.62; p=0.0104) (Reeves et al., 2015). This association was reported in wealthy nations with large social protection systems and secure welfare mechanisms, which spent up to 20% or more of their gross domestic product on these social protections. This starkly differs from low and middle-income countries where the burden of TB is high and less than 10% of gross domestic product is spent on social protection.

The financial burden on households in high burden TB countries such as South Africa is compounded by the social determinants of poverty, poor access to health, and low levels of education in poorer communities. As poverty has been linked to an increased risk of infection as well as poor health outcomes and health seeking behaviour, reducing the cost of the illness is of great importance. Furthermore, the disease also worsens poverty by reducing the patients’ physical ability to work and earn an income (Daftary, Padayatchi, & O'Donnell, 2014; Foster et al., 2015). Within South Africa, the financial impact may be catastrophic when considering that 30% of the world’s incident cases of HIV-associated TB occur in South Africa and the country experiences a high rate of unemployment at 29% (Statistics South Africa, 2019). Studies investigating the costs associated with TB disease often only investigate direct, out-of-pocket expenditure related to transport or medication. The indirect costs associated with the disease (namely, loss of time at work and loss of ability to seek employment due to ill health or having to take care of another who is ill) are often not considered or quantified.

2.3 Magnitude of the TB Epidemic in South Africa

Within South Africa, TB is a disease occurring predominantly in poorer communities (Lutge, Lewin, Volmink, Friedman, & Lombard, 2013), in part due to the legacy of Apartheid which not only divided a nation along racial lines but also left the marginalised with unequal access to health care, inferior education, and ultimately poor prospects for QoL. Although 25 years after democracy the country has made significant strides in providing more accessible health care for all, it has yet to have similar success in combating the TB epidemic (National Department of Health, 2014). In the most recent Global TB Report (World Health Organisation, 2019), South Africa, based on a population of 58 million (2018), recorded 301 000 TB infections and 64 000 TB related deaths. With an estimated incidence rate of 520 per 100 000 (including those with HIV co-infection) the country is still one of the 30 high-burden countries identified by the WHO. These figures have seen a reduction since 2017 where 322 000 people fell ill with TB, with an incidence rate of 567 per 100 000. Regarding the profile of those affected with TB, South Africa follows the global trend with more adult males (54%) than adult females (37%) affected by the disease. The age category most affected is 15-55 years, which corresponds to the most productive working years.

The country has seen certain gains in the treatment coverage rate, which has increased from 68% in 2016 to 76% in new and relapsed cases in 2017. The treatment success rate fell from 82% in 2016 to 77% in 2017, which falls short of the 90% target for both indicators by 2022. These small gains may be attributed to continued domestic and international TB funding. Despite TB having been reported as the leading cause of death in South Africa in 2018, TB deaths for the same calendar year decreased from 78 000 deaths in 2017 to 64 000 deaths in 2018. According to the Western Cape Department of Health (Western Cape Department of Health, 2019), the Khayelitsha community recorded 4 095 new TB cases in 2018, of these, the proportion of cases that were known HIV co-infected was 57.5% (2356) (Western Cape Department of Health, 2019). Despite the total number of TB cases (new and re-infection) for the period 2016–2018 increasing each year, the number of new TB cases between these years was not substantial and relatively stable (see Table 1 below).

Table 1. Khayelitsha Aggregated Data for Tuberculosis (TB) 2016–2018.

	2016	2017	2018
New TB cases			
Total no. of Pulmonary TB	2 499	2 383	2 527
Total no. of Extra Pulmonary TB	598	652	633
TOTAL NEW TB CASES	**3 097**	**3 035**	**3 160**
Re-Treatment cases			
Total no. of Pulmonary TB	393	482	493
Total no. of Extra-Pulmonary TB	64	104	109
TOTAL NO. OF RE-TREATMENT CASES	**457**	**586**	**602**
Other	**425**	**347**	**333**
TOTAL ALL TB CASES (HIV + included)	**3 979**	**3 968**	**4 095**

Source: *Western Cape Department of Health, All Tuberculosis Cases by Age and Gender Q1–4 2016–2018, The Electronic Tuberculosis Register.*

The target of achieving a 90% treatment coverage and success rate by 2022 became challenging when factors such as poor adherence to medication, development of MDR-TB, extreme drug resistant TB, and a high prevalence of HIV-positive patients with TB are considered (Daftary et al., 2014; Shargie, Lindtjorn, & Lindtjørn, 2007; World Health Organisation, 2019). In addition to factors focused on the medical aspect of the disease, the psychological factors such as stigmatisation, isolation (Aggarwal, Gupta, Janmeja, & Jindal, 2013; Atif et al., 2014; Bauer, Leavens, & Schwartzman, 2013; Louw et al., 2012; Marra et al., 2004), and patient preference of adherence to HIV medication instead of TB treatment further compounds the effective management of the disease (Daftary et al., 2014).

2.4 Mechanism of Lung Damage in TB

Understanding the mechanism of how *mycobacterium tuberculosis* affects the lung is important as it explains why pulmonary impairment after TB is present. Before the 1950s, the understanding was that the formation of caseating granulomas was the main characteristic of both primary and post-primary TB infection (Hunter, 2011; Stek et al., 2018). Granulomas are considered a key characteristic of primary TB, with cavitation occurring only in post-primary TB (Hunter, 2011; Ravimohan, Kornfeld, Weissman, & Bisson, 2018). Tuberculosis damage was described by Hunter (2016) as a "three-act play" as follows:

> First, primary TB is a war of attrition which begins with infection that spreads through the lymphatics and blood stream, before inducing systemic immunity which contains and controls the organism with granulomas.

> Second, post-primary TB, a sneak attack, develops during latent TB as an asymptomatic obstructive lobular pneumonia in persons with effective systemic immunity. It is a paucibacillary process with no granulomas that spreads via bronchi and accumulates mycobacterial antigens and host lipids for 1-2 years before suddenly undergoing caseous necrosis. Third, the fallout, is responsible for nearly all clinical post-primary disease. It begins with caseous necrotic pneumonia that is either retained to become the focus of fibrocaseous disease or is coughed out to leave a cavity (p. 497).

Simply, pulmonary cavitation occurs, which is a process by which pulmonary tissue is obliterated, involving caseous necrosis of lipid pneumonia lesions producing cavitating pneumonia in the post-primary TB setting. During this process, alveolar cells and septa are destroyed as well as the surrounding vessels, and bronchi and cavities form when these areas of caseous pneumonia liquefy, break-up, and are released through coughing (Ravimohan et al., 2018; Singh et al., 2018). In addition to this process, pulmonary fibrosis may occur as a result of the long-term injury that replaces normal lung parenchyma with collagen tissue, which alters the structure of the lung through thickening and stiffening of the lung walls (Ravimohan et al., 2018; Stek et al., 2018). Furthermore, inflammation also plays an important role in lung damage in TB as both *mycobacterium tuberculosis* and the host response play a significant role in lung damage. An investigation of the targeted inflammatory responses in TB, it appeared that a small number of *mycobacterium tuberculosis* organisms start an inflammatory cascade that could result in extensive tissue damage, complications, or death (Friedland, 2014). In immunosuppressed patients, as in the case of HIV-co-infected patients, TB often also presents atypically with normal CXRs, suggesting that lung damage may be less in HIV co-infected patients (Mathur, Badhan, Kumari, Kaur, & Gupta, 2017), but at the same time, immune reconstituted inflammatory syndrome may cause excessive inflammation and ultimately more lung damage in patients who are co-infected with HIV (Meintjies & Sonderup, 2011).

2.5 HIV Co-infection with TB

In sub-Saharan Africa, the TB incidence is higher than in Europe, in part due to the high prevalence of HIV infection (Bekker & Wood, 2010; Gao, Zheng, & Fu, 2013; World Health Organisation, 2019). A systematic review and meta-analysis of the prevalence of TB/HIV co-infection outside China reported a prevalence rate of TB/HIV co-infection of 23.5%, nearly double the rate (13%) reported by the WHO in 2011 (Gao et al., 2013). The higher prevalence reported in this study may be attributed to the fact that more than half the studies included in the review were conducted in high-burden countries such as South Africa, Zambia, Nigeria, Ethiopia, Zimbabwe, India, and Thailand (Griffiths et al., 2000; Lutge et al., 2013). This finding is not surprising as the Africa region accounts for nearly three-quarters (72%) of the estimated number of HIV-positive TB cases globally (World Health Organisation, 2019).

According to the WHO, in 2018 South Africa had one of the highest co-infection rates in the African region, with a reported 59% of patients with TB also being HIV positive (World Health Organisation, 2019). A study conducted in South Africa, which investigated the impact of anti-retroviral treatment on TB fatality in HIV-positive patients, reported that TB case fatality was strongly associated with a CD4 count of <350cells/uL (Kaplan, Caldwell, Middelkoop, Bekker, & Wood, 2014). The study further reported the risk of death for those with a CD4 count between 200 and 350cells/uL at 1.87 (95% CI: 1.46–2.42) compared to patients with a CD4 count greater than 500cells/uL ($p<0.001$). This risk, however, was reduced in patients who received anti-retroviral therapy (Kaplan et al., 2014).

Although research regarding the epidemiology and management challenges of HIV and TB interaction is readily available (Kaplan et al., 2014; Middelkoop et al., 2015), there appears to be a gap in research investigating the impact of these diseases on lung function when they present concurrently. In one of the first longitudinal studies to investigate lung function decline in HIV-positive patients in the absence of TB, it was reported that those infected with HIV were, over time, more likely to have COPD than their HIV-negative counterparts (Drummond et al., 2013). The same study reported a 76ml/year greater decline in FEV_1 and an 86ml/year greater decline in FVC amongst HIV-positive individuals with a viral load of more than 75 000 copies/ml than in HIV-negative individuals ($p<0.01$). Furthermore, the authors reported that HIV-positive individuals with CD4 counts of less than 100cells/µl had a 57ml/year more rapid decline in FEV_1 and an 86ml/year more rapid decline in FVC than HIV-negative participants ($p=0.018$ and $p=0.001$, respectively). In a cross-sectional study conducted in rural Uganda which investigated the association between HIV infection, pulmonary tuberculosis, and COPD, it was reported that FEV_1 was lower amongst older participants and those with a history of TB (North et al., 2018).

In a study of 269 participants, 143 participants living with HIV had a percentage predicted FEV_1 that was lower amongst those with detectable viral loads (−26.7 percentage predicted, 95% CI −41.4 to −12.0, $p<0.001$) and those with lower CD4 counts (<350 versus >500: −9% predicted, 95% CI −17.8 to −0.1, $p<0.05$), which aligns with the findings reported by Drummond et al. (2013) (North et al., 2018). A recent South African study which investigated the association between HIV infection and pulmonary function in a rural village in the Limpopo province reported that after multivariate analysis HIV was not significantly associated with a decline in the post-bronchodilator FEV_1/FVC ratio (β -0.017, $p=0.18$). However, when a history of pulmonary infection was removed from the final model, HIV was significantly related to the post-bronchodilator FEV_1/FVC ratio (β -0.026, $p<0.03$) (Varkila et al., 2019).

Varkila et al. (2019) and North et al. (2018) both identified the need for further investigation of pulmonary function in a HIV co-infected TB population to better understand the association between pulmonary function and these diseases.

2.6 Pulmonary Impairment after TB

Tuberculosis-related morbidity and its treatment is under-reported and therefore a neglected area of research (Aggarwal et al., 2013). Post-TB treatment research has revealed that pulmonary impairment due to structural changes within the lung parenchyma, as described above, is evident after cure and is still present six months post treatment completion (Ehrlich et al., 2011; Pasipanodya et al., 2007; Ralph et al., 2013; Singh et al., 2018; Vecino et al., 2011). Therefore, microbial cure from TB does not equate to full recovery. Pulmonary impairment may be present in many patients post TB cure due to pulmonary sequelae. These pulmonary sequelae are often characterised by alterations in the bronchial and parenchymal structures found within the lung (Di Naso, Pereira, Schuh, & Unis, 2011), including broncho-vascular distortions, bronchiectasis, and fibrosis (Maguire et al., 2009; Pasipanodya et al., 2007). The disease can also involve the airways, leading to mucosal oedema, hypertrophy, and hyperplasia of mucous glands, which further leads to increased mucous secretion and smooth muscle hypertrophy (Dean et al., 2019). All the above may affect the calibre of the airways, resulting in decreased airflow within the airways (Pasipanodya et al., 2010; Pasipanodya et al., 2007), ultimately causing lung function abnormalities (Cruz et al., 2008).

An emerging body of research details the lingering effects of TB on lung function, namely a decrease in lung function parameters and a contribution to the development of COAD (Akkara et al., 2013; Allwood et al., 2013; Baig et al., 2010; Cole et al., 2016; Cruz et al., 2008; Ehrlich et al., 2011; Maguire et al., 2009). A literature review of South African studies on respiratory symptoms following TB reported that despite successful treatment for drug-susceptible TB, survivors were likely to develop COAD (Ehrlich et al., 2011). In one of the few studies exploring the long-term outcomes for patients with TB in India (14–18 years post successful TB treatment), lung function abnormalities were present in 66% of participants (Banu Rekha et al., 2009). In this study, with a sample of 148 patients, only 35% of patients had normal lung function 14–18 years post successful treatment.

A systematic review which measured the QoL of people with active TB, concluded that TB has lasting negative effects on patient QoL, which persists long after patients are medically cured (Guo et al., 2009). Despite this emerging evidence, few studies have “quantified pulmonary impairment after TB cure” (Allwood et al., 2013).

Treatment strategies that look beyond microbial cure are essential for addressing lung function abnormalities and improving QoL for those affected. Research into the long-term consequences for individuals with TB with regard to COAD and subsequent management of this consequence is limited (Atif et al., 2014; Hansel et al., 2004).

The authors of a systematic review investigating the association between TB and COPD concluded that amongst the nine studies included in the review, the strongest association was observed in countries with a high incidence of TB and that efforts to improve long-term lung health should be included in PTB care. However, the authors did not provide a clear definition of lung health nor what treatment strategies/care bundles should be considered towards promoting lung health care (Byrne, Marais, Mitnick, Lecca, & Marks, 2015).

In another study conducted in Brazil which investigated the prevalence of chronic respiratory symptoms and pulmonary dysfunction amongst indigenous and non-indigenous patients with post-TB (n=121), a high prevalence of both was reported (Nihues et al., 2015). The authors observed chronic respiratory symptoms in 45% of participants even after completion of TB treatment. Pulmonary dysfunction was reported in 41% of the participants, with most reporting obstructive disorders.

Similarly, studies in sub-Saharan Africa have investigated the prevalence of chronic airway obstruction in patients (n=70) recently cured from TB (De La Mora, Martínez-Oceguera, & Laniado-Laborín, 2015). A study by De La Mora et al. (2015) reported that unlike patients with smoking-related COPD, these patients were much younger (<50 years) and had an FEV_1 <60% than predicted, which clinically impacts on patients' QoL. The mean number of TB episodes in their study was significantly greater amongst subjects with chronic airway obstruction than those without (1.9 ±0.7 vs. 1.4 ± 0.6 episodes; $p<0.009$).

The studies above (Byrne et al., 2015; De La Mora et al., 2015; Nihues et al., 2015) all align with the scoping review by Van Kampen et al. (2018), which reported that TB is an important risk factor for the development of chronic respiratory disease due to the residual lung damage after cure. The scoping review, the first to provide comprehensive oversight of the present literature regarding post-tuberculosis lung disease (PTLD), found only three international guidelines that referred to TB sequelae and none which described how to identify or treat the condition. The authors concluded that a gap in the literature exists regarding the above, and therefore a need exists for research to investigate the appropriate management options particularly for high-burden TB countries.

2.6.1 Extra-pulmonary manifestations in TB and COPD

The few studies that have been conducted to ascertain the impact of TB on the HRQoL of patients during TB treatment reported that although an improvement in HRQoL had been observed from commencement to completion of TB treatment, participants still showed compromised physical and mental health at end of treatment (Atif et al., 2014; Jaber & Ibrahim, 2019). Those affected by COPD are disposed to developing musculoskeletal dysfunction which is linked to physical inactivity and compounded by compromised nutrition (Jaitovich & Barreiro, 2018; R. Jones et al., 2017; Sharanya et al., 2019). Skeletal muscle dysfunction affects both the respiratory muscles as well as non-ventilatory muscles, particularly that of the lower extremities which then negatively affects the patients' ability to execute activities of daily living (Jaitovich & Barreiro, 2018). Loss of the ability to perform activities of daily living often result in mental health issues such as anxiety, depression, and demotivation (Jaber & Ibrahim, 2019; R. Jones et al., 2017). According to Jaber and Ibrahim (2019), mental health was particularly negatively affected even at one year post TB treatment completion. Both the physical and mental impairment found in patients with COPD have been observed to improve with PRP.

2.6.2 Pulmonary rehabilitation in COPD

Chronic obstructive pulmonary disease is an umbrella term for chronic respiratory diseases that are primarily caused by smoking. It is commonly defined as: "a slowly progressive airflow obstruction which is only partially reversible" (Senior & Anthonisen, 1998)(p. 139). In the 2019 report by the Global Initiative for Chronic Obstructive Lung Disease, COPD had been reported as the cause of death for more than 3 million people in 2012 and projected to be the third leading cause of mortality by 2020. Chronic respiratory diseases such as COPD, asthma, bronchiectasis, and PTLD are reportedly commonly neglected non-communicable diseases which affect patients across their lifespan (Meghji et al., 2021). They contribute to higher care costs, morbidity, activity limitation, and recurrent exacerbations which require acute hospital admissions (Global Initiative for Chronic Obstructive Lung Disease, 2019; Meghji et al., 2021). Chronic obstructive pulmonary disease is therefore a major health concern as it not only affects mortality but also morbidity. The holistic management of COPD has become important to reduce both mortality and morbidity (Global Initiative for Chronic Obstructive Lung Disease, 2019).

In recent years the terms 'lung health' or 'respiratory health' have been associated with improved morbidity for those with respiratory disease. However, no clear understanding has been provided in the literature as to what this term entails nor what treatment strategies or care bundles should be implemented to improve lung health outcomes (Allwood et al., 2020).

In a recent study exploring the identification of lung health, the authors concluded that the over simplistic definition of good respiratory health being defined as the absence of lung disease requires a paradigm shift to better understand the risk factors that shift an individual from good lung health to that of poor or impaired lung health (Reyfman et al., 2018).

At the first international symposium on post-tuberculosis lung health held in South Africa, it was determined that the absence of consensus terminology for post-TB has hampered research in this area and contributed to lack of research in the holistic management of patients with PTLD. Specific mention had been made regarding the inadequacy of the existing TB guidelines in addressing the prevention, diagnosis, and treatment of PTLD for which no guidelines exist. In addition, consensus was reached that at the very least, lung function assessment should be conducted to determine who would present with lung impairment and hence would benefit from additional care in the form of pulmonary rehabilitation. In a letter to the editor in response to the publication by authors Allwood et al. (2020), Harries, Dlodlo, Brigden, and Chakaya (2021*)* noted: *"*first, it is vital that the WHO and the Stop TB Partnership recognise that post-TB lung health is an integral part of person-centred care and prevention" (p. 161). The symposium highlighted the urgent need for research on the effectiveness and comparative cost of PTLD treatment options which should include education on self-management, airway clearance, bronchodilators, and pulmonary rehabilitation particularly in high-burden TB countries (Allwood et al., 2020; Van Kampen et al., 2018). Pulmonary rehabilitation is an element of the standard care for patients with chronic lung disease (Fahy, 2004; Gloeckl, Schneeberger, Jarosch, & Kenn, 2018; McCarthy et al., 2015; Puhan et al., 2011; Ries et al., 2007; Spruit et al., 2013). By definition, pulmonary rehabilitation is a comprehensive intervention that includes, but is not limited to, physical activity (aerobic training), education, and behavioural change (R. Jones et al., 2017). Pulmonary rehabilitation is widely accepted as a means to improve standard therapy, reduce symptoms, minimise hospitalisation due to acute exacerbations, and optimise function in those living with chronic lung disease (Oliveira et al., 2018; Pedersen & Saltin, 2015; Rochester et al., 2015; Spruit et al., 2014). The primary aim of pulmonary rehabilitation is therefore to restore the patient to the highest possible level of function and in so doing help them gain control of their symptoms. In addition to pulmonary rehabilitation being beneficial to the patient, carers and significant others are taught about the disease and its related coping methods.

In 1997, the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) published a set of evidence-based guidelines for pulmonary rehabilitation (Ries et al., 1997).

The guidelines include both therapeutic and important health outcomes. The topics covered for the therapeutic outcomes include upper and lower limb training, ventilatory muscle retraining, and psychosocial/behavioural interventions. The components related to health outcomes include psychosocial/behavioural outcome measures, dyspnoea, QoL, health care utilisation, and survival. In these guidelines, the panellists provided recommendations based on the strength of evidence for each topic. Regarding lower limb training and reducing dyspnoea, the panellists found level 1A evidence for the recommendation of the inclusion of lower limb training and noted that dyspnoea reduced markedly for patients who participated in a PRP and therefore was an important outcome measure. For the inclusion of upper limb training, ventilatory muscle retraining, and QoL, level 1B evidence was found as routine use of ventilatory muscle retraining was not supported as an essential part of pulmonary rehabilitation but was beneficial for selected individuals who had decreased respiratory muscle strength. For upper limb training, beneficial effects were reported as they increased exercise capacity in the arms and reduced metabolic and ventilatory demand.

As for including outcome measures related to QoL, the panellists concluded that comprehensive pulmonary rehabilitation had been shown to improve the QoL of patients with chronic lung disease. Psychosocial/behavioural changes and education components had level 1C evidence to support its inclusion in PRPs. This was primarily due to no evidence at the time to support short-term interventions. Although not supported by evidence at the time of the review, the expert opinion was that educational and psychosocial interventions should be included in PRPs. Since these initial guidelines, the ACCP/AACVPR has been updated by Ries et al. (2007) with new evidence that cements the previous recommendation of lower and upper extremity training. In this update, new evidence that supports longer PRPs and the incorporation of education as beneficial is noted; it concludes that pulmonary rehabilitation is beneficial in COPD as well as in other chronic lung diseases.

Several studies have reported on various populations where PRPs have been implemented for patients with a diagnosis of COPD and chronic lung disease (Altenburg, De Greef, Ten Hacken, & Wempe, 2012; Cambach, Chadwick-Straver, Wagenaar, van Keimpema, & Kemper, 1997; Chavannes, Vollenberg, Van Schayck, & Wouters, 2002; Embarak, Mansour, & Mortada, 2015; Gibellino & Mammana, 2014; Kagaya et al., 2009). Most studies implementing PRPs in COPD patients have reported success in various settings including hospitals and out-patient clinics, as well as in community-based and home-based settings.

In a study conducted by Incorvaia et al. (2014) in an urban hospital, 190 patients with COPD underwent a PRP with drug therapy as recommended by the Global Strategy for the Diagnosis, Management, and Prevention of COPD's Global Initiative for Chronic Obstructive Lung Disease (Global Initiative for Chronic Obstructive Lung Disease, 2019) and 67 were treated with drugs (over three years only). Results from this study reported that the PRP group had improved FEV_1 values from 1240ml to 1252.4ml after three years, compared to the control who had 1367ml at baseline and 1150ml after the three-year period, which was a significant difference ($p<0.001$). The authors concluded that in patients with stable COPD receiving standard drug therapy, pulmonary rehabilitation may slow or even stop the decline of FEV_1. Incorvaia et al. (2014) suggested that the currently overlooked role of pulmonary rehabilitation should be considered and warrants randomised trials to extend the evidence.

In an out-patient setting, Bakry Elkhateeb, Elhadidi, Masood, and Mohammed (2015) reported that a short-term PRP of six to eight weeks had the capacity to "break the vicious cycle of dyspnoea, increasing inactivity, and exercise intolerance." In their study of 45 COPD patients divided into three groups, namely aerobic training (n=15), respiratory training (n=15), and a CG (n=15), the authors reported a significant improvement in spirometric values of FEV_1 ($p=0.006$) and FVC ($p=0.002$) in the aerobic training group compared to the respiratory training group and the CG.

Similarly, a recent quasi-experimental study by Machado, Oliveira, Valente, Burtin, and Marques (2020) conducted a community-based PRP on individuals with acute exacerbations of COPD and reported that those in the experimental group presented with improved outcomes. Outcome measures included were dyspnoea scale (modified Medical Research Council), quadriceps muscle strength, sit-to-stand test, and the impact of COPD assessment test. These outcome measures were assessed within 48 hours of the acute exacerbation of COPD onset and after a three-week PRP. In all the above measures, the experimental group showed significant improvements compared to the CG who showed no significant improvements. The results for the experimental group were as follows: quadriceps muscle strength (Pre: 21.0 vs. Post: 25.0, $p=0.012$), COPD assessment test (Pre: 23.0 vs. Post: 14.5, $p=0.008$), symptoms of dyspnoea at rest (Pre: 3.0 vs. Post: 1.0, $p=0.008$), SpO_2 (Pre: 94.0 vs. Post: 96.0, $p=0.031$), and respiratory rate (Pre: 24.0 vs. Post: 20.5, $p=0.004$). In an earlier study by Sewell, Singh, Williams, Collier, and Morgan (2006), a shorter duration a of four week PRP was also acknowledged as having equivalent outcome benefits to that of a seven week PRP. In their study, 100 participants with stable COPD were randomised into either a four-week or a seven-week programme and received supervised PRP in an out-patient facility.

Participants in both groups made significant within-group improvements. However, there were no statistically significant differences between the two groups at seven weeks or at the six month follow-up, except in the four-week group which attained a higher endurance shuttle walk test (p=0.024) at the seven-week time point (Sewell et al., 2006).

Gibellino and Mammana (2014) reported on the effects of pulmonary rehabilitation on lung function in patients with COPD and noted a significant difference in symptoms, health status, exercise capacity, as well as lung function before and after pulmonary rehabilitation. The authors concluded that their findings held clinical significance as this evidence strengthened previous recommendations that pulmonary rehabilitation should be included in the standard care for patients with COPD. This comment is cemented by the Cochrane Review conducted by McCarthy et al. (2015), where the author concluded:

> Pulmonary rehabilitation relieves dyspnoea and fatigue, improves emotional function and enhances the sense of control that individuals have over their condition. These improvements are moderately large and clinically significant. Rehabilitation serves as an important component of the management of COPD and is beneficial in improving health-related quality of life and exercise capacity. It is our opinion that additional RCTs comparing pulmonary rehabilitation and conventional care in COPD are not warranted. Future research studies should focus on identifying which components of pulmonary rehabilitation are essential, its ideal length and location, the degree of supervision and intensity of training required and how long treatment effects persist. This endeavour is important in the light of the new subgroup analysis, which showed a difference in treatment effect on the Chronic Respiratory Questionnaire between hospital-based and community-based programmes but no difference between exercise only and more complex pulmonary rehabilitation programmes (p.2).

2.7 Summary of the Literature

There is a clear gap in the literature related to large scale population-based studies which considers at the overall lung health of patients with TB. Despite the literature that cure after treatment for patients may be the start of COPD, uptake of continuum of care research has been slow, particularly in endemic TB countries and needs to be prioritised. The present study aimed to provide evidence that lung function impairment is present even in first time drug susceptible patients with TB and that there is a clear rationale that PRPs as an adjunct to standard chemotherapy would be beneficial to improving lung function, functional capacity, QoL, and subsequently overall long-term lung health. It was also anticipated that the present study would be able to provide information on the type of exercise as well as the intensity of the activities which is often not provided in PRP guidelines.

CHAPTER THREE: CROSS-SECTIONAL PREVALENCE STUDY (STUDY 1)

The present chapter provides a brief background to the first study, a cross- sectional prevalence study, followed by the methodology, results, and a discussion of the study findings.

3.1 Background to Study 1

Research regarding TB has been primarily focused on mortality, early detection, and the development of new drugs. Often, the impact of the disease on functional capacity and QoL (morbidity) have been under recognised areas of research (Aggarwal, 2010). To provide meaningful holistic management for patients with TB, one must understand the prevalence of abnormal lung function and how the disease impacts on the individual's QoL. In this, the first of three studies for this PhD thesis, the researchers set out to identify the prevalence of abnormal lung function present in patients diagnosed with first time drug susceptible TB, the presence of functional impairment, as well as QoL to better inform what additions to the continuum of care should be considered.

3.2. Methodology of Study 1

3.2.1 Study design

The present study employed a cross-sectional prevalence design using a sample of convenience.

3.2.2 Subjects

Patients who presented at the Ubuntu HIV/TB site and Michael Mapongwana Community health clinic in Khayelitsha were recruited for inclusion in the study. Potential participants comprised all adults with confirmed first-time, drug-susceptible TB who were registered at either clinic and were receiving treatment, with or without HIV co-infection, and who were receiving TB treatment for at least four months (16 weeks). This time point was chosen as most patients would be on the continuation phase of treatment by this time.

3.2.3 Inclusion and exclusion criteria

Adult male and female participants were recruited into the study from both clinics if they met the inclusion criteria of age, namely 18–80 years with confirmed (smear positive or by CXR) drug susceptible TB for which they had been on treatment for at least four months at the time of recruitment (with only pulmonary involvement not extra-pulmonary TB pericarditis TB or Pleural TB).

Participants were excluded from the study if they had had previous TB episodes, recent severe chest trauma (within the previous three months), a recent history of pneumonia, known atopic asthma, chronic bronchitis, emphysema, bronchiectasis prior to TB diagnosis, cardiac failure, or any other unrelated respiratory disease as reported in their medical folder. Exclusion of existing atopic asthma, bronchiectasis, chronic bronchitis, and emphysema was implemented in an attempt to control for any abnormalities in lung function that may have been attributed to TB, and not to include pre-existing lung disease or diseases related to smoking. Selection bias was minimised by inviting all potentially eligible participants to enrol in the study. As described below (Section 3.2.4), potentially eligible participants were identified using the TB registers. However, despite this, not all potentially eligible patients were enrolled as issues of incorrect contact details, missing contact details, or non-updated details hampered enrolment. Unfortunately, a logbook to keep track of the number of patients who were not reached was not kept and this is therefore a recommendation for future studies.

3.2.4 Sample size determination

The sample size was determined using the following formula

$$n = \frac{\mathrm{p}\,(1-\mathrm{p})Z^2}{e^2}$$

where:

- p is the estimated prevalence of abnormal lung function of 60% (based on similar studies (Vecino et al., 2011);
- z is the level of confidence (measure of precision) set at 95% with a z value of 1.96; and
- e is the significant level set at 5%.

Therefore, based on the sample size calculation, an estimated sample of 369 participants was required for this prevalence study.

3.2.5 Recruitment

The research team comprised of a qualified physiotherapist, a research assistant, and an isiXhosa speaking translator (to assist participants who were not fluent in English), who were responsible for the recruitment and screening of potential participants. The study was advertised at the clinics by means of posters both in English and isiXhosa from January 2016. The primary source of recruitment was the use of the TB registers at both clinics to identify potential participants that met the inclusion criteria. The contact details of these potential participants were obtained from their patient records. Potential participants were subsequently contacted telephonically to invite them to participate in the study. In addition, the research team screened clinic attendees awaiting treatment at Ubuntu Site B TB clinic daily for potential participants as this was the primary data collection site.

Ubuntu TB clinic staff also assisted in the screening process and informed the research team of potential participants. Once identified as a potential participant, the research team accompanied the patient to a consultation area away from the general waiting area and provided the details of the study. Potential participants were then given the opportunity to agree to or decline participation. Informed consent was then taken by the research team, with or without the use of the isiXhosa translator as per the participants' request. Only one participant requested consent in Afrikaans.

3.2.6 Procedure

Participants who met the inclusion criteria and provided consent (Appendix B) were escorted to an available, well-ventilated consultation room adjacent to the clinic to complete the questionnaires. The following three questionnaires were then administered to all participants, once-off, by the research team who were trained in the administration thereof:

- A self-designed clinical research form (Appendix C) which collected basic demographic data regarding age, sex, socio-economic status, medical history, and information regarding TB and HIV status and treatment;
- The St Georges Respiratory Questionnaire (SGRQ) (Appendix D) which gathered information regarding the patients' history of chest-related problems/difficulties such as breathlessness, coughing frequency, and whether activities were limited by breathlessness; and
- The EQ-5D-3L (Appendix E), a QoL questionnaire consisting of five domains pertaining to mobility, self-care, usual activities, pain, and anxiety/depression. The questionnaire was also available in isiXhosa (Appendix F).

After completion of all forms, participants were escorted to a separate area to perform the lung function test (spirometry), the six-minute walk test (6MWT), and a CXR, in that order. Details pertaining to the standardised procedure for both the spirometry (Appendix G) and the 6MWT (Appendix H) were explained to participants. The only instances where the testing sequence was not followed was as a result of inclement weather, which required the participant complete the 6MWT first, as the walking area was situated outside the assessment room at the clinic and only provided partial cover when raining. In this event, after the 6MWT, participants were taken for a CXR and the spirometry was performed last to ensure recovery from the 6MWT.

Firstly, the technique for spirometry was explained to the participant by the research team in the participant's preferred language (either English or isiXhosa). This was followed by a demonstration by the research team and a mock execution by the participant to establish whether they understood the actions required. In addition, the research team also utilised a short video clip for participants who were unclear during the mock execution or demonstration. The video clip was presented in isiXhosa and demonstrated the correct and incorrect methods for spirometry. A minimum of three and a maximum of eight attempts were completed by each participant as per the standardised guidelines (Graham et al., 2019; Koegelenberg et al., 2013; Miller et al., 2005). The best value from the three best acceptable spirometry attempts was recorded as the patient's lung function parameters. At this stage, participants who had an unacceptable lung function test due to non-reproducibility between attempts were excluded in analyses pertaining to lung function specifically. Data regarding functional and HRQoL measures outcomes were, however, still analysed for these participants.

Functional capacity was assessed objectively by means of the 6MWT. The 6MWT is a self-paced test using a measured demarcated distance where the patient is required to walk on a flat indoor surface for six minutes using two cones 30m apart. Although the guidelines for the 6MWT (Crapo et al., 2002) state that the cones be placed 30m apart, this was not possible at the research site as there was no viable indoor space of sufficient in length for patients to execute the guidelines exactly. Hence, a pragmatic approach was used to execute the guidelines as best possible, which comprised of a 20m space between two clinic structures that was largely sheltered from the elements. All other aspects of the guidelines, however, such as standardised instructions including no additional prompting during the execution of the 6MWT were adhered to. The primary measurement for this test was the total distance the patient covered in the allocated time. Prior to commencement of the 6MWT, participants had their resting blood pressure, heart rate, and oxygen saturation levels measured by means of electronic blood pressure monitor (Rossmax CH155F Digital Blood Pressure Meter) and a portable oxygen saturation probe (Pulse Oximeter Fingertip CMS-50DL with LED Display) respectively, as well as again immediately after the test as per the 6MWT guidelines (Crapo et al., 2002). Furthermore, the Modified Borg Dyspnoea Scale (Kendrick, Baxi, & Smith, 2000) was also noted prior to commencing the test and again immediately afterwards. Both the spirometry and the 6MWT were administered by either the qualified physiotherapist or the research assistant who had been trained in the execution of both assessments.

Finally, participants had a CXR (posterior-anterior view) taken by the clinics resident research radiographer. The CXR was taken on the same day as the lung function test and the 6MWT as a rule; however, if the radiographer was unavailable on the same day due to either other commitments or the machine being unavailable for operational reasons, participants were asked to return the following day for their CXR. If patients did not return the following day, they were contacted telephonically as a reminder. All participants who were required to return on an additional day to the clinic for the CXR were reimbursed to the value of R30 for travel expenses. The CXRs were used to assess the radiological profile of lung involvement due to TB in relation to spirometry results. An adapted version of the Timika scoring system (Kriel, Lotz, Kidd, & Walzl, 2015) was used, which specified the percentage of abnormal lung without specifying the abnormality other than cavities.

3.2.7 Instrumentation used as outcome measures for Study 1 (prevalence)

3.2.7.1 Spirometry

The primary outcome measures for both studies were lung function parameters, specifically FEV_1, FVC, and the ratio of FEV_1/FVC. The Medical International Research (MIR) Spirolab III desktop spirometer was used to obtain all parameters. The standardised procedure was used for lung testing as described by Miller et al. (2005) (refer to Appendix G), which is similar to the update version by Graham et al. (2019). A reusable MIR turbine was used in conjunction with a disposable mouthpiece with a built-in filter for each participant to reduce the risk of infection. Mouth pieces were disposed of in a medical waste bin after use by each participant. The reusable turbine was disinfected daily. There are no published studies validating this specific spirometer, although spirometry in general is considered as the most commonly reproducible test for lung function assessment (Vogelmeier et al., 2017). Calibration of the spirometer was performed daily by the research assistant using a 3L calibration syringe.

Spirometry was graded using the quality control grading system of the MIR Spirolab III desktop spirometer, which grades each FVC or FEV test based on a scale from A–F as follows:

- A: at the end of two acceptable attempts, the variation of the two highest FEV_1 values and the two highest FEV_6 values are less than or equal to 100 mL;
- B: at the end of two acceptable attempts, the variation of the two highest FEV_1 values is between 101 and 150 mL;
- C: at the end of two acceptable attempts, the variation of the two highest FEV_1 values is between 151 and 200 mL;

- D: only one attempts was acceptable or there is more than one acceptable attempt but the variation of the two highest FEV_1 values is greater than 200 mL; and
- F: no acceptable attempts.

Following a discussion with a lung function technician and the research supervisors, it was agreed that only Gradings A and B would be accepted for analysis.

3.2.7.2 The six-minute walk test for functional capacity

Numerous methods are used in research to measure functional capacity, including the 6MWT, the shuttle-walk test, stair climbing, and specific activity scales for cardiac patients such as the New York Heart Association Classification and cardiopulmonary exercise stress testing (Vogelmeier et al., 2017). The gold standard for functional capacity testing is cardiopulmonary exercise stress testing; however, as it requires expensive equipment and trained personnel to execute, its accessibility is limited (Bernstein, 2012). The 6MWT is inexpensive and can be conducted easily in a resource-limited setting to assess changes in functional exercise capacity (Bernstein, 2012; Guessogo, Mandengue, Ndemba, Medjo, & Minye, 2016; Holland et al., 2014). According to Holland et al. (2014), the 6MWT is valid and reliable when used to assess functional exercise capacity. It is a self-paced test which measures the distance the patient walks on a flat surface for six minutes. The primary measurement is the total distance the patient covers in the allocated time. Measurement of dyspnoea and level of fatigue can also be ascertained as secondary outcomes using the Modified Borg Dyspnoea Scale (Pryor & Prasad, 2002), which was utilised in this study (Enright, 2003; Jenkins, 2007). The distance measured within the six minutes provides a standardised, objective, and integrated assessment of the cardiopulmonary and musculoskeletal system that is relevant to daily activities (Enright, 2003; Guessogo et al., 2016) and therefore it was used as a generic, one-time measure of functional status for participants (Sivaranjini, Vanamail, & Eason, 2010). The use of the 6MWT in patients with TB has shown that the test is reliable and valid as an outcome measure for functional capacity in this population (Guessogo et al., 2016).

3.2.7.3 Health-related quality of life

The EQ-5D-3L and the SGRQ were used in both Studies 1 and 3. Two HRQoL questionnaires were used in order to cover both the functional capacity as well as the impact of the respiratory symptoms on function. The EQ-5D-3L, translated into isiXhosa (Appendix F) and Afrikaans (Appendix I), has been validated in several South African studies (Jelsma, Mkoka, Amosun, & Nieuwveldt, 2004).

The research assistant was trained to administer the questionnaires. However, it must be noted that due to the high illiteracy rate, very few (approximately 10/314) participants in Study 1 were able to self-administer the questionnaires, and the few who did requested the English versions in preference to the isiXhosa translated versions. Therefore, in Study 1, although the EQ-5D-3L was available in isiXhosa, it was seldom used. Hence in both Study 1 and Study 3 (intervention), the questionnaires were in administered predominantly in English and the research assistant would translate into isiXhosa where required.

3.2.7.4 EQ-5D-3L

The EQ-5D-3L is the most widely used generic, preference-based measure of HRQoL, which produces utility scores anchored at 0 for dead and 1 for perfect health (Cuthbertson, Scott, Strachan, Kilonzo, & Vale, 2005; Rowen, Brazier, & Roberts, 2009). The EQ-5D-3L is brief and provides an overall summary index; its health state classification is based on the combination of answers to five items, each with only three possible answers (Alemayehu et al., 2017; Nordlund, Ekberg, & Kristenson, 2005). The descriptive system has five dimensions (mobility, self-care, usual activity, pain/discomfort, and anxiety/depression) and three levels (no problems, some problems, and extreme problems) which create 243 unique health states (Rowen et al., 2009). The five attributes translate to the patient not being confined to bed, being unable to wash or dress themself, being unable to perform usual activities, being in extreme pain or discomfort, and being extremely anxious or depressed (Cuthbertson et al., 2005). The EQ-5D-3L is reliable and has been validated in the South African population in various contexts (Jelsma et al., 2004). The EQ-5D-3L has also been translated into isiXhosa and Afrikaans and been found to be reliable; it was used for participants who preferred these languages (Jelsma et al., 2004).

3.2.7.5 St George's Respiratory Questionnaire

The SGRQ is a questionnaire consisting of three domains: symptoms, activity, and impacts (psycho-social) with 50 items to assess QoL. It was primarily developed to measure health impairment in asthma and COPD patients, although it has been used in a variety of diseases including TB (Ralph et al., 2013). A minimum change in score of four units was established as clinically relevant after patient and clinician testing (P. W. Jones, 1992). The SGRQ is a reliable and validated tool to measure the health impairment for individuals living with COPD and respiratory disease in general (Pasipanodya et al., 2007). In Study 1 (prevalence), the SGRQ was used as a once-off, baseline assessment of respiratory health. In Study 3 (intervention), the SGRQ was taken at baseline, at six weeks, and at 12 weeks post intervention.

The SGRQ is similar to other HRQoL questionnaires that assess symptoms, activity, and the impact of the disease on the health status of the individual. The 15 SGRQ questions are divided into two parts relating to three components namely: symptoms score (part one), and activity and impact score components (part two). Questions related to part one covers the patients' recollection of respiratory symptoms over a period of three months, while part two addresses the patients' current state of well-being, how they are able to perform activities of daily living at present, and whether it impacts on their lives. A total score is calculated by totalling all weighted positive responses in each component and expressing it as a percentage of the total weight of the questionnaire. A score of zero indicates the best possible health status and a score of 100 equates to the worst possible health status.

3.2.8 Chest radiography

The use of basic chest radiography remains an integral element for the assessment of an individual suspected of having TB, particularly in high-burden, low-income countries (Pinto et al., 2013). Although there are limitations due to the intra- and inter-observer variability, it is an affordable instrument to supplement TB diagnosis in resource-limited facilities. A simple semi-quantitative scoring system based on the Timika scoring system (Ralph et al., 2010) and adapted by Kriel et al. (2015) was used to analyse the participants' CXR. The scoring system was shown to have good inter- and intra-reader reliability by Kriel et al. (2015), who used the scoring system to evaluate the radiological severity score to predict outcome in adults with TB. In brief, the scoring system consists of four steps for analysis of CXRs which consist of the following (Kriel et al., 2015):

- **Step 1:** demarcation of six zones – here the CXR is divided into six sections of relatively similar size. The lines in general are at the level of the inferior border of the fifth or six rib at the costovertebral joint bilaterally, and at the level of the inferior border of the eighth or ninth rib at the costovertebral joint bilaterally but the demarcation was subjective. Equal size of lung zones is important.
- **Step 2:** chest x-rays were read systematically from top to bottom and right to left to estimate the overall percentage of affected lung for each zone. Each zone would then be scored for the percentage of active involvement from 5% or 10–100% in 10% increments. In this step, the most visible opacification type in each zone is identified – either nodular or homogenous (refer to Glossary of Terms).

Standard proportions are applied for zones with mainly nodular infiltrates (0.5), or (1.0) for mainly homogenous infiltrates which are then multiplied by the proportion of lung affected in the zone, e.g., a zone that is 70% diseased with mainly homogenous infiltrates will score – 70% x 1.0 = 70% and a zone with 70% disease primarily with nodular infiltrates will score – 70% x 0.5 = 35%.

- **Step 3:** determine whether a cavity is present. A cavity is defined as a hypodense area greater than or equal to 1cm in diameter. If a cavity is present, then a constant value of 40 is added to the overall percentage.
- **Step 4:** calculate the final Timika score by adding all of the zones and dividing by 600 x 100% then add the constant for the cavity if applicable. For example:

Table 2. Example of Timika Score Calculation.

ALL ZONES		FINAL SCORE
25	0	= 75/600 x 100%
10	40	=**12.5%** diseased lung with no cavities
0	0	=12.5% +40* =**52.5% diseased lung with cavities**

Scoring was carried out by two independent doctors who were familiar with reading pulmonary tuberculous CXRs and were trained to use the scoring system as described. Each scorer documented scores on a self-designed clinical research form (Appendix J). If the scores between readers had a difference of greater than 10%, they were required to reach a consensus. If consensus was not possible a third scorer, a pulmonologist, would resolve the discrepancy. A trial of 20 CXRs was performed by the two readers prior to reading the study CXRs to ensure inter-rater reliability using the self-designed clinical research form (Appendix J).

3.2.9 Statistical analysis and data management

Statistical analysis was performed using Stata version 15 (Stata Corp, Texas, USA, 2017). Univariate and bivariate descriptive statistics were used to summarise the characteristics of patients, which included clinical and socio-demographic characteristics, QoL, physical activity levels, TB treatment and HIV status, and lung function parameters. Univariate and stepwise multivariate logistic regression models were used to identify factors independently associated with abnormal lung function. Spearman's correlation was used as data did not meet tests of normality. Spearman correlation findings were categorized as follows: 0-0.19 very weak, 0.2-.39 weak, 0.4-0.59 moderate, 0.6-0.79 strong and 0.8-1.0 very strong. Fischer's exact tests were performed on categorical variables

respectively to measure degree of association between the two variables. Missing data was excluded on a variable basis. All data collected was entered on an Excel spreadsheet, cleaned, and organised for analysis. The data files were password protected and stored on a server, backed up by an external hard drive. Both were firewall protected.

3.2.10 Ethical considerations for Study 1

The study adhered to the Declaration of Helsinki (World Health Organisation, 2001). Ethical approval was obtained from the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences at the University of Cape Town (HREC/REF:725/2015, Appendix K). Approval was also obtained from the Western Cape Department of Health and from all the relevant stakeholders of the various clinics before the commencement of Study 1 (Appendix L).

3.2.10.1 Autonomy and beneficence

Participants were informed that participation in the study was voluntary and that it would not affect their scheduled visits, or the standard of care provided at the clinic. As participation was voluntary, participants were informed that they could withdraw from the study at any stage without being penalised. An information sheet was provided to each participant in their preferred language, which was either English (Appendix B) or isiXhosa (Appendices B_1), to read or have it read to them by the research assistant who was fluent in both languages. Informed consent was obtained from participants recruited into the study who met the inclusion criteria. All demographic and personal information of participants remained confidential as each participant was provided with a study number. Data collected was stored on a password protected external hard drive, and all hard copies, which were coded with only study numbers, were kept in a secure locked cabinet away from the clinic. Participants received reimbursement for travel costs (R30) as well as refreshments (water and some fruit) on enrolment.

3.2.10.2 Non-maleficence and risks

In Study 1, participants were asked to perform two functional assessments, namely spirometry and a 6MWT for lung function and functional capacity respectively. The risks relating to participating in the study were low as participants performed once-off assessments and therefore would not experience any negative, long-term effects as a result of the testing. Participants were informed that they may experience some dizziness or shortness of breath immediately after blowing into the spirometer or performing the 6MWT, however this should have resolved within five minutes of completing the

activities. If participants experienced any continued shortness of breath or dizziness, they were immediately referred to the clinic doctor.

During Study 1, no such adverse events occurred. Participants were informed that they would be required to disclose their HIV status and that for some this may cause discomfort, however counselling was made available where required.

3.2.10.3 Justice

The intention of Study 1 was to assess the prevalence of lung function abnormality, ascertain functional capacity, physical activity, and the HRQoL of individuals with TB, with or without HIV co-infection. Participants were included as they were close to the completion of their TB treatment and lived in an area in which TB was endemic. Participants were made aware that the results of the study would be published in an accredited medical/health care journal to create awareness of the prevalence of lung function abnormality still present five months after TB treatment and the impact this may have on lung function, functional capacity, and QoL.

3.3. Results of Study 1

3.3.1 Introduction

In this section, the results are presented following the objectives set out in Section 1.2 above. Socio-demographic data is presented first, followed by clinical data. Data regarding the outcome measures is then reported using the following structure:

- *Lung function parameters (FEV_1, FVC and FEV_1/FVC);
- *Classification of lung function abnormalities;
- 6MWT;
- QoL measurements (EQ-5D-3L and SGRQ); followed by
- CXR.

**only for participants with acceptable lung function tests (A-LFTs)*

All the above is reported on in the following manner: first, the total sample (n=314); second, those participants who performed acceptable lung function tests (A-LFT); third, those participants who had unacceptable lung function tests (U-LFT); and fourth, per HIV status in all three of the above categories. The flow chart of recruitment is presented in Figure 4 below.

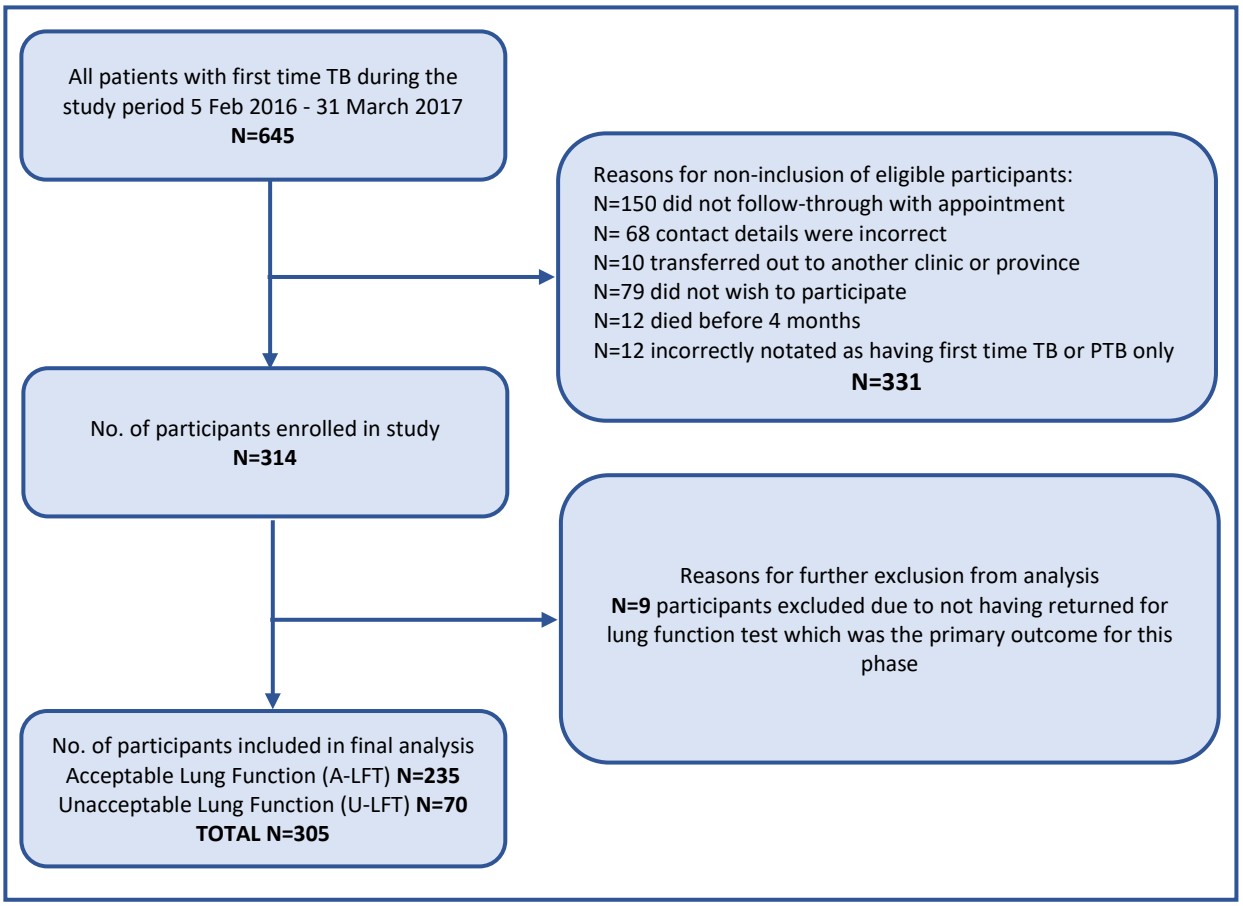


Figure 4. Flowchart of Recruitment.

A sample of 314 participants met the inclusion criteria and provided consent. However, nine participants were excluded after enrolment as they did not complete the lung function testing (spirometry) which was the primary outcome. Hence, the total sample analysed for Study 1 was 305 participants. Of these 305 participants, 235 (77%) had an A-LFT and the remaining 70 (23%) participants had an U-LFT. Due to the larger than expected proportion of participants with U-LFT, post hoc analysis was performed.

Socio-demographic characteristics of participants are described first, followed by the clinical characteristics. Participants resided in Khayelitsha and were recruited from two TB clinics, namely Ubuntu Site B clinic and the Michael Mapongwana community health centre. The majority of participants (90.3%, n=224) were recruited from Ubuntu Site B clinic.

3.3.2 Socio-demographic characteristics

The socio-demographic profile of the total sample is presented in below. Regarding sex, 55.1% (n=168) of the total sample were male and 44.9% (n=137) were female. Similar percentages were noted when comparing the group that had A-LFT tests versus those who had U-LFTs. The median age for the total sample as well as the A-LFT and U-LFT participants was the same at 36 years (IQR:28–43).

In general, participants were shack dwellers, had running water close to their shack (less than 5m), did not have a flushing toilet inside their shack, and used electricity as the main power source for cooking and heating. The median number of persons living in a shack of an average size of 2m x 2m was 3.5. Two-thirds (61.1%) of the participants in the study were unemployed at the time of enrolment. Educational levels were similar in the A-LFT and U-LFT participants, with 72.3% and 72.9% having obtained a secondary level education respectively.

Table 3. Socio-Demographic Profile of the Total Sample and those with Acceptable (A-LFT) and Unacceptable (U-LFT) Lung Function Tests.

CATEGORY	DESCRIPTION	TOTAL (N=305) N (%)	A-LFT (N=235) N (%)	U-LFT (N=70) N (%)
SEX	**Total**	305	235	70
	Male	168 (55.1)	130 (55.3)	38 (54.3)
	Female	137 (44.9)	105 (44.7)	32 (45.7)
AGE GROUPS (YEARS)	**18–25**	50 (16.4)	39 (16.6)	11 (15.7)
	26–35	97 (31.8)	74 (31.5)	23 (32.9)
	36–45	92 (30.2)	68 (28.9)	24 (34.3)
	46–55	44 (14.4)	35 (14.9)	9 (12.9)
	56–65	16 (5.2)	15 (6.4)	1 (1.4)
	65+	6 (2.0)	4 (1.7)	2 (2.9)
	Median age, (IQR)	36 (28–43)	36 (28–43)	36 (28–43)
HOUSING AMENITIES	Brick house	119 (39.0)	92 (39.1)	27 (38.6)
	Shack dwelling	169 (55.4)	128 (54.5)	41 (58.6)
	Running water inside	120 (39.3)	94 (40.0)	26 (37.1)
	Running water outside (<5m away)	131 (43.0)	104 (44.3)	27 (38.6)
	Running water outside (>5m away)	37 (11.8)	23 (9.8)	14 (20.0)
	Flushing toilet (inside)	99 (31.5)	72 (30.6)	23 (32.9)
	Flushing toilet (outside)	156 (49.7)	123 (52.3)	30 (42.9)
	Bucket toilet	26 (8.3)	15 (6.4)	11 (15.7)
	No toilet	4 (1.3)	2 (0.9)	2 (0.9)
	Electricity	271 (86.3)	205 (87.2)	59 (84.3)
	Biomass (wood) for cooking/heating	5 (1.6)	4 (1.7)	1 (1.4)
	Paraffin for cooking/heating	18 (5.7)	14 (6.0)	4 (5.7)
	Gas for cooking/heating	13 (4.1)	8 (3.4)	5 (7.1)
	Median no. of people living in dwelling	3	3	3.5
EDUCATION	Primary or less	76 (24.9)	59 (25.1)	17 (24.3)
	Secondary	221 (72.5)	170 (72.3)	51 (72.9)
	Tertiary	8 (2.6)	6 (2.6)	2 (2.9)
EMPLOYMENT STATUS	Employed	117 (38.4)	96 (40.9)	21 (30.0)
	Unemployed	188 (61.6)	139 (59.1)	49 (70.0)

3.3.3 Clinical characteristics

The clinical characteristics of participants are provided in Table 4 below. Fewer than 9% of participants had hypertension, fewer than 5% had any type of diabetes mellitus, and only 1% had documented angina. Only 2.2% of the total sample had two or more co-morbidities. In the total sample 51% reported a HIV-positive status which differed slightly between the A-LFT and U-LFT participants (50.6% and 52.9% respectively). The median BMI for the total sample was 22.8kg/m^2 (IQR: 20.6–26.8) and fell in the healthy BMI category as described by the National Institute of Health's BMI calculator (National Institute of Health, 2014). Male participants had a lower median BMI of 21.9kg/m^2 (IQR: 20.0–23.8), which was similar for both A-LFT and U-LFT participants. Females, however, had a median BMI of 25.2kg/m^2, which is categorised as overweight; this did not differ between the A-LFT and U-LFT participants. When comparing the mean BMI of the A-LFT and U-LFT participants, there was no significant difference (p=0.6).

Table 4. Clinical Characteristics of Participants in the Total Sample and those with and without Acceptable Lung Function Tests.

CATEGORY	DESCRIPTION	Total (N=305) N (%)	A-LFT (N=235) N (%)	U-LFT (N=70) N (%)
REPORTED CO-MORBIDITIES	Hypertension	25 (8.2)	20 (8.5)	5 (7.1)
	Diabetes M Type 1	13 (4.3)	10 (4.3)	3 (4.3)
	Diabetes M Type 2	7 (2.3)	5 (2.1)	2 (2.9)
	Angina	2 (0.7)	1 (0.4)	1 (1.4)
	Other	10 (3.3)	9 (3.8)	1 (1.4)
	>2 morbidities	7 (2.2)	6 (2.6)	1 (1.4)
MEDIAN BMI KG/M^2, (IQR)	**Total**	22.8 (20.6–26.8)	22.8 (20.7–26.9)	22.8 (20.2–26.4)
	Male	21.9 (20.0–23.8)	22.0 (20.1–24.1)	21.7 (19.8–23.0)
	Female	25.2 (22.0–29.5)	25.2 (22.0–29.0)	25.4 (21.8–31.8)
HIV STATUS	Positive	156 (51.1)	119 (50.6)	37 (52.9)
	Negative	139 (45.6)	110 (46.8)	29 (41.4)
	Unknown	10 (3.3)	6 (2.6)	4 (5.7)
SMOKING HISTORY	Ever smoked (incl. current)	140 (46.1)	112 (47.9)	28 (40.0)
	Never smoked	164 (53.9)	122 (52.1)	42 (60.0)
PACK YEARS (MEAN, SD)	Total	2.2 (4.3)	2.4 (4.4)	1.8 (3.7)
	Male	3.8 (5.2)	4.0 (5.4)	3.1 (4.6)
	Female	0.3 (0.9)	0.4 (1.0)	0.2 (0.6)
RECREATIONAL DRUG USERS	Total	24 (7.8)	12 (5.1)	12 (5.1)
MEDIAN DURATION ON TB TREATMENT IN WEEKS, (IQR)	Total	19 (18–22)	19 (17–22)	20 (18–22)
	Male	19 (18–22)	19 (17–22)	20 (18–22)
	Female	19 (18–21)	19 (17–21)	18 (18–22.5)

Regarding smoking history, participants were classified as either having previously smoked tobacco or never previously smoked tobacco. In the total sample, participants who had previously smoked comprised 45.9%. There was minimal difference between the A-LFT and U-LFT participants on smoking history at 47.9% and 40% respectively (p=0.25). The median time on TB treatment at time of enrolment was 19 weeks (IQR:18–22) for the overall sample and there was no significant difference between the A-LFT and U-LFT participants (Table 4). As part of the inclusion criteria (refer to Section 3.2.3 above), all participants had to have received at least four months (16 weeks) of treatment.

3.3.4 Lung function parameters

Acceptable lung function tests were performed by 235 participants. An A-LFT was defined as being acceptable and reproducible, having a grading of A or B using the MIR Spirolab III (refer to Section 3.2.7.1). Seventy participants had U-LFT as they were not reproducible and were graded C–F using the MIR Spirolab III (refer Appendix M). Analyses were only performed and reported on for the 235 participants with A-LFT.

The Global Lung function Initiative reference equation for predicted values of lung function parameters (which were pre-programmed in the SPIROLAB III) was used for FEV_1 and FVC (Quanjer et al., 2012). In addition, the FEV_1/FVC ratio (refer to Glossary of Terms) is also reported below as these are the parameters used to classify lung function into normal, obstructive, restrictive, or mixed abnormalities.

3.3.4.1 Forced expiratory volume in one second

Forced expiratory volume in one second is defined as the volume of air that can be forced out in one second after taking a deep breath and is used in the assessment of severity of lung diseases (Heuer & Scanlan, 2017). The absolute value and the percentage predicted FEV_1 value, which is based on height, weight, and race are presented in Table 5 below. The median value for absolute FEV_1 for the sample was 2.5 litres/sec (L/sec) with an IQR:2.0–3.0 (Table 5). There was no statistically significant difference when comparing the percentage predicted FVC values by sex.

Table 5. Absolute and Percentage Predicted Values for Forced Expiratory Volume in one second (FEV_1) by Sex.

	FEV_1 (L/sec)			PERCENTAGE PREDICTED FEV_1		
	Total	**Female**	**Male**	**Total**	**Female**	**Male**
N	235	105	130	235	105	130
MEDIAN	2.5	2.2	2.8	89	91	87
IQR	2.0–3.0	1.9–2.6	2.3–3.3	75–101	77–98	75–87

The mean FEV_1 in relation to HIV status in the A-LFT is depicted in Figure 5 below. Forced Expiratory Volume in one second between the HIV-positive and HIV-negative participants was tested. No statistical comparison to unknown HIV status was performed due to the small number (n=10). There was, however, no statistically significant difference between HIV status (p=0.400) when examining the mean FEV_1.

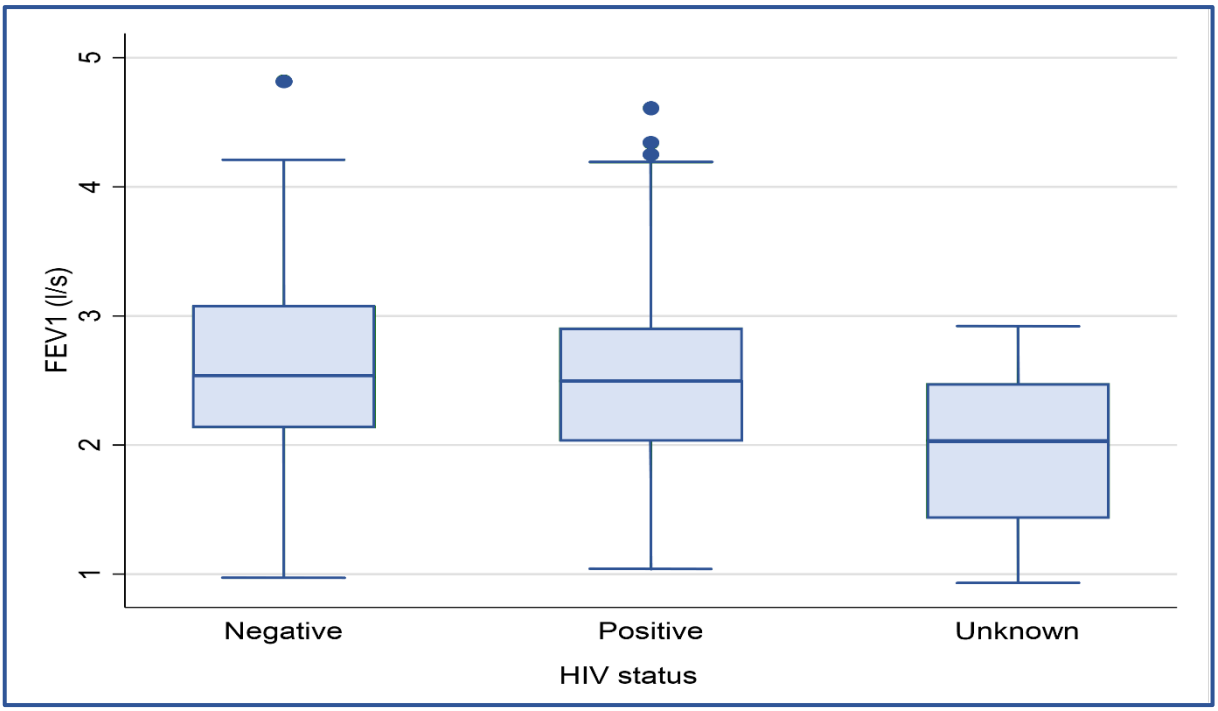


Figure 5. Mean Forced Expiratory Values in one second (FEV_1) for Acceptable Lung Function Tests (A-LFT) in Relation to HIV Status.

3.3.4.2 Forced vital capacity

Forced vital capacity is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. Measurements may be used to help diagnose lung disease, determine its severity and progression, and assess an individual's ability to tolerate surgery. The absolute median value for FVC was 3.2L for the entire sample, and 2.7L and 3.7L respectively for female versus male participants (Table 6). There was no statistically significant difference when comparing the predicted FVC percentage values by sex (p=0.6).

Table 6. Absolute and Percentage Predicted Values for Forced Vital Capacity (FVC) by Sex.

	FVC (L/sec)			PERCENTAGE PREDICTED FVC		
	Total	**Female**	**Male**	**Total**	**Female**	**Male**
N	235	105	130	235	105	130
MEDIAN	3.2	2.7	3.7	94	93	94.5
IQR	2.6–3.9	2.4–3.1	3.2–4.2	81–107	81–105	82–107

3.3.4.3 Forced expiratory volume in one second/Forced vital capacity

The FEV_1/FVC ratio is a measurement used in conjunction with the FEV_1 value to determine the pattern of lung function abnormality, i.e., obstructive, restrictive, mixed lung function abnormality, or normal lung physiology. It represents the proportion of a person's vital capacity that they are able to expire in the first second of forced expiration in relation to the full FVC. The median FEV_1/FVC ratio for those who had acceptable lung function tests was 79.7% (IQR:73.5–84.2) (Table 7).

Table 7: Absolute and Percentage Predicted Values for the Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC) Ratio.

	FEV/FVC RATIO			PERCENTAGE PREDICTED FEV/FVC RATIO		
	Total	**Female**	**Male**	**Total**	**Female**	**Male**
N	235	105	130	235	105	130
MEDIAN	79.7	81.1	78.5	95	95	94.5
IQR	73.5–84.2	74.9–84.4	70.5–83.1	88–100	90–100	87–100

3.3.5 Classification of lung function

The FEV_1/FVC ratio and FEV_1 are the parameters used to determine classification of lung function into obstruction and restriction and the severity of the abnormality respectively. A FEV_1/FVC ratio value is considered normal when the ratio is equal to or above 70% for the individual. Classification of lung function used in this study to determine normal, obstructive, restrictive, and mixed lung functions and severity is outlined below (Table 8).

Table 8. Lung Function Classification and Severity.

CLASSIFICATION	LUNG FUNCTION PARAMETERS
NORMAL	FVC and FEV_1 are within 80% of the predicted value FEV_1/FVC ratio is ≥70% of predicted values
OBSTRUCTION	FEV_1/FVC ratio <70% Severity: Stage 1: FEV_1 % PRED >= 80 Stage 2: 50 >= FEV_1 % PRED <80 Stage 3: 30 >= FEV_1 % PRED <50 Stage 4: FEV_1 % PRED <30
RESTRICTION	FVC <80%, FEV_1/FVC ratio >=70% Severity: No restriction: FVC % PRED >= 80 Mild restriction: 65 >= FVC % PRED <80 Moderate restriction: 50 >= FVC %PRED <65 Severe restriction: FVC %PRED <50
MIXED	Both of the above criteria are present in the individual

As can be seen in Figure 6, overall, participants had normal lung functions (68%) with only 32% having abnormal lung function. Restrictive abnormalities were the main abnormality at 15% (n=36) while obstructive and mixed lung abnormalities made up 11% (n=25) and 6% (n=15) respectively.

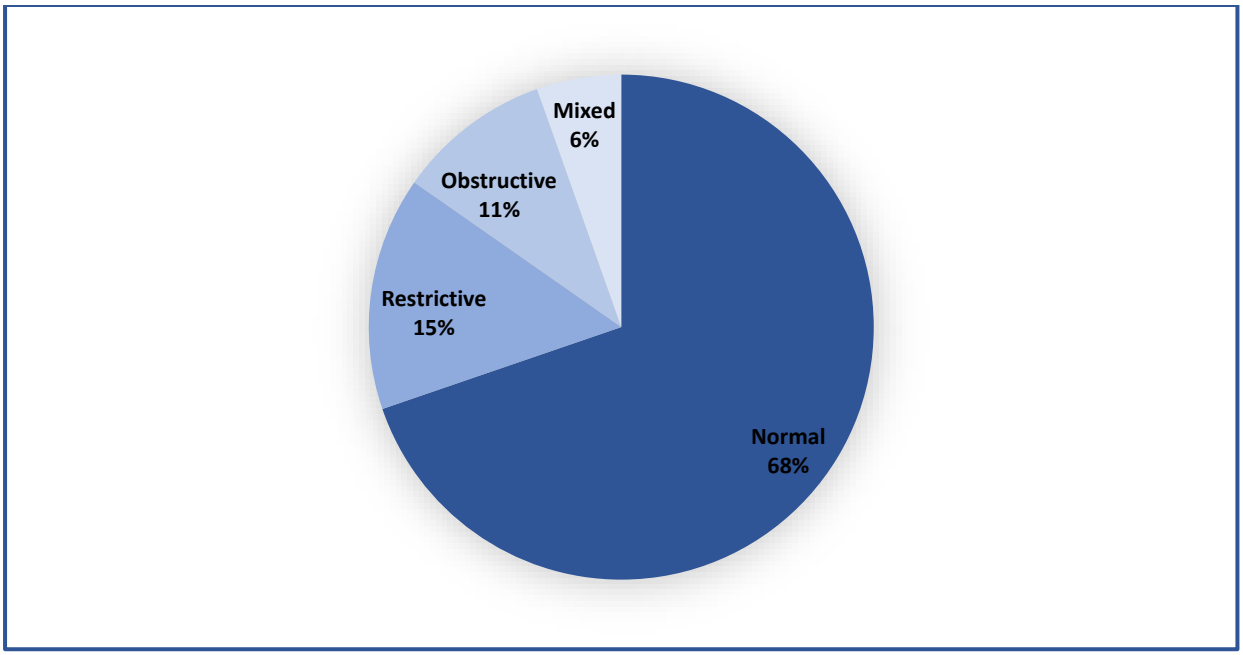


Figure 6. Classification of Lung Function Abnormalities for Acceptable Lung Function Test (A-LFT) Participants (N=235).

3.3.6 Severity of lung function abnormalities

As per the criteria listed in Table 8 above, further analysis was carried out on those participants with abnormal lung function to identify the severity of their restriction and obstruction (Figure 7 and Figure 8 respectively). Nearly half (45%) of the participants with obstructive lung abnormalities were further classified as having stage 2 severity of obstruction, which is equivalent to a moderate obstruction (Figure 8).

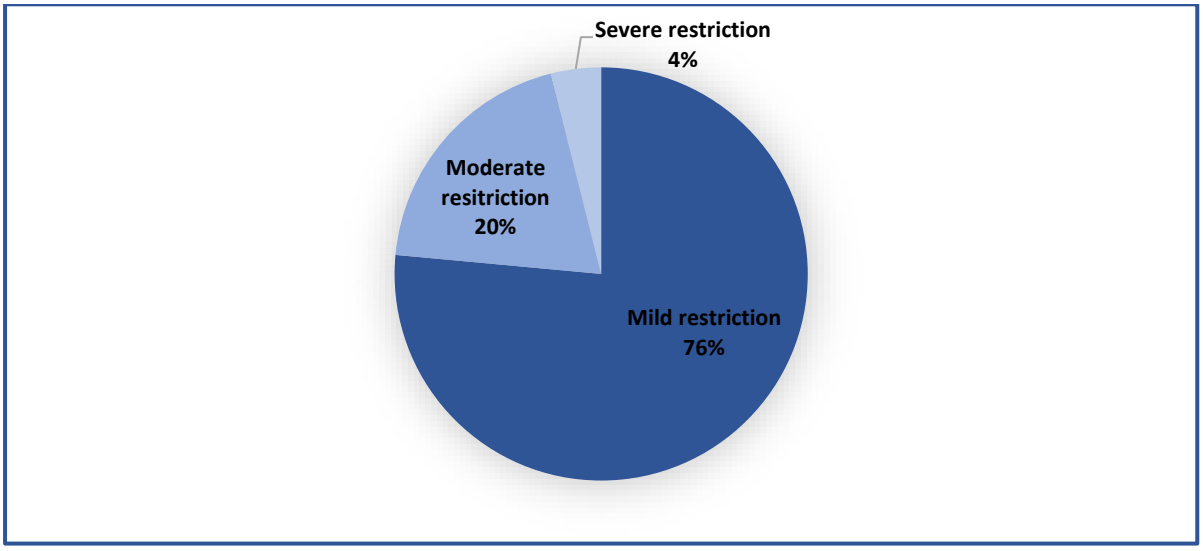


Figure 7. Severity of Restriction of Participants with Abnormal Lung Function (N=36).

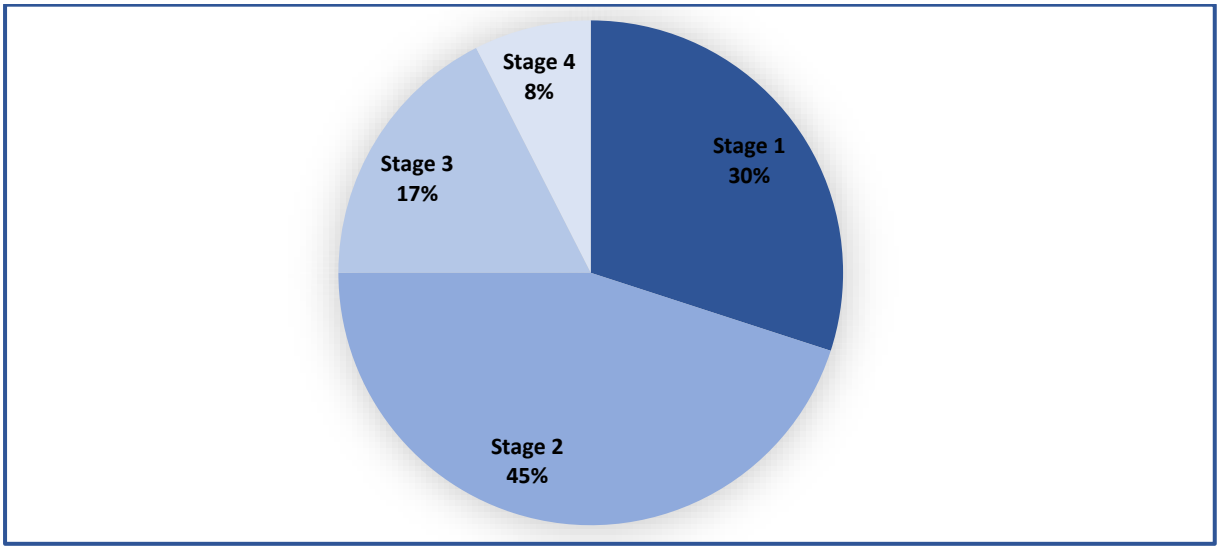


Figure 8. Severity of Obstruction of Participants with Abnormal Lung Function (N=25).

3.3.7 Chest x-ray

Of the 305 participants, only 284 participants had a CXR performed. Twenty-one participants had no CXR taken due to the unavailability of the CXR machine on the day of assessment due to servicing (n=5); 16 participants left the clinic before the CXR was taken and did not return despite follow-up messages and telephone calls; and one participant had an unreadable CXR according to the two independent scorers and was therefore excluded from the analysis. Of the 284 CXRs taken, 218 participants had A-LFT with the remaining 66 participants having U-LFT. The overall mean, median, IQR, and SD are reported in Table 9 for all of the 284 participants, as well as for the A-LFT and U-LFT groups. The median CXR score was 4.0%, 3.9%, and 4.2% for the overall, A-LFT, and U-LFT respectively. There was no statistically significant difference in the means for the A-LFT and U-LFT CXR scores (p=0.2017). Cavities on the CXRs were present in only 27 (9.5%) participants. When stratified by lung function classification (obstructive, restrictive, and mixed), no significant difference was noted (Table 10).

Table 9. Chest X-Ray (CXR) Scores for the Total Sample.

FINAL CXR SCORES	OVERALL (N=284)	A-LFT PARTICIPANTS (N=218)	U-LFT PARTICIPANTS (N=66)
MEAN	9.9	10.5	7.8
SD	15.1	15.8	12.2
RANGE	0–77.9	0–65.8	0–77.9
MEDIAN	4.0	3.9	4.2
IQR	0.9–11	0.9–11	0.9–9.6

Table 10. Odds Ratio for Lung Function and Cavity.

	ODDS RATIO*	95% CI		P-VALUE	N
OBSTRUCTIVE	0.90	0.09	4.23	0.89	21
RESTRICTIVE	1.42	0.38	4.34	0.51	35
MIXED	0.6	0.01	4.47	0.64	15

*For reference: normal lung function has a value of 1

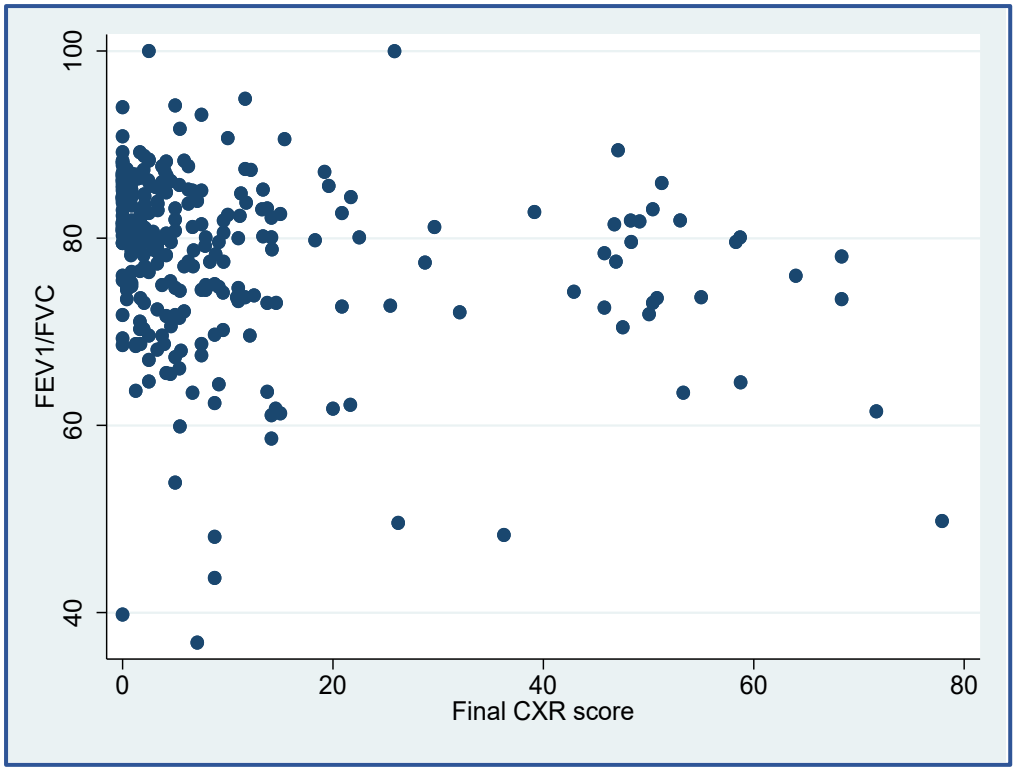


Figure 9. Final Chest X-Ray (CXR) Score and Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC) for the Overall Sample (N=284).

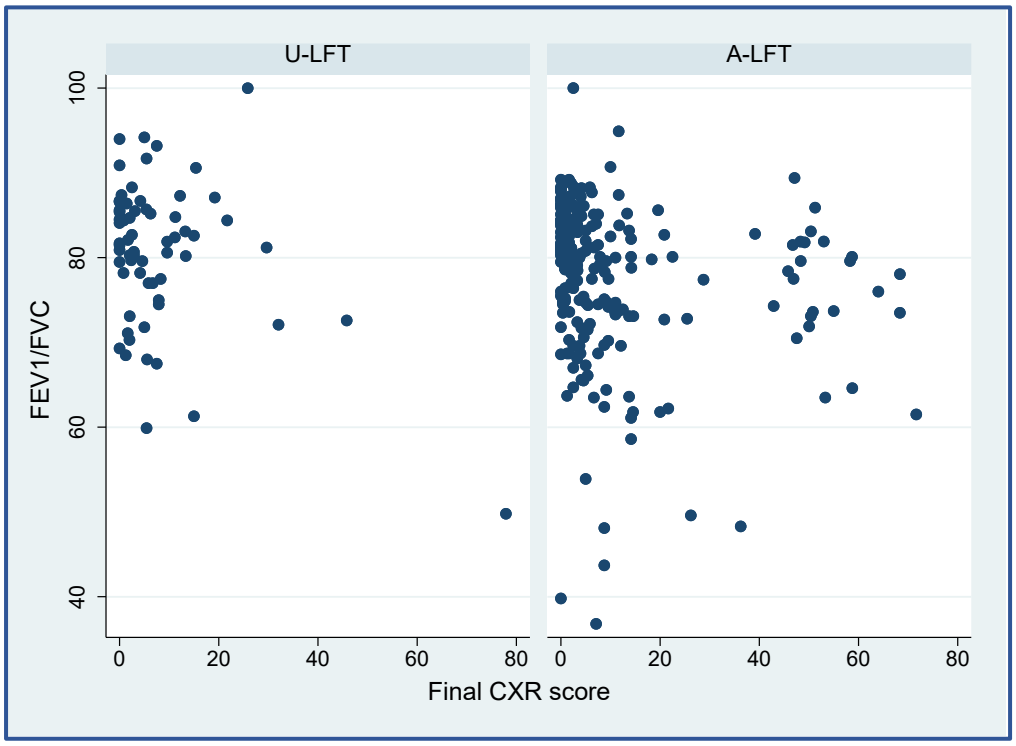


Figure 10. Final Chest X-Ray (CXR) Score for Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC) Values Comparing Unacceptable Lung Function Test (U-LFT) with Acceptable Lung Function Test (A-LFT) Participants.

There is significant correlation between CXR scores and FEV1 for the combined, U-LFT, and A-LFT groups (Table 11, Figure 11, Figure 12). There is a significant correlation between CXR scores and FEV1/FVC ratio for the combined and A-LFT group, while there is no correlation in the U-LFT group.

Table 11. Correlation between Lung Function Parameters Forced Expiratory Volume in one second (FEV_1) and Forced Expiratory Volume in one second/Forced Vital Capacity (FEV_1/FVC) with Final Chest X-Ray (CXR) Scores.

	U-LFT		A-LFT		COMBINED	
	SPEARMAN'S CORRELATION COEFFICIENT	P-VALUE	SPEARMAN'S CORRELATION COEFFICIENT	P-VALUE	SPEARMAN'S CORRELATION COEFFICIENT	P-VALUE
FEV_1/FVC VS FINAL CXR SCORE	0.1479	0.2361	0.3435	0.0000	0.3031	0.0000
FEV_1 VS FINAL CXR SCORE	0.4844	0.0000	0.3572	0.0000	0.3828	0.0000

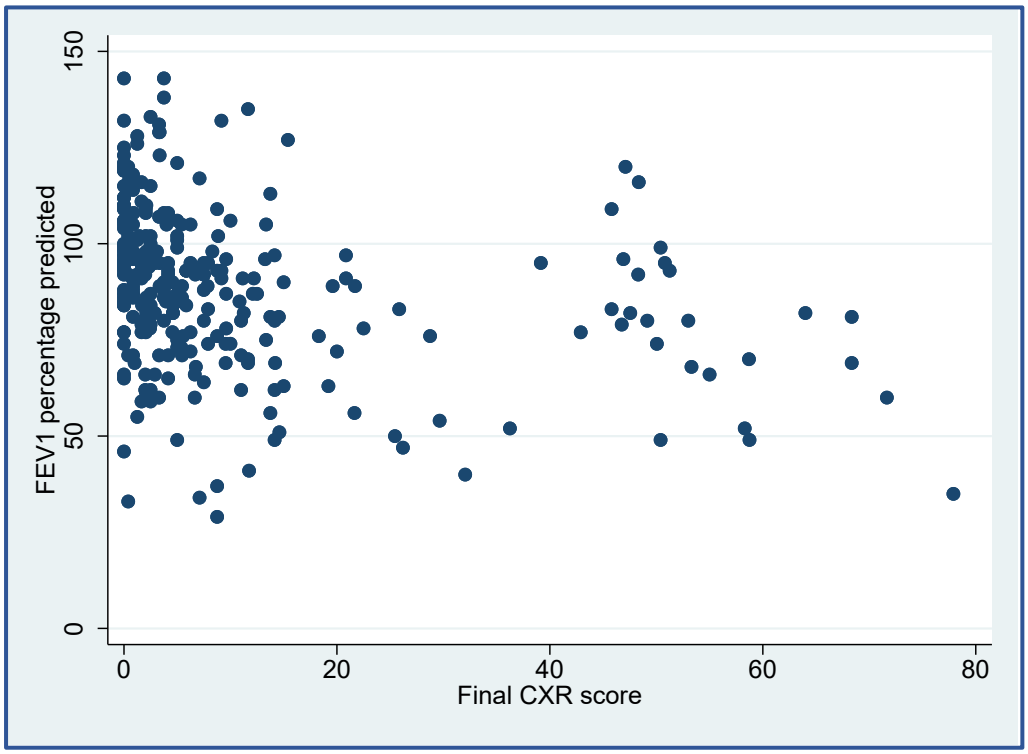


Figure 11. Final Chest X-Ray (CXR) Scores and Forced Expiratory Volume (FEV_1) Percentage Predicted Values for the Sample (N=284).

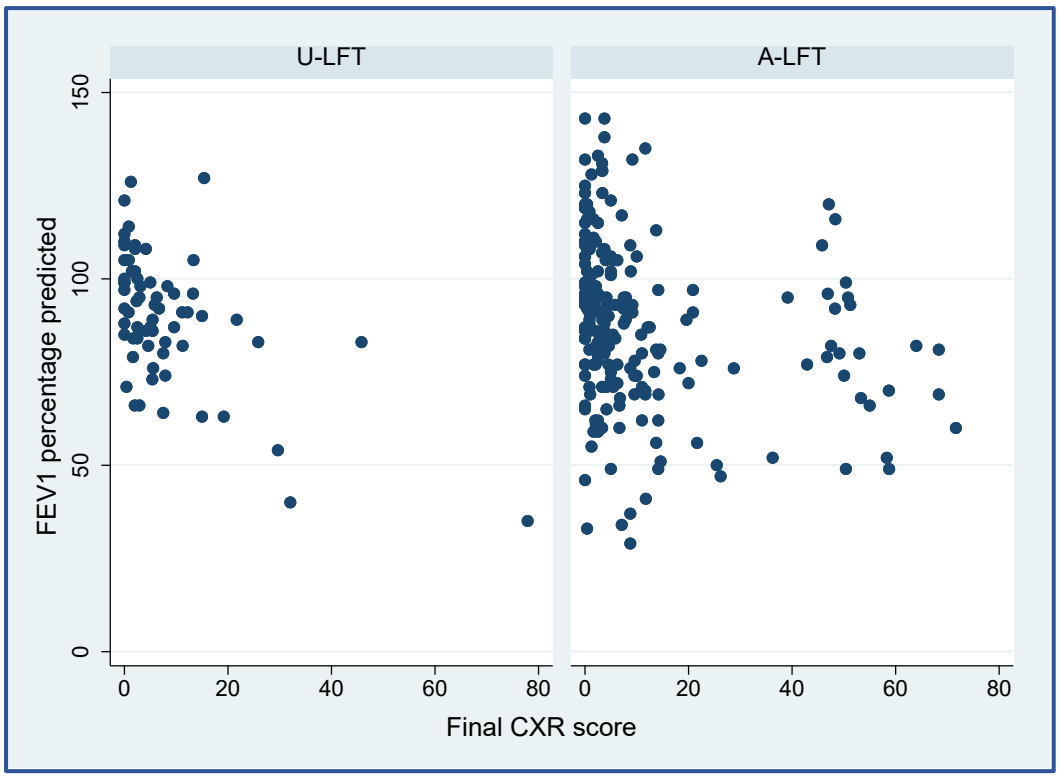


Figure 12. Final Chest X-Ray (CXR) Scores for Forced Expiratory Volume in one second (FEV_1) Percentage Predicted for Unacceptable Lung Function Test (U-LFT) versus Acceptable Lung Function Test (A-LFT) Participants.

3.3.8 Six-minute walk test

Of the 305 participants, only 299 completed the 6MWT (230 in the A-LFT and 69 in the U-LFT). The remaining six participants were unable to complete this outcome measure due to inclement weather (n=4) and high blood pressure readings at rest prior to the start of the test that did not lower after five minutes (n=2). The participants with raised blood pressure were referred to the clinic doctor for further management. The four participants who were unable to perform the 6MWT on the day of enrolment due to inclement weather were asked to return the next day to perform the assessment but did not, despite follow-up SMS/WhatsApp messages and telephone calls. As seen in Table 12, the mean and median distance covered for the total sample was 484.1m and 487m respectively, with a range of 86–802m (SD=96.3m). The mean distance covered in the A-LFT was higher than in the U-LFT group and the difference was statistically significant (p=0.006).

Table 12. Distance Covered in Six-Minute Walk Test (6MWT) in Metres.

	MEAN	SD	RANGE	MEDIAN	IQR
TOTAL SAMPLE (N=299)	484.1m	96.3m	86–802m	487m	430–544
A-LFT SAMPLE (N=230)	492.7m	86.7m	200–802m	490.5m	435–554
U-LFT SAMPLE (N=69)	455.5m	119.3m	86–734m	485.5m	400–524

3.3.8.1 Six-minute walk test in relation to lung function classification

With regard to distance covered by participants in the A-LFT group in relation to their lung classification, participants with obstructive lung classification covered the least distance (463.2m) when compared to those who had a restrictive or mixed classification (Table 13). There was however no significant difference when comparing the mean distance covered by lung function classification (Table 14).

Table 13. Distance Covered in Six-Minute Walk Test (6MWT) by the Acceptable Lung Function (A-LFT) Group.

	MEAN	SD	RANGE	MEDIAN	95% CONF. INTERVAL	
NORMAL LUNG FUNCTION *(N=158, 1 missing distance)*	497.9m	84.8	252–802	497	484.5	511.2
OBSTRUCTIVE DISEASE *(N=24, 1 missing distance)*	463.2m	84.7	200–605	479	427.5	499
RESTRICTIVE DISEASE (*N=33, 3 missing distance)*	488.6m	91.6	287–660	484	456.2	521.1
MIXED (N=15)	494.8m	98.6	360–711	475	440.2	549.4

Table 14. P-values Comparing the Mean Distance Covered by Lung Function Classification.

	OBSTRUCTIVE	RESTRICTIVE	MIXED
NORMAL	0.0638	0.5758	0.8954
OBSTRUCTIVE	-	0.2907	0.2946
RESTRICTIVE	-	-	0.8337

3.3.8.2 Six-minute walk test in relation to HIV status

The distance covered by participants when analysed in relation to HIV status for the total sample and those with A-LFT and U-LFT are presented in Table 15. The mean and median distances covered by the HIV-negative participants were higher than the mean and median distances covered by the HIV-positive participants in the overall group, the A-LFT, and the U-LFT, with a statistically significant difference between the groups (p=0.0067, p=0.0064, and p=0.007 respectively).

Table 15. Distance Covered in Six-Minute Walk Test (6MWT) when Grouped for HIV Status.

OVERALL DISTANCE COVERED IN RELATION TO HIV STATUS					
	MEAN	**MEDIAN**	**RANGE**	**SD**	**N**
NEGATIVE	499.6m	501.5m	86–711	88.6	136
POSITIVE	470.4m	472.0m	120–802	103.2	154
UNKNOWN	484.3m	480.0m	435–570	43.0	9
TOTAL	484.1m	487m	86–802	96.3	299
DISTANCE COVERED BY ACCEPTABLE-LFT (A-LFT) PARTICIPANTS IN RELATION TO HIV STATUS					
	MEAN	**MEDIAN**	**RANGE**	**SD**	**N**
NEGATIVE	509.2m	505.0m	334–711	78.1	107
POSITIVE	477.5m	466.5m	200–802	92.9	118
UNKNOWN	498.0m	490.0m	440–570	50.8	5
TOTAL	492.7m	490.5m	200–802	86.7	230
DISTANCE COVERED BY UNACCEPTABLE-LFT (U-LFT) PARTICIPANTS IN RELATION TO HIV STATUS					
	MEAN	**MEDIAN**	**RANGE**	**SD**	**N**
NEGATIVE	464.1m	494.0m	86–620	114.5	29
POSITIVE	447.2m	477.0m	120–734	130.2	36
UNKNOWN	467.3m	467.5m	435–499	28.1	4
TOTAL	455.5m	485.5m	86–734	119.3	69

3.3.9 Quality of life

3.3.9.1 EQ-5D-3L

In Figure 13 below, the EQ-5D-3L health profile of the total sample is described per domain. Only two participants (0.32%) reported having severe problems in the domains of usual activity and anxiety/depression. Overall, participants reported having no problems in most of the domains (see Figure 13). The domain of pain and discomfort was where participants reported the highest percentage of problems (n=52; 17%).

A few problems were reported in the domains of self-care and usual activities but were negligible (1% and 2% respectively). The domains of mobility and anxiety/depression were 7% and 6% respectively.

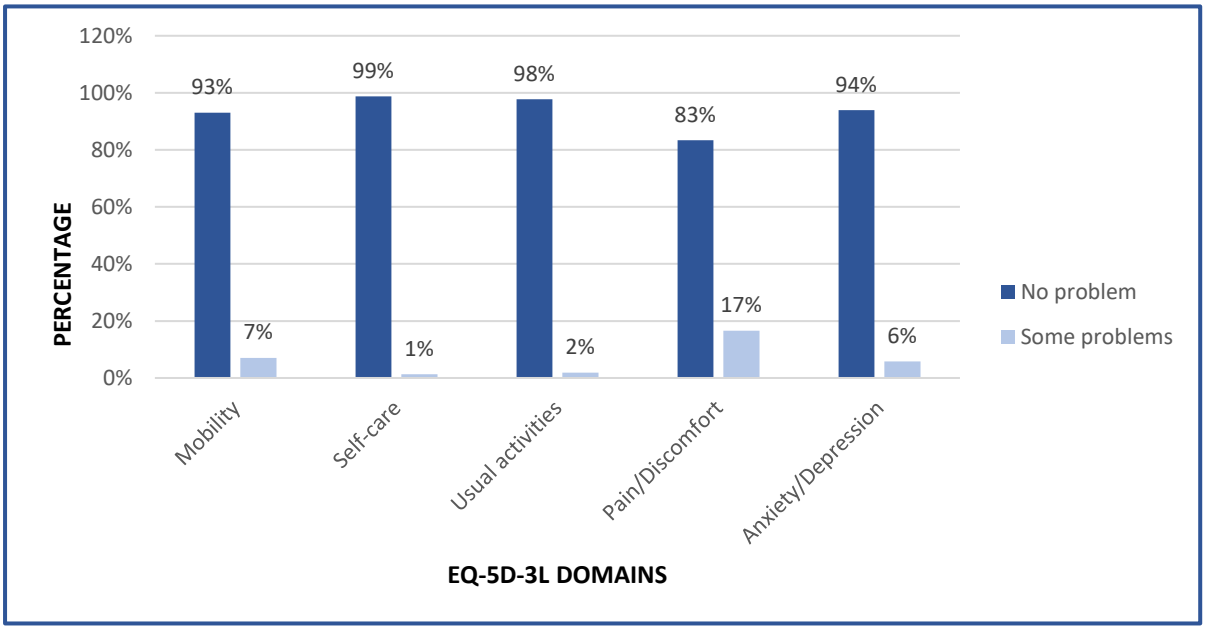


Figure 13. Percentage of Reported Problems for the Total Sample (N=305).

When reporting the percentage of problems in the five domains between those participants with both A-LFT and U-LFT, there were no differences despite having a higher percentage in the domains of mobility and pain/discomfort compared to A-LFT participants or the total sample (Figure 14 and Figure 15).

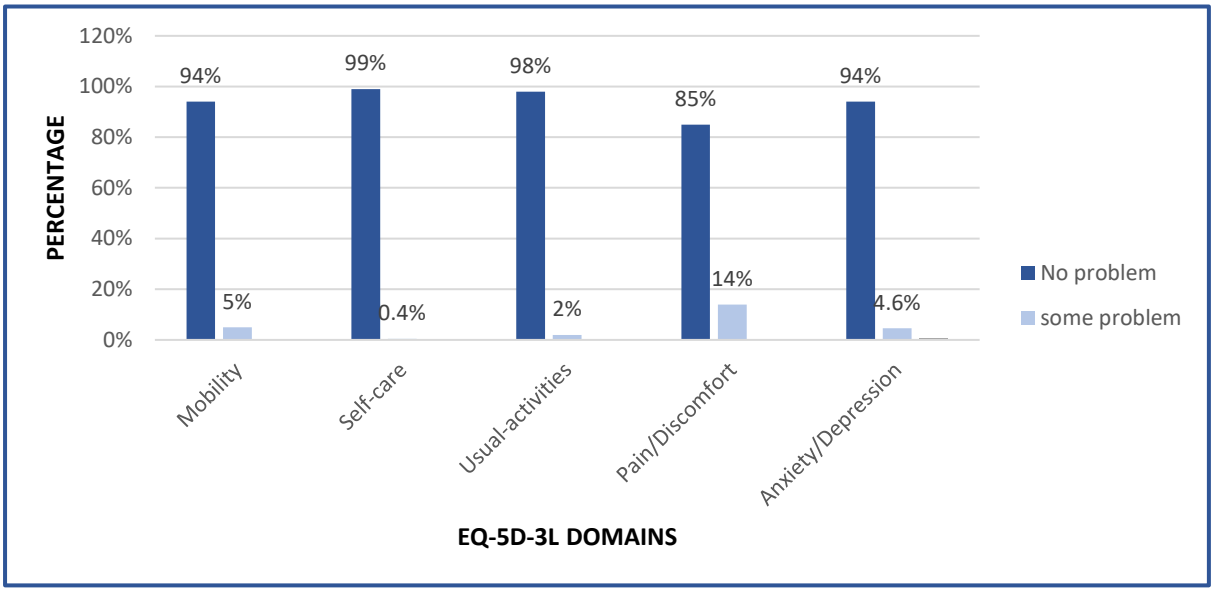


Figure 14. Percentage of Reported Problems for Participants with Acceptable Lung Function (A-LFT) (N=235).

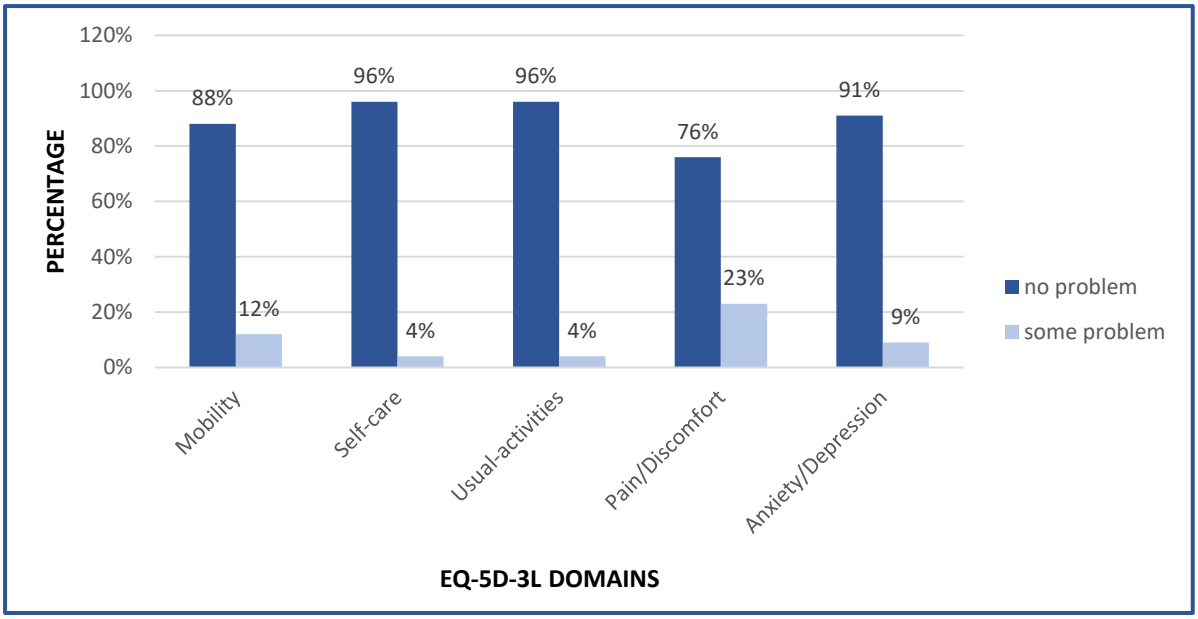
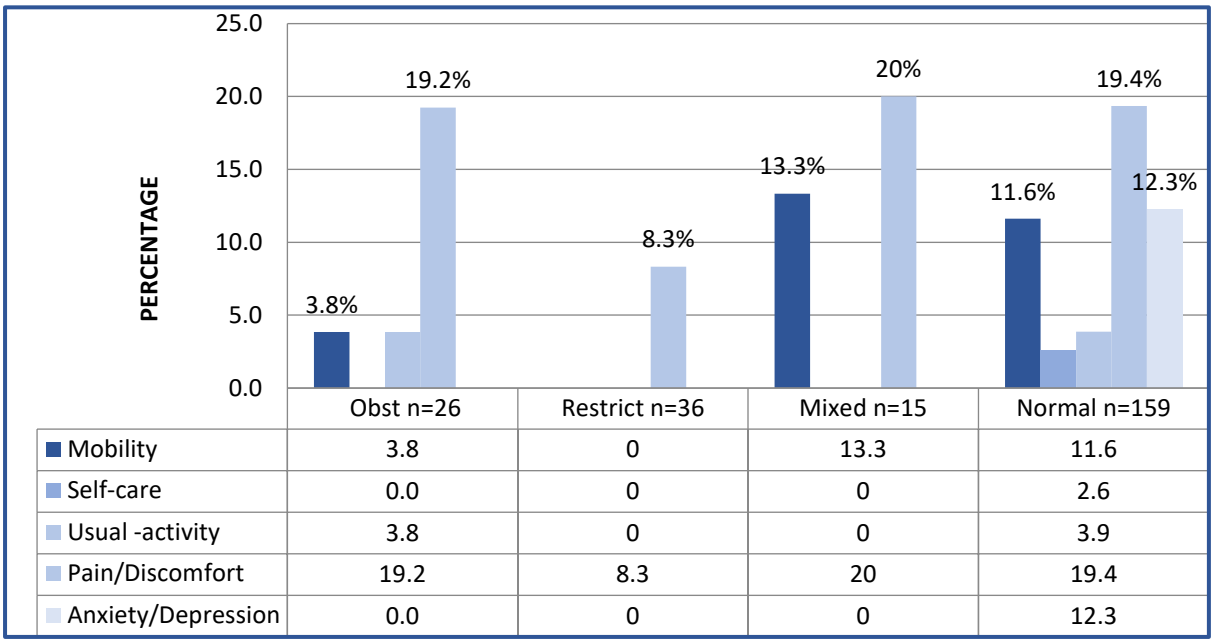


Figure 15. Percentage of Reported Problems for Participants with Unacceptable Lung Function (U-LFT) (N=70).

3.3.9.2 EQ-5D-3L relating to lung classification for acceptable lung function test group

In Figure 16 below, the percentage of problems in each domain is depicted for participants with A-LFT in relation to abnormal lung classification. Patients with obstructive and mixed abnormal lung function classification reported the highest percentage of pain/discomfort (19.2% and 20% respectively). Participants with mixed abnormal lung function classification reported the highest percentage of problems with mobility (13.3%) when compared to those with obstructive lung abnormality (3.8%). Interestingly, participants with normal lung function also reported problems with mobility similar to those in the mixed lung abnormality classification. Due to the small number in each lung classification, statistical testing was not possible.



	Obst n=26	Restrict n=36	Mixed n=15	Normal n=159
Mobility	3.8	0	13.3	11.6
Self-care	0.0	0	0	2.6
Usual -activity	3.8	0	0	3.9
Pain/Discomfort	19.2	8.3	20	19.4
Anxiety/Depression	0.0	0	0	12.3

Figure 16. EQ-5D-3L in Relation to Lung Function Classification for Acceptable Lung Function (A-LFT) participants (N=235).

3.3.9.3 St George's Respiratory Questionnaire

Analysis of the SGRQ was performed for 234 of the 235 A-LFT participants. One participant was excluded from the analysis as more than 50% of the data was missing. The mean, median, and range for symptom, activity, and impact scores are presented in Table 16 below. The mean for the total score was 9.9. A graphic representation of the symptom, activity, and impact scores is depicted in Figure 17. As can be seen from both Table 16 and the box plot in Figure 17, participants in general self-reported to be relatively healthy as the total score was not more than 10, although the ranges for both the symptom and activity scores were large. No association was found between SGRQ score and that of lung function parameters (see Appendix N).

Table 16. Mean, Median, and Range of the St George's Respiratory Questionnaire (SGRQ) Scores.

	ACTIVITY SCORE	SYMPTOM SCORE	IMPACT SCORE	TOTAL SCORE
MEAN	10.6	19.2	6.9	9.9
SD	19.2	22.1	9.8	12.4
RANGE	0–100	0–100	0–61.5	0–70.7
MEDIAN	0	11	3.8	5.1
IQR	0–12.9	2.7–27.7	0–8.1	2.1–12.9

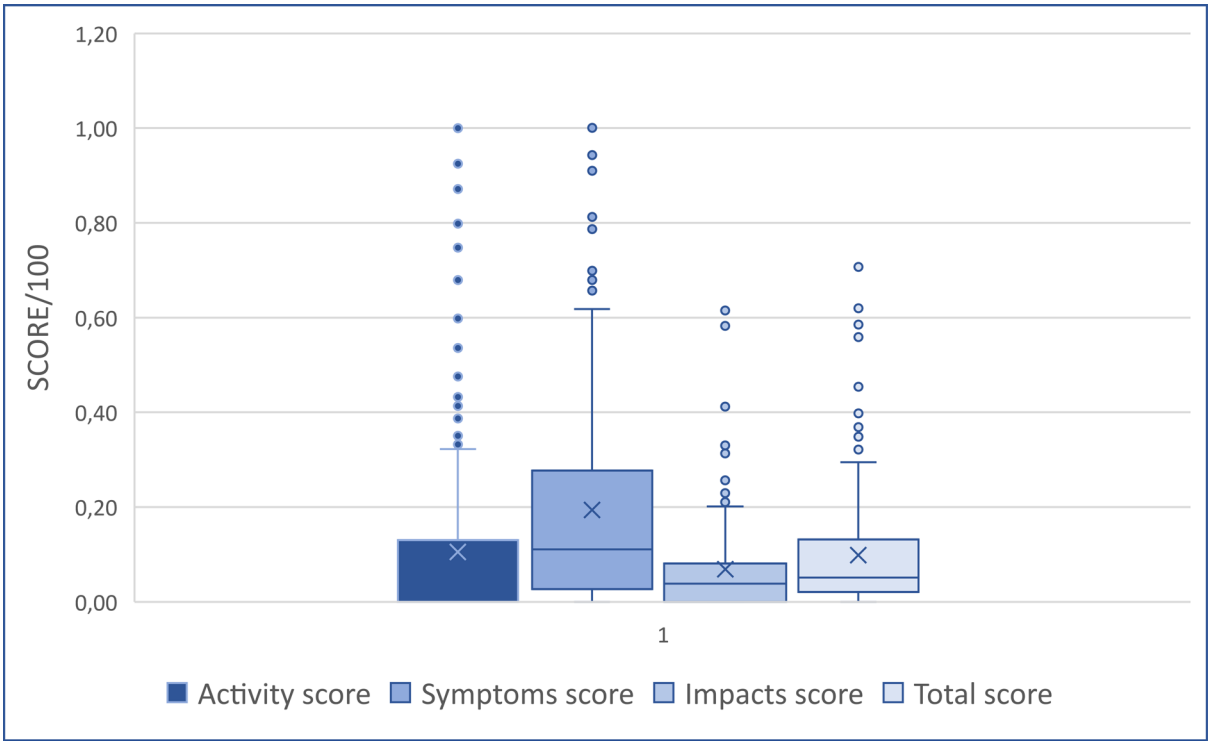


Figure 17. St George's Respiratory Questionnaire (SGRQ) Scores for the Various Domains for Participants with Acceptable Lung Function Tests (A-LFT).

3.3.10 Measures of association of overall data with all independent variables

As an objective of Study 1 (refer to Section 1.2), an analysis to measure any associations with the dependent variable of FEV_1 was performed. Univariate and stepwise multivariate logistic regression was performed on the socio-economic and clinical characteristics of patients at the 5% significance level (Table 17 and Table 18). The significant variables in Table 18 were female sex, primary education, age older than 45 years, being HIV negative, having a primary education, and being obese.

Table 17. Univariate Logistic Regression for Forced Expiratory Volume in one second (FEV_1).

CHARACTERISTIC	REFERENCE GROUP	OR	P-VALUE	95% CI	
Sex: Male	Female	0.2092	0.0000*	0.1494	0.2929
AGE GROUP					
26–35	18–25	1.8750	0.3630	0.4845	7.2564
36–45	18–25	2.2373	0.2400	0.5845	8.5632
46–55	18–25	4.1538	0.0460*	1.0237	16.8553
56–65	18–25	8.0000	0.0090*	1.6700	38.3230
65+	18–25	12.0000	0.0330*	1.2193	118.0999
BMI		0.9520	0.2080	0.8818	1.0278
height		1.0706	0.0010	1.0290	1.1139
weight		1.0093	0.4690	0.9844	1.0348
HIV status: Positive	**negative**	0.4811	0.0410*	0.2387	0.9697
hypertension	no	1.6759	0.3460	0.5729	4.9029
diabetestype1	no	1.2051	0.8180	0.2464	5.8943
diabetestype2	no	1.2000	0.8720	0.1306	11.0226
Angina /heart disease	no	1.0000	-	-	-
other disease	no	1.0000	-	-	-
LEVEL OF EDUCATION					
Secondary Education	primary	0.4709	0.0380*	0.2310	0.9600
Tertiary education	primary	1.0000	-	-	-
Employment	unemployed	1.2791	0.4760	0.6500	2.5170
Cigarettes /ex-smoker	no	1.8196	0.0960	0.9000	3.6788
BMI					
Normal weight	underweight	0.4033	0.1220	0.1276	1.2747
Overweight	underweight	0.7150	0.5920	0.2093	2.4424
Obese	underweight	0.0917	0.0380*	0.0095	0.8807

**significant p<0.05*

However, results of the multivariate logistic regression related to the socio-economic and clinical characteristics of participants showed that being older, specifically in the age group of 56–65 years and being obese were significant and associated with abnormal lung function (Table 18).

Table 18. Logistic Regression Analysis of All Socio-Demographic and Clinical Variables for Forced Expiratory Volume in one second (FEV_1).

CHARACTERISTIC	REFERENCE GROUP	OR	P-VALUE	95% CI	
GENDER: Male	Female	1.92	0.20	0.70	5.23
AGE GROUP (YEARS)					
26–35	18–25	2.02	0.33	0.49	8.35
36–45	18–25	2.24	0.28	0.52	9.60
46–55	18–25	3.15	0.17	0.61	16.23
56–65	18–25	10.13	0.02*	1.32	77.84
65+	18–25	5.78	0.21	0.37	91.43
BMI CATEGORY					
Normal weight	underweight	0.39	0.17	0.10	1.50
Overweight	underweight	0.80	0.77	0.18	3.54
Obese	underweight	0.06	0.04*	0.00	0.85
HIV status: Positive	negative	0.44	0.06	0.19	1.03
LEVEL OF EDUCATION					
Secondary Education	primary	0.86	0.75	0.33	2.23
Tertiary education	primary	1.00	0.00	0.00	0.00
Employment	unemployed	1.17	0.71	0.51	2.67
Cigarettes ex-smoker	no	1.10	0.83	0.47	2.56
Hypertension	no	1.56	0.57	0.34	7.19
Diabetes type I	no	0.44	0.44	0.05	3.53
Diabetes type II	no	1.05	0.98	0.05	21.26
Angina/heart disease	no	1.00	0.00	0.00	0.00
Other disease	no	1.00	0.00	0.00	0.00

**significant p<0.05*

In an analysis of whether an association existed between smoking history, CXR scores, and smoking and lung function classification, only the latter had an association (Table 19). Participants were 2.63 times more likely to have an obstructive lung function abnormality than those who had never smoked (p=0.03). As can be seen in Table 20 below, an association was present regarding the domain of mobility and usual activity in the EQ-5D-3L outcome measure and lung function (p=0.005 and p=0.05 respectively).

Table 19. Association between Smoking History and Lung Function Classification.

	ODDS RATIO	95% CI		P-VALUE
OBSTRUCTIVE	2.63	1.00	7.44	0.03*
RESTRICTIVE	0.88	0.39	1.95	0.74
MIXED	2.48	0.73	9.63	0.10

**significant p<0.05*

Table 20. Measures of Association between Lung Function and Quality of Life (QoL) Measures EQ-5D-3L.

	MOBILITY			MEASURE OF ASSOCIATION P-VALUE
Lung function	**1†**	**2‡**	**TOTAL**	
Normal lung function	188	6	194	0.005*
Abnormal lung function	34	6	40	
TOTAL	222	12	234	
	SELF-CARE (SC)			**MEASURE OF ASSOCIATION P-VALUE**
Lung function	**1**	**2**	**TOTAL**	
Normal lung function	193	1	194	1.00
Abnormal Lung function	40	0	40	
TOTAL	233	1	234	
	USUAL ACTIVITY (UA)			**MEASURE OF ASSOCIATION P-VALUE**
Lung function	**1**	**2**	**TOTAL**	
Normal lung function	191	3	194	0.05*
Abnormal lung function	39	1	40	
TOTAL	230	4	234	
	PAIN AND DISCOMFORT (PD)			**MEASURE OF ASSOCIATION P-VALUE**
Lung function	**1**	**2**	**TOTAL**	
Normal lung function	165	39	194	0.41
Abnormal lung function	36	4	40	
TOTAL	201	33	234	

	ANXIETY AND DEPRESSION (AD)				MEASURE OF ASSOCIATION P-VALUE
Lung function	**1**	**2**	**3§**	**TOTAL**	
Normal lung function	183	10	1	194	0.68
Abnormal lung function	39	1	0	40	
TOTAL	222	11	1	234	

† value of 1 given for no problems in EQ-5D-3L, ‡ value of 2 given for some problems in EQ-5D-3L,
*§ value of 3 given for severe problems in EQ-5D-3L, ** significant p<0.05

The Fisher's exact test yielded no association between lung function abnormality and HIV status, which was further confirmed with a logistic regression analysis which showed no significance (OR 0.60, 95% CI: 0.31–1.14). This may be due to the small numbers in the data set (Table 21).

Table 21. Association of Lung Function and HIV Status.

	HIV STATUS				MEASURE OF ASSOCIATION (FISHER'S EXACT TEST) P-VALUE
	NEGATIVE	**POSITIVE**	**UNKNOWN**	**TOTAL**	
LUNG FUNCTION					
Normal lung function	85	105	5	195	0.21
Obstructive disease	25	14	1	40	
TOTAL	110	119	6	235	
RESTRICTION					
No restriction	86	94	4	186	0.82
Mild restriction	18	20	1	39	
Moderate restriction	5	4	1	10	
Severe restriction	1	1	0	2	
TOTAL	110	119	6	235	

3.4 Discussion of Study 1

3.4.1 Outline of discussion

The results of Study 1 will be discussed in this section in relation to the determined objectives which were to:

- Determine baseline clinical profile (age, sex, HIV status, TB treatment, smoking history, and BMI) and socio-economic profile (level of education, amenities, employment, and exposure to biomass);
- Measure lung function parameters of FEV_1, FVC, and FEV_1/FVC ratio as well as the predicted percentage of FEV_1 and FVC after at least four months on TB treatment;
- Establish the proportion of participants who have normal or abnormal (obstructive, restrictive, or mixed) lung function;
- Ascertain the severity of lung function abnormalities;
- Determine the baseline information pertaining to the QoL outcome measures of EQ-5D-3L and the SGRQ;

- Determine correlation of lung function abnormalities with CXR abnormalities;
- Establish whether a relationship exists between lung function and measures of QoL; and
- Identify the predictors (HIV, age, sex, and smoking status) of lung function abnormality in individuals being treated for active TB.

3.4.2 Socio-demographic and Clinical characteristics of participants

The demographic data for Study 1 specifically considered individuals who had been diagnosed with drug susceptible pulmonary TB and were receiving treatment for the first-time. Significant research has been carried out on individuals who have had multiple TB episodes, have had MDR-TB, or extensively drug-resistant TB (Gandhi et al., 2010; De La Mora et al., 2015; Manji et al., 2016). Generally, these studies have investigated the mortality and efficacy of drug therapy. In the present study, however, we aimed to describe and measure the effects of a first-time episode of TB on lung function, functional capacity, and QoL for individuals with no previous lung disease or TB.

3.4.2.1 Socio-demographic characteristics

The socio-economic findings from Study 1 were typical of an urban African township setting. In this context, participants lived in primarily low-lying areas that are damp and often flooded during the Cape winter months. Most participants lived in shacks constructed of tin sheets and plywood, which are on average 2m x 2m in size with minimal openings for ventilation. In addition to poor ventilation, these informal shacks are constructed in close proximity (see Figure 3). Participants who lived in shacks (n=169) also had no running water (n=168; 54.8%) or toilet facilities (n=156; 49.7%) within the living space but had access to these facilities within a 5m radius, with 8.3% still using a bucket system for sanitation. Despite the poor infra-structure for amenities such as sanitation and electricity, most shack dwellers reported using electricity for preparing food and for heating. Just over 10% of participants used alternative fuel (wood, paraffin, and gas) for preparing food or heating their homes. Household air pollution (HAP) affects nearly 3 billion people globally and each year almost 3.8 million people die prematurely from illnesses attributed to the use of biomass fuels. Several early studies have reported that exposure to biomass fuel increases the risk of respiratory diseases such as chronic bronchitis, emphysema, and TB (Kurmi, Sadhra, Ayres, & Sadhra, 2014; Sood, 2012). However, a recent scoping review by Simkovich et al. (2019) which considered the health implications of HAP and respiratory disease found opposing findings on whether a relationship exists between HAP and the risk of developing TB. Simkovich et al. (2019) further reported that other than the two systematic reviews conducted by Kurmi et al. (2014) and Lin et al. (2014), no studies have been published that clearly show an association between HAP exposure and TB.

In the systematic review conducted by Kurmi et al. (2014) and pooled data of 12 peer-reviewed studies that evaluated active TB and controlled for smoking, the authors concluded that an individual exposed to HAP had a 43% increased risk of developing active TB compared to those that used clean fuels (pooled OR 1.43 [95% CI 1.07-1.9]). However, a review published in the same year by Lin et al. (2014) concluded the opposite, stating that there was no "strong evidence for a positive association of HAP and TB". Therefore, although there appears to be a risk of developing respiratory disease (including active TB) due to increased exposure to HAP, the evidence is still inconclusive.

Educational disparities in South Africa still exist, with Black South Africans still having lower levels of education than their White South African counterparts (Branson, Garlick, Lam, & Leibbrandt, 2012). Only 2.6% (n=8) of participants in the present study had completed tertiary education and nearly a quarter (24.9%, n=76) had only completed primary education or less. Similar levels of education in patients with TB have been reported in other lower income countries such as India (Miandad, Nawaz-Ul-Huda, Burke, Hamza, & Azam, 2016) and upper middle income countries such as Brazil (Steffen et al., 2010). In the study by Steffen et al. (2010), which investigated the cost and cost-effectiveness of TB treatment in directly observed treatment short courses and non-directly observed treatment short courses facilities in Rio de Janeiro, only 5.5% (n=12/218) had completed tertiary education and under two-thirds had only completed primary education or less (60.5%, n=132). Lower levels of education have also been associated with a delay in presenting at clinics for TB testing (Miandad et al., 2016; Steffen et al., 2010). In a study conducted in Karachi, India that investigated educational status and awareness amongst patients with TB, results showed that male participants were more educated than their female counterparts (Miandad et al., 2016). Also, in a recent study that investigated educational disparities in TB mortality between 1990 and 2003 in 16 European countries in urban versus rural populations, the authors reported that TB mortality was greater in countries where the educational disparities were greater (Álvarez Morán et al., 2011). These authors also noted that "people living in disadvantaged circumstances are known to have poorer health, more disability and shorter lives than those that are more affluent" (Álvarez Morán et al., 2011).

Educational disparities in patients with TB both locally and internationally have primarily focused on the association of educational levels with identifying TB symptoms, the early reporting of these symptoms to health care facilities, and adherence to drug treatment.

In the present study, no association was present between patients with lower levels of education and the inability to perform the lung function or the functional capacity testing.

When reporting on the data collected regarding lung function testing specifically, the level of education between the A-LFT and U-LFT groups was similar (25.1% vs 24.3% with primary or less, 72.3% vs 72.9% with secondary, and 2.6% vs 2.9% with tertiary education). Although not an objective of the present study, it is important to pose the following questions: why was such a large proportion of participants unable to execute the lung function test correctly, could education level impact future implementation of proposed PRPs in the current context, and does this impact relate to an aspect of learning behaviour and not educational level? It can only be speculated that perhaps one of the reasons 25% of participants were unable to perform the lung function testing correctly was due to the procedure being unfamiliar; it was a technique that participants had not encountered in their previous visits to a health facility. Research has shown that most patients with TB have residual lung damage long after TB cure which could develop into COPD. Therefore, a recommendation would be that lung function testing should be included in the assessment measures taken to better track improvement or decline of lung function, thereby familiarising patients with the skill required to perform the test accurately.

Further to the questions posed regarding education level playing any role in future PRPs, the contextual setting of the present study must also be considered and cannot truly be separated from education level and socio-economic circumstances. In Khayelitsha, the unemployment rate is high (60%), with those who have employment often holding unskilled and low-level positions such as that of a domestic work or labourer in the construction industry. Therefore, exposure to rehabilitation programmes and structured exercise training for general health is not a priority. Similarly to lung function testing, individuals living with TB and accessing future rehabilitation programmes may require pre-training to acquire familiarity with these exercises and the terminology used so as to effectively benefit from such programmes.

3.4.2.2 Clinical characteristics of participants

The clinical characteristics of the participants in Study 1 reflect the typical gender and age spread reported in the WHO Global TB report (World Health Organisation, 2019) that more males (55.1%) had active TB disease than women (44.9%) (Global TB Report 2019). In this cohort, the median age was 36 years with an IQR of 28–43. The median age was for males was 38 years (IQR: 29–44) and 34 years for females (IQR: 27–42).

These statistics are in accordance with the latest WHO Global TB report for South Africa, which reported that the notified age groups for 2017 were concentrated in the 25–44 age category for both men and women (World Health Organisation, 2019). According to the quarterly labour report for South Africa, the working population is between 15–64 years of age. This age group represents the most productive age group in terms of employment. However, in South Africa, this is also the age group that has the highest unemployment levels and therefore a high level of discouraged work seekers (Statistics South Africa, 2019).

In agreement with specific reporting for the African region (World Health Organisation, 2019), a high burden of co-infection with HIV was observed in Study 1, with just over half (51.1%) of the participants being co-infected with HIV. This finding is unsurprising, and it confirms the data from the 2019 WHO Global TB report which reported that 60% of all TB cases (new and re-lapse) in South Africa were co-infected with HIV. South Africa has been ranked as one of 14 countries with an overlap of TB, TB/HIV, and MDR-TB. The 2019 WHO Global TB report for South Africa estimated the incidence of TB/HIV+ in 2017 was 340 per 100 000 individuals. It is well established that HIV drives TB incidence, and in the sub-Saharan region this is evident as it contributes to nearly 72% of the global TB/HIV cases (Daftary et al., 2014; Granich et al., 2012; World Health Organisation, 2019; Yoko, Tumbo, Mills, & Kabongo, 2017).

In the present study, other comorbidities related to cardiovascular disease including hypertension, angina, and diabetes mellitus type I and II were also reported; however, they made up less than 10% of the sample population (refer to Table 4). It must be noted that, for the most part, these comorbidities were self-reported during the assessment period and could possibly have been under ascertained. In this cohort, diabetes mellitus type I and type II constituted 4.3% and 2.3% respectively. Low rates of diabetes mellitus (0.9%) were also reported in a recent South African study by Yoko et al. (2017), who conducted a retrospective record review of the characteristics of patients with TB in the North West Province of Moses Kotane. In both the present study and that by Yoko et al. (2017), less than one percent of the sample had two or more comorbidities. A recent study also conducted in South Africa investigated the prevalence and determinants of active TB amongst diabetes patients in the same research setting of Khayelitsha, and found a prevalence of 3% of active TB in their sample of 440 diabetes patients (Berkowitz et al., 2018; Oni et al., 2017; Wood et al., 2010). This percentage prevalence was four-fold higher than the national prevalence, which is not surprising considering that systematic screening for diabetes amongst patients with TB or vice-versa often uncovers substantial undiagnosed disease.

More than half the of participants (54%) in the present study reported never having smoked cigarettes or tobacco products. Those who were current or previous smokers constituted 46% but had a mean pack year of only two years.

The use of recreational drugs such as methaqualone (commonly known as mandrax), cannabis (also known locally as dagga), and crystal methamphetamine (more commonly known as tik in South Africa) collectively represented only 3.5% of the total study sample. Several studies have shown that active smoking is an independent risk factor for the development of active TB (Altet-Gómez, Alcaide, Godoy, Romero, & Hernández Del Rey, 2005; Davies et al., 2006). In the study by Altet-Gómez et al. (2005), the authors reported that smokers had more pulmonary disease and cavitary lesions compared to patients with TB who were non-smokers. In this study, the researchers were unable to draw the same conclusion as Altet-Gómez et al. (2005) regarding cavitation on the CXR, as this sample excluded participants with previous TB episodes who may have had more cavitation on the CXR. Also, in this study cohort, CXRs were taken only once, at four to five months of TB treatment, with no consistent previous CXR to compare with. The researchers that acknowledge not having a comparative CXR is a limitation, and this is highlighted further in the section identifying the study's limitations. When analysing whether a relationship existed between smokers and classification of lung function disorders (obstructive, restrictive, and mixed pulmonary disease), smokers were 2.63 times more likely to have obstructive disease than those who had never smoked.

Although the majority of participants were non-smokers, passive smoking is also a predictor for the development of both active TB (hazard ratio [HR], 1.49; 95% CI, 1.01–2.19) and culture-confirmed TB (HR, 1.70; 95% CI, 1.04–2.80) as reported in a study by Leung et al. (2010). The present study did not collect data regarding smoking within the household and were therefore unable to draw any conclusions regarding the cohort's second-hand exposure to smoking.

3.4.3 Lung function

Of the 305 participants that met the inclusion criteria for the prevalence study, analysis of lung function data was performed for only 235 participants who had performed an A-LFT. Acceptability of the lung function test was based on whether the attempts met the criteria of acceptability and repeatability of lung parameters of FEV_1 and FVC, using the MIR SPIROLAB III model. Only reports that were graded as either grade A or B were considered acceptable (refer to Section 3.2.7.1).

The classification of participants' lung function into obstructive, restrictive, or mixed lung abnormalities was based on the Global Lung Initiative criteria (see Table 8). Using this classification, the prevalence of abnormal lung function was 32%, disaggregated into obstructive (11%), restrictive (15%), and mixed (6%) lung function categories. This is lower than the range of 40–87% of abnormal lung function reported in other TB studies that considered lung function abnormality (Amaral et al., 2015; Baig et al., 2010; Manji et al., 2016; Mbatchou Ngahane et al., 2016).

In the study by Manji et al. (2016) conducted in Tanzania, 74% of the study population presented with abnormal lung function at a similar time point of at least 20 weeks of TB treatment. Values for obstructive lung function and mixed patterns were also higher at 42% and 19% respectively. Similarly, in a study conducted by Mbatchou Ngahane et al. (2016) in Cameroon, the authors reported higher abnormal lung function in their cohort with 45.5% of participants presenting with abnormal lung function after the successful completion of TB treatment.

Points to consider as reasons for the lower prevalence of abnormal lung function recorded include that previous studies were conducted in individuals who had multiple TB episodes, MDR-TB, and had a higher smoking history (Akkara et al., 2013; Mbatchou Ngahane et al., 2016; Ralph et al., 2013). A further reason may be that patients access a TB diagnosis more rapidly in Khayelitsha as there are more than 10 public sector TB clinics in the community that provide free treatment, which may be different to other low-income countries. Earlier access and diagnosis of TB results in is less lung damage at the commencement of TB treatment.

This contrasts with the present study where all participants had a first-time drug susceptible TB diagnosis, with participants excluded if they had extra-pulmonary TB. The timing of the data collection may be another factor for the lower prevalence rates as it was carried out near completion of TB treatment – namely at four to five months of treatment. Although the study by Manji et al. (2016) reported a similar time point for data collection, their participants were not restricted to first time TB episodes and included those with recurrent TB. The present study's finding of a lower percentage of abnormal lung function in first-time, drug susceptible patients with TB is similar to a recent study conducted in Russia, which is also a high-burden TB country. In the study by Dudnyk et al. (2018), TB-induced airflow obstruction was reported in 29.97% of new TB cases. An additional reason for the lower abnormal lung function seen in the recent study may be that none of the participants had undergone any surgery related to their TB diagnosis as was the case in earlier studies where participants had undergone thoracotomies and lobectomies (Akkara et al., 2013).

Unlike other studies (Lee, Kim, Kim, Oh, & Lee, 2011; Vecino et al., 2011) where patients with a history of COPD were included, the present study excluded those with confirmed COPD in an attempt to minimise confounding variables. Despite reporting a lower percentage of lung function abnormalities in Study 1, it is of clinical significance to note that up to a third of the current cohort with an active, first time TB episode still had some form of lung abnormality near completion of their TB treatment and may potentially be at risk for developing COPD.

Over and above the reasons already discussed regarding the lower prevalence of abnormal lung function, one cannot omit a discussion of the 23% of participants who were unable to provide acceptable lung function testing. The most common cause of unacceptable lung function testing in the literature is ascribed to inadequate instructions by the pulmonary technician (Cheung & Cheung, 2015; Miller et al., 2005; Ranu, Wilde, & Madden, 2011). In the study by Cheung and Cheung (2015), the authors reported that having accurate equipment, regular calibration, sufficient patient co-operation, and optimal patient effort are requirements for obtaining A-LTFs. Inconsistent effort by patients is often the reason for unacceptable results, which are in turn due to poor coaching or instructions provided by the individual conducting the test (Cheung & Cheung, 2015). Additionally, it is acknowledged that the execution of an A-LFT is based on the patients clear understanding of the rather complex manoeuvre, which is physically demanding (Graham et al., 2019). Further, health status at the time of the test should also be considered. In the present study, these prerequisites were considered as the researcher underwent training by a pulmonary technologist prior to data collection. Calibration of the equipment was performed daily and additional parameters such as providing a video of the correct execution in the participant's first language of isiXhosa was produced. The research assistant fluent in isiXhosa was present with each test, demonstrating and encouraging the patient to provide maximum effort. Despite this, participants were still unable to execute the technique and 23% had unacceptable results. The researcher postulates that in the context of the study setting, participants may not have been familiar with the concepts that the test required for the correct execution. Hence, as recommendation for future studies, the researchers propose that familiarity and exposure to lung function testing sessions prior to taking the test (as part of an assessment or screening) be put in place to ensure that the execution of the technique is optimal in order to provide acceptable results for interpretation.

As noted in Section 3.4.1, one of the objectives of this phase was to identify any predictors of abnormal lung function in individuals being treated for active TB. Multivariate logistic regression analysis identified only one age category of 56–65 years as well as being obese as significant (p=0.02 and p=0.04 respectively). Neither of these findings are unexpected as it is known that lung function declines in older persons as a normal physiological occurrence. Similarly, having an increased BMI impacts on lung function. Unlike in other studies, a positive smoking history and HIV-positive status (Ferrara et al., 2012; Silva et al., 2018) were not found to be independent risk factors (p=0.83 and p=0.06 respectively) for having an abnormal lung function. Regarding lung function and CXR abnormalities, also no association was observed.

3.4.4 Chest x-ray (CXR) score

The CXR scores in the sample for Study 1 were low, with a median score of 3.9% which translates to minimal abnormalities on CXR, with under 10% of participants having cavities on the CXR. This score is comparable to a study by Stek et al. (2018) who investigated the effect of HIV-associated TB, immune reconstituted inflammatory syndrome, and prednisone on lung function. The study by Stek et al. (2020), which was conducted in the same research setting and used the adapted Timika scoring system for the CXR, also reported a low median CXR score (4%). In their study, the authors followed participants at week 0 and week 28 of treatment and reported a significant correlation between CXR scores and respiratory symptoms, 6MWT, and FEV_1. For every increase of 10 points in the CXR score, an OR of 1.51 for symptoms (95% CI 1.13–2.03; p=0.006) was observed, the six-minute walk distance (6MWD) decreased by 21m (95% CI 11–31; p<0.001), and an average predicted FEV_1 percentage decreased by 3.3% (95% CI 1.9–4.8; p<0.001). As Study 1 only collected once-off data to establish prevalence, the researchers had no serial CXR for the participants, and therefore the scores observed were a cross-sectional assessment near completion of TB treatment. The significant p-values seen in our CXR must be viewed with the R-values which showed a weak correlation (r =0.14 correlation).

The scatter plots for the CXR score and lung function parameters clearly display a biphasic pattern which may be due to the fact that cavities are more weighted (refer to Section 3.2.8). Without serial CXRs taken prior to the assessment, the researchers were unable to determine whether a higher CXR score may have presented earlier in the disease. Therefore, a clear limitation of this outcome measure exists in that serial CXRs were not taken in order to observe any improvement or deterioration. Furthermore, one should also consider whether the weighting of cavities in the Timika scoring should be further explored as it does appear to have polarised the scores observed in the present study.

3.4.5 Six-minute walk test and six-minute walking distance

In TB treatment, outcome measures are traditionally focused on mortality, laboratory, or radiological improvement of the patient (Guessogo et al., 2016). Outcome measures related to functional ability and QoL are often not included in large TB studies. However, growing research into the long-term effects of TB post cure has warranted focus on this under-recognised area of research. Functional tests such as the 6MWT are often used as a simple means of evaluating functional capacity in individuals with chronic disease (Sivaranjini et al., 2010). The 6MWT is a quick, inexpensive, and low resource test which provides valuable information regarding a patient's QoL, as the ability to ambulate reflects the ability to perform activities of daily living (Batista et al., 2012; Rahmani, Erwinanto & Andean 2015). Several studies have validated the 6MWT and confirmed its reliability and validity in various conditions, including TB (Casanova et al., 2011; Heresi & Dweik, 2011).

The median 6MWD covered by the current cohort was 487m (range 86–802m). This is much lower when compared to a study which established reference standards for the 6MWD in healthy subjects across seven countries, and reported a mean distance of 571± 90m (range 380–782m) (Casanova et al., 2011). Similarly, in a study conducted in Portugal assessing the 6MWD for healthy Caucasian Portuguese adults between the ages of 18 and 70 years, the mean distance for the overall study was 627.8m ± 73 (Oliveira et al., 2018). However, in a study conducted in India that compared the 6MWD of healthy participants to participants with TB, the distance covered by TB participants was even lower than in the present study at 285±79.2m for males and 245.5± 73.1m for females compared to their healthy counterparts who walked 482 ± 45.9m and 408± 39.9m respectively (Sivaranjini et al., 2010). It must be noted that in the aforementioned study, the participants' mean age for both healthy (57.7±5.6 male and 56.4 ±5.2 female) and TB participants (56.1±5.1 male and 56.3 ±5.2 female) was higher than in the present study (38.4 for males and 35.7 for females). Increased age has been observed to be an independent factor in the decrease in 6MWD in healthy subjects (Dourado, 2011). Furthermore, specifics as to which stage participants were in when completing the assessment were not explicitly mentioned other than stating that the patients were stable on TB treatment at time of enrolment. One can therefore only speculate that the participants in the study may have been assessed for the 6MWT at an earlier stage of their treatment where they may have been at a higher severity of illness, with symptoms such as productive cough and shortness of breath. This is in contrast to the present study cohort in which participants were near completion of TB treatment with minimal residual symptoms (median time on treatment being 19.7 weeks).

Unfortunately, there are no normative values for a healthy South African population regarding the 6MWD for comparison. Research equations have been used in European subjects to establish normative values (Casanova et al., 2011). However, in a recent review of the literature regarding reference equations for 6MWT, Dourado (2011) concluded that European reference equations were not applicable to his Brazilian cohort as they could not explain the variability in the distance covered. Dourado (2011) recommended providing specific reference equations for each population.

With regard to the 6MWD in relation to the lung classification of the current cohort, participants with normal lung function had a median 6MWD of 497.9m, versus 463.2m for those with obstructive, 488.6m for restrictive, and 494.8m for participants with a mixed lung function classification. It is known that patients who have obstructive lung disease have diminished functional capacity (Gloeckl et al., 2018; Jenkins, 2007; Kapella, Larson, Covey, & Alex, 2011).

The greater 6MWD observed in the mixed lung function classification is unexpected but may be skewed due the small number of participants (n=15) which presented with this classification. In addition, the severity of the obstruction may have been less severe than those with pure obstructive lung disease as Gardner, Ruppel, and Kaminsky (2011) reported regarding the overestimation of obstruction in mixed lung function abnormalities. In their study, Gardner et al. (2011) hypothesised that by adjusting the FEV_1 for the decrease in total lung capacity, a truer estimate of obstruction severity in mixed lung function abnormalities would be observed. Their study examined a large pulmonary function testing database; using their adjusted model, severe obstruction was reduced from 76% to only 33% in 199 cases with mixed lung function abnormalities. Although the present study did not adjust FEV_1 values in relation to total lung capacity, this is a plausible reason for why, despite having a mixed lung abnormality, participants were still able to perform better than their counterparts who had a pure obstruction.

The median 6MWD in the present study was lower in participants who were HIV positive (472m) compared with their HIV negative counterparts (501.5m), and this difference was significant in the overall group, the A-LFT, and the U-LFT (p=0067, p=0064, and p=0007 respectively). This finding is supported by a recent study conducted in the United States of America that investigated the effects of HIV on 6MWD compared to HIV-negative controls, which reported HIV as an independent risk factor for reduced 6MWD (Robertson et al., 2019). In a study by Abebe et al. (2010), it must be noted that the participants were not co-infected with TB.

The effects of TB on the lungs are well documented and must be considered (Khosa et al., 2020; Manji et al., 2016; Stek et al., 2018). An HIV positive status may explain the lower 6MWD observed in the present study.

As reported in the results, linear regression modelling with continuous variables of lung function parameters with SGRQ (refer to Section 3.3.9.3), CXR scores (refer to Section 3.3.7) yielded no association. It can only be speculated that this was observed as the current study cohort was younger, had no previous TB history, and primarily comprised of non-smokers. This is in comparison to the previously cited literature (Davies et al., 2006; Yoshida et al., 2006), all of which observed an association (negative impact) on the aforementioned outcome measures. In addition, the data obtained must be viewed against the backdrop that no normative data is available for either 6MWD, CXR scores, or lung function parameters in the South African population.

3.4.6 Quality of life measures

Health related QoL measures are often overlooked in research related to TB (Aggarwal, 2010; Babikako, Neuhauser, Katamba, & Mupere, 2010; Brown et al., 2015; Deribew et al., 2009; Rajeswari, Muniyandi, Balasubramanian, & Narayanan, 2005). The focus in most studies related to TB is morbidity. However, with improved cure rates for many countries globally (World Health Organisation, 2019) more attention should be focused on the impact of QoL the disease causes (Olufemi et al., 2018). Although there are numerous QoL outcome measure tools available, there is limited implementation in TB research. Few studies have considered the feasibility and reliability of QoL measures in the TB population and even less so in sub-Saharan Africa where the burden of the disease is high (Babikako et al., 2010). In a recent South African study, the authors noted the lack of attention paid to the impact of HRQoL amongst patients with TB, whether at the commencement or completion of treatment (Louw et al., 2012).

Overall, the QoL for participants in Study 1 was reported to be good and could be attributed to the timing of the assessment. Quality of life measurements were taken near completion of TB treatment (median of 19 weeks) and it would be expected that participants would be feeling better with fewer respiratory symptoms. A similar finding of improved QoL was reported in a South African study by Louw et al. (2012), which reported a significant improvement in the physical component of the HRQoL using the SF-12 instrument after six months of treatment (p=0.016).

The primary domain in which participants continued to report problems was pain and discomfort. According to several studies conducted in TB populations, both physical and mental discomfort is common for people living with TB (Babikako et al., 2010; Louw et al., 2012; Olufemi et al., 2018; Rajeswari et al., 2005). This may explain why participants with normal lung function still reported the highest percentage of problems with pain and discomfort (19.4% vs. 19.2% obstructive vs. 8.3% restrictive), anxiety and depression (12.3% vs. 0% for all abnormal lung function categories), and mobility (11.6% vs. 3.8% for obstructive vs. 0% restrictive). A recent study conducted in Nigeria, which investigated the HRQoL of patients with TB at the commencement and completion of the intensive phase of treatment, reported that participants had the highest score in the pain domain when assessed using the Short Form 36 (SF-36); although it improved significantly at the end of the intensive phase, it was still present (Olufemi et al., 2018). In the same study, the authors also reported that the domain of emotional wellbeing improved the least from commencement of treatment to the completion of the intensive phase (minimum clinically important difference of 4.24, p=0.05).

According to Aggarwal et al. (2013), who investigated the HRQoL of patients with TB in an Indian population, despite improvement in overall HRQoL with TB treatment, patients often had to manage psychological and financial problems which impacted their QoL even after completion of treatment. Unlike in the present study which also investigated lung function in relation to QoL, few studies have considered the impact of impaired lung function caused by TB on QoL. Despite pulmonary impairment after TB as a known phenomenon, research that combines this with QoL is limited, particularly in endemic areas. Although the percentage of participants with obstructive, restrictive, and mixed lung function was low (32%) and not statistically significant, the QoL for participants with mixed lung function was more greatly marked in the domain of mobility and pain/discomfort.

The other QoL measurement reported on in Study 1 was the SGRQ, which specifically assessed the respiratory health of participants. The SGRQ has been validated for use in pulmonary TB (Pasipanodya et al., 2007) as it not only includes respiratory symptoms but also activity limitation and the impact of these scores on QoL. A score of zero reflects optimal respiratory health status, with higher scores indicative of worse respiratory health status. Overall, participants had good QoL at the time of assessment as reflected by the median score of less than 10% for any of the three subscales (symptom=9.9%, activity=0%, and impact=3.8%).

These findings are not unexpected at near completion of TB treatment. However, studies that that have been conducted in TB populations that assessed QoL using the SGRQ have had varied results, reporting both worsening and improved SGRQ scores. In a study conducted in Indonesia, the mean SGRQ score at completion of TB treatment (six months) was 44.6%, which is much higher than the present study which reported 9.9% at around five months of TB treatment. Although the study by Maguire et al. (2009) also had predominantly drug susceptible patients with TB with no previous history of TB treatment, they included participants who had any drug resistance as well as patients with MDR-TB in their sample, which may be a reason for the higher baseline SGRQ score noted. Alternatively, participants in their study may also have had delays in diagnosis where symptoms may have been worse. In another study conducted in the United States of America (Pasipanodya et al., 2007), the authors reported a significant increase in SGRQ scores (worsening respiratory status) when comparing their active TB participants with those with latent TB. Also, a higher SGRQ score was associated with patients who had a greater deficit in lung function (Pasipanodya et al., 2007). In the present study, however, the median total score was 5.1%, which reflects a better overall QoL for the study sample (despite reporting on pain and anxiety) and could be related to the time of assessment which was near completion of TB treatment where one would expect improved QoL.

However, a limitation of the present study was that the data was not compared to population norms for lung health as they are not available in South Africa. Hence, inferences cannot be made as to whether the low score for respiratory health was improved or worse than population norms. To the researcher's knowledge, this is the first South African study with a large sample size that investigated a population-based prevalence on pulmonary TB in first-time, drug susceptible patients during treatment, and therefore no comparative data for SGRQ scores were available. This has highlighted the need for population-based normative data regarding lung health.

3.4.7 Concluding summary of Study 1

In summary, the sample of 305 participants in Study 1 was primarily male and had a median age of 36 years, measured at 19.7 weeks after the initiation of TB treatment. Lung function results were interpretable in 77% of patients (n=235). Overall, 32% of the sample presented with abnormal lung function, which is lower than comparable studies that investigated lung function in TB populations. For most participants, QoL was considered good at the time of assessment. Participants who had obstructive lung function abnormalities covered less distance when compared to those who with restrictive or mixed lung function abnormalities; however, there was no statistically significant difference (p=0.29).

After logistic regression analysis of clinical and socio-demographic variables (multi-variate), only older age (56–65 years old) and an obese BMI result were statistically significant (p=0.02 and p=0.04 respectively). When considering QoL, the domains of mobility and usual activity were statistically associated with abnormal lung function (p=0.005 and p=0.05 respectively).

The limitations of Study 1 related to the absence of normative data for a healthy population relating to lung function and 6MWD with which to compare the findings in this TB population. Recommendations for future research includes establishing normative data for the outcome measures. Regarding lung function testing, it is recommended that training of correct execution of the spirometry techniques is performed prior to assessment as this technique may be unfamiliar when compared to the routine tests administered at clinic visits for individuals receiving TB treatment. It is recommended that a practice run of the 6MWT is performed prior to the test being administered. Furthermore, the polarised CXR scores reported in Study 1 may suggest that cavities using the Timika scoring system are weighted too high, which requires further consideration. Future studies should make use of a logbook to track the reasons why eligible patients did not consent to participate so that barriers to effective recruitment and enrolment are understood and can be addressed.

In conclusion, the overall objective to ascertain the prevalence of lung abnormalities in patients with first time drug susceptible TB was achieved. Although the percentage of abnormal lung function reported in Study 1 (32%) was lower than other studies conducted in TB populations, it must be noted that participants in the present study had not undergone any previous lung surgery nor had been previously diagnosed with any other lung illnesses. These findings contribute knowledge to current research that abnormal lung function should be screened for in patients with TB at the commencement and also the termination of TB treatment to identify those who would benefit from continued care to maintain lung health.

CHAPTER FOUR: IS PULMONARY REHABILITATION EFFECTIVE FOR PATIENTS WITH TB? (STUDY 2)

4.1 Introduction

Pulmonary TB was the leading cause of death from an infectious disease in 2017 globally and remains a significant health problem affecting marginalised communities in low- and middle-income countries (World Health Organisation, 2019). Despite being curable, individuals living with TB, whether with a first-time or a recurrent episode, are likely to have pulmonary impairment post completion of chemotherapy (Di Naso et al., 2011; Pasipanodya et al., 2010; Vecino et al., 2011). In studies conducted in the past five years, as many as 60% of patients with TB have developed some form of COPD which contributes to the global morbidity and mortality rates as a result (Baig et al., 2010; Byrne et al., 2015; Manji et al., 2016). Individuals with COPD have reduced lung function and functional capacity which may hinder their ability to carry out activities of daily living (Mohammed, Nagla, Morten, Asma, & Arja, 2015). Despite this, PRPs, which are known to be effective in treating long-term consequences resulting from COPD, are not widely implemented in patients with current or previous TB (Di Naso et al., 2011; Manji et al., 2016; Pasipanodya et al., 2010; Vecino et al., 2011). In a recent non-systematic review by Muñoz-Torrico et al. (2016), the authors considered the necessity of a rationale for pulmonary rehabilitation after successful completion of chemotherapy for TB and concluded that the evidence available suggested "that TB is definitely responsible for functional sequelae, primarily causing an obstructive pattern on spirometry, and that there is a rationale for pulmonary rehabilitation" (Muñoz-Torrico et al., 2016).

4.2 Pulmonary Rehabilitation as a Continuum of Care for Patients with TB

Despite numerous studies identifying pulmonary sequelae after TB (Cruz et al., 2008; Maguire et al., 2009; Pasipanodya et al., 2010; Vecino et al., 2011), the management of patients with TB has not expanded past the mainstay of chemotherapy. Over the past decade, research into the long-term effects of TB has emerged providing evidence that TB is a predictor of COPD (Allwood et al., 2013; Amaral et al., 2015; Byrne et al., 2015; Ehrlich et al., 2011). Unlike patients with pulmonary impairment from TB, patients with smoking-related COPD are managed both pharmacologically with the use of inhalers and with non-pharmacological intervention in the form of PRPs to address the long-term effects of the disease on respiratory function, functional capacity, and QoL.

In a recent scoping review analysing international research and guidelines on post-TB chronic lung disease, the authors found that only seven guidelines considered at patient follow-up after TB treatment (Van Kampen et al., 2018). Furthermore, only three of these guidelines mentioned pulmonary TB sequelae, with the remaining four focused on relapse management. More importantly, none of the guidelines provided insight into how potential pulmonary TB sequelae are to be identified or managed (Van Kampen et al., 2018). The above findings are not surprising as the global focus for TB control has been early detection, vaccine development, and a reduction of case incidence and mortality from the disease. The shift to invest more research and resources to morbidity and long-term management has therefore been slow.

Pulmonary rehabilitation is not a novel intervention for the treatment of patients suffering from smoking-related COPD, and has long been established as an appropriate and effective method of management for this condition (Ries et al., 2007). Pulmonary rehabilitation programmes to manage COPD have demonstrated that patients have improved QoL and are also better able to manage their disease and maintain lung wellness (Ries et al., 2007). The guidelines established in 1997 by the joint ACCP and the AACVPR, updated in 2010, set out the clear benefits of PRPs (Ries et al., 2007). These guidelines also provide systematic evidence-based recommendations as to what should be included in such a programme, to whom it should be provided, and for how long a PRP should be implemented. According to the guidelines, a comprehensive PRP commonly includes components such as exercise training, education regarding the disease (on how it progresses and self-management), respiratory and chest physiotherapy techniques, as well as psychological support to aide positive outcomes with regard to QoL. Furthermore, the guidelines state that there is good evidence (level 1a) that pulmonary rehabilitation reduces the number of hospital days during acute exacerbation and other measures of health care utilisation in patients (Cuthbertson et al., 2005; Nordlund et al., 2005). However, data pertaining to specific programmes, intensity level, and optimal timing for PRPs is lacking.

In a recent Cochrane Review on the effectiveness of PRPs for COPD patients, McCarthy et al. (2015) concluded that, “additional RCTs comparing pulmonary rehabilitation and conventional care in COPD are not warranted” (p. 2). McCarthy et al. (2015), however, also recommended that:

> Future research studies should focus on identifying which components of pulmonary rehabilitation are essential, its ideal length and location, the degree of supervision and intensity of training required, and how long treatment effects persist.

> This endeavour is important in the light of the new subgroup analysis, which showed a difference in treatment effect on the chronic respiratory questionnaire between hospital-based and community-based programmes, but no difference between exercise only and more complex pulmonary rehabilitation programmes (p. 2).

In light of the above, Study 2 comprised of a systematic review of PRPs in patients with TB.

4.3 Aim

The aim of the systematic review was to determine the effect of exercise based PRPs, primarily on the lung function of individuals living with TB, followed by functional capacity, and QoL.

4.4 Methodology

4.4.1 Protocol and registration

The protocol was published in the international Prospective Register of Systematic Reviews (PROSPERO) database (registration number: CRD42015026774). The reporting of this systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Template for Intervention Description and Replication (TIDier) checklist and guide (Hoffmann et al., 2014; Moher, Liberati, Tetzlaff, & Altman, 2009).

4.4.2 Eligibility criteria

4.4.2.1 Types of studies

Studies that investigated the effectiveness of pulmonary rehabilitation or exercise therapy on lung function as their primary outcome, and functional capacity and QoL as secondary outcomes were eligible for inclusion. Included study designs for eligibility were RCTs, pre-post-test interventions, or quasi-experimental studies. Eligible full-text articles were included irrespective of language or publication status.

4.4.2.2 Types of participants

Study participants had to be adults (18 years and older) with confirmed TB, with or without HIV co-infection on directly observed treatment short courses or non-directly observed treatment short courses regimens for anti-tubercular therapy. A TB diagnosis could be current or previous. Studies were included in both new and re-treatment cases, as well as those conducted in either or both sexes. Studies were excluded if the TB diagnosis was related to extra-pulmonary TB or in a paediatric population.

4.4.2.3 Types of outcome measures

The primary outcome of interest was lung function, specifically FEV_1, FVC, and FEV_1/FVC. These parameters were chosen as they are used in the classification of lung abnormalities (obstructive, restrictive, or mixed abnormalities). Secondary outcome measures were functional capacity including, but not limited to, the 6MWT and QoL.

4.4.3 Search strategy for identification of studies

4.4.3.1 Electronic search

The search strategy was designed with the help of a research librarian familiar with systematic reviews to identify studies consisting of PRP or physical therapy in adult patients with TB investigating the effectiveness of pulmonary rehabilitation on lung function outcomes (refer to Appendix O). The principal authors, Shamila Manie and Ameer Hohlfeld, independently searched seven databases (MEDLINE via Pubmed, CENTRAL, CINAHL, PEDro, Web of Science, Scopus, Science Direct, and African Index Medicus, including Google Scholar) for the period January 1995 to December 2016, with an updated search in November 2018. An initial search with the librarian indicated that the term pulmonary rehabilitation, as defined as an exercise programme, was used more frequently in publications after 1995. Furthermore, the reference lists of pertinent articles were searched for additional studies. When deemed necessary, further information was requested via email. Non-English, full-text articles potentially meeting the inclusion criteria based on the title and abstract screening were translated before deciding whether they definitively met these criteria. The search was conducted concurrently with the commencement of Study 1 in 2016.

4.4.4 Data collection and analysis

4.4.4.1 Study selection

The principal authors independently screened the titles and abstracts of studies returned by the electronic searches. Thereafter, the full texts of the selected studies were obtained and further assessed for eligibility using standardised eligibility criteria. Disagreements were settled through consensus or submitted to a third reviewer, Quinette Louw, to reach a decision.

4.4.4.2 Data collection process

The principal authors used homogenous data extraction forms to independently extract the data, followed by a verification process which involved cross-checking each other's data extraction forms for irregularities. Disagreements were resolved by discussion. The authors of the included studies were contacted where clarification was required.

4.4.4.3 Data items

Information extracted from the studies is provided in Table 22. The outcome data of primary interest was that of FEV_1 and FEV_1/FVC ratio after PRP or exercise therapy. The explanatory variables extracted included study design, description of participants, duration of TB therapy, previous TB episodes, activities in the PRPs and the duration of intervention, and the time points at which lung function parameters were measured. Lung function parameters were selected as the primary outcome on recommendation from a study confirming that pulmonary rehabilitation had the ability to significantly reduce the decline of lung function ($p<0.001$) (Incorvaia et al., 2014). In addition, lung function and not QoL nor functional capacity was used to identify patients with COPD and hence selected as primary outcome.

4.4.4.4 Risk of bias in individual studies and across studies

The authors assessed the quality of the studies using the McMaster Guidelines for Critical Review of Quantitative Studies (Law et al., 1998). This review tool includes several experimental study designs and comprises nine classifications, namely citation, study purpose, literature, design, sample, outcomes, intervention, and results, including conclusions and implications (see Section 4.5.5).

4.4.4.5 Summary measures and synthesis of results

All included studies varied in their study designs, so it was impossible to combine the outcome data to conduct a meta-analysis (Green & Higgins, 2011). Therefore, the findings are reported as a narrative synthesis. The contributions of each study were described through a structured synthesis and summarised in Table 22. The synthesis includes a description of the participants, intervention, outcomes, and the study design.

4.5 Results

4.5.1 Study selection

In total, 1 705 studies were obtained from the search. Once duplicate studies were removed, 1 220 studies remained. The titles and abstracts of these studies were screened resulting in 1 210 studies being excluded. Therefore, 10 studies were potentially eligible. Once the full-text articles were assessed, four studies met the inclusion criteria**.**

Figure 18 depicts the PRISMA flow diagram of the search as well as the reasons for exclusion. Of the included studies, only one was a RCT, two studies were single arm before and after studies, and one study was a prospective non-randomised open trial (two arms). A summary of the included studies is provided in Table 22.

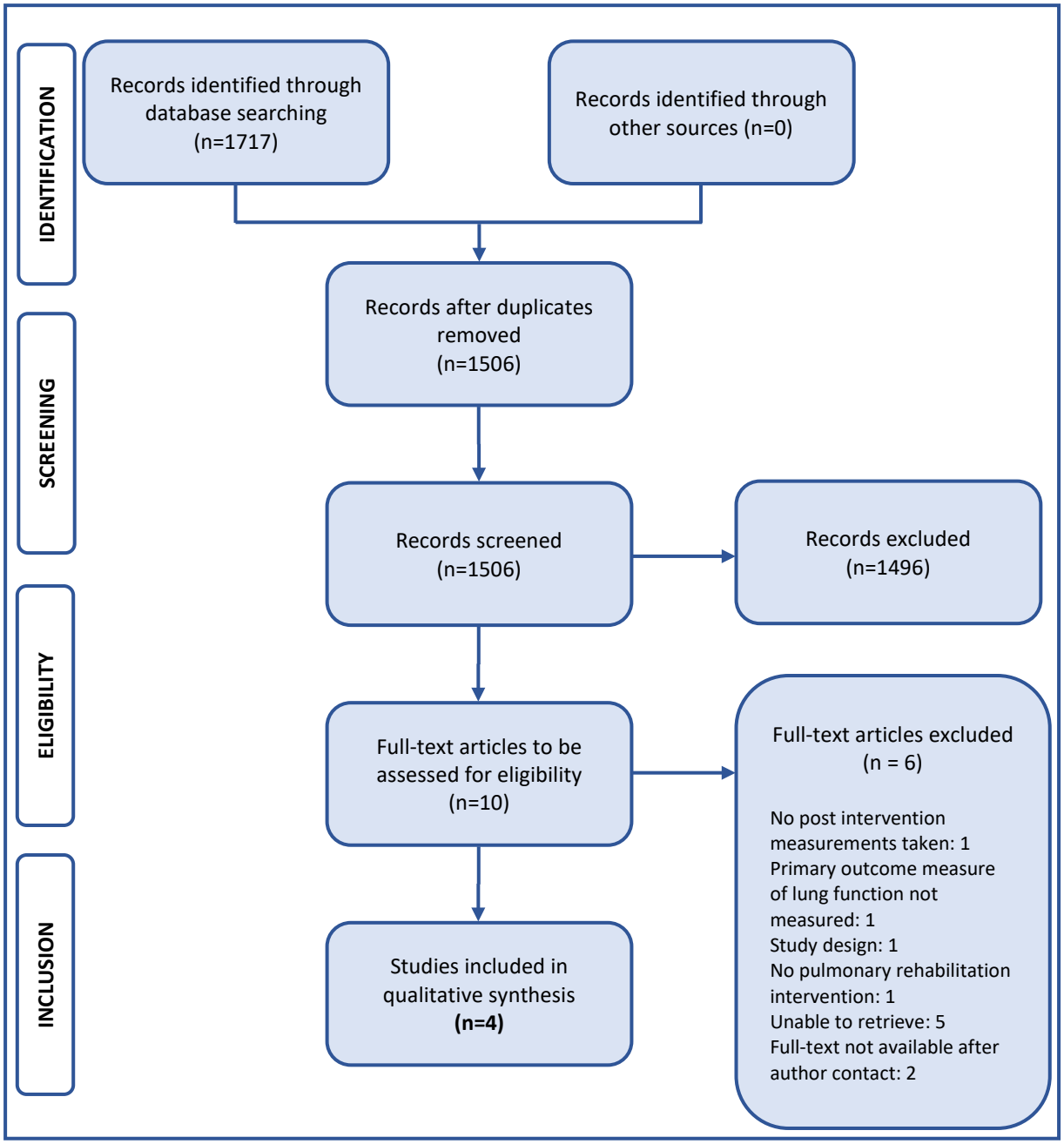


Figure 18. Flow Chart of Included and Excluded Studies using PRISMA.

4.5.2 Participant characteristics

Table 22 provides an overview of the characteristics of the included studies. In total, there were 178 participants in the studies, with sample sizes ranging from 10 to 67 participants. All four selected studies had both male and female participants; however, overall, male participants were the majority with 69% vs. 31% females (sex ratios were not described by Ando et al. (2003). The mean age for participants was 70 years of age (Ando et al., 2003; Tada et al., 2002; Yoshida et al., 2006).

However, one study did not report the mean age but only included participants between 18 and 65 years of age (De Grass et al., 2014). Only one study reported on HIV status and included HIV-positive participants (De Grass et al., 2014). No other co-morbidities were reported.

In the intervention arm of the study by Ando et al. (2003), 25 participants had undergone thoracoplasty for TB between 30–40 years ago. Similarly, in the study by Yoshida et al. (2006), eight participants had undergone thoracic surgery for thoracoplasty, pneumonectomy, or lobectomies. The mean number of years post-surgery was 33.6 years. Thirteen participants had undergone lung surgery in the study by Tada et al. (2002). The study by De Grass et al. (2014) was the only study whose participants had not undergone any surgery. Apart from De Grass et al. (2014), where participants were in the continuation phase of chemotherapy (four to six months of TB treatment), all other study participants were post-TB treatment.

Table 22. Characteristics of Included Articles.

AUTHOR (YEAR)	TITLE	STUDY DESIGN	TYPE OF TB	PARTICIPANT PRE-INTERVENTION (N)	PARTICIPANT POST-INTERVENTION (N)	SETTING	OUTCOME	FEV1†	FVC‡	FEV_1/ FVC*
Ando et al. (2003)	The Effect of Pulmonary Rehabilitation in Patients with Post-tuberculosis Lung Disorder	Prospective non-randomised open trial	Post –TB disorder	64: N=32 IG N=32 CG-COPD matched patients	64	Out-patient PRP 9-week duration, (once a week)	6MWT, PFT MRC dyspnoea grade, BDI, TDI, and ADL	X		
De Grass et al. (2014)	Effectiveness of a home-based pulmonary rehabilitation programme in pulmonary function and health-related quality of life for patients with pulmonary tuberculosis: a pilot study	RCT	Current TB and previous TB	67 N=34 IG N=33 CG	67	Home-based PRP 6-week duration (daily sessions)	6MWT, PFT, and EQ5D	X	X	X
Tada et al. (2002)	Effects of Pulmonary Rehabilitation in Patients with Pulmonary Tuberculosis Sequelae	Uncontrolled single-arm before-after study	In patients with TB sequelae	37	37	Hospital setting 3 to 8-week duration (not provided)	6MWT, PFT, and QoL – non-validated tool	X		
Yoshida et al. (2006)	Exercise Training for the Improvement of Exercise Performance of Patients with Pulmonary Tuberculosis Sequelae	Observational pre-and post-intervention (single arm)	TB sequelae	10	10	Hospital setting – 2wks duration, (daily sessions)	6MWT and PFT	X		X

Legend: CG – Control group; IG – Intervention group; BDI – baseline dyspnoea index; MRC – Medical Research Council; TDI – Transition dyspnoea index; ADL – Activity of daily living; QoL – quality of life; 6MWT – Six-minute walk test; PFT – pulmonary function test; EQ-5D – a quality of life outcome measure; **†** -Forced expiratory volume in one second; **‡** -Forced vital capacity; ***** -ratio of forced expiratory volume in one second and forced vital capacity

4.5.3 Interventions across studies

Across the four included studies, the intervention to improve exercise tolerance in patients with TB was exercise-based (Table 22). In the study by De Grass et al. (2014), a home-based, self-administered programme was provided to participants enrolled in the intervention arm. Participants in the intervention arm were required to perform a six-week, home-based exercise programme to improve functional capacity/exercise tolerance, lung function, and QoL. The programme included cardiovascular, low-impact exercises such as upper and lower limb range of movements, wall push-ups, repeated sit-stand movements, calf raises, and walking. The pulmonary component included activities such as pursed-lip breathing, diaphragmatic breathing, as well as postural correction. The activities were demonstrated to participants in detail by the researcher who also provided printed illustrations and instructions. Instructions included the number and duration of repetitions and sets required. In addition, participants were provided with educational information regarding TB, its symptoms, treatment, and prevention. However, detail regarding the intensity level of each activity was not described. Furthermore, as the intervention was home-based, the researchers had to assume that participants were honest in reporting the execution of the programme as intended.

Similar to De Grass et al. (2014), participants in the study by Ando et al. (2003) took part in a nine-week outpatient PRP. An hour-long, group format exercise session was provided once-a-week at an out-patient facility, run by a qualified physiotherapist and a respiratory physician. The programme consisted of breathing retraining, exercise, and education. Breathing retraining exercises were described as relaxed breathing techniques, pursed lip, and slow breathing activities. The exercise component of the study included low-intensity strength training of the upper and lower extremities and level walking for 15 minutes. Patient education was performed for 20 minutes during each outpatient visit. Over and above the weekly visits, participants were required to continue with the exercises daily and record this using a training diary. The details of how many repetitions were performed for each activity were not reported. Intensity level was described only as low intensity for strength training with no mention of increased intensity over the nine-week period. The authors also did not report whether any modifications or tailoring of the programme were performed during its execution.

Yoshida et al. (2006) guided participants in breathing techniques such as pursed lip and diaphragmatic breathing in various positions for a week prior to the assessment. The exercise training primarily consisted of walking on a level walkway in the hospital. Participants were instructed to commence walking at their maximum walking speed which was established with baseline treadmill testing.

The walking time was 15 minutes per set and participants had to perform two sets per day for two weeks, supervised by a physiotherapist during the week and performed independently over the weekends.

In the study by Tada et al. (2002), participants received an in-hospital exercise programme, consisting of breathing retraining that included pursed lip breathing and abdominal breathing while lying on their backs, sitting, standing, or walking. The exercise component consisted of weight training of the upper limbs, as well as ergometer and treadmill exercises five times per week for 30–60 minutes. Ergometer and treadmill exercises started with a low workload (not specified) for a short period and increased over time (also not specified). Exercise intensity was set as breathing difficulty below moderate, SPO_2 >90%, with the heart rate no more than 10 above (138-age x 0.5). Participants' initial parameters were expected to return to baseline within three minutes of completing the workout. Respiratory muscle training was performed using the INSPIREX to provide resistance to inspiration. Details regarding the number of repetitions and sets as well as the actual duration for each session by the participant were not provided. As part of the PRP, participants were provided with educational sessions on a range of topics including anatomy and physiology of the lungs, clinical conditions of chronic respiratory failure, physiotherapy, drug therapy, oxygen therapy, nutrition, smoking cessation, and everyday lifestyle. These sessions were presented by a multidisciplinary team comprising of doctors, nurses, physiotherapists, nutritionists, and pharmacists.

In all of the studies, instructions were provided to participants by a qualified physiotherapist and/or respiratory therapist/physician. Except for De Grass et al. (2014), who had a community, home-based PRP, training programmes were in a hospital or clinic-based setting. All studies provided supervision and/or instruction in the programmes by a qualified physiotherapist for the duration of the studies (Table 22).

4.5.4 Outcome measures

All studies measured the lung function parameter of FEV_1 and the 6MWT as the functional capacity test. The study by De Grass et al. (2014) was the only study that measured the patients' QoL using a validated tool, namely the EQ-5D-3L questionnaire. Tada et al. (2002) used an unvalidated questionnaire developed for patients using home oxygen therapy. The educational component of the PRPs was tailored and described in three of the studies with only Yoshida et al. (2006) not providing any information.

4.5.4.1 Lung function results

Studies included various measured lung function parameters; however, FEV_1 was measured in all studies. In all four studies, there was no significant difference in FEV_1 parameters from baseline to the end of intervention (see Table 23). Similarly, the two studies that reported FEV_1/FVC also did not report statistical significance between the CG and IG.

Table 23. Lung Function Results for Baseline and Post-Intervention.

STUDY	FEV_1 (L) BASELINE	FEV_1 (L) post INTERVENTION	FEV_1/FVC (%) BASELINE	FEV_1/FVC (%) POST INTERVENTION
Ando et al. (2003)	0.820 (CG) 0.840 (IG) *p>0.05*	0.850 (CG) 0.868 (IG) p>0.05	Not documented	
De Grass et al. (2014)	1.47 (CG) 1.60 (IG) *p=0.57*	1.54 (CG) 1.77 (IG) *p=0.1*	0.95 (CG) 0.96 (IG) *p>0.05*	0.94 (CG) 0.96 (IG) *p>0.05*
Tada et al. (2002) Pre- versus post	0.93	1.02 *	Not documented	
Yoshida et al. (2006) Pre- versus post	0.95	0.95*	68.8%	70.1%*

*Legend: *p-value given as p>0.05; FEV_1 – forced expiratory volume in 1 second, FEV_1/FVC – Forced expiratory volume in 1 second/Forced vital capacity; IG – Intervention group; CG – Control group*

4.5.4.2 Six-minute walk test

The 6MWT was used as the functional outcome measure in all four studies. The baseline 6MWT across the studies ranged from 303m to 401m (Table 24). Statistically significant results were reported in all studies after pulmonary rehabilitation.

Table 24. Six-Minute Walk Test (6MWT) Distance at Baseline and Post-Intervention.

STUDY	BASELINE MEAN DISTANCE (m)	P-VALUE	POST INTERVENTION MEAN DISTANCE (m)	P-VALUE
Ando et al. (2003)	333 (CG-COPD patients) 342 (IG-post TB)	0.01	380 (CG-COPD patients) 384 (IG-post TB)	0.01
De Grass et al. (2014)	340 CG 401 IG	0.01	356.97 (CG) 411.03 (IG)	0.007
Tada et al. (2002)	303		339	0.001
Yoshida et al. (2006)	399		467	0.01

Legend: IG – Intervention group; CG – Control group; COPD – chronic obstructive pulmonary disease

4.5.5 Study characteristics

4.5.5.1 Quality of studies included

The articles included in this review were primarily non-randomised studies, hence a critical review to assess the quality of the studies using the Law Tool for quantitative studies was used (Law et al., 1998). A scoring system adapted from the McMaster Law tool was used, using an 18-point score to assess the quality of the study (Table 25), which was based on the following questions:

1. Was the purpose of the study clearly stated?
2. Was relevant background literature reviewed?
3. Was the study design clearly stated?
4. Appropriateness of the study design?
5. Selection or sample biases?
6. Measurement/Detection biases?
7. Allocation biases?
8. Performance biases?
9. Was the sample described in detail?
10. Was the sample size justified?
11. Were the outcome measures reliable?
12. Were the outcome measures valid?
13. Was the intervention described in detail?
14. Was contamination or co-intervention avoided?
15. Results reported in terms of statistical significance?
16. Was analysis appropriate?
17. Was their clinical importance reported?
18. Were drop-outs reported?

Table 25. Assessment of the Quality of the Included Articles.

	1	2	3	4	**5**	**6**	**7**	**8**	9	10	11	12	13	**14**	15	16	17	18	**SCORE**
Ando et al. (2003)	+	+	+	+	≠	≠	≠	≠	—	—	+	+	—	+	+	+	+	+	**11**
De Grass et al. (2014)	+	+	+	+	—	—	—	—	≠	≠	+	+	—	—	+	+	+	—	**9**
Tada et al. (2002)	+	+	≠	+	≠	≠	≠	≠	+	—	+	—	—	—	+	+	+	—	**8**
Yoshida et al. (2006)	+	—	+	+	≠	≠	≠	≠	+	≠	+	+	+	≠	+	+	+	+	**11**

Legend: *+ criterion achieved; – criterion not achieved; ≠ not discussed. High: >75% of the criteria has been fulfilled (14/18), Moderate: 50–75% of the criteria has been fulfilled (9–13/18) and Low: <50% of the criteria has been fulfilled (<8/15). Bolded number (5–8 and 14) relate to risk of bias questions*

4.5.5.2 Risk of bias within included studies

Despite the quality of the studies scoring at a moderate level, the questions on risk of bias (questions 5–8 and 14) were either not achieved or not discussed at all in all four studies (Table 23). Selection bias was present in the study by De Grass et al. (2014) as participants were referred by clinic staff or volunteered to participate in the study. Also, allocation concealment and blinding of the participants and personnel were not performed. In the study by Yoshida et al. (2006), it was unclear as to whether the same therapist provided the intervention, and no mention was made of blinding the outcome assessor at the end of the intervention. The study by Ando et al. (2003) had inherent problems being a controlled before and after study. Neither allocation concealment nor blinding of participants was possible. However, there was no loss to follow-up (LTFU), and it was unclear whether selective reporting was present as the authors mentioned a low BORG scale score at baseline but did not provide measures of these in the results section.

4.6 Discussion

This is the first systematic review to evaluate the effects of PRPs on pulmonary lung functions for patients' post-treatment TB or being treated for active TB. Despite a large body of evidence on TB sequelae (Banu Rekha et al., 2009; Crothers et al., 2011; Cruz et al., 2008; Guo et al., 2009; Maguire et al., 2009) and effective medical management of TB, the present systematic review illustrated that there is scant research on the impact of non-pharmacological interventions to ameliorate the effects of the disease on lung function parameters.

The articles included in this study, of which only one was an RCT, had varied study designs and therefore a meta-analysis was not possible. The findings of the four included studies did not provide conclusive evidence to support or negate the effects of PRPs for patients with current or previous TB. However, they do provide relevant clinical information that PRPs for patients with TB or post-TB lung disease may be beneficial, suggesting that there may be benefit in terms of improved functional capacity. Unfortunately, the review was not able to address the second objective, which was to ascertain the most suitable components of a PRP in the context of the study and hence the intervention in Study 3 was informed by the guidelines for pulmonary rehabilitation.

Although all the participants from the included studies had TB, they were all at different stages of the disease. De Grass et al. (2014) was the only study where participants were still receiving TB treatment while participating in the study. The participants from the other included studies were all post TB treatment and/or had undergone a surgical intervention such as thoracoplasty, thoracotomy, or lobectomy. In the study by Ando et al. (2003), 78% (25/32) of enrolled participants had undergone thoracoplasty 30–40 years previously, which inevitably negatively affected their baseline lung function. Similarly, in the study by Yoshida et al. (2006), 57% (8/14) of participants had undergone a surgical intervention with TB treatment. In addition, the average age for the latter two studies was 72 and 71 years respectively, which could explain why minimal improvement was observed in lung function parameters (FEV_1) in these two studies, as there is also a decrease in lung function with increased age (Pruthi & Multani, 2012; Sharma & Ahluwalia, 2006).

The clinical improvement observed in FEV_1 in the study by De Grass et al. (2014) may be attributed to participants having a better baseline function (see Table 22) as none had undergone any surgery and they were of a younger age. The other measured lung function parameter was the FEV_1/FVC score, which is clinically important as it is used to indicate the severity of obstructive and restrictive lung diseases (Quanjer et al., 2012). However, in the two studies (De Grass et al., 2014; Yoshida et al., 2006) that measured FEV_1/FVC, there was a slight improvement, although not statistically significant, which may be due to the studies' small sample size.

Although the studies by De Grass et al. (2014) and Tada et al. (2002) both used PRPs following the guidelines set by the ACCP for COPD, their programmes were different. Both studies used breathing techniques such as pursed lip breathing, but participants in the study by Tada et al. (2002) also used an inspiratory handheld device that provided resistance to breathing.

The lack of statistical improvement in lung function corresponded to similar results for the functional outcome of the 6MWT in all but the study by Tada et al. (2002) which had a significant improvement in 6MWT despite not having improved lung function. The authors did not provide any reason for this and were not contactable to provide additional input.

The 6MWT is a reliable and validated outcome measure for functional capacity. It has been validated in several study populations, including TB populations recently (Sivaranjini et al., 2010). Although not the gold standard for functional capacity, in low to middle income countries such as South Africa, it is a cost-effective outcome measure. Participants across the included articles of this review showed an increase in the distance covered during the 6MWT, despite having no significant improvement in FEV_1. The functional improvement may be as the test considers exercise tolerance more than lung function capacity alone to execute the activity. In addition, the execution of the 6MWT may have had the investigator motivating participants to improve the distance covered. However, the only RCT, which had the most methodological rigour, reported the least improvement and the change was not statistically significant. We hypothesise that the co-morbidity of HIV, which was reported in more than 60% of participants, contributed to the least improvement in distance covered by participants in the study by De Grass et al. (2014).

With regard to QoL, no significant difference (p=0.78) was observed in QoL between the IG and the CG in the study by De Grass et al. (2014) at the end of the six-week programme. This may be attributed to the small sample size and the LTFU at the end of the six-week programme. While noting the benefits of the studies reviewed in this systematic review, the need for the establishment of minimum clinically important parameters for the PRP in patients with TB is worth considering for future studies.

4.7 Limitations and Recommendations

As the included studies varied in design and were primarily non-RCTs, a meta-analysis was not possible. In addition to this, when assessing risk of bias (refer to items 5–8 and 14 in Table 25), the studies were of high risk as they did not adequately address issues of potential bias. Inherently, two studies were prone to bias (Ando et al., 2003; De Grass et al., 2014) as allocation concealment and blinding of personnel and participants were impossible. Furthermore, the remaining two studies (Tada et al., 2002; Yoshida et al., 2006) may have implemented a form of blinding to the outcome assessment, however it is unclear whether this was performed. As the search was also not limited to English studies, the study by Tada et al. (2002) was published in Japanese and required a translator which was difficult to obtain, with no way to verify whether the translation was correct.

The outcome measures used also varied with the exception of the FEV_1 and 6MWT, with no explicit mention of validation in the TB population. The programmes used across the included studies were self-developed and although all had the components of pulmonary rehabilitation, they did not provide sufficient detail. Regarding lung function outcome measures, a guideline as to all of the parameters that should be reported on would be beneficial to ensure that future studies include them. The researchers recommend that future research investigates the extent of pulmonary sequelae in patients after completion of TB chemotherapy in large-scale studies. Long-term follow-up in individuals who have had TB without surgical intervention should be prioritised to understand the extent of lung function disorders in this population, particularly in countries that have a high burden of the disease. A further recommendation is for well executed RCTs that control for biases to investigate pulmonary rehabilitation in TB populations to be prioritised as there is a need to develop an evidence-based continuum of care for this patient population.

4.8 Conclusion

The present systematic review was unable to support or negate the use of PRP for patients with TB, primarily due to the lack of well-designed and executed RCTs. In the included studies, no effect on FEV_1 was demonstrated. Secondary outcomes of QoL were not reported in all studies and there is a need for the use of validated tools to assess QoL in this population. Statistical significance was reported for the functional outcome measure of the 6MWT across the studies.

However, the strength of this review is that it may be a useful summary informing consumers such as patients, health care workers (e.g., doctors including pulmonologists, and physiotherapists), policymakers, and stakeholders regarding the current pulmonary rehabilitation landscape and options available for patients with TB. It also provides relevant clinical information highlighting how patients with TB may benefit from pulmonary rehabilitation. The researchers conclude that there is a dire need for future research in this area, particularly studies with larger sample sizes and better methodologically rigour.

CHAPTER FIVE: RANDOMISED CONTROL TRIAL (STUDY 3)

5.1 Background to Study 3

Study 3 was a RCT which was primarily informed by the prevalence study conducted in Study 1 (refer to Figure 1). In Study 1, a 32% prevalence of abnormal lung function in patients who were diagnosed with first time drug susceptible TB near completion of their treatment was observed. This finding, though not surprising, indicated that despite being compliant with TB chemotherapy, patients were still not cured and now presented with potentially long-term lung health concerns. Despite the literature identifying a rationale for the implementation of PRPs for patients with TB, there has been no official guidelines regarding this and a slow uptake of PRPs in TB endemic countries (Van Kampen et al., 2018).

5.2 Methodology for Intervention Study

Study 3 is described in two sections, namely the pilot study for the intervention and the intervention itself**.** Although the same outcome measures (EQ-5D, SGRQ, and spirometry) were used in the intervention study as in Study 1, there were certain differences in implementation and execution and will therefore be described again. The functional outcome measure changed from the 6MWT to the three-minute step test (3MST), which is described in detail. A pilot study was conducted recruiting participants from the prevalence study. However, participants for the intervention, which was an RCT, were newly recruited. The inclusion/exclusion criteria, recruitment, screening, enrolment, and actual procedure for the pilot study and then the intervention is described first, followed by statistical analysis, and ethical considerations.

5.2.1 Pilot study for the intervention

The overall aim of the pilot study was to ascertain the feasibility and comprehension of the process of the planned intervention. The specific objectives were to:

- Ascertain whether enrolled participants understood instructions for each exercise/activity;
- Ascertain whether demonstration, instruction, or a combination of both by the therapist was preferred by participants;
- Establish whether participants correctly used the heart rate monitors to ensure that they effectively recorded heart rate during the activity;

- Document any adverse events such as extreme dizziness (subjectively measured), fainting, desaturation (using portable battery-operated finger pulse oximeter to measure oxygen saturation level during activity), and dyspnoea (measured by Modified Borg Dyspnoea Scale-with smiley descriptors) which may occur during the exercise component of the PRP; and
- Ascertain whether having only one instructor during PRP sessions was sufficient.

After conducting the pilot study, the following was established and used to adjust the intervention and its delivery for the full study:

- Participants were exercise naïve and instructions using conventional exercise terminology such as star-jumps or squats were unfamiliar;
- Exercises needed to be demonstrated at each session rather than by verbal instruction only;
- Participants would require supervision when putting on the heart rate monitor body strap to ensure correct placement of the sensor at each session;
- No adverse events occurred during the pilot study and therefore the planned activities were deemed safe for participants; and
- Due to space constraints, participants in the IG needed to not exceed six participants per group, therefore one instructor during the PRP sessions would be sufficient.

5.2.1.1 Recruitment, inclusion, and exclusion criteria for the pilot study

Participants were recruited from Study 1. Consent to recruit participants from Study 1 was included in the consent form (Appendix B). In addition, participants were required to have at least one zone of infiltrate on CXR on their baseline CXR taken in Study 1 as an indicator of lung abnormality and to pass the American College of Sport Medicine's (ACSM) new pre-participation health screening questionnaire (Appendix P) to qualify for enrolment into the pilot study. Once the screening criteria had been met, participants were eligible for enrolment into the pilot study. At this point, baseline parameters for lung function, functional capacity, and QoL were performed.

5.2.1.2 Sample size

Only four participants were enrolled from Study 1 as per the inclusion criteria mentioned above despite having recruited more than 10 participants. Due to the slow uptake, it was decided that instead of waiting to enrol more participants for the pilot study and delay recruitment for the main study, only the four participants that had provided consent would participate in the pilot study.

5.2.1.3 Procedure

Once enrolled into the pilot study, participants participated in a PRP over a period of two weeks to assess the comprehension of the process and the feasibility of the intervention. The intervention for the pilot study was the same for the intervention (refer to Section 3.2). Participants attended two weekly 45-minute sessions of the PRP. The dates for these sessions and the time at which the PRP would start were negotiated with the participants, but the duration of each session was consistently set a 45-minutes. The PRP sessions for the pilot study took place at the clinic in an open-air space which had artificial grass between two containers and had been screened off on one side to protect against inclement weather conditions.

Participants were provided with a yoga mat, a set of TheraBands of different resistances, and a bottle of water at the start of the session. The researcher fitted participants with a chest strap and a watch heart rate monitor (Polar heart rate monitors – Model A330) before commencing the session. Participants at this point were shown how to read the heart rate on the watch and were required note where the monitor was situated on their chest. In addition, pulse oximetry and Modified Borg Dyspnoea Scale was also taken at start of the session. The quantitative data, however, was not analysed as the purpose of the pilot was to test the feasibility of the method planned for the RCT. The researcher, a qualified physiotherapist, was the instructor. Each exercise was demonstrated to the participants at least three times before asking the participants to execute the activity. Clear instructions using simple English and basic isiXhosa words such as bend (goba), knee (indolo), and breathe in and out (phefumla) were used during the sessions to encourage and engage with participants. Participants were corrected on their execution of an activity by the researcher where required. At the end of the two-week period, the assessments and outcome measures were repeated. Thereafter, participants were also provided an opportunity to complete a questionnaire regarding the process, as well as their perceived benefits and experience of the PRP (Appendix Q). No changes were made to the PRP as there were no comments regarding this in the feedback forms other than that the open-air space would be cold during winter months. This was addressed and an alternate facility was sourced for the intervention. No adverse events occurred during the pilot PRP sessions.

5.2.2 Study design for the intervention

A pilot, randomised, single blinded, pre-test-post-test design was used. The trial was designed to assess the superiority of the experimental intervention over standard of care in a RCT. The assessors were blinded to group allocation, while the researcher who implemented the PRP, was not.

5.2.3 Participants

Patients who presented at the Ubuntu HIV/TB site in Khayelitsha were recruited for inclusion in the study. All adult participants who were between the ages of 18 and 65 years, who had a current confirmed TB diagnosis by Gene-Xpert or smear microscopy, with or without HIV co-infection at time of diagnosis, but still within the first week of TB treatment were screened for eligibility. Participants who had experienced previous episodes of TB were not excluded.

5.2.4 Recruitment

For the intervention, participants were newly recruited from the clinic. Pamphlets were posted at the clinic informing clients attending the TB clinic of the study. As there were two additional observational studies running concurrently (February 2018 to Dec 2018) at the site also recruiting newly diagnosed TB clients, permission was obtained from the HREC to co-enrol participants if they so wished. Potential participants were identified using the confirmed National Health Laboratory Services reports of positive Gene Xpert results which were accessed daily by the research doctors on site. The research assistant would contact these individuals and invite them to be screened for the study. In addition, the research assistant also recruited potential participants in the waiting area daily. Although the TB clinic staff were not responsible for recruitment, they would occasionally inform the researcher or research assistant of potential participants.

Patients were informed as to the length of the study and that participation in the study was not part of their routine treatment and therefore completely voluntary. Patients who wished to participate were asked to report to a designated consultation room away from the general waiting area after receiving their medication. Participants who were interested in participating in the study were also permitted to see the research team after receiving their medication to ensure that they did not lose their place in the queue. In the privacy of the consultation room, details pertaining to the intervention study were provided, which included information regarding the type of assessments required at enrolment (spirometry, 3MST, and completion of the EQ-5D-3L and SGRQ questionnaires), how long the intervention sessions would be if allocated to the IG, and how many follow-up sessions were involved for each group.

Although the intention was for a three-month post-intervention follow-up, only five participants returned for their three-month follow-up. All attempts to encourage participants from both the CG and the IG to return for a three-month follow-up were unsuccessful; these measures included home visits as well as telephone calls. Participants were informed of the potential benefits and risks associated with participation.

In the privacy of a consultation room, potential participants were given an opportunity to ask any questions and were provided with answers related to their participation should they enrol. Thereafter, informed consent took place which allowed the patient the freedom to decline participation once all information pertaining to the study had been provided. Potential participants were also given time to consider consenting and returning on another day if they so wished. They were also allowed to bring a family member to find out about the trial and assist with their decision if they so wished. The above measures were in place to reduce any undue influence that the researcher or research assistant may appear to have imposed.

5.2.5 Inclusion and exclusion criteria

All adult patients with TB between the ages of 18 and 65 years who were diagnosed and being treated for TB at the TB clinic, whether it was their first-time having TB or not, with or without HIV co-infection, with or without COPD were eligible for inclusion. Participants had to be in their first week (seven days) of treatment with a confirmed positive Gene Xpert or smear and compliant with their treatment. Compliance with treatment was established by checking participants' clinic records/cards. Those who had missed any treatment session within the first two weeks of treatment were excluded. Continued compliance throughout the intervention and follow-up was required and this was monitored by checking their follow-up appointments at the clinics using their medical records, for which consent was obtained during the screening and enrolment process (Appendices R and S respectively). In addition, during the exercise sessions participants were encouraged to remain compliant with TB treatment, even if they felt better. Those in the CG were reminded about being compliant with treatment throughout the study via SMS and follow-up visits until the completion of their TB treatment. In addition, recruited participants must have had at least one area of infiltration/consolidation on CXR to be enrolled into the study trial. A further inclusion criterion was that participants had to have passed the ACSM's new pre-participation health screening questionnaire (Appendix P). The PRP consisted of aerobic exercises, therefore participants were required to be independently ambulant and free of cardiac problems to participate.

Participants were excluded from the intervention study if they were adult patients with only extra-pulmonary TB, recent severe chest trauma (within the past three months), a recent history of pneumonia (within one month), known atopic asthma, cardiac failure, any other unrelated respiratory disease as reported in their medical folders, or who had poor adherence as described above. Patients who failed the ACSM's new pre-participation health screening questionnaire, were unable to ambulate due to paralysis or amputation, or did not provide informed consent were also excluded.

5.2.6 Screening and enrolment

Patients were first screened before being invited to enrol in the study. A screening information sheet and a consent form presented in English (Appendix T) or in their language of preference (isiXhosa – Appendix T_1) was provided for those who were literate. Largely, recruited participants who were screened for eligibility preferred to have the screening information sheet explained or read to them by the research assistant, who was isiXhosa speaking, before consenting. During this time, participants were also given the opportunity to ask any questions and have them answered by the research team.

Potential participants who provided consent to be screened (Appendix T) had a CXR taken to confirm that at least one segment of lung was affected, and cleared the ACSM's new pre-participation health screening questionnaire (Appendix P) which screened for readiness to start an exercise programme, and were then eligible for enrolment. Female participants were requested to perform a pregnancy test prior to having the CXR taken to ensure that additional measures to reduce radiation were taken. Once screening consent was obtained and the criteria met as stated above, participants were invited to enrol in the study.

Participants who fulfilled the inclusion criteria were provided with details regarding the trial and requested to complete an enrolment consent form (Appendix R) if they were so inclined. Once enrolment consent had been obtained, baseline data pertaining to demographics, socio-economic status, QoL, and lung function parameters was taken. HIV status and information pertaining to CD4 count, viral load, and time on anti-retroviral therapy were also recorded from the patients' medical folder. The research assistant and researcher performed the baseline assessments. Randomisation (as described in Section 5.2.8) was only completed after the baseline assessments had been completed.

At this point, participants were informed that at subsequent assessment follow-up dates (six weeks and 12 weeks of intervention and three, six-, and 12-months post intervention) they were not to inform the assessor which group they had been allocated to. Participants who met the screening and enrolment criteria and provided consent were compensated for travel and time to the value of R150 on the day. Participants who were enrolled into the IG received R100 per session attended and R150 on the days when they attended the clinic for the follow-up re-assessments according to the timeline.

5.2.7 Sample size determination

It was estimated that the change in FEV_1, the primary outcome measure, for the IG would be approximately 220ml, and 120ml in the control group (Vecino et al., 2011). With power of 90%, an alpha of 5%, and a standard deviation of 80ml, the total sample size required was 30 participants.

However, to allow for a drop-out rate of up to 50%, or potentially detect a smaller difference in improvement with the IG, a total sample size of 60 was used, with 30 participants in each group.

5.2.8 Randomisation

A random, computer-generated sequence was developed by a statistician to ensure that enrolled participants were randomly allocated to an intervention arm. This list, using participant study numbers only, was provided by the statistician prior to commencement. These numbers, which were linked to an IG receiving PRP or the CG receiving standard care, were concealed in opaque envelopes, and stored consecutively for allocation. Allocation of enrolled participants was performed by an independent research assistant who was not present on site. The researcher would contact the independent researcher after the enrolment of the participant and request an allocation. The use of sequential sealed envelopes as well as an independent researcher that allocated the envelopes was performed to ensure allocation concealment.

Randomisation into intervention arms using the concealed envelopes was executed only after all inclusion and screening criteria had been met and baseline assessments had been performed by the research team. The process aimed to control selection and measurement bias, with the researcher blinded at time of baseline assessment. In addition, when more than one participant was enrolled at the same time on the same day, participants were informed telephonically the next day as to which group they had been allocated to reduce the contamination of groups.

Due to the nature of the intervention, it was impossible to blind the interventionist (the researcher) from the process. However, the assessor responsible for follow-up assessments (six weeks and 12 weeks) was independent from the study and blinded to the IG to reduce detection bias. It must be noted that this was not always possible as the assessment days may be similar for both intervention arms and participants may have involuntarily informed the assessor. The assessor, however, reminded participants on the assessment day that they should not inform them or the fellow participants which group they had been allocated to.

5.2.9 Procedure

Once participants had provided consent and had been enrolled into the trial, following procedure was observed:

- Baseline data collection for enrolled participants was conducted in a well-ventilated consultation room away from the clinic waiting area. This afforded participants privacy while providing answers regarding their health.

- Baseline data of participants pertaining to demographic, QoL questionnaires (EQ-5D-3L and SGRQ), and where applicable, data pertaining to HIV status and management (whether on anti-retroviral therapy) were also collected using a self-designed clinical research form which had been slightly modified since its use in Study 1 (Appendix S).
- Participants in the IG received two 45-minute PRP sessions per week over a 12-week period, completing a minimum of 16 sessions (allowing for missed appointments). Due to the nature of recruitment and enrolment, initial PRP sessions were individual but progressed to small group classes not exceeding six participants due to space constraints.
- The exercise class was provided in the community hall situated close to the clinic as it was well ventilated and allowed the class to continue in the event of inclement weather. Other practical infection control measures such as drinking their own water (supplied by researcher) and instruction on cough hygiene were adhered to. These sessions were led by the researcher who is a qualified physiotherapist. The two sessions per week were arranged to suit both the therapist and participants as far as possible to ensure maximum attendance. The negotiated time for sessions related only to the time of day and not the duration of the session.
- As with the pilot study, for the intervention pulse oximetry and Modified Borg Dyspnoea Scale was also taken at start of each session.
- An educational session was provided to the IG only as part of the PRP and was presented every three weeks. Topics related to TB/HIV as well as general health information related to the benefits of smoking cessation, leading an active lifestyle, and identifying common symptoms of diabetes, and the importance of continued TB therapy was covered.
- Participants in the CG were provided with an information leaflet (Appendix U) regarding TB and its treatment. They were also reminded that they would be contacted for follow-up assessments even though they were not participating in the structured PRP.
- The participants for both the CG and IG were assessed at baseline (at enrolment – month 0), midway through the intervention (six weeks), and at completion of the study (12 weeks). The midway assessment was performed at week six and was included to assess participants progress and to encourage continuation.
- Long-term follow-up at three, six, and 12 months, although initially planned, was not possible due to poor retention of participants at three months (with only five returning for assessment at three months after the 12-week intervention), time constraints, as well as funding limitations.
- Participants in both the IG and CG were reminded via SMS/call/WhatsApp of their follow-up appointments. In addition, the IG was provided with appointment cards for their exercise sessions.

5.2.10 The intervention

Pulmonary rehabilitation programmes are typically conducted at outpatient facilities which often have basic exercise equipment such as stationary bicycles, dumbbells, rowing machines, or treadmills. The PRP for Study 3 was conducted at a community hall as the outpatient facility at the clinic (Ubuntu Site B) had neither the space nor the basic exercise equipment noted above. Therefore, this had to be considered when creating the PRP and as a result most of the exercises used participants own body weight for resistance, while TheraBands were used instead of dumbbells as a cost effective alternative (Lopes et al., 2019).

As set out in the pulmonary rehabilitation guidelines, the exercise component of the PRP consisted of a warm-up (10 minutes), an aerobic component (30 minutes), and a cool down (5 minute) (Garvey et al., 2016; Spruit et al., 2013). The ACCP/AACVPR guidelines (as mentioned in Section 2.1) provide updated guidelines for the components of a PRP but fall short of outlining the specific activities. Therefore, the activities listed in each of the exercise components that follow are activities selected in an attempt to address this gap. The warm-up session consisted of breathing exercises (diaphragmatic and pursed lip breathing) and stretches for all major muscle groups for both the upper and lower extremities. These exercises were in line with information obtained from the systematic review, where three out of the four studies included breathing exercises.

The aerobic component of the PRP consisted of a combination of cardio and upper and lower limb strengthening exercise as there was level 1a evidence to support the inclusion of these types of activities in the COPD PRP guidelines. Upper limb strengthening exercises included bicep curls, triceps extensions, abduction with resistance bands, push ups, and sit ups. Aerobic/cardio components such marching on the spot, jumping jacks, and boxing punches were used between strength components. Lower limb activities included high knees, side jacks with arm punches, high knee marching, superman's, walking lunges, standing calf raises, squats and wall squats for those who were unable to do the technique correctly while free standing, as well as 'air cycling.' Appendix V provides details regarding the intervention related to level of intensity, incremental increase, and number of repetitions. Skipping rope activities were initially included in the intervention but had to be excluded as not all participants were able to perform this activity.

In the initial two weeks of the programme, the participants' own body weight was used as a form of resistance. From week three onwards, resistance was increased with the introduction of resistance bands for upper limb activities. The cool down component consisted of large muscle group stretching for both the upper and lower limbs as well as relaxation techniques such as yoga poses.

As participants reported that they were not participating in any form of regular/conventional exercise programmes and primarily watched television in their spare time, activities were introduced at a lower intensity (refer to Glossary of Terms) for the first two weeks of programme. This was to ensure that participants executed each activity correctly and to familiarise them with the basic exercise terminology used during the class. Intensity levels were progressively increased as participants became more conditioned. At week three, participants were advanced from low intensity to moderate intensity and from week six until the end of the intervention, participants were advanced to a higher intensity. Each activity was performed twice (two sets) with a repetition range of six to eight in the first two weeks for each activity. As participants had not previously participated in a structured exercise programme, learning the correct technique for each activity was important, and as a result a short repetition range was implemented to reduce the 'burn' of the activity and to allow the participant enough practice to execute the movement correctly. A range of six to eight repetitions, instead of a fixed number, allowed the researcher to objectively measure when weights/resistance or repetitions should be increased for progression (Gloeckl et al., 2018).

Maximal heart rate for each participant (for cardiovascular endurance) was calculated prior to commencement of the PRP. The calculation for maximal heart rate is 220 less the age of the patient (Lato & Polar, 2020). Participants worked at a submaximal heart rate percentage of 40% to 50% (low intensity) at the start of the programme (first two weeks) and progressed accordingly (50% to 60% from the third week, coinciding with moderate intensity activities and then to 60% to 75% of maximum heart rate). The exercise component of the PRP was followed by an educational session held every third week for 15 minutes, with topics related to TB/HIV as well as general health information related to the benefits of smoking cessation, having an active lifestyle, and identifying common symptoms of diabetes. During this time, participants were also given time to ask the therapist any questions related to the exercise programme or their general health.

The execution of the PRP was led by a qualified physiotherapist, with more than 20 years' experience, who provided instructions and demonstrated all activities to participants and corrected them where and when necessary. Due to the nature of enrolment, sessions were initially individual but as participants' enrolment increased, a group format was introduced with a maximum of six participants due to space and resource limitations. Recovery periods between activities were 10–30 seconds in duration. Participants were encouraged to participate maximally according to their heart rate and to hydrate throughout the sessions. A chair was provided for each participant to use in the session when required for activities, as well as for rest periods.

Participants' effort tolerance was monitored actively (via a heart rate monitor) and subjectively using the Borg rating of perceived exertion scale (RPE) (Appendix W) throughout to ensure they did not overexert themselves. Participants were requested to perform activities at a light intensity in the initial two weeks while getting accustomed to activities (RPE =1–3) which was then progressed accordingly to a moderate intensity (RPE= 4–6).

Only two adverse events occurred during the intervention programme that were reported to the clinic doctor. In both instances, the participants fainted. The reason for one of the participants fainting was related to not having eaten for two days prior to the session due to her shack having caught alight destroying all her belongings. For the other participant, the cause was unknown. Both participants were immediately taken to the trauma unit at the nearby clinic where they were observed and later discharged.

Participants in the IG were reminded via SMS/calls/WhatsApp to attend the upcoming PRP session in addition to providing them with a clinic card. The participants allocated to the CG were offered the same number of educational sessions on topics relevant to TB, such as the importance of nutrition and smoking cessation. Participants in the CG were provided with an information leaflet regarding TB and benefits of staying healthy/active (Appendix U).

5.2.11 Re-assessment at various time points

On completion of the PRP, participants in both groups were re-assessed for the outcome measures pertaining to lung parameters (FEV_1, FEV_1/FVC and FVC), functional capacity (step test), CXR, and QoL (EQ-5D-3L and SGRQ). The assessors were blinded as to which group was being assessed and only provided with study numbers to contact participants for assessment dates. The assessors also reminded study participants that they should not inform the assessor which group they had been assigned to when attending the follow-up assessments. As noted in Section 5.2.9, follow-up at three months was attempted but had a very poor response with only five participants returning. Due to financial constraints, time constraints of the researcher, as well as lack of responses from participants, the long-term follow-up at three, six and 12 months could not be executed.

5.2.12 Functional outcome measure used in Study 3 (intervention) only

The same outcome measures used in Study 1 for lung function (spirometry) and HRQoL (EQ-5D-3L and SGRQ) were used in Study 3 and therefore not repeated here (refer to Section 3.2.7). The additional or alternate outcome measures used for Study 3 are described below.

5.2.12.1 Exercise pre-participation health screening questionnaire for exercise professionals

The exercise pre-participation health screening questionnaire was recently published by the ACSM (Magal & Riebe, 2016). The tool allows professionals to establish whether an individual should participate in physical activity and consists of three steps, namely: symptoms of cardiac disease, current activity level, and medical conditions (Appendix P). Participants who answer 'no' to all questions were deemed fit to commence physical activity without medical clearance. The questionnaire also provides recommendations for patients who are unable to commence physical activity due to various medical conditions. In Study 3, the ACSM new exercise pre-participation health screening questionnaire was used as a screening tool for recruited participants as part of the inclusion criteria for enrolment into the RCT.

5.2.12.2 Three-minute step test

Both walking and step tests are considered to be low technology and have been widely performed in patients with respiratory disease to inform prognostic and therapeutic management due to their ease of execution (Costa et al., 2017). In Study 3, a RCT providing an exercise-based intervention, the 3MST, was used as the functional outcome measure.

The step test, as its name suggests, is a test in which participants have to complete a number of steps within in a given time frame, using a '2-step' platform, with a standardised step height of at least 20cm (Costa et al., 2017; de Andrade, Cianci, Malaguti, & Dal Corso, 2012). The step test may be used as both an assessment and an outcome tool. Measuring the heart rate before and after completion of the test is a simple assessment of an individual's cardiovascular fitness level (de Andrade et al., 2012; Pessoa, Arcuri, & Labadessa, 2014). The number of steps measured during the test is used to ascertain any improvement in functional capacity. When compared to the 6MWT, the 3MST is a valid and reliable tool to measure exercise capacity in patients with COPD (Beaumont et al., 2019). Unlike the 6MWT which requires a 30m unobstructed corridor indoors, which is usually available in a hospital setting (but was not available at the assessment site), the 3MST requires much less space and can be performed more easily for non-hospitalised patients. Therefore, the use of the 3MST was deemed fit for the resource limited setting, specifically regarding space resources.

5.2.13 Statistical analysis and data management

Data collected for the intervention study was analysed using the Stata data management programme. Analysis for the primary outcome of lung function parameters (FEV_1, FEV_1/FVC, and FVC) followed the intention to treat principle. Descriptive statistics were used to describe the demographic data, QoL, TB treatment and HIV status, and lung function parameters in both groups.

Differences between the baseline and final lung function test values, namely FVC, FEV_1, and FEV_1/FVC ratio (primary outcome measures) were calculated. A Shapiro-Wilk test was performed to determine normality for all continuous data. If the data were normally distributed, the paired t-test was performed to determine whether there were within-group differences from pre- to post-intervention. Independent t-tests were used to determine whether there were between-group differences at the commencement of the intervention as well as post intervention.

Where the data were not normally distributed, equivalent non-parametric tests were formed (Sign test and Mann Whitney U test). Pre-test measures were compared to post-test measures. Analysis of Variance (ANOVA) across time and intervention/control group as well a post-hoc Tukey tests were performed to establish whether change did take place and at what stage. Sub-group analysis was carried out with comparisons between HIV-positive and HIV-negative groups. Correlation was assessed through scatterplots and correlation tests were conducted using the Spearman's coefficient to measure the strength of the association between continuous variables and the direction of the relationship (Schober, Boer, & Schwarte, 2018). Spearman correlation findings were categorized as follows: 0-0.19 very weak, 0.2-.39 weak, 0.4-0.59 moderate, 0.6-0.79 strong and 0.8-1.0 very strong. Missing data was excluded on a variable basis.

5.2.14 Ethical considerations for Study 3

The study adhered to the Declaration of Helsinki (World Health Organisation, 2001). Ethical approval was obtained from the HREC, Faculty of Health Sciences, University of Cape Town (HREC/REF:323/2017, Appendix X). Similar to Study 1, approval was also obtained from the Western Cape Department of Health and from the relevant stakeholders of the various clinics, i.e., site managers. Furthermore, the RCT was registered with the Pan African Clinical Trial Registry (PACTR) registry (PACTR201706002153485, Appendix Y). The researcher also completed a Good Clinical Practice course (Appendix Z) to ensure compliance prior to the commencement of the RCT.

5.2.14.1 Autonomy

Participants were informed that participation in Study 3 was voluntary and that it would not affect their scheduled visits or standard of care provided at the clinic. As participation was voluntary, participants were informed that they could withdraw from the study at any stage without being penalised. An information sheet was provided to each participant in their preferred language (Appendix R) which was either English or isiXhosa (Appendix R_1) to read or have it read to them by the research assistant who was fluent in both languages. Informed consent was obtained from

participants recruited into the study who met the inclusion criteria. To ensure that participants understood the nature of randomisation prior to signing the consent form and enrolling into Study 3, they were questioned regarding this (see Appendix R).

All demographic and personal information of participants remained confidential as each participant was provided with a study number. The data collected was stored on a password protected external hard drive, and all hard copies, which were coded with only study numbers, were kept in a secure locked cabinet away from the clinic.

5.2.14.2 Beneficence

Participants who were screened and enrolled into the study received reimbursement for travel to the value of R150, which was provided using a card-less cash withdrawal system. Subsequently, participants in the IG received R100 at each session attended as reimbursement for travel costs (also using the card-less cash withdrawal system). In addition to this, participants in the IG were provided with a 500ml bottle of water, a sandwich with a protein filing (peanut butter, cheese, or cold meat), and fruit at each session. Reimbursement for time and travel to the value of R150 was also provided at each assessment point after enrolment for both the IG and the CG.

Participants who screened negative for commencement for physical activity due to high blood pressure or any other cardiac problems were excluded from the study but referred to the doctors at the clinic for further management. As participants were patients at the clinic, they were not an additional load to the clinic due to the study.

5.2.14.3 Non-maleficence and risks

In Study 3, an exercise-based intervention, great care was taken to minimise the risk of participants sustaining an injury during the PRP. In the event of such an incident taking place, the participant would receive immediate post-injury care by referral to the clinic doctor or nearest hospital for management as applicable. The researcher responsible for the intervention was a qualified physiotherapist and had completed a cardio-pulmonary resuscitation certification. First aid kits were also available during every session. In the event of a participant feeling unwell during the exercise session, the participant would be immediately referred to the clinic doctor for appropriate management. Participants in the PRP were screened using the ACSM's new pre-participation health screening questionnaire exercise guidelines (Appendix P) to exclude any risk factors for participating in an exercise programme. Similar to Study 1, participants also had spirometry and functional capacity assessed at enrolment and at follow-up assessment points (refer to Section 3.2.7).

5.2.14.4 Justice

The research aim of Study 3 was to improve pulmonary function, functional capacity, physical activity, and HRQoL of people with TB, with or without HIV co-infection. This group of participants was chosen particularly because they lived in areas with poor infrastructure and inadequate resources. Participants were made aware that the results of the study may be published in an accredited medical/health care journal to create awareness of the outcome of the study and any possible benefits of a PRP for patients with TB, with or without HIV co-infection. A final study report was also provided to the facility manager on completion of the thesis.

5.3 Results of Study 3

In this section, the results from the intervention, which was an exercise based PRP executed as a pilot RCT are reported. As in Chapter 3, the results are presented in relation to the objectives previously set out in Chapter 1 (see Section 1.2). Socio-demographic data will be presented first, followed by the clinical data. Data regarding the outcome measures will then be reported using the following structure:

- Lung function parameters (FEV_1, FVC and FEV_1/FVC);
- Classification of lung function abnormalities;
- A step test (3MST); and
- The QoL measurements of EQ-5D-3L and SGRQ.

5.3.1 Socio-demographic characteristics

Regarding sex and age, the two groups were well matched. With reference to housing and amenities, the CG and IG were also comparable as most participants were shack dwellers (CG=18 vs IG =16). Both the CG and IG groups had similar amenities regarding access to water, electricity, and use of alternate sources for heating and cooking, as presented in Table 26 below. The median number of people living in a dwelling with the TB participant was three for the CG and four for the IG. Education levels were comparable; most participants in each group had obtained secondary education (CG=20 and IG=23). Majority participants were unemployed irrespective of group allocation (Table 25).

Table 26. Socio-Demographic Profile for Control Group (CG) and Intervention Group (IG).

	CG (n=29)	IG (n=29)
SEX		
Female	11 (37.9%)	10 (34.5%)
Male	18 (62.1%)	19 (65.5%)
AGE GROUPS (YEARS)		
18–25	0%	6 (20.7%)
26–35	12 (41.4%)	12(41.4%)
36–45	14 (48.3%)	4 (13.8%)
46–55	2 (6.9%)	4 (13.8%)
56–65	1 (3.4%)	3 (10.3%)
MEAN AGE (YEARS)		
Total	**36.9** (SD ± 7.8)	**35.8** (SD ± 11.9)
Females	34.5 (SD ± 5.1)	32.3 (SD ± 6.7)
Males	38.4 (SD ± 8.9)	37.6 (SD ± 13.7)
HOUSING AND AMENITIES		
Brick house	10 (34.5%)	14 (48.3%)
Shack dwelling	18 (62.1%)	16 (55.2%)
Running water (inside)	15 (51.7%)	18 (62.1%)
Running water (outside)	18 (62.1%)	15 (51.7%)
Flushing toilet (inside)	13 (44.8%)	16 (55.2%)
Flushing toilet (outside)	19 (65.5%)	17 (58.6%)
Bucket toilet	3 (10.3%)	2 (6.9%)
Electricity	23 (79.3%)	26 (88.7%)
Biomass (wood) for cooking /heating	0%	1 (3.4%)
Paraffin for cooking/heating	5 (17.2%)	2 (6.9%)
Gas for cooking/heating	4 (13.8%)	3 (10.3%)
Median no. of people living in dwelling	**3**	**4**
EDUCATION		
Primary or less	7 (24.1%)	5 (17.2%)
Secondary	20 (69.0%)	23(79.3%)
Tertiary	1 (3.4%)	1 (3.4%)
EMPLOYMENT		
Employed	10 (35.7%)	9 (31.1%)
Unemployed	15 (53.6%)	15 (51.7%)
Studying	0	2 (6.9%)
Pensioner	1 (3.6%)	0
Unemployed due to poor health	2 (7.1%)	(10.3%)

5.3.2 Clinical characteristics of the groups

The participants' clinical characteristics in the RCT are summarised in Table27. There were 29 participants in each group. Regarding number of co-morbidities, the two groups were well matched. Like that of participants in Study 1, few participants had more than two comorbidities. Hypertension was the most prevalent comorbidity amongst participants and was similarly distributed for both groups and genders. Overall, participants in this study were similar to those in Study 1 with the exception that those with a prior TB infection were not excluded.

Regarding HIV status, the CG had more participants who were HIV positive (n=22) and on anti-retroviral therapy (n=11) than their IG counterparts (n=13 and n=5 respectively). The median BMI for both groups fell within the normal range category (CG=19.4kg/m2; IG=19.9kg/m2). When comparing BMI by sex, females had a higher median BMI in the CG (CG=24.8kg/m2 vs IG=23.2kg/m2) when compared to their male counterparts (see Table 26).

Approximately half of the participants were first time TB patients, with more participants in the IG reporting recurrent TB episodes (n=16 vs n=13). When comparing smoking history between the CG and IG, the CG had a longer pack year history than the IG.

Table 27. Clinical Characteristics of Control group (CG) and Intervention group (IG).

	CG (N=29)	IG (N=29)
REPORTED CO-MORBIDITIES		
Hypertension	2 (6.9%)	3 (10.3%)
Diabetes Mellitus Type I	2 (6.9%)	0 (0%)
Diabetes Mellitus Type II	0 (0%)	2 (6.9%)
Angina	0 (0%)	0 (0%)
>2 co-morbidities	**1 (3.4%)**	**1 (3.4%)**
MEDIAN BMI (kg/m^2)		
Totals	**19.4 (IQR: 17.8–22.8)**	**19.9 (IQR 18.4–22.7)**
Females	24.8 (IQR:19.4–31.6)	23.2 (IQR:22.4–25.1)
Males	18.5 (IQR: 17.6–21.1)	19.0 (IQR: 18.2–21)
HIV STATUS		
Positive	22 (75.9%)	13 (44.8%)
Negative	6 (20.7%)	16 (55.2%)
Unknown	1 (3.4%)	0 (0%)
Mean CD4 count (cells/µL)	**190* (*n=15)**	**205* (*n=10)**
ANTI-RETROVIRAL TREATMENT STATUS		
Total	*(n=22)*	*(n=13)*
Current	11 (50%)	5 (38.5%)
Previous	3 (13.6%)	2 (15.4%)
Never	8 (36.4%)	4 (30.8%)
		(2 missing data)
SMOKING HISTORY		
Ever smoked (incl. current)	15 (51.7%)	16 (55.2%)
Never smoked	13 (44.8%)	13 (44.8%)
Recreational drug users	**2 (6.9%)**	**3 (10.3%)**
Pack years (mean)	**5.5**	**2.9**
PREVIOUS TB EPISODES		
First episode	16 (55.2%)	13 (44.8%)
1 previous episode	8 (27.6%)	6 (20.7%)
2 previous episodes	5 (17.2%)	9 (31.0%)
3 previous episodes	0 (0%)	1 (3.4%)

**CD4 counts were only available for these number of participants in each group at time of data collection; BMI-Body mass index*

5.3.3 Summary of assessments completed at each time point

Details pertaining to assessments and questionnaires completed in each arm of the study at various time points are presented in Table 28 below. At six weeks, there was a LTFU of 24.1% and 27.6% in the CG and IG respectively. Reasons for LTFU in the CG at six weeks were attributed to withdrawal due to finding employment (n=3), withdrawal without reason (n=1), and being unable to contact the participant for follow-up (n=3). In the IG group, LTFU was attributed to similar reasons: finding temporary employment (n=2), withdrawal without reason (n=3), being unable to contact the participant for follow-up (n=2), and death (n=1).

After 12 weeks, there was further LTFU in the CG group by one participant from the six week follow-up and loss of an additional four participants in the IG group. The reason for additional LTFU at 12 weeks for both the CG and IG was solely attributed to being unable to contact the participants despite several follow-up calls, WhatsApp messages, and even home visits. Loss to follow-up from baseline to 12 weeks was therefore 28.6% in the CG, versus 41.4% in the IG.

Table 28. Summary of Assessments for Control Group (CG) and Intervention Group (IG) at the Various Time Points.

	N (%)	N (%)
BASELINE (TOTAL N=58)	**CG (N=29)**	**IG (N=29)**
A-LFT	21 (72.4)	21 (72.4)
QoL questionnaires	29 (100%)	29 (100%)
3MST	27 (93.1%)	27 (93.1%)
Unacceptable LFTs	8 (27.6%)	8 (27.6%)
6 WEEKS (TOTAL N=43)	**CG (N=22)**	**IG (N=21)**
A-LFT	21 (95.5%)	20 (95.3%)
QoL questionnaires	22 (100%)	21 (100%)
3MST	21 (95.5%)	20 (95.3%)
Unacceptable LFTs	1 (4.5%)	1 (4.7%)
Loss to follow-up from baseline	7 (24.1%)	8 (27.6%)
12 WEEKS (TOTAL N=38)	**CG (N=21)**	**IG (N=17)**
LFT	21 (100%)	17 (100%)
QoL questionnaires	21 (100%)	17 (100%)
3MST	21 (100%)	17 (100%)
Loss to follow-up from baseline	8 (27.6%)	12 (41.3%)

Legend: 3MST- three-minute step test; A-LFT=Acceptable lung function test, QoL=Quality of life.

5.3.4 Lung function parameters

5.3.4.1 Forced expiratory volume in one second (FEV_1)

In Table 29 below, the median and IQR values in relation to the absolute and the percentage predicted FEV_1 values are presented for the overall group, CG, and IG respectively at the various timepoints. The absolute median FEV_1 at baseline for the overall sample was 2.27 litres, with 2.26 litres in the CG, and 2.31 litres in the IG.

There was no significant difference between the means for the CG and IG at the 5% significant level using the t-test at all the timepoints for absolute FEV_1 and the percentage predicted FEV_1.

Table 29: Absolute and Percentage of Predicted Lung Function for Forced Expiratory Volume at one second (FEV_1) at the Various Assessment Timepoints.

	BASELINE MEDIAN (IQR)	N	6 WEEKS MEDIAN (IQR)	N	12 WEEKS MEDIAN (IQR)	N
OVERALL						
Absolute FEV_1	2.27 (1.93–2.75)	42	2.4 (1.87–2.84)	41	2.49 (2.01–2.94)	38
Percentage of Predicted FEV_1	75.50 (61–92)		81 (68–95)		84 (65–97)	
ABSOLUTE FEV_1						
Control group (CG)	2.26 (1.93–2.75)	21	2.26 (1.87–2.76)	21	2.53 (2.02–2.93)	21
Intervention Group (IG)	2.31 (1.97–2.72)	21	2.45 (1.68–2.84)	20	2.44 (1.6–2.94)	17
P-value (comparison of means)	0.62		0.73		0.39	
PERCENTAGE OF PREDICTED FEV_1						
Control group (CG)	82 (61–92)	21	82 (68–96)	21	86 (70–99)	21
Intervention group (IG)	74 (69-85)	21	81 (66.5-92.5)	20	84 (65-87)	17
P-value (comparison of means)	0.52		0.43		0.26	

5.3.4.2 Forced vital capacity

The median absolute FVC for the overall sample was 3.22L, and 3.06L and 3.28L for the CG and IG respectively. The medians for the percentage predicted FVC value for the CG and IG were 93% and 85% respectively at baseline (Table 30). The percentage predicted for FVC in the CG declined at six weeks (89%) but returned to baseline values at week 12. In comparison, the IG had a lower baseline percentage predicted FVC (85%), improved to 92.5% at six weeks, and then decreased to 87% by week 12. However, the percentage predicted FVC in the CG remained the same from baseline to 12 weeks, while the IG saw an upward trend over the same period. The magnitude of all these changes was small and could have been related to technical variability or variability in performance of the lung function testing rather than representing significant changes in lung function. There was no significant difference between the means for the CG and IG at the 5% significant level using the t-test at any of the timepoints for absolute FVC and percentage predicted FVC.

Table 30. Absolute and Percentage Predicted Forced Vital Capacity (FVC) at the Various Assessment Timepoints.

	BASELINE MEDIAN (IQR)	N	6 WEEKS MEDIAN (IQR)	N	12 WEEKS MEDIAN (IQR)	N
OVERALL						
FVC	3.22 (2.68–3.61)	42	3.29 (2.41–3.65)	41	3.19 (2.63–4.04)	38
Percentage of Predicted FVC	88.50 (58–488)		90 (45–488)		91 (51–131)	
ABSOLUTE FEV_1						
Control group (CG)	3.06 (2.68–3.64)	21	3.04 (2.41–3.65)	21	3.48 (2.7–3.84)	21
Intervention Group (IG)	3.28 (2.12–3.55)	21	3.29 (2.30–3.66)	20	3.16 (2.35–4.04)	17
P-value (comparison of means)	0.48		0.65		0.32	
PERCENTAGE OF PREDICTED FEV_1						
Control group (CG)	93 (73–104)	21	89 (74–110)	21	93 (77–110)	21
Intervention group (IG)	84 (70.1–102)	21	91 (65.5–100.5)	20	87 (70–102)	17
P-value (comparison of means)	0.51		0.38		0.21	

5.3.4.3 Forced expiratory volume in one second/Forced Vital Capacity ratio

The FEV_1/FVC ratio for the two groups is presented in Table 31. The absolute value and percentage predicted values for the FEV_1/FVC ratio were similar for both the CG and IG at baseline and at 12 weeks.

Table 31. Absolute and Percentage of Predicted Forced Expiratory Volume in one second/Forced Vital Capacity Ratio (FEV_1/FVC) at the Various Assessment Timepoints.

	BASELINE MEDIAN (IQR)	N	6 WEEKS MEDIAN (IQR)	N	12 WEEKS MEDIAN (IQR)	N
OVERALL						
FEV_1/FVC	74.15 (68.1–79.5)	42	76.6 (70.6–81.5)	41	75.7 (68.8–81.6)	38
Percentage of EV_1/FVC	88.5 (82.94)		91 (87–95)		91.5 (85–97)	
ABSOLUTE FEV_1						
Control group (CG)	74.1 (68.7–78.9)	21	74.2 (70.4–81.8)	21	74.3 (68.8–82.5)	21
Intervention Group (IG)	75 (67.2–80.8)	21	77.15 (71.9–81.45)	20	76.9 (72.4–79.1)	17
P-value (comparison of means)	0.83		0.87		0.87	
PERCENTAGE OF PREDICTED FEV_1						
Control group (CG)	89 (83–94)	21	91 (87–96)	21	92 (85–98)	21
Intervention group (IG)	87 (80–94)	21	91 (86.5–95)	20	91 (85.–94)	17
P-value (comparison of means)	0.99		0.76		0.76	

There was no significant difference between the means for the CG and IG at the 5% significant level using the t-test at all the timepoints for the absolute FEV_1/FVC ratio and percentage predicted FEV_1/FVC ratio.

5.3.5 Lung function classification

5.3.5.1 Classification and severity of lung function at baseline

At baseline, 43% of all participants presented with normal lung function, with the remaining 57% of participants being classified as having either obstructive (26%), restrictive (21%), or mixed (10%) lung function (see Figure 19).

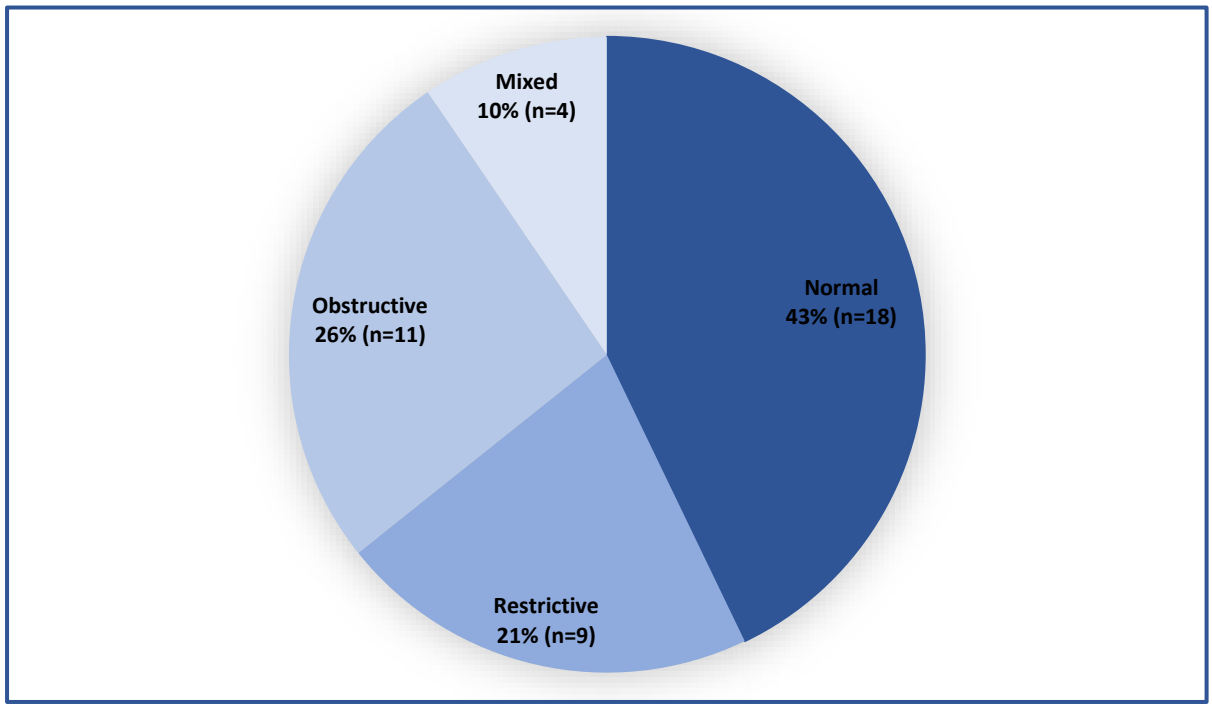


Figure 19. Overall Lung Function Classification at Baseline (N=42).

When comparing baseline lung function classification between the CG and IG, the number of participants with lung function abnormality in the CG was less than their counterparts in the IG (Figure 20). The number of participants with obstructive lung function was 1.5 times greater in the IG group than in the CG (n=7 [33%] vs n=4 [19%]) and the number of participants with restrictive lung function was also greater in the IG when compared to the CG (n=5 [24%] vs n=4 [19%]).

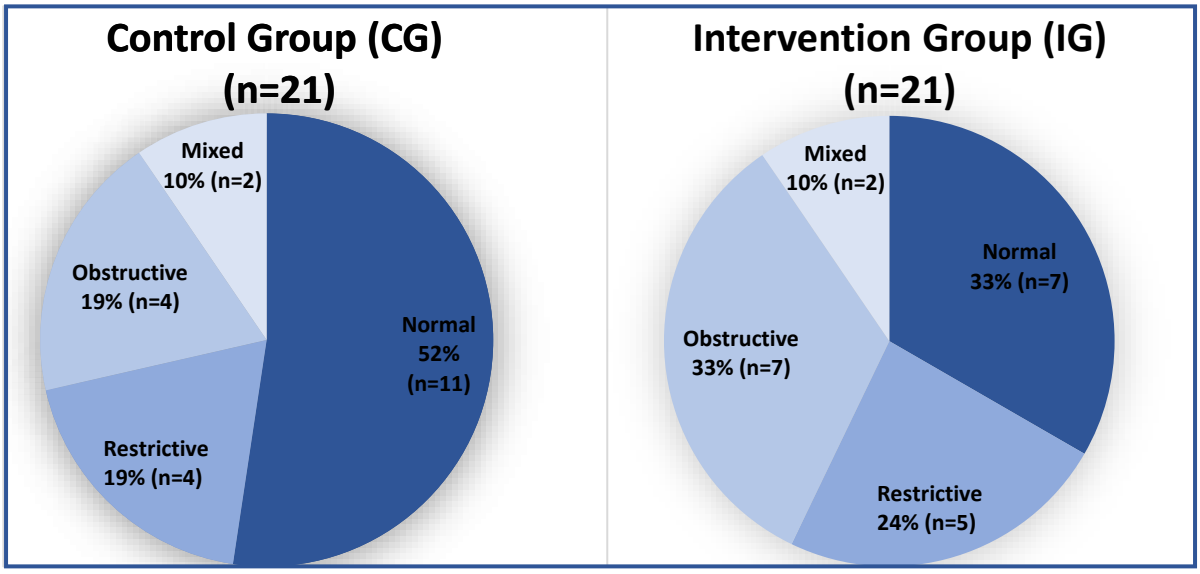


Figure 20. Lung Function Classification per Group at Baseline.

Obstructive/mixed lung function abnormality was further classified into four stages of severity of obstruction as: stage 1 – mild, stage 2 – moderate, stage 3 – severe, and stage 4 – very severe (refer to Table 8). In both groups, most participants had stage 2 (moderate) obstructive lung function (CG=67% and IG=56%). However, in the IG the proportion of participants with stage 1 (mild) obstruction was twice that of the CG (IG=33% vs CG=16%) at baseline (Figure 21).

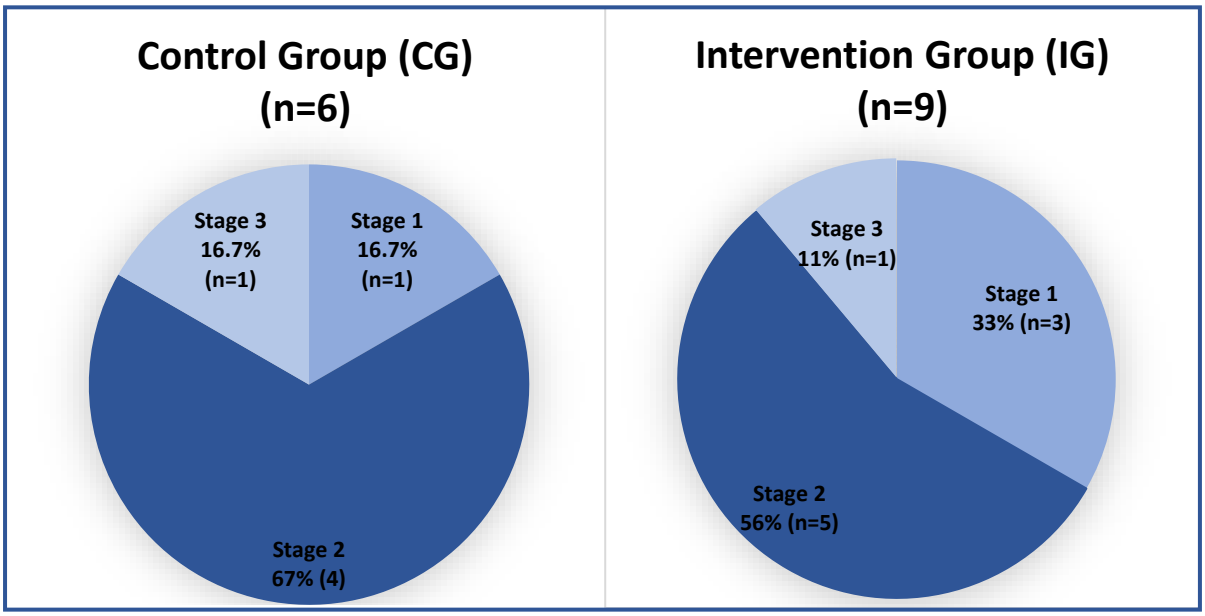


Figure 21. Severity of Obstructive Lung Classification per Group at Baseline.

Similarly, the severity of lung function for restrictive/mixed lung classification was further classified as mild, moderate, or severe restriction. At baseline, severity of restriction differed between the CG and IG. Participants who presented with restrictive lung function in the CG mostly presented with mild restriction (83%). On the contrary, those in the IG presented with primarily moderate restriction (71%) (Figure 22).

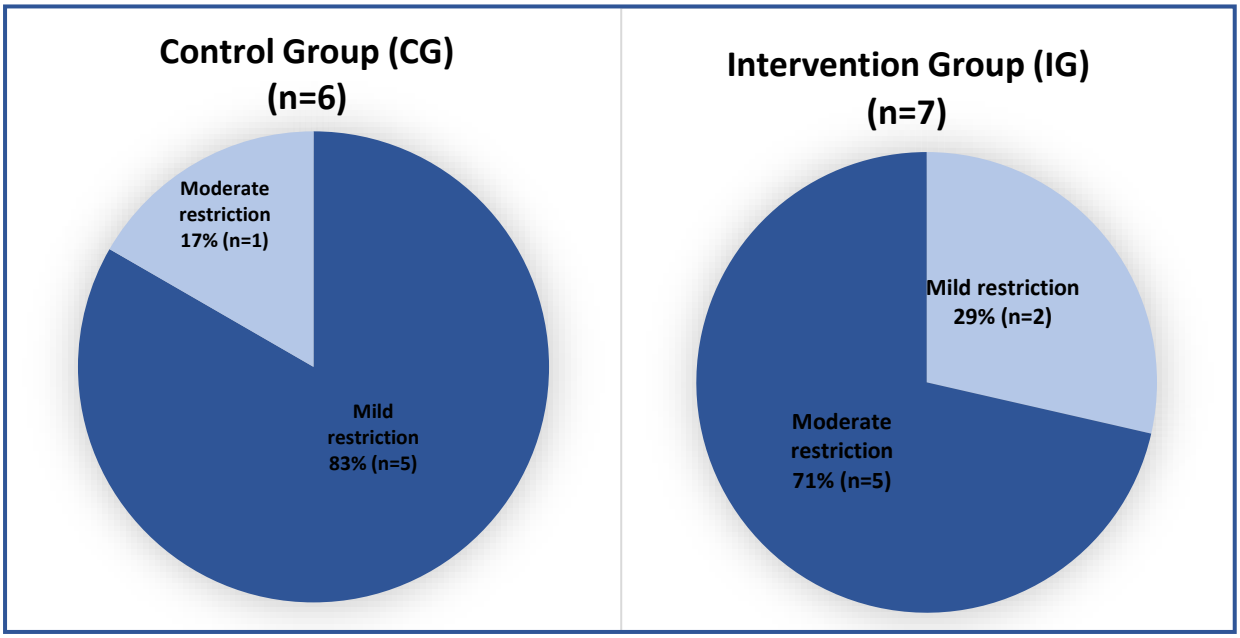


Figure 22. Severity of Restrictive Lung Function Classification at Baseline in Control Group (CG) and Intervention Group (IG).

5.3.5.2 Classification and severity of lung function at 12 weeks

In Figure 23, the lung classification for both the CG and IG is depicted. At 12 weeks, the CG had remained similar in terms of lung classification in comparison to the baseline assessment. At 12 weeks, however, a shift in lung classification was observed in the IG when compared to the baseline lung classification. This shift, although not statistically significant, was observed in the obstructive lung function classification at 12 weeks in the IG, from 33% at baseline to 12% at 12 weeks (p=0.15). Statistical analysis regarding the changes observed in the CG and IG from baseline to 12 weeks are tabled below (Table 32).

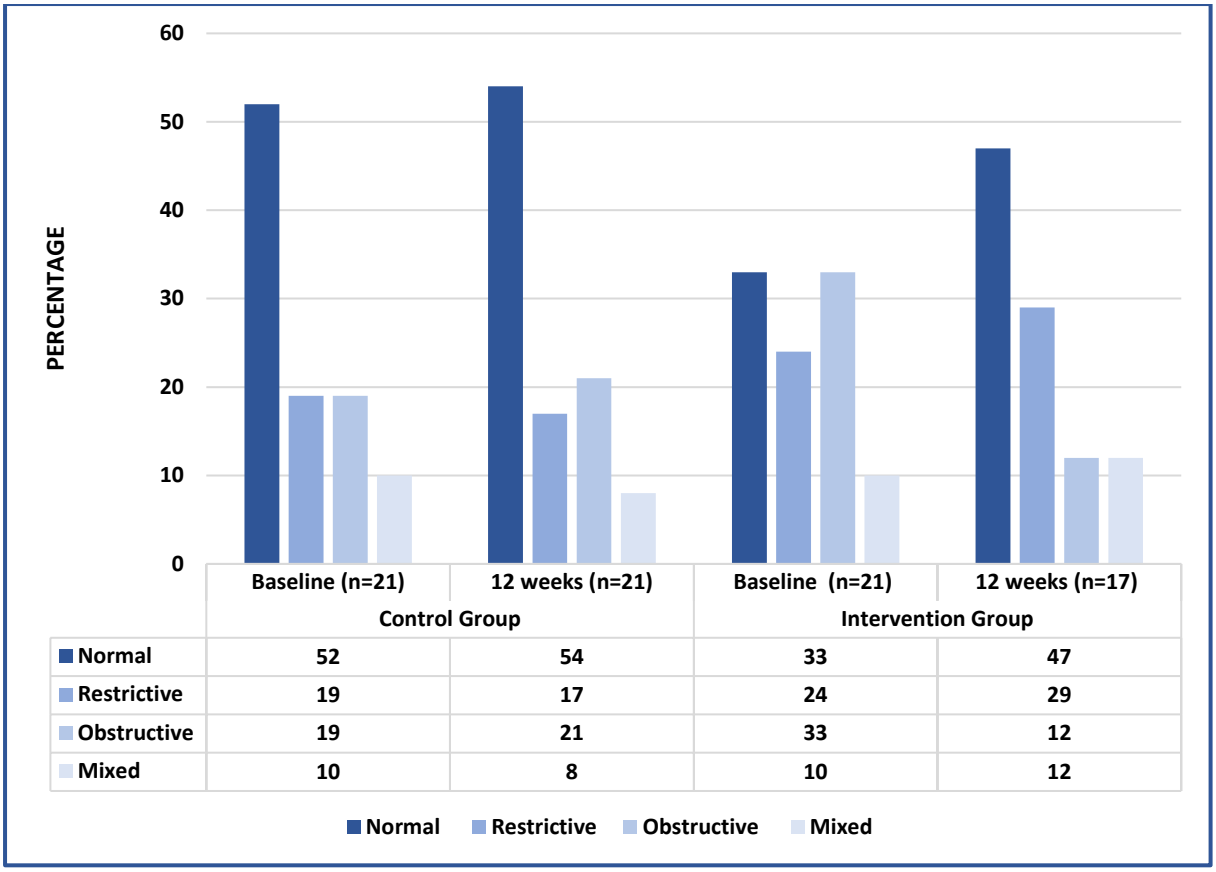


Figure 23. Classification of Lung Function of the Control Group (CG) and Intervention Group (IG) at Baseline and Week 12.

Table 32. Classification of Lung Function, Odds Ratio, and Confidence Interval for the Control Group (CG) versus Intervention Group (IG) at Baseline and Week 12.

LUNG FUNCTION	REFERENCE (CONTROL)	INTERVENTION TIME	OR	95% CI	P
NORMAL	Baseline	12 weeks	1.034	0.233–4.531	0.960
RESTRICTIVE	Baseline	12 weeks	1.000	0.109–9.175	1.000
OBSTRUCTIVE	Baseline	12 weeks	4.375	0.406–61.711	0.147

Although a statistically significant difference was not reached when analysing the continuous data (refer to Table 29, Table 30, and Table 31) or lung classification (Table 32), there was a tendency for participants in the IG to have a 67% decrease in obstructive lung classification at 12 weeks, which has clinical significance. There was also 3% increase in normal lung function at 12 weeks in the IG compared to the CG at baseline, though the effect was not significant.

While there was no difference in restriction in the CG and IG at baseline compared to at 12 weeks, there was a decrease of 4.4 times in obstructive lung function at six-weeks in the IG compared to the CG at baseline, although the effect was not significant, and this is probably due to the small number of participants remaining at 12 weeks in both groups.

5.3.6 Three-minute step test

The 3MST was the functional capacity outcome measure used in the present clinical trial. The 3MST was assessed at baseline, six weeks, and finally at completion of the intervention at 12 weeks for both groups. The median baseline number of steps taken by the CG was 79 steps (IQR 42–134) vs 117 steps (IQR 84–154) by the IG (Table 33).

Table 33. Summary of Steps Taken in the Three-Minute Step Test (3MST).

TIME POINT	GROUP ALLOCATION	MEDIAN	IQR	N
STEPS: BASELINE	Control	79	42–134	27
	Intervention	117	84–154	27
	Total	106.5	62–142	54
STEPS: 6 WEEKS	Control	99	68–143	21
	Intervention	168.5	115–199	20
	Total	143	81–181	41
STEPS: 12 WEEKS	Control	128	109–166	21
	Intervention	167	147–215	17
	Total	152	116–187	38

When comparing females to males in the respective groups, the median number of steps for males was greater in both the CG and IG at baseline and six weeks, but less at week 12 (Table 34). The t-test conducted to test the difference between means for the CG and IG was statistically significant (p=0.002) at six weeks only (Table 34).

Table 34. Summary of Steps Compared by Sex.

		FEMALES			MALES		
	GROUP	**MEDIAN**	**IQR**	**N**	**MEDIAN**	**IQR**	**N**
STEPS: BASELINE	Control	78	36–85	10	96	68–142	17
	Intervention	110	60–123	9	141,5	90–159	18
	Total	78	36–123	19	117	78–156	35
STEPS: 6 WEEKS	Control	81	68–142	9	113	68–168	12
	Intervention	165	150–179	6	180,5	111–200	14
	Total	142	68–166	15	149	84–192	26
STEPS: 12 WEEKS	Control	111	104–128	9	141,5	116–169.5	12
	Intervention	175	139.5–188	4	167	147–230	13
	Total	116	109–170	13	162	130–211	25

Table 35. Comparison of Means for the Three-Minute Step Test (3MST) at the Various Timepoints Comparing the Intervention Group (IG) and Control Group (CG).

BASELINE P-VALUE	6 WEEKS P-VALUE	12 WEEKS P-VALUE
0.09	0.002*	0.13

** significant p<0.05*

Due to the reduced number of participants at 12 weeks, a statistically significant difference was not achieved at the 5% significance level for the IG, despite a considerable increase in the median number of steps taken compared to the CG. However, the change observed in the CG may be attributed to the Hawthorne effect, where a participants' behaviour changes as a result of being observed (Figure 24).

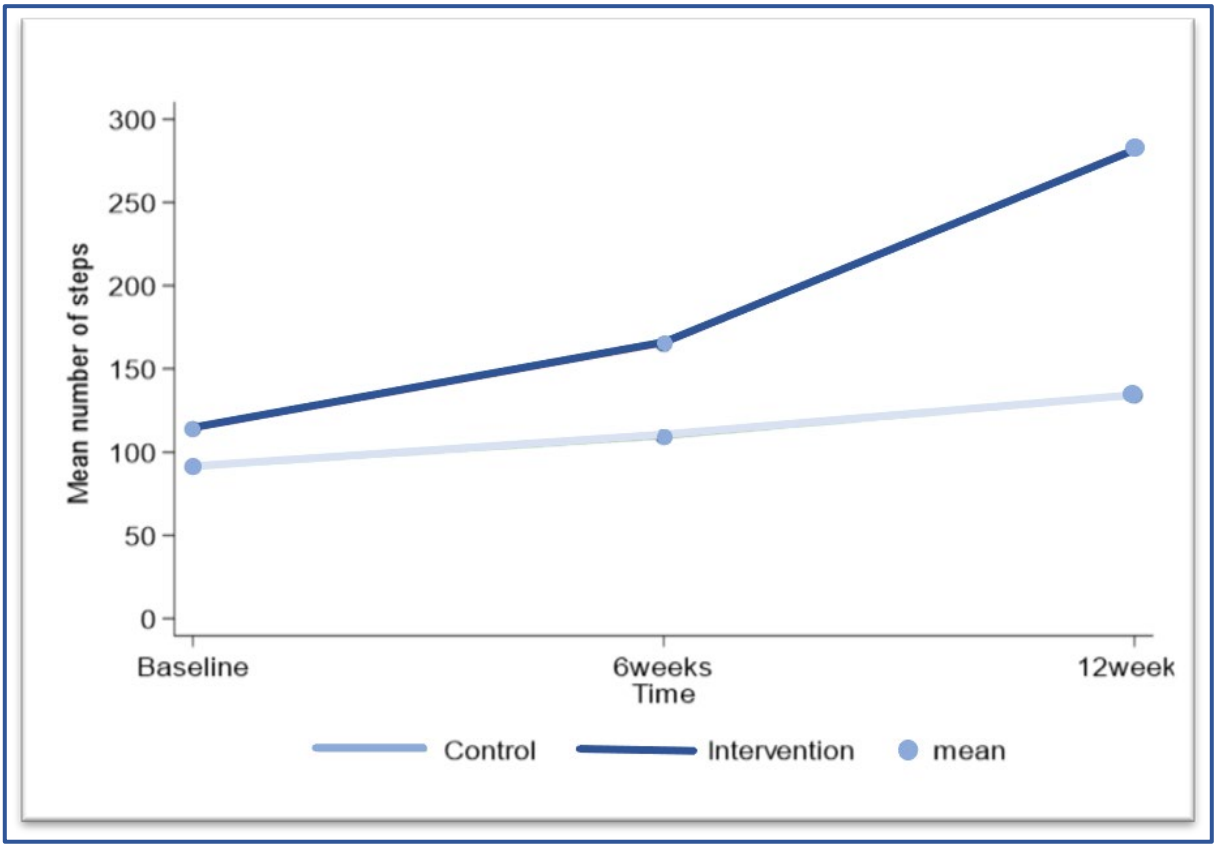


Figure 24. Difference in Mean Number of Steps between Control Group (CG) and Intervention Group (IG).

The summary table below presents the percentage change in the median number of steps in the CG, IG, and overall sample (Table 36). Females in the CG had a 42% change in baseline to 12 weeks while their counterparts in the IG group had a 59% improvement. However, males faired differently with a 47% and 18% change observed in the CG and IG respectively.

Table 36. Percentage Change in Medians for Number of Steps from Baseline to Week 12.

PERCENTAGE MEDIAN CHANGE	FEMALES	MALES	TOTAL
CONTROL	142%	147%	162%
INTERVENTION	159%	118%	143%
TOTAL	149%	138%	143%

5.3.7 Quality of life measurements

5.3.7.1 EQ-5D-3L at baseline

Quality of life for the overall sample for each of the domains in the EQ5D-3L is presented in Table 37 below. Overall, most participants had no problem with mobility, self-care, or usual care at all time points. However, in the domain of pain/discomfort as well as anxiety/depression, participants in the overall sample reported some problems (n=26 and n=8 respectively) at baseline.

When comparing the QoL of participants in the CG and IG, the majority had no problem in the domains of mobility, self-care, and usual activity at baseline, six weeks, and 12 weeks. However, participants reported having some problems in the domain of pain/discomfort (CG [n=14] and IG [n=12]) and anxiety/depression (CG [n=5[and IG [n=3]) at baseline. At six weeks, both the CG and IG still reported some problems with the domains of pain/discomfort (CG [n=5] and IG [n=4]) and anxiety/depression (CG [n=7] and IG [n=2]). A downward trend in the number of affected participants was noted for both domains at six weeks in each group but they were not statistically significant (p=1.000 and p=0.132 respectively). Similarly, there was no statistically significant difference in the number of participants in the CG and IG who reported problems in the domains of pain/discomfort (p=0.672) and anxiety/depression (p=0.197) at 12 weeks.

Overall, health as scored by participants using the visual analogue scale within the EQ-5D-3L questionnaire was 62%, 79%, and 80% at baseline, six weeks, and 12 weeks respectively. There was no statistically significant difference between the means for the CG and IG at the 5% significant level using the t-test at all the timepoints for visual analogue scale (Table 38).

Table 37. Summary of EQ5D-3L for the Overall Sample, Control Group (CG), and Intervention Group (IG).

	BASELINE (N=58)			6 WEEKS (N=43)			12 WEEKS (N=38)		
	CG	IG	TOTAL	CG	IG	TOTAL	CG	IG	TOTAL
					MOBILITY				
No Problem	27	26	53	21	21	42	21	16	37
Some Problem	2	3	5	1	0	1	0	1	1
p-value		**1.000**			**1.000**			**0.447**	
					SELF-CARE				
No Problem	28	27	55	22	21	43	21	17	38
Some Problem	1	2	3	0	0	0	0	0	0
p-value		**1.000**			**-**			**-**	
					USUAL ACTIVITY				
No Problem	28	27	55	21	21	42	21	16	37
Some Problem	1	2	3	1	0	1	0	1	1
p-value		**1.000**			**1.000**			**0.447**	
					PAIN/DISCOMFORT				
No Problem	15	17	32	17	17	34	17	15	32
Some Problem	14	12	26	5	4	9	4	2	6
p-value		**0.792**			**1.000**			**0.672**	
					ANXIETY/DEPRESSION				
No Problem	24	26	50	15	19	34	16	16	32
Some Problem	5	3	8	7	2	9	5	1	6
p-value		**0.706**			**0.132**			**0.197**	

Table 38. Comparison of Means of Visual Analogue Scale for the Control Group (CG) and Intervention Group (IG).

	BASELINE P-VALUE	6 WEEKS P-VALUE	12 WEEKS P-VALUE
VISUAL ANALOGUE SCALE (%)	0.129	0.887	0.765

5.3.7.2 St Georges Respiratory Questionnaire

Only 57 participants completed the SGRQ at baseline. The median SGRQ score for the overall sample was 21.9 at baseline and 8.7 at 12 weeks. As in Table 39 below, the median SGRQ score at baseline and 12 weeks for the CG was 14.1 and 10.3 respectively. The median SGRQ score for the IG was the highest at baseline (30.7) and observed a downward trend at the end of 12 weeks (6.6).

Table 39. Summary of St Georges Respiratory Questionnaire (SGRQ) from Baseline to Week 12.

	MEDIAN	IQR	N
		BASELINE	
Control	14.1	5.1–27.5	28
Intervention	30.7	10.7–38.7	29
Total	**21.9**	**6.2–33.1**	**57**
		6 WEEKS	
Control	15.9	5.2–28.2	21
Intervention	6.1	1.4–21.3	20
Total	**8.1**	**3.3–23.7**	**41**
		12 WEEKS	
Control	10.3	3.0–25.4	21
Intervention	6.6	2.9–15.6	16
Total	**8.7**	**3.0–18.1**	**37**

There was no correlation between SGRQ scores and lung function parameters (FEV_1 percentage predicted and FEV_1/FVC ratio percentage predicted) as depicted in the series of scatter plots below for either the CG or IG at baseline (Figure 25, 26 and 27), six weeks (Figure 28, 29 and 30), and 12 weeks (Figure 31, 32, and 33).

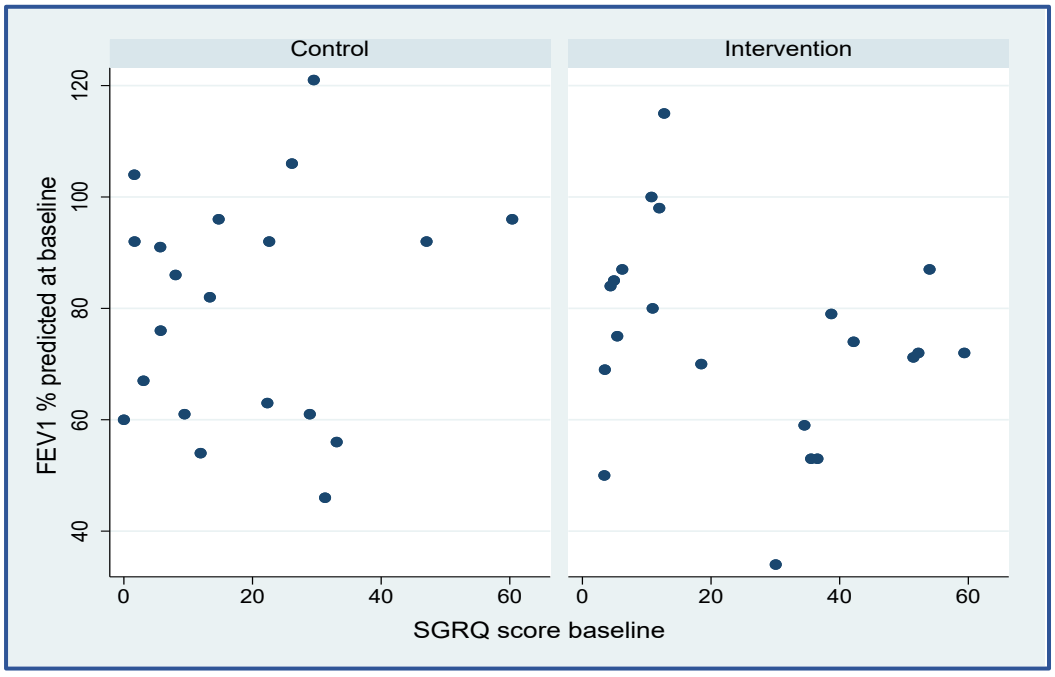


Figure 25. Scatter Plot for St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Expiratory Volume at one second (FEV_1) for Control Group (CG) and Intervention Group (IG) at Baseline.

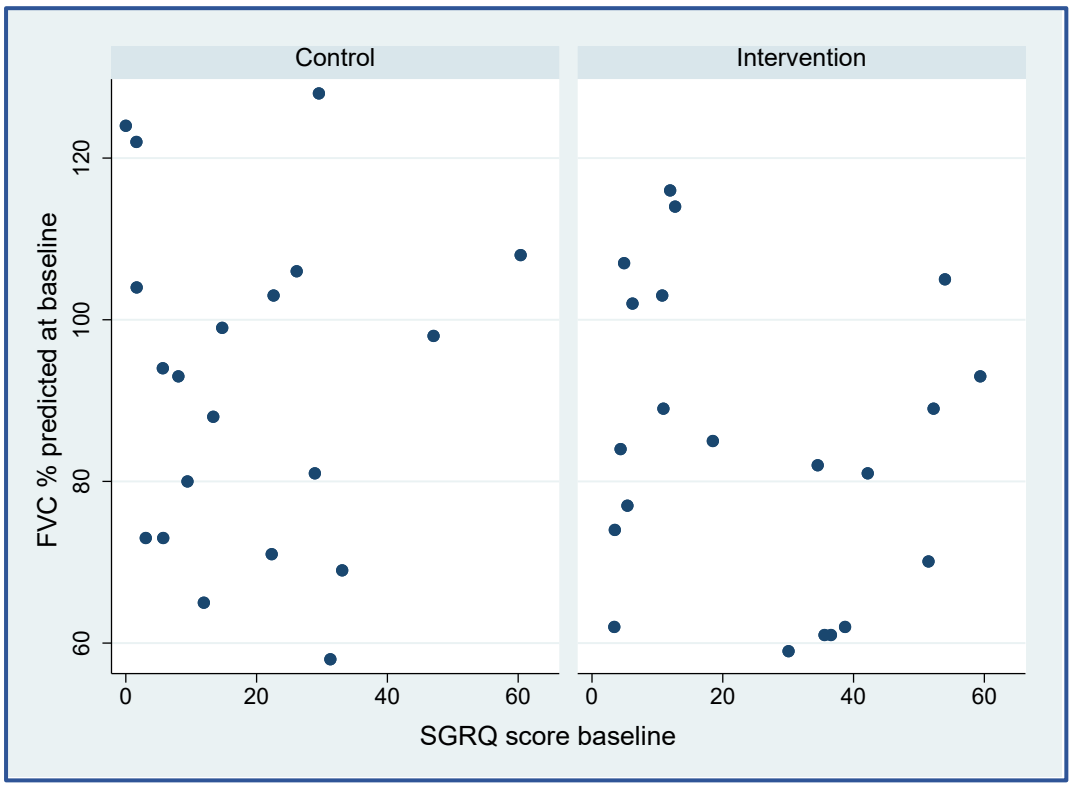


Figure 26. Scatter Plot for St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Vital Capacity (FVC) for the Control Group (CG) and Intervention Group (IG) at Baseline.

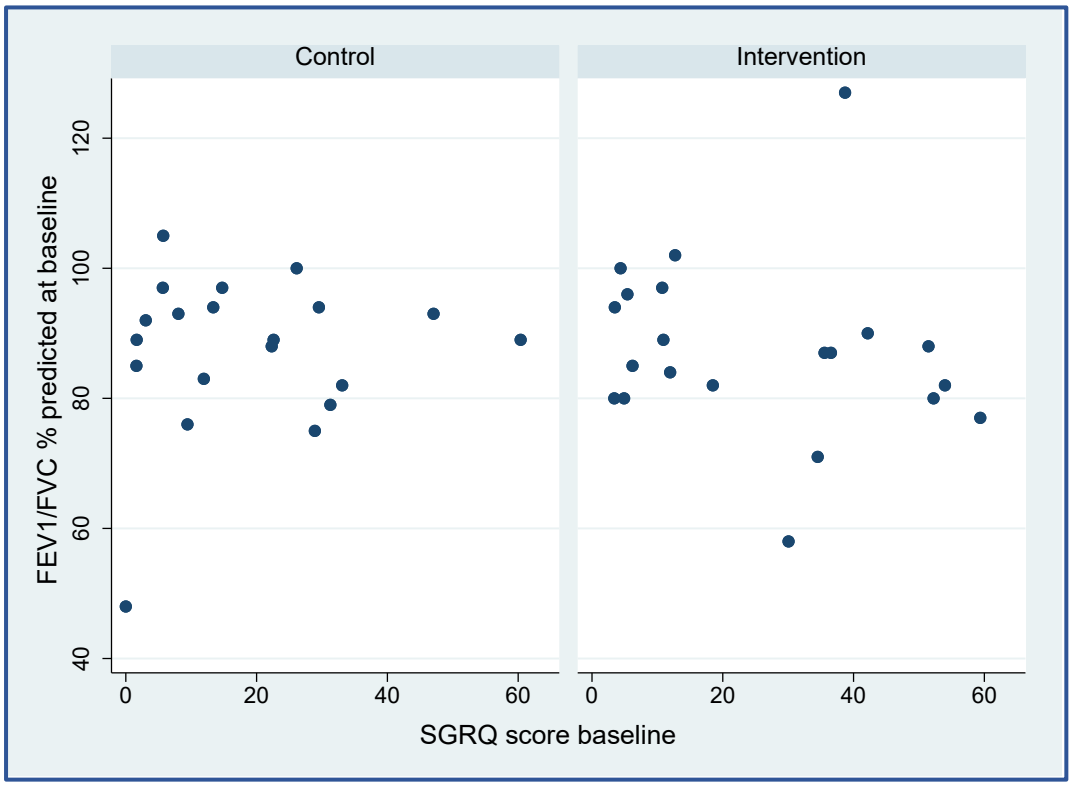


Figure 27. Scatter Plot of St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Expiratory Volume in one second/Forced Vital Capacity Ratio (FEV_1/FVC) for the Control Group (CG) and Intervention Group (IG) at Baseline.

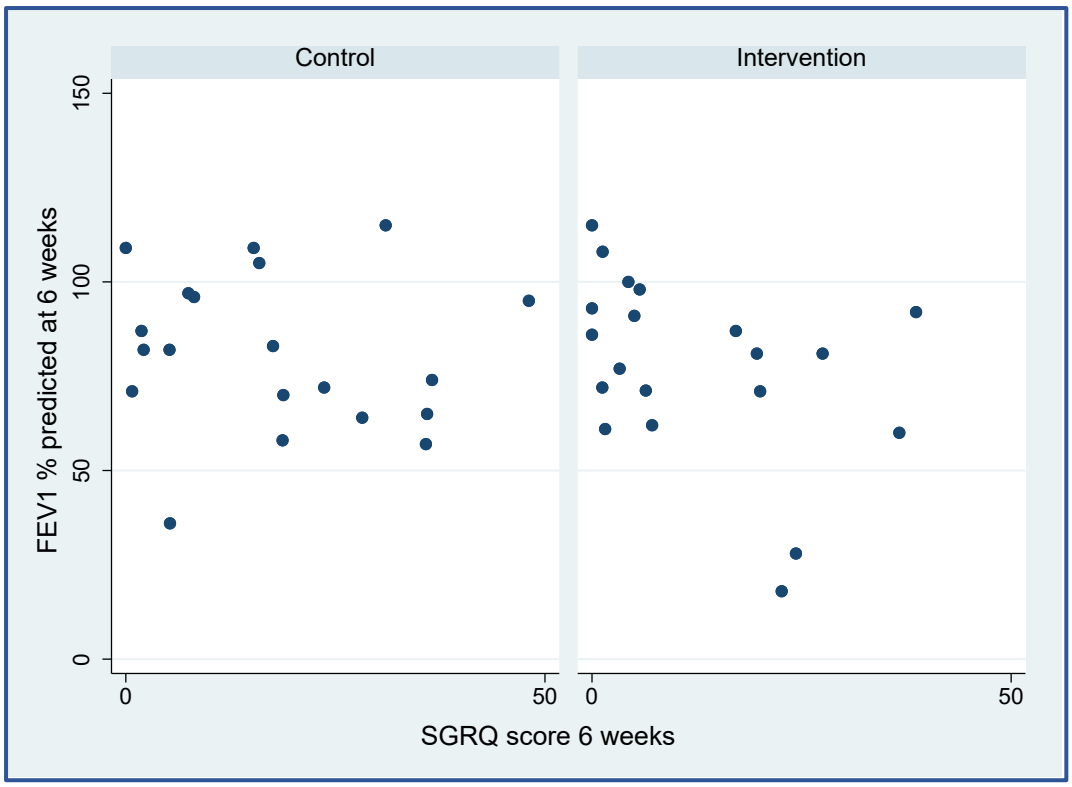


Figure 28. Scatter Plot of St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Expiratory Volume in one second (FEV_1) for the Control Group (CG) and Intervention Group (IG) at Week Six.

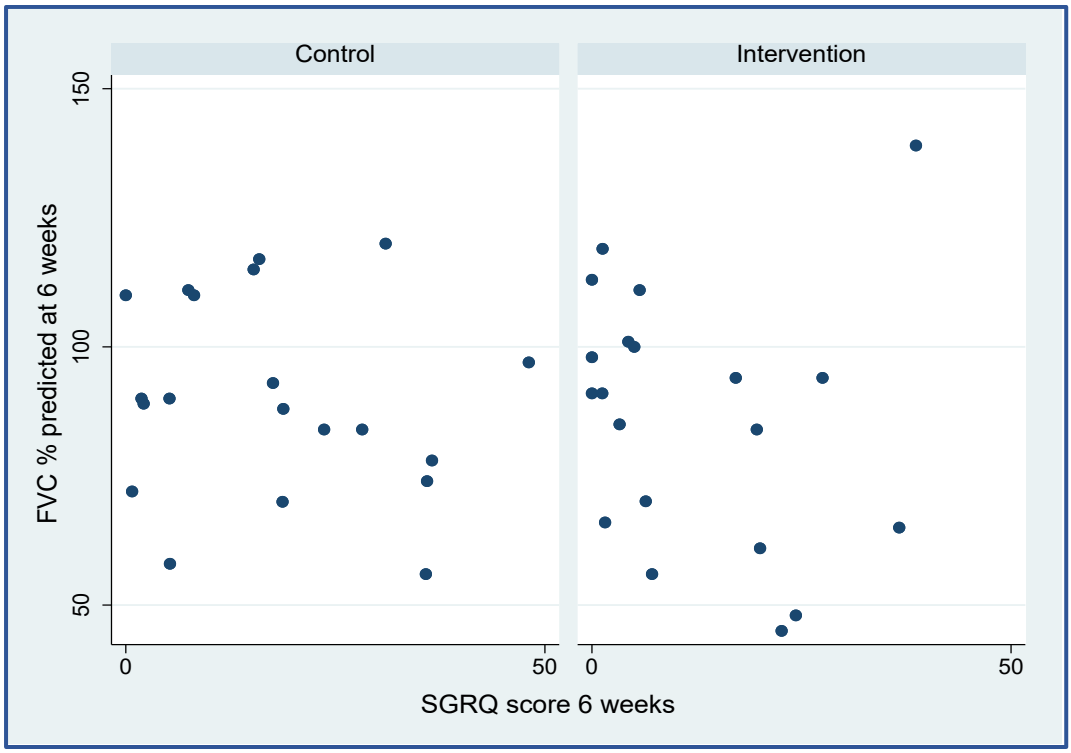


Figure 29. Scatter Plot of Scatter Plot of St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Vital Capacity (FVC) for the Control Group (CG) and Intervention Group (IG) at Week Six.

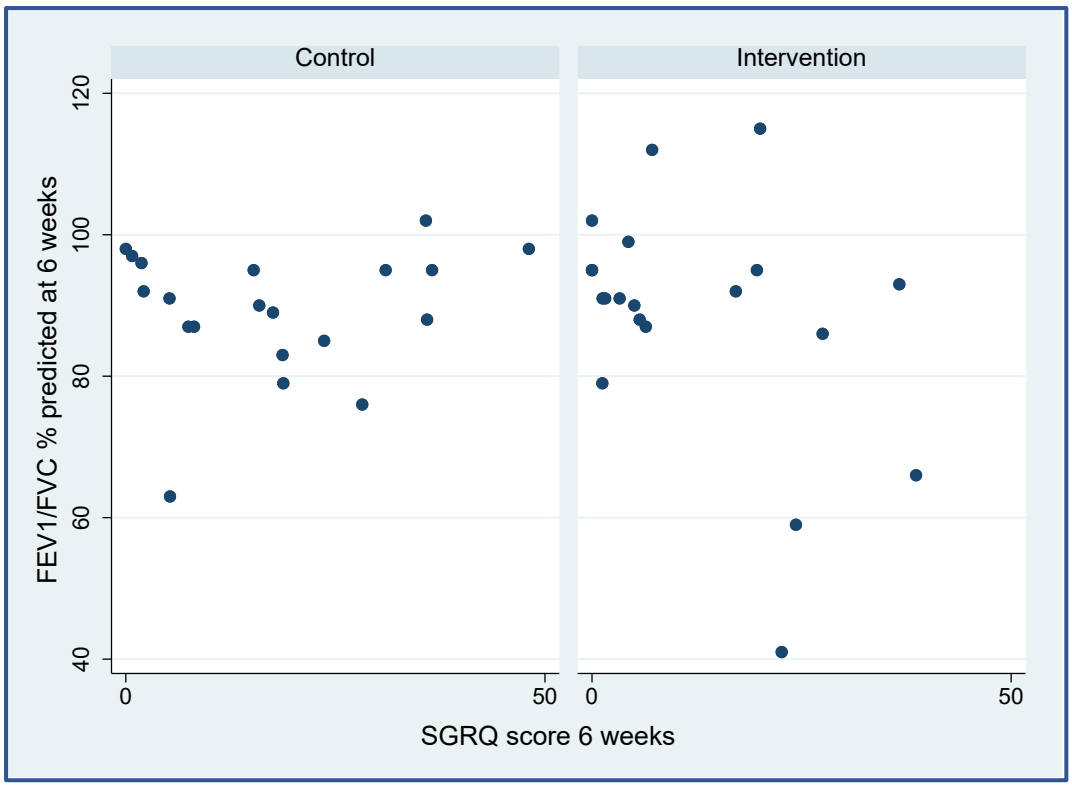


Figure 30. Scatter Plot of Scatter Plot of St Georges Respiratory Questionnaire (SGRQ) and Percentage Predicted Forced Expiratory Volume in one second/Forced Vital Capacity Ratio (FEV_1/FVC) for the Control Group (CG) and Intervention Group (IG) at Week Six.

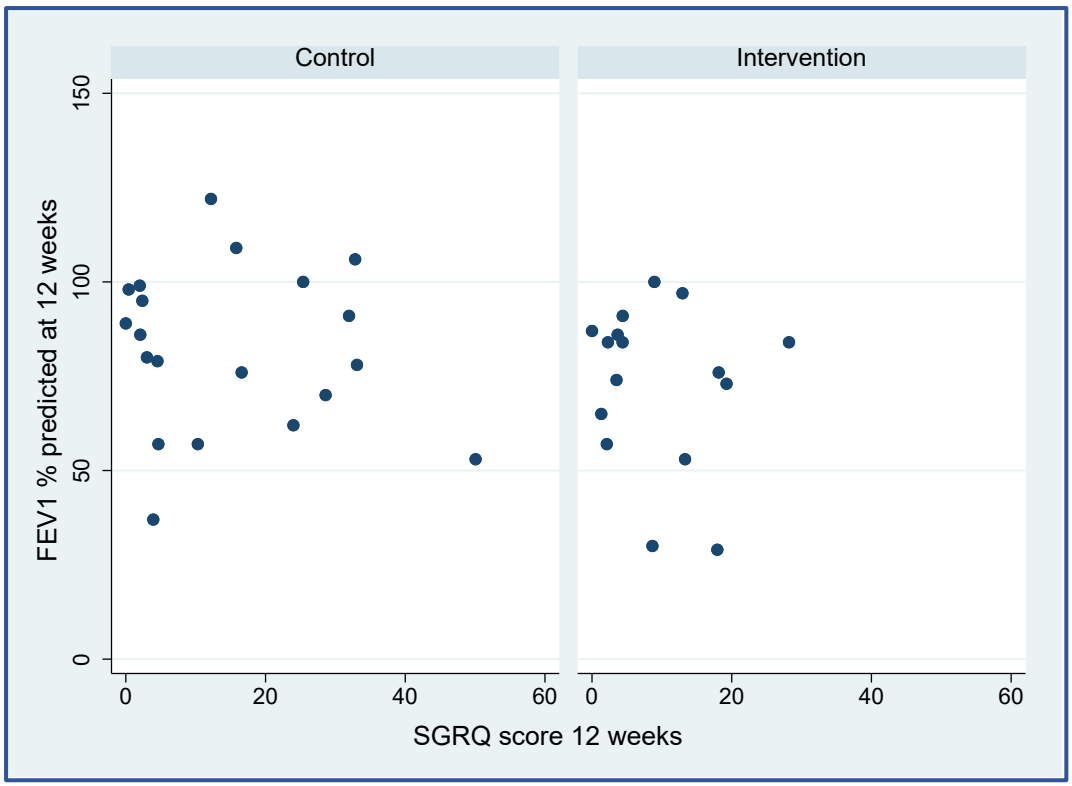


Figure 31. Scatter Plots of the Percentage Predicted Forced Expiratory Volume in one second (FEV_1) for the Control Group (CG) and Intervention Group (IG) at Week 12.

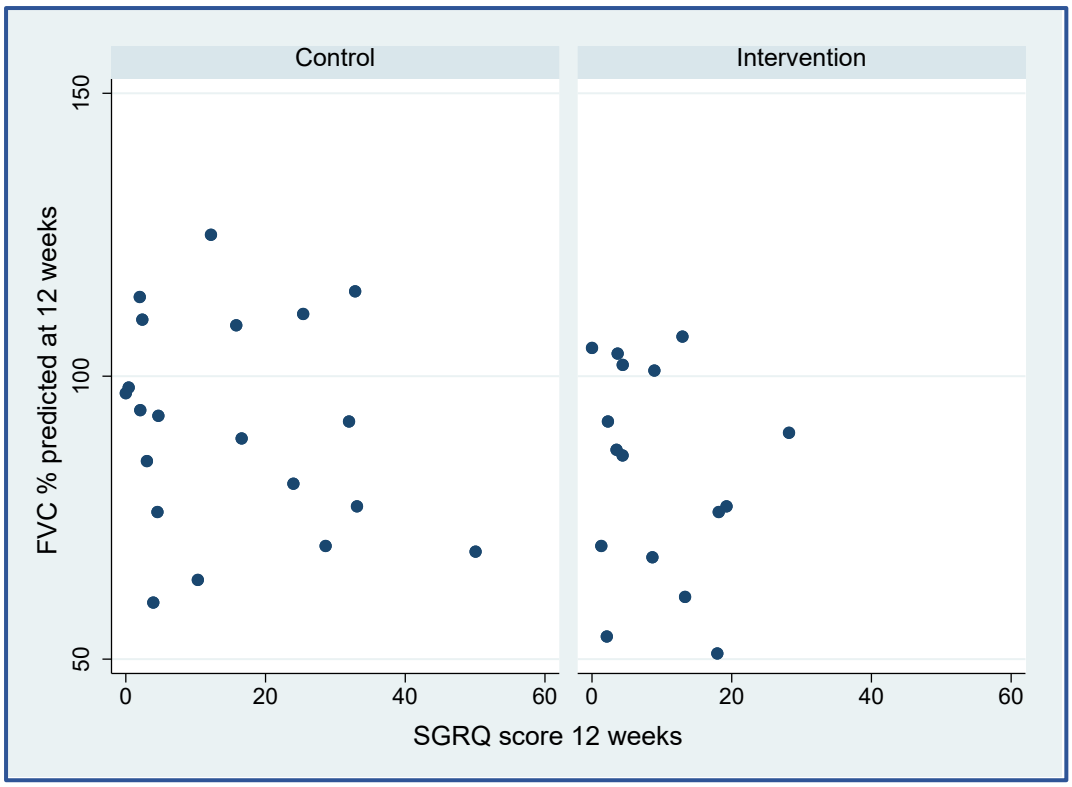


Figure 32. Scatter Plots of Percentage Predicted Forced Vital Capacity (FVC) for Control Group (CG) and Intervention Group (IG) at Week 12.

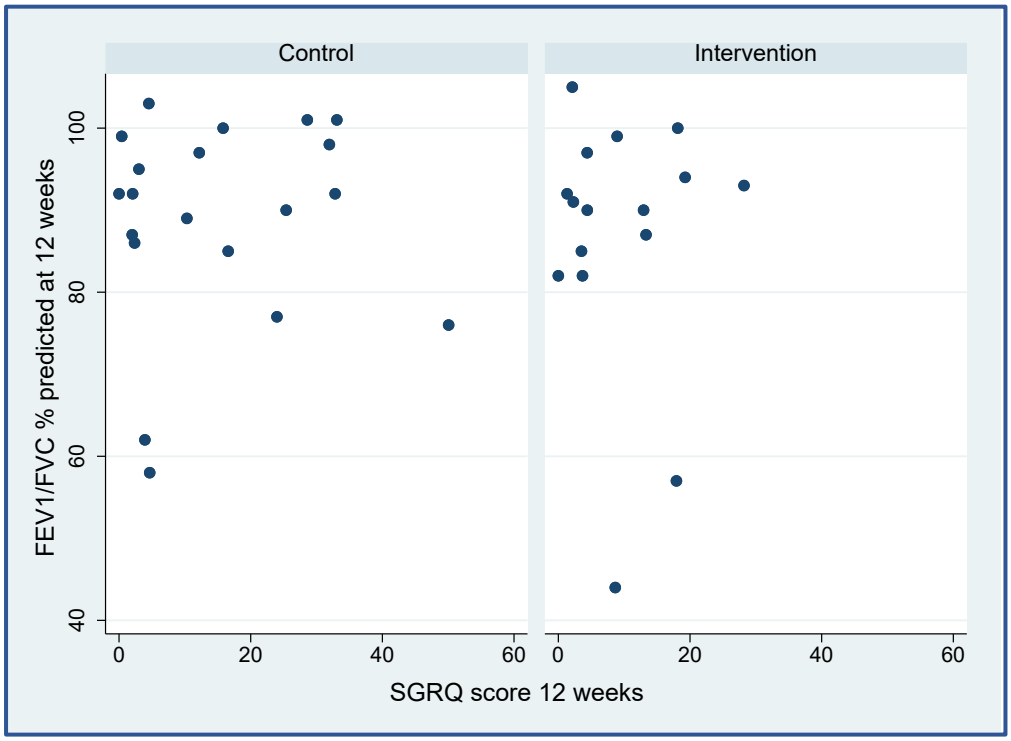


Figure 33. Scatter Plots Percentage Predicted Forced Expiratory Volume in one second/Forced Vital Capacity Ratio (FEV_1/FVC) for the Control Group (CG) and Intervention Group (IG) at Week 12.

As in Table 40 below, there was no statistical difference for any of the lung function parameters and SGRQ scores for either group at any of the timepoints.

Table 40. Assessment for Correlation between Lung Function Parameters and St Georges Respiratory Questionnaire (SGRQ) Scores for Both Groups.

	CONTROL		INTERVENTION	
	CORRELATION COEFFICIENT	P-VALUE	CORRELATION COEFFICIENT	P-VALUE
		BASELINE		
FEV_1 % predicted vs SGRQ	0.1178	0.6209	-0.2597	0.2556
FVC % predicted vs SGRQ	-0.0148	0.9507	-0.2005	0.3834
FEV_1/FVC % predicted vs SGRQ	0.1113	0.6405	-0.1719	0.4562
		6 WEEKS		
FEV_1 % predicted vs SGRQ	-0.0998	0.6754	-0.4032	0.0780
FVC % predicted vs SGRQ	-0.1534	0.5185	-0.1540	0.5169
FEV_1/FVC % predicted vs SGRQ	0.1518	0.5230	-0.3933	0.0863
		12 WEEKS		
FEV_1 % predicted vs SGRQ	-0.1033	0.6649	-0.1412	0.6020
FVC % predicted	-0.1802	0.4470	-0.5059	0.4443
FEV_1/FVC % predicted vs SGRQ	0.0724	0.7615	-0.0528	0.8461

5.4 Discussion of Study 3

Tuberculosis remains one of the major global health problems, despite advances in early detection, treatment, and vaccine research. In the latest SDG for 2030 (see Appendix A), the United Nations has identified the need for research and a focus on the education, self-care, and the continued care of individuals with TB (WHO Sustainable Development Goals, 2018). However, international guidelines has placed very little focus on the management of patients with TB with pulmonary function impairment beyond their microbiological cure (Van Kampen et al., 2018). In the systematic review conducted by Van Kampen et al. (2018), the authors concluded that research is required regarding early detection of post-TB lung disease and subsequent management options, particularly in high burden countries.

Similarly, an earlier non-systematic review which focused on pulmonary rehabilitation for patients with TB, Muñoz-Torrico et al. (2016) concluded that the increased evidence of long-term lung function impairment provides the rationale for pulmonary rehabilitation to be evaluated in this population.

The present series of three studies builds on the earlier study by De Grass et al. (2014), which was a home-based rehabilitation programme which recommended that a RCT be conducted. The present study builds on this study by establishing the extent of lung impairment for patients nearing completion of TB treatment first (Study 1), but also in addressing the need for management options in the form of a PRP for patients identified with abnormal lung function, reduced functional capacity, and QoL with TB lung disease (Study 3).

5.4.1 Outline of the discussion

The results of the intervention are discussed in the following section, and will addresses the objectives set out for the present pilot RCT. From the outset, it must be noted that it was not possible to obtain data from long-term follow-up (three, six, and 12-months post intervention) as initially planned due to several reasons, which included LTFU, the data collection period for both Study 1 and Study 3 taking three times longer than anticipated, and research funding limitations. The objectives for this phase of the study were to:

- Measure baseline parameters pertaining to lung function, functional capacity, and QoL prior to enrolment into an RCT at 0 months (time of TB diagnosis);
- Measure any changes in lung function at six weeks into the intervention and at 12 weeks (completion of intervention) as well as three, six, and 12-months post intervention;
- Measure any changes in functional capacity at six weeks into intervention and at 12 weeks (completion of intervention) as well as three, six, and 12-months post intervention;
- Measure any changes in QoL at six weeks into intervention and at 12 weeks (completion of intervention) as well as three, six, and 12-months post intervention; and
- Compare the baseline parameters of lung function, functional capacity, and QoL to the mid (six weeks) and completion intervention (12 weeks) points.

5.4.2 Socio-demographic and Clinical characteristics of participants

Although the participants in this phase were from the same community, had been recruited at the same research site, and had also been diagnosed with TB, they differed from the Study 1 participants primarily in that previous TB episodes did not exclude them from being eligible to participate. The general profile of participants in Study 3 was once again reflective of global TB data, in that more males than females were represented (World Health Organisation, 2019). Regarding sex, the CG and IG were similar. The mean age for the CG was only slightly older at 36.9 years compared to that of the IG at 35.8 years of age.

Regarding the socio-economic status for the CG and IG, participants in both groups had similar SES characteristics. Education levels and unemployment rates were comparable between the groups and similar to Study 1 (refer to Section 3.4.2). Regrettably, our study was underpowered and therefore did not allow us to draw any conclusions as to whether the profile of having recurrent TB or whether being HIV positive with a positive smoking history led to an increased risk of developing abnormal lung function as reported in other studies (Jung et al., 2015; Park et al., 2018).

The greatest difference between the clinical characteristics of the CG and IG was that of HIV status and smoking history, with more participants being HIV positive and on anti-retroviral therapy in the CG, with nearly double the smoking pack year history than those in the IG (Table 26). In a review by Ferrara et al. (2012) smoking history was identified as an independent risk factor for developing active TB. Similarly, Altet-Gómez et al. (2005) reported on the clinical and epidemiological aspects of smoking and TB, and observed that smokers developed more severe pulmonary disease (aOR1.5) and increased cavitary lesions (aOR 1.9) than the non-smoking TB control. However, the researchers of the present study were unable to perform any analysis to ascertain whether having a positive smoking history was a predictor of abnormal lung function due to the small sample size. In an Indian study by Prasad and Gupta (2004), the authors reported that duration of smoking (>10 years) was more significantly associated ($p<0001$) with the development of TB.

Regarding previous TB episodes, the IG had a higher percentage of participants with previous TB episodes (55.1%) compared to the CG with 44.8%. It is well established in the literature that having multiple TB episodes leads to fibrotic changes and increased cavitation within the lungs, which then affects lung function (Mkoko et al., 2019; Naidoo et al., 2018; Park et al., 2018). The link between having a previous TB infection and the development of COPD has been established in recent years with recurrent episodes of TB resulting in increased severity of COPD (Allwood et al., 2013; Park et al., 2018). In Study 3, the researchers reported that participants in the IG had a non-significant trend towards a greater percentage of abnormal lung function at baseline compared to the CG. This trend may be related to the higher proportion with previous TB episodes in line with other research findings having reported that those with recurrent or prior TB episodes are more likely to develop COPD (Allwood et al., 2013).

5.4.3 Lung function

In this pilot RCT, the baseline prevalence of abnormal lung function of any kind was 57%, with the prevalence of obstructive, restrictive, and mixed patterns being 26%, 21%, and 10% respectively. This finding is reflective of a large burden of pulmonary function abnormalities in patients with TB, during TB treatment. These findings are similar to other studies conducted elsewhere in the world, which reported similar burdens even post TB treatment (Daniels et al., 2019; Gupte et al., 2019; Manji et al., 2016; Pasipanodya et al., 2007). In the study by Manji et al. (2016) conducted in Tanzania, the authors reported a prevalence of abnormal lung function in 74% of their study participants (obstructive 42%, restrictive 13%, and mixed 19%) after completion of TB treatment. The authors attributed this high prevalence of obstructive lung function particularly to childhood pneumonias, pertussis, measles, and low birth weights, as these diseases have been identified as contributing to obstructive airway disease. In another study by (Pasipanodya et al., 2007), which was conducted in the United States of America and investigated pulmonary impairment in patients with active and latent TB, 59% of study participants in the active TB group had abnormal lung function (obstructive 15%, restrictive 31%, and mixed 13%) with those in the latent TB group having significantly ($p<0.05$) less pulmonary impairment overall with only 20% (obstructive 3%, restrictive 16%, and mixed 1%). A recent descriptive South African study by Daniels et al. (2019) which investigated the lung function of 45 participants in the Brede Valley in the Western Cape, reported that 48% of their participants had abnormal lung function (obstructive 21%, restrictive 25%, and mixed 2%) near completion of the treatment. The study by Daniels et al. (2019) did not indicate whether their sample only included patients being treated for TB for the first time or whether those with recurrent TB had also been included.

The prevalence in Study 3 therefore falls in the range of abnormal lung function observed in patients with TB in other studies. Compared to Study 1, the higher overall percentage of abnormal lung function observed in Study 3 may be attributed to the fact that many participants reported multiple episodes of TB. In the IG, more than half of the participants (55.1%) had one or more prior TB episodes compared to 44.8% of participants in the CG. In studies conducted in global TB populations both in high-burden and low-burden TB countries, having recurrent TB episodes has been associated with abnormal lung function (Hnizdo et al., 2000; Lee et al., 2011; Manji et al., 2016; Park et al., 2018). In the study by Manji et al. (2016), patients who presented with recurrent TB episodes were 2.8 times more likely to have abnormal lung function at the end of treatment than individuals with a first-time TB infection. Similarly, the study by Lee et al. (2011), which was a population-wide Korean study, reported that previous TB predicted almost a threefold higher risk of obstructive disease. In a systematic review by Allwood et al. (2013), the authors reported a positive association between history of TB and the presence of chronic airway obstruction in patients with TB.

Despite there being no statistically significant difference between the IG and CG in the classification of lung function or in the lung parameters of FEV_1, FVC, and FEV_1/FVC from baseline to 12 weeks (Table 29, Table 30, Table 31, and Table 32), there was a clinically significant reduction (67%) in the percentage of obstructive lung function in the IG. There were also modest improvements in the lung parameters in both groups. These findings are similar to other studies that reported improvements but were not statistically significant (Singh et al., 2018; Yoshida et al., 2006). Due to the LTFU, particularly in the IG from baseline to 12 weeks, meaningful analysis to assess whether participants in the IG indeed had worse lung function parameters were not possible to perform. However, as stated above, there was an observation that the IG, which had more participants with multiple TB episodes, had a downward trend of patients having an obstructive lung disease from baseline to 12 weeks (33% to 12%).

5.4.4 Three-minute step test

Step tests are a valid and reliable method of assessing functional capacity as an alternative to more complex methods in resource constrained research settings (Buckley, Sim, Eston, Hession, & Fox, 2004; Ritchie, Trost, Brown, & Armit, 2005). The median baseline number of steps for the CG and IG at baseline were 79 (IQR:42–134) and 117 (IQR:84–154) respectively. At six weeks, there was a statistically significant difference between the means of the CG and IG (p=0.002). This difference may be partly attributed to baseline differences between groups. This time point coincides with the start of the continuation phase of TB treatment where patients are likely to have improved symptoms. As a result, the researchers are cautious of solely attributing the differences at six weeks to the PRP. At 12 weeks, the median number of steps of participants in the CG and IG were 128 (IQR:68–143) and 167 (IQR:147–215) and the difference between the means was not statistically significant at the 5% level (p=0.13).

Although the results were not statistically significant at 12 weeks, an upward improvement in the number of steps in the IG compared to the CG can be seen from baseline to 12 weeks and from six weeks to 12 weeks (see Figure 24). The LTFU at 12 weeks may explain why statistical significance was not reached for the IG at this time. The improvement in the CG (as depicted in Figure 24) may be attributed to the fact that participants in the CG may have started to alter their behaviour near the end of the 12 weeks because they were aware of being assessed for improvement, known as the Hawthorne effect. The TB treatment itself may have also resulted in the changes observed in the CG. No comparative studies using this functional capacity test in a TB population could be found. In a systematic review by de Andrade et al. (2012), the lack of studies using a step test in patients with lung disease was identified.

We acknowledge that the 6MWT could have been selected as the functional capacity outcome measure in Study 3 once again but decided against this as the larger prevalence study did not yield any significant findings regarding the 6MWT and that in the context of the setting and habitual walking by participants, this would not have been the best functional measure. The latter reason is supported by a large multicentre study that reported great variability in the distance covered by their participants, which could not be explained by anthropometric factors even after an adjustment for percentage predicted HRmax/HRmax. Casanova et al. (2011) further postulated that the difference observed may have been due to other factors such as the speed of habitual walking, or cultural, lifestyle, and motivational aspects. In the context of the present study cohort, participants resided in an informal settlement and were largely unemployed and as result habitual walking to move around is the rule rather than the exception. In addition, it was possible to execute the step test within a confined space and the covered indoor area (30m of unobstructed flat surface), which is required for the 6MWT, was not needed.

5.4.5 Quality of life

Research into the assessment and impact of TB disease on the QoL in TB populations has only been in the foreground in recent years. It is well known that TB is a leading cause of morbidity in many regions globally (World Health Organisation, 2019). The need to understand the QoL for patients with TB is critical if the targets set by the End TB campaign (World Health Organisation, 2015a) are to be met, as QoL data may influence the effectiveness of interventions to improve patient care, as well as new preventative and treatment strategies. Data from QoL studies also has a direct impact on economic evaluations (Brown et al., 2015; A. V. Jones et al., 2019).

In the present study, QoL measures were added to better understand the impact of an intervention such as a PRP on participants affected by TB. Quality of life was assessed in Study 3 using both the EQ-5D-3L and the SGRQ. Overall, the participants in both the CG and IG had relatively good QoL at baseline and this improved over time in both groups but was not statistically significant. Nevertheless, the potential clinical benefit of the change in the SGRQ scores at 12 weeks is worth noting. In the CG, the score moved from 14.1 to 10.3, a 27% change. In the IG, however, the score moved from 30.7 to 6.6, a 78% change. A minimum change in score of four units in the SGRQ score is considered clinically relevant (P. W. Jones, 1992), hence a 24.1-point change in QoL for the IG is significant and maybe attributed to the PRP given that a change of similar magnitude was not observed in the CG. This said, the results should still be interpreted with caution as the number of participants that this was noted in was much less at completion due to LTFU. In addition, the self-reporting nature of the SGRQ did not allow the researcher to verify the changes reported.

It is documented that social desirability and recall bias are known biases in self-reported questionnaires (Althubaiti, 2016). The former may be at play in present study as the patients may have reported what they thought the desired outcome should be. Similarly, recall bias may have also been a factor as participants had to report on their health over the previous week. Therefore, although the change is significant, it should be noted that it may have been contributed to by these biases.

According to a systematic evaluation of health status and QoL in TB by Brown et al. (2015), the authors reported that "evidence regarding the QoL associated with TB, its treatment and long-term impact is limited" (p. 73). Furthermore, the authors contest that providing a single numeric value to summarise the impact of TB on an individual is impossible and as a result data obtained from quantitative studies related to QoL varies greatly. The issue related to comparison of data related to QoL for patients with TB is also problematic as the disease is often associated with poverty and comparison of HRQoL to the general population may be misleading. In the present intervention study, the CG was similar as participants were from the same socio-economic background and had active TB, with or without HIV co-infection. However, despite the small sample size and LTFU, QoL and lung function improvement, though not statistically significant, was observed in the IG from baseline to 12 weeks with modest improvements in the CG in the lung function test.

A qualitative study conducted in Uganda that investigated whether the implementation of a PRP altered the lived experience of people with chronic respiratory disease reported that a PRP was beneficial and had the potential to restore the physical, mental, and social functioning in patients with chronic respiratory disease (R. Jones et al., 2018). In contrast, purely pharmacological interventions have much narrower effects on individuals lived experiences. Pulmonary rehabilitation programmes offer a major new option for the treatment of a neglected group of patients. Singh et al. (2018) conducted a PRP in patients with chronic lung impairment post completion of TB treatment and reported that a PRP is an effective intervention for improving functional capacity and QoL.

According to A. V. Jones et al. (2019), who held a stakeholder's consensus event regarding outcome measures for exercise rehabilitation programmes for COPD and chronic heart failure, HRQoL was ranked the most important category to assess both for clinical and research purposes. This finding was supported by Smith et al. (2018), who conducted a Delphi study in 13 countries with a 26-perseon expert panel with the intention of developing a core outcome measure for multimorbidity research. The lack of a specific QoL outcome measure designed for TB and, more specifically an outcome measure that is valid and reliable in the context of low to middle income countries where the burden of TB disease is greatest, is a gap in TB research.

Although the Delphi study by Smith et al. (2018) supports the present research's QoL outcome measure used, it must be noted that the panellists were all from high-income countries (United Kingdom, United States of America, Australia, Canada, Netherlands, Sweden, and Italy) where the burden of TB disease is less severe.

5.4.6 Concluding summary of Study 3

The results obtained in Study 3 yielded no statistical difference in lung function parameters from baseline to 12 weeks between the IG and CG. However, classification of lung function did change between the CG and IG from baseline to 12 weeks. Due to the present study being underpowered, the change observed in the IG, from 33% of participants having obstructive lung function compared to 12% at the end of 12 weeks, compared to the CG which increased from 19% to 21%, is not statistically significant but does reflect a tendency towards improvement in the IG. This change, however, holds clinical significance for rehabilitation professionals as participants with obstructive lung patterns are prone to repeated infections, which lead to hospital admissions and in turn increases the financial burden on both the state and the participants themselves. Functional capacity for the IG was statistically significantly higher at six weeks compared to the CG ($p=0.002$). Despite continued improvement in functional capacity for the IG at 12 weeks, statistical significance was not maintained due to LTFU in the IG. Finally, differences in QoL reached clinical significance (24.1% change in SGRQ score) for the IG group compared to the CG at 12 weeks.

In conclusion, although it is fundamentally true that a PRP may not influence the components of the lung that already have fibrosis, it is still unknown to which degree PRPs would be able to address the non-fibrotic changes, namely: airway secretions, inflammation, as well as respiratory muscle function caused by PTLD. This does not mean that these patients should not be treated. On the contrary, rehabilitation professionals such as physiotherapists should provide care that could maintain residual lung function to maintaining good lung health, improve functional capacity, develop coping strategies for people with TB to manage their PTLD, and importantly improve overall QoL.

CHAPTER SIX: OVERALL DISCUSSION, LIMITATIONS, RECOMMENDATIONS, AND CONCLUSION

6.1 Discussion

The outcomes of the three studies have been previously discussed separately. To avoid repetition, the following chapter discusses and links the cross-cutting findings across the three studies. The discussion focuses on three key points namely i) evidence related to lung function abnormality as provided in Study 1, ii) the gap in literature related to knowledge regarding rehabilitation programmes for patients with TB as in Study 2, and iii) the potential benefit of a PRP in the continuum of care for patients with TB identified with abnormal lung function as in Study 3.

In these studies, the researchers aimed to assess the lung function abnormalities in adult patients with TB in a high HIV-prevalent setting. We also aimed to establish whether the provision of a PRP would positively impact lung function, functional capacity, and QoL for patients in a high TB burden, low to middle income, country such as South Africa. To our knowledge, the present research study is amongst the first to assess the lung abnormalities found in patients at the start of their TB treatment and provide a structured, community based PRP as an adjunct to the standard drug therapy. The researchers adopted this approach as we found that studies conducted in TB commonly quantified the lung abnormalities after completion of TB treatment but seldom investigated this at the commencement of treatment. The few that considered lung abnormalities were also often reported for patients who had surgical interventions such as lobectomies and thoracotomies and not in populations who had non-surgical treatment alone. Very few studies have evaluated PRPs as an adjunct to TB drug therapy despite there being a rationale to do so from the smoking-related COPD research. The presented study made use of a community-based, supervised, structured PRP rather than an unsupervised, home-based PRP. The evidence is still inconclusive as to which programme results in better outcomes (Horton et al., 2018).

The present study's findings relating to lung function for both Study 1 and Study 3 were aligned with other studies that reported similar ranges of lung function abnormalities. It is noteworthy that 32% of first-time, drug-susceptible TB participants with no previous lung pathology presented with lung abnormalities near completion of their TB treatment. The failure rate of participants to execute the spirometry in Study 1 was not expected by the researcher as all measures to ensure understanding and repeatability were implemented as per the guidelines provided by Graham et al. (2019).

These guidelines, which speak to clear instruction and demonstration of the test, which in the present study was conducted in the participants preferred language of isiXhosa, as well as the use of a short video clip demonstrating the technique in isiXhosa was implemented to negate this. One can only speculate that due to the participants not being familiar with the test and not having repeated tests conducted over time (Study 1 was cross-sectional in nature) the participants were not able to learn the method required to execute the spirometry correctly.

The percentage of lung abnormalities observed in Study 3 was expected as participants with previous TB episodes were included in the study. Unfortunately, LTFU in the IG compromised our ability to obtain statistical significance in the outcome measures of both the functional capacity (3MST) and QoL (EQ-5D-3L and SGRQ). Additionally, the researchers acknowledge that the lack of specificity of at least 20 minutes of aerobic training followed by 20 minutes of resistance training may have contributed to the statistically non-significant results observed in Study 3. This said, improvements in both these outcome measures were noted for the IG compared to the CG. We acknowledge that the results obtained for Study 3, particularly related to the improvement seen in both the 3MST and QoL outcomes, although not significant, may have been due to chance particularly as Study 3 was underpowered. We have provided additional knowledge as to the extent of lung function abnormalities that exist even in patients with first-time, drug-susceptible TB as well as during the intensive phase of TB treatment.

Although PRPs are not a new intervention, it is an approach that has, to date, not garnered traction in the management of patients with TB despite growing research that PTLD exists for many patients after microbiological cure. Granted that the present intervention did not yield statistically significant differences in the CG with regard to improvement in lung function parameters specifically, we were able to show clinical improvement in both the functional capacity and QoL measures of participants in the IG. Perhaps this did not yield statistical significance at week 12 due to the limited sample size at this time point. Physiological parameters such as an increased FEV_1 or FVC do not automatically relate to improved function or ability to perform activities of daily living without problems. From the patients' perspective, being able to walk without any pain or discomfort or having less anxiety is relevant even if it does not reach a statistically significant difference.

Therefore, it is our view that the present research demonstrates that there is potential benefit for patients to be provided with a PRP not just after TB cure but also during treatment. If PRPs are prescribed to patients with TB earlier as an adjunct to chemotherapy, there may be a potential benefit for improvement in QoL and functional capacity and it would also address the lung wellness and self-management aspects which relate to the United Nations' SDG goals. Furthermore, physiotherapists who primarily provide PRPs for patients with COPD are well positioned to extend this intervention to include patients with TB.

The systematic review was inconclusive as to whether PRPs were effective in improving lung function as the primary outcome, but it must be noted that very few studies have been conducted in populations with TB, particularly in endemic TB countries such as South Africa. It also did not provide a clear guideline as to which activities should be provided but more clearly identified the need for future research to address the need for these guidelines.

6.2 Limitations of the Study

For both Study 1 and Study 3, the original sample size (n=369) was not attained which impacted on the results obtained. In Study 1, the sample size was calculated using an estimated prevalence of abnormal lung function of 60%, a confidence interval of 95%, and precision of 0.05. It was estimated that a timeframe of six months would be sufficient to obtain this in the research setting as it has the highest prevalence of HIV and incidence of TB in the Cape Metro. However, it took 14 months to obtain the sample of 314 participants for Study 1. Reasons for the protracted recruitment and enrolment into Study 1 can be attributed to the very specific inclusion and exclusion criteria, which were that only first-time, drug-susceptible TB participants near completion of their treatment, with only pulmonary TB were enrolled. Patients with extra-pulmonary TB were excluded was as well as any patient with existing COPD. Another reason for the longer time taken to achieve the planned sample can be ascribed to the mobility of the patients in the peri-urban informal settlement of Khayelitsha. Patients in this area also often travel annually to the Eastern Cape, Northern Cape, or other provinces from late November to end of January. During this period, patients are accommodated with a two- to three-month medication prescription from the recruitment sites and therefore did not attend the clinics during this period. In addition, most participants were unemployed and dependent on either public transport or walking to the clinic, which was hampered as a result of inclement weather or if finances did not allow them to get to the appointment. Furthermore, if a work opportunity presented itself on the appointed day, participants would forfeit the research appointment in lieu of employment, even if it was of a temporary nature.

Another reason for the slow recruitment rate can be attributed to record keeping practices at the clinics where contact details were often taken down incorrectly, with missing digits, which made recruitment challenging.

Regarding lung function testing, the findings of Study 1 did not reach statistical significance as nearly a quarter (24.5%) of the sample were unable to produce an acceptable lung function test for analysis. As discussed in Chapter 3 (Section 3.4.7), this may be attributed to the lack of familiarity of performing a spirometry test by both the patient and the research assistant. Although the research assistant had been trained to perform a spirometry and was isiXhosa speaking, we acknowledge that the research assistant was not a qualified lung function technician and therefore instructor error could not be ruled out as a limitation. Regarding the CXR findings in Study 1, we acknowledge that not having a comparative CXR from earlier during the TB treatment was a limitation. However, the implementation of routine CXR at the commencement of the TB treatment when it is no longer the primary or the recommended method of confirming TB diagnosis has cost implications and research to assess the cost benefit to improve outcomes for patients with TB would be required for it to be implemented.

Although the 6MWT was demonstrated to all participants in both studies before performing the test, a practice test was not performed by the participant. This may have affected the execution and the outcome of the test. A recommendation would be for future studies using the same outcome test provide a practice session 24 hours before to ensure that the patient understands instructions and correct execution of the test.

In Study 3, the sample size was based on the estimation that the change in FEV_1, the primary outcome measure for the IG would be approximately 220ml and 120ml in the CG (Vecino et al., 2011). Therefore, using a power of 90%, alpha of 5%, and standard deviation of 80ml, the total sample size would be 30 participants. However, to allow for LTFU of 50%, a total sample size of 60 was used, with 30 participants in each group. Despite the inclusion criteria being broader in Study 3 (multiple TB episodes, inclusion of COPD diagnosis), recruitment also took nearly double the amount of time (11 months instead of six months). Slower recruitment in Study 3 may also be a result of the timing and the site used. At the time of recruitment for Study 3, two additional HIV/TB studies were running concurrently at the research site with similar inclusion criteria, which had not been envisaged, and which subsequently resulted in slower enrolment. The LTFU also reduced the power of the study. Additionally, the researchers did not collect data pertaining to the TB regimen the participants were prescribed in either Study 1 or Study 3 which may have affected their willingness to participate in either study due to potential negative drug side-effects.

Lack of access to dedicated transportation to collect participants to attend either the assessment or intervention sessions was a further limitation of Study 3 in particular. Service delivery protests during 2018 were frequent in the research setting, which also impacted negatively on participants being able to safely use public transport to attend scheduled sessions.

The lack of a dedicated space for the intervention sessions was another factor that negatively impacted on the participation of the IG group as sessions had to be cancelled or postponed due to the occasional non-availability of the community facilities. Participants in Study 3 were LTFU (27.6% and 24.1% for the IG and CG respectively) due to various reasons, but primarily to financial and transport related challenges. Most participants in Study 3 were unemployed and therefore either relied on a state social services grant or part-time employment. One would presume that attending treatment sessions when not gainfully employed would then not be challenging, but when health must compete with financial/food security, the former was less important. Patients would miss intervention sessions if gainful employment was possible, even if it was only for a limited period. The few participants in the both the CG and IG who were permanently employed could not attend sessions if it clashed with their working hours, even if these times were negotiated early and a medical certificate for attendance was provided.

Despite recording participants' contact details and residential addresses at enrolment, follow-up using these methods to retain participation was still challenging. In some instances, participants cell phones were stolen, and in others they provided contact numbers of next of kin when they did not have their own, which led to messages not being relayed to them at all or not passed on timeously. In addition, participants also often had two cell phone numbers but did not disclose this at enrolment. This was uncovered during the sessions when the research assistant would ask why they had not responded to a WhatsApp message or an SMS and was informed that they had different contracts/cell phone numbers for cellular calls and WhatsApp/SMS. Similarly, with home visits using existing clinic structures of community health care workers, participants still did not return for the sessions. In certain instances, participants had moved but had not informed the clinic or the research assistant of the change of address or provided no forwarding address. Although withdrawal from the study without reason was stated as acceptable at enrolment, one participant in the IG cited personal safety and increased crime in the research setting of Khayelitsha as the reason for moving and hence their withdrawal from the study. Certain participants also cited feeling symptomatically better for their withdrawal from the IG.

Therefore, all the above factors impacted on retention of participants particularly in the IG, which then also impacted on the ability for a sufficiently statistically powered study to draw conclusions regarding the efficacy of the intervention over standard care. Another limitation was that the later assessments were not able to be performed.

6.3 Recommendations for Future Studies

In this thesis, Study 1 supported the hypothesis that patients with TB could benefit from a PRP as a continuum of care. Unfortunately, Study 2 did not provide the contents of the PRP. It is recommended that an updated systematic review be conducted. The aim of Study 3 was to assess the benefits of the PRP in patients being treated for TB. It was intended as a pilot study. The hypothesised effect on lung functions was perhaps too ambitious and the sample size therefore too small. Our view is that the findings of our pilot trial justify plans to conduct a larger trial. The larger studies should ensure that adequate statistical powered analysis can be carried out to draw conclusions regarding interventions in clinical trials.

The optimal timing of the commencement of a PRP is uncertain. Initiation of such a programme at approximately eight weeks after chemotherapy may be considered, as at six weeks, both the CG and IG had some upward improvement which continued for the IG at 12 weeks. The PRP should also target those patients who would benefit from it the most. Therefore, patients should be routinely screened with spirometry at baseline and then again at eight weeks to identify those with impaired lung function despite having reduced TB symptoms. Perhaps a better targeted trial enrolling only those patients with impaired lung function during early TB treatment who are most likely to benefit would have the potential to demonstrate greater benefits from a PRP. Long-term follow-up (at two to five years) is strongly recommended for patients who have had a TB episode, as research has shown that microbial cure does not equate to return to normal health for all. Once identified as still having pulmonary impairment post TB, patients should be offered a PRP as there is literature from COPD research to support this rationale. Furthermore, patients who are identified to have developed COPD due to TB should be afforded the same continuum of care, namely inhaler therapy and PRPs, to manage the chronic condition similarly to those diagnosed due to smoking, as set out in the revised guidelines of the ACCP/AACVPR. In addition, qualitative data collection regarding patients' lived experiences when provided with interventions such as PRPs will assist in assessing the acceptability of such interventions in the future.

As for the use of lung function as a primary outcome measure for PRP, there is room for debate as the first symposium on post-TB lung health identified the need for lung function assessment to better identify the development of PTLD and for further care in the form of treatments such as pulmonary rehabilitation, education regarding self-management, and airway clearance as part of the 'post-TB toolbox' (Allwood et al., 2020). Regarding the execution of the 6MWT, it is recommended that a practice run is implemented before the actual assessment to ensure that patients are familiar with the assessment.

The execution of an RCT is heavily dependent on resources both human and financial to ensure that all operating procedures are executed correctly and that quality control measures at each step of the data collection process are in place to ensure that missing data is minimised as far as possible. A recommendation for future studies wanting to implement a PRP in a low socio-economic environment would be to provide transportation for participants to improve attendance at intervention and follow-up assessment sessions. A dedicated facility or space to execute the PRP is another recommendation. Although community spaces are mostly freely available, they are in high demand and often subject to booking and availability, and as a result a structured routine is difficult to establish. The hiring of a dedicated space for the duration of the programme would be highly recommended, alternatively an assured space needs to be provided by local government structures.

Regarding recruitment and sample size, a multicentred approach is also recommended as it may enable the pooling of data and address the issue of slow recruitment at a single facility. Long-term follow-up studies (two to five years) of varied TB populations should be conducted and should include MDR-TB survivors.

Finally, the recording and aggregation of normative data for the South African population regarding 6MWT, 3MST, and QoL measures for individuals in the general population and in the same socio-economic contexts are highly recommended to provide context for the data collected regarding PTLD in South Africa.

6.4 Conclusion

As one of the few South African studies focused on PTLD, the present three linked studies have identified the prevalence of lung function abnormalities in this patient population. These findings highlight the need to screen patients with TB during pharmacological treatment for lung function abnormalities.

The findings also highlight the need for future studies to address the effects and management of PTLD in endemic countries such as South Africa to improve the long-term lung health of these individuals and contribute to the long-term goals of the WHO to ensure lung health.

As a Physiotherapist, the researcher acknowledges the potential benefit of the PRP in patients with TB who participated in this study. The standard care for patients with TB in South Africa does not include pulmonary rehabilitation except when there are severe complications. The outcome of this pilot RCT would suggest the need for the assessment of lung function abnormality early in TB treatment to better identify those who would benefit from a rehabilitation programme to maintain good lung health and the assessment of rehabilitation programmes in larger numbers of patients with TB.

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APPENDICES

Appendix A: World Health Organisation Sustainable Development Goal 3

ENSURE HEALTHY LIVES AND PROMOTE WELL-BEING FOR ALL AT ALL AGES

We all know how important it is to be in good health. Our health affects everything from how much we enjoy life to what work we can perform. That's why there's a Goal to make sure everyone has health coverage and access to safe and effective medicines and vaccines. In the 25 years before the SDGs, we made big strides—preventable child deaths dropped by more than half, and maternal mortality went down by almost as much. And yet some other numbers remain tragically high, like the fact that 6 million children die every year before their fifth birthday, or that AIDS is the leading cause of death for adolescents in sub-Saharan Africa. We have the means to turn that around and make good health more than just a wish.

Appendix B: Information Sheet and Consent (Study 1: English Version)

University of Cape Town:

The research obtained in this study will be used as a part of a post-graduate dissertation conducted by a PhD candidate Shamila Manie enrolled at the University of Cape Town in 2015. This study will adhere to the ethical principles outlined in the Declaration of Helsinki Brazil, 2013)

Title of the research

The assessment of lung function abnormalities in adult patients with pulmonary tuberculosis in a high HIV-prevalent setting to ascertain the impact of a pulmonary rehabilitation intervention to improve functional outcomes

Why are we doing the study?

The purpose of this study is to find out how well my lungs work after receiving TB treatment, whether I am HIV positive or not. Research has shown that TB affects the way some people's lungs work even after they have completed their TB treatment. We want to find out how your lungs are working now that you are nearly finished with your TB treatment whether I am HIV positive and on ARVs or not. We want to see if knowing how well the lungs of people living with TB work, whether we as physiotherapist could give you any treatment that can help you improve the way your lungs work if the TB has caused them not to work as well as before.

Why have I been asked to consider volunteering taking part in this study?

I have been asked to think about volunteering for this study because I have TB for the first time and responding well to the drug therapy. We are looking for volunteers that are almost finished with their TB treatment.

What information will the study ask of you?

You will need to complete four questionnaires: one regarding your medical history and demographic information, two regarding quality of life (EQ-5D and SGRQ) and another about your everyday physical activity (GPAQ). Some of this information may require me to have access to your clinic folder. After you finish filling in these questionnaires, which will take about 30–40 minutes to complete, we will take your height and weight. We will then ask you to blow through a machine- called a spirometer- to measure how well your lungs are working. Lastly, we will ask you to perform a 6-minute walk test. We will then look at all the information we got from all the other participants - representing the data in the form of tables and graphs. This data will be used to determine how many people have a problem with their lungs after completing five months of TB treatment. We will also report on how well your lungs work.

What is needed from me if I agree to participate in the study?

I will be required to attend one session where I will answer questions to four written questionnaires truthfully and to the best of my ability. These questions will require me to provide demographic information such as where I live, how old I am and report on issues of quality of life (QoL) – how I feel about my health as well as access to my medical/clinic folder to obtain laboratory results and

other information which you may not readily know or remember. The researcher assistant will then measure my height with a tape measure and weigh me using a scale. How well my lungs are working will then be tested with a machine called a spirometer. In a seated position, I will need to hold a mouthpiece to my mouth, taking a deep breath in and then blowing out through the mouthpiece as hard and fast as I can. This process may be repeated between 3 and 8 times depending on how well I perform this test. Rest periods will be given in between each time I blow through the mouthpiece. The spirometer will then record and print out the findings which we will explain to you. I will be asked to perform a walking test to see how fit I am. The process should take between 3–50 minutes. No follow-up testing session is required. However, I may be approached later to participate in a pilot study that will test how well a pulmonary rehabilitation programme works. The information the tests give the researcher will only be used for this research study.

What are the risks if I participate in this study?

Participating in this study is voluntary. I will still receive all my standard care at the clinic whether I volunteer to participate in this phase of the study or not. I will not lose my place in the queue if I wish to participate in the study as I can see the researcher after I finish with my clinic visit. With regard to the tests I will be asked to do, I should not experience any negative long-term effects. I may, however, experience some dizziness or shortness of breath immediately after blowing into the machine (spirometer) or doing the walking test (6-minute walk test). I may also experience some discomfort in talking about my HIV status and personal health. If I have a problem with how well my lungs are working, I will be referred by the researchers to my nearest health clinic for further assessment and treatment.

How will participating in this study benefit me?

I will gain knowledge of how well my lungs are working and be informed as to whether I have any problems with my lungs. If there are problems with my lungs, I will be referred to my nearest health facility.

Will I receive any reimbursement for participating in this study?

I will get money to the value of R30 once only, for taking part in this phase of the study. This money is to help me with paying to travel to the clinic. I will get something to eat and/or drink when I finish with filling in the forms and finishing the tests.

Alternatives to participating in the study

As this study is not a treatment study, the only alternative to participating in the research is for me not to participating in this phase of the study.

Voluntary participation

I will be taking part in this study out of my own free will and do not have to participate. I have not been forced to participate in this phase of the study by any of the research team (researcher, research assistant or isiXhosa translator).

Right to withdraw from study

I have the right to withdraw from the study at any point, and for any reason. I do not have to tell anyone why I don't want to be in the study anymore. I will still receive my normal treatment at the clinic even if I don't wish to participate in this study.

Confidentiality

Your identity will remain strictly confidential. A number will be placed on each consent form and after the consent is obtained, the individual identity of a person will no longer be referred to. Instead, the participants will be referred to by a number. It will not be possible for researchers to link personal responses to individual identities when using this method. All assessments and consent to participate in the study will be in a consultation room away from the general waiting area.

All data will be processed using password protected computer files and only researchers will have access to the data. Upon finishing the study, data will be stored in a password-protected folder.

Compensation/treatment in event of injury

If patients experience any dizziness or shortness of breath, researchers are trained in teaching breathing techniques to alleviate symptoms. The study is covered by UCT no-faults insurance policy which states that:

"UCT undertakes that in the event of you suffering any significant deterioration in health or well-being, or from any unexpected sensitivity or toxicity that is caused by your participation in the study, it will provide immediate medical care. UCT has appropriate insurance cover to provide prompt payment of compensation for any trial-related injury according to the guidelines outlined by the Association of the British Pharmaceutical Industry, ABPI 1991. Broadly speaking, the ABPI guidelines recommend that the insured company (UCT), without legal commitment, should compensate you without you having to prove that UCT is at fault. An injury is considered trial-related if, and to the extent that, it is caused by study activities. You must notify the study doctor /researcher immediately of any side effects and/or injuries during the trial, whether they are research-related or other related complications.

UCT reserves the right not to provide compensation if, and to the extent that, your injury came about because you chose not to follow the instructions that you were given while you were taking part in the study. Your right in law to claim compensation for injury where you prove negligence is not affected. Copies of these guidelines are available on request"

What will you do with the results of the research?

Results of the study will be made available to the facility manager of your clinic from which you were recruited. The researcher will use the results from this study to help inform potential rehabilitation treatment for patients with TB. If you wish to be contacted in order to be informed of the results of the study, you may contact the researcher or give your contact numbers so that they can contact you.

Who can I contact for further information?

Participants may contact the following persons for more information regarding the research:

M Shamila Manie (primary investigator)

Address: F56 Old Main Building, Groote Schuur Hospital, Observatory 7925

Contact numbers: Tel: +27 (0) 21 406 6428; Mobile: 083 225 1736;

Fax: +27 (0) 21 406 6323/0866111883

Email address: shamila.manie@uct.ac.za

Prof. Dele Amosun (primary supervisor):

Address: F45 Old Main Building, Groote Schuur Hospital, Observatory 7925

Contact numbers: Tel: +27 (0) 21 406 6428 Fax: +27 (0) 21 406 6323/0866111883

Email address: seyi.amosun@uct.ac.za

Prof. Graeme Meintjes (co-supervisor):

Email address: Graeme.meintjes@uct.ac.za

You may also contact the Human Research Ethics Committee if you have any questions regarding your rights as a research participant.

Address: Room E52-24, Old Main Building, Groote Schuur Hospital, Observatory, 7925.

Telephone: 021 406 6338 Fax: 021 406 6411

Email: shuretta.thomas@uct.ac.za, Website: www. Health.uct.ac.za/research/humanethics/forms

Appendix B_1: Information Sheet and Consent (Study 1: isiXhosa Version)

University of Cape Town:

The research obtained in this study will be used as a part of a post-graduate dissertation conducted by a PhD candidate Shamila Manie enrolled at the University of Cape Town in 2015. This study will adhere to the ethical principles outlined in the Declaration of Helsinki Brazil, 2013)

Title of the Research

The assessment of lung function abnormalities in adult patients with pulmonary tuberculosis in a high HIV-prevalent setting to ascertain the impact of a pulmonary rehabilitation intervention to improve functional outcomes

injongo yophando

Olu nakekelo/kujongwa kwemiphunga inengxaki kubantu abane TB apho Ininzi khona.

Kuthen sisenza olu Phando?

Injengo yolu phando kukufumanisa ukuba iphile/okanye isebenze njani emva kokuba ufumene unyango lwe TB, une HIV okanye ungenayo. Uphando lufumanise ukuba. TB chaphazela imiphunga yabantu ngendlela efanayo nokube sele ugqibile ukuyinyanga. Sifuna ukufumanisa ukuba isebenza njani imiphunga kubantu ebatya iTB,s ibe thina si physiotherapist singekumke nayiphine into/treatmet ukukunceda kuphuculwe indlela imiphunga esebenza ngayo ukube iTB yiyo ebangele uuibe ingasebenzi ngendlela ibisebenza ngayo ngaphambili.

Kutheni ndicelwa ukuba ndithathe inxaxheba kolu phando?

Ndiyacelwa ukuba ndicinge ngokuthatha inxexheba kolu phando kuba ndine TB okokuqala/ndiyaqala ukuba ne TB yaye lusebenze kakuhle kum unyango. Sifuna abantu ebesele bezokugqiba ukunyangelwe iTB.

Zeziphi incukacha ezizakubuzwa kolu phando?

Kuzekufuneka uphendule imibuzo emine: omnye unxulumene nemeko yakho yezempilo nendleha enihlala ingayo eyesibini imeko enlte yezempilo kubomi bekho(EQ-5D and SGRQ) enye indlela owenza ngayo izinto zemihla ngemihla. Ezinye zengxelo ngawe siza kuzifumana kwifolder yakho yalapha eklinic . Xa sigqibile siza kuqokelela yonke le mibuzo, yonke lento izokuthata malunga nemizuzu eyi 30-40 ukeyigqiba, sizakujonga isikali nobude bakho. Emva koko sizakucela uphefumle ngokuvuthela kumatshini wethu ukujonga ukuba iphile kangakanani na imiphunga yakho okokugqibela sizakucele uhambe imizuzu emithandathu(6) siza kujonga lonke olu lwazi silufumeneyo ngawe/ngabatu bonke ngokuthi siifake kwidata. Le data izakusetyenziselwa ukubona bangaphi abantu abanengxaki ngemiphunga xa begqiba ukunyangelwa iTB emva kwenyanga ezintlanu (5months) sizekuchaza nendlele ephile ngayo imiphunga yakho.

Yintoni efunekayo kum ukuba ndiyavuma ukuthatha inxaxheba kolu phando?

Ndizakucelwe ndize kwi session enye apha ekliniki ndize ndiphendule le mibuzo mine ngokunyenisekileyo ngoko ndikwaziyo. Le mibizo izakuchezela mna ngokuthi ndinike incukacha ezinje ngokuba ndhlala phi, ndineminyaka emingaphi nokuchaza ngemeko endiphila ngayo kubomi bam (QOL) nedlela endiziva ngayo ngempilo yam. Kwakunye nokujonga nakwi folder yam iziphumo zamagazi nezinye izinto endisazikhumbulayo ,ndizakujongwa ngomye waba thathisi nxexheba isikali, iweight nobude bam. Ingaba nephunga yakho iyasebenza apho baya kuvavanywa kumashini obizwa ngokuba ispirometer, Kwindlela endihleli ngayo, kuya kufuneka ndifake imouth piece kumlomo wam, ndibizele umphefulo zendivuthele ngomlomo ngamandla ngokukhawuleza endinako. Le ndima iyakuphindwa phindwa kathathu 3 okanye kasibhozo 8 kuxhomekeka ukuba ndivuthele kakuhle kangakanani na

Ixesha lokuphumla liya kunikezelwa qho ndigqiba ukuvuthela. Isipirometer siye kucishilela isiphumo eziya kuchaza ukuba ndenze njani. Ndiyakucelwa ndihanjiswe kwaye kuya kwenziwa nex-ray ukujonga isifuba. Le indima iyathuthatha imizuzu eyi 30 ukuye kweyi 50. Akuzu kwenziwa lulandelelo uzakubonwa kube kanye. Ekuhambeni ndinganyulwa, ndibe ngumthathi inxatheba kuvavanyo lwe-pilobat, apho kuya kuvanywa ingabe rehabilitation. Isebenza njani ngabi ulwazi olunikezelwa luvavanyo luya kusetyenziswa kuphela gabaphandi.

Yintoni eyakwenzeka xandithathe inxaxhebe kolu phando

Ukuthatha inxaxheba kolu phando yinto ndiyakuyifuma kunyango ekliniki nokuba ndithatha inxaxheba koluphando okanye hay. Andisokuze ndiphosakale kwikliniki yakho ndifuna ukuthatha inxaxheba kuphando, kuba ndisebabona abaphandi emva kweklinik yam. Emva kuvavanyo miphumela yexesha eli endiyakuyifumana. Ndise nekuba nesiyezi ekanye iphika ngakukhawuleza emva kokuvuthela okanye uhambo. Xa ndingumntu ongumama kufuneka phambi kokuba ndithatwe ix-ray funeka ndihlolwe ukuba andikhulelwanga na, kodwa ukuba kunjalo kofuneka ndifumane ukhuseleko. Ndise nokungonwabi ukuthatha malunga nentsholongwane okanye izinto zam. Ukuba ndifumaniseke ndinengxaki nemiphunga yam ukuba isebenza njani ndiyakuthunyelwa kwikliniki ekufutshane ukuya kuhlolwa ndifumane nonyango.

Yintoni endiyakuyizuza koluphando?

Ndiyakufumana indlela izintso zam ezisebenza ngayo, ndixelelwe ukuba ndinengxaki nemiphunga yam. Ukuba ndinengxaki ndiyakuthunyelwa kwiikliniki ekufutshane.

Ingaba ndiyakufumana inkxaso ngoku thatha inxaxheba kolu phando?

Ndiyakufumana imali engange R30 kube kanye, ngokuthathe inxaxheba. Le mali iya kundinceda ukukhwela ukuza ekliniki. Ndiyakufumana into etyiwayo okanye isiselo emva kokuba ndigqibile ukuphendule amaphepha novavanyo.

Alternative

Olu phando ayilo phando lonyango kokuba ndithathe inxaxheba ukuwenzela mna.

Voluntary Participation

Ndiya kuthatha inxaxheba kolu phando ngoku zifunela kunga nyanzelekanga. Andinyanzeliswanga kolu phando nangomnye wophando.

Imvume yokuba ndingayeka kolu phando

Ndivayo imvume yokuyeka kolu phando nanini na nange siphi isizathu. Andina kuxelela nakubani na isizathu sokunga qhubeki nophando. Ndiya kuqhubekeka ndilufumane unyango lwam ekliniki nokuba andithathi nxaxhebe kolu phando.

Imfhlelo (Confidential)

Inkcukacha ngam ziya kuhlala ziyimfihlelo kolu phando. Inombolo iya kufakwa kwi consent nganye nasemva kokuba kugqityiwe . Umthathi nxaxheba waya kudluliswa ngokwa manani. Zonke inkukacha okanye iconsent ziyakugcinwa kwigumbi elilodwa . Apho kulindelwa khona. Inkcukacha ezikwicomputor ziya kubonwa ngokuvulwa ngaba phandi kuphela.

I mbuyekezo/unyango xa uthe wafumana umonzakalo

Ukuba isigulana sifumaniseke sinesiyezi okanye iphika, abaphandi bafundisiwe indlela yokuphefumlisa ukujonga impawu. Uphando lukhuselwe yi UCT no faults insurance policy. iUCT ithatha inxaxheba kwimpilo yakho xa uthe kwenzeka uphazamiso malunga nokukatha inxaxheba .Iya kuhlawulela xa kukho umonakalo ye Association yase British Pharmaceutical industry ABPI 1991. Xa uthe wabona into xela ngokukhawuleza kumphandi okanye kugqira.

Ndiza kwenza ntoni ngeziphumo zophando

Iziphumo zohlala zikhona ukunceda kuphando kwi rehabilitation kumyango kwi zigulana. Ukuba ufuna ulwazi ngeziphumo tsalela umphandi akunike iziphumo.

Ozikhona kumphati wekliniki yakho apho besikufumana khona. Umphandi uyakusebenzisa iziphumo
Ngubani oyakunxulumana malunga nolwazi

Izigulana ziyakutsalela aba bantu balandelayo maunga nolwazi.

M Shamila Manie (primary investigator)
Address: F56 Old Main Building, Groote Schuur Hospital, Observatory 7925
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Prof. Graeme Meintjes (co-supervisor):
Email address: Graeme.meintjes@uct.ac.za

Dr. Brian Allwood (co-supervisor):
Email address: brianallwood@gmail.com

Unga qhagemshela Human Research Ethics Committee ukuba unemibuzo kuba ungumthathi nxeba.

Address: Room E52-24, Old Main Building, Groote Schuur Hospital, Observatory, 7925.
Telephone: 021 406 6338 Fax: 021 406 6411
Email: shuretta.thomas@uct.ac.za, Website: www. Health.uct.ac.za/research/humanethics/forms

Appendix C: Self-Designed CRF – Includes Six-Minute Walk Test – Study 1

DOA:01/01/16 ***Participant no:*** ***Initials of participant: XY*** ***Interviewer: SM***

STUDY: Prevalence of lung function abnormalities in adult patients with TB in a high HIV setting ***Study reference number: HREC/REF:725/2015*** ***Clinical trial site/unit: Khayelitsha Site B ☐ Michael Mapongwana ☐***	
Participant no	
Folder no.	
DEMOGRAPHIC DATA	
Address: ***Contact no.:***	Date of Birth: DD MM YR ☐☐ ☐☐ ☐☐☐☐
Gender	Male Female
MEDICAL HISTORY	
Do you have or has the doctor ever said you have one of the following diseases: Hypertension Diabetes Type 1 Diabetes Type 2 Angina/***heart disease*** Any other medical condition not listed above? _____	**Tick all that apply:** ☐ ☐ ☐ ☐
SOCIO-ECONOMIC INFORMATION:	
Tell me about the house you live and amenities: Brick house Shack /backyard dwelling ***Electricity*** ***Running water inside the house*** ***Running water outside the house, <5m away*** ***Running water outside of house, > 5m away*** ***Flushing toilet inside house.*** ***Flushing toilet outside of house*** ***Bucket toilet outside of house*** ***No toilet*** ***Other*** ***How many people on average sleep in your house per night, in the last month?***	**Tick all that apply:** ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐☐

Do you cook in your home using:	**Tick all that apply:**
Wood/coal/dung	☐
Paraffin	☐
Electricity	☐
Other	☐
If yes to the 1st two, for how many years?	☐
What level of schooling did you complete?	**Tick all that apply:**
Finished Primary school (Std.5 / Gr 7)	☐
Primary school (less that Std. 5/Gr. 7)*	☐ ☐
Finished high school (Std. 10/ Gr. 12)	☐
High school (less than Std. 10/ Gr. 12)*	☐ ☐
Diploma course	☐
University degree	☐
None	☐
Unknown	☐
****note which grade completed***	
Employment	**Tick one box only**
1. ***Employed full time***	☐
2. ***Employed part-time***	☐
3. ***Self-employed***	☐
4. ***Currently unemployed, looking for work***	☐
5. ***Not working because of poor health***	☐
6. ***Full time house person***	☐
7. ***Full time student***	☐
8. ***Pensioner***	☐
9. ***Other***	☐
Is your work place very dusty? Or does your work entail a lot of dust?	☐
What kind of work do you do?	☐
How many years are you doing this current job?	☐
SMOKING HISTORY	
Do you smoke:	**Tick all that apply**

	Current	Ex-smoker	Never	No. of yrs
1. Cigarettes				
2. Cigars				
3. Pipe tobacco				
4. Dagga				
5. TIK (Methamphetamines)				
6. Mandrax				
7. Other				

Age or year you started smoking	
Age or year you stopped smoking	
How many cigarettes etc. do you smoke a day	
*Pack year calculation	

TB INFORMATION			
	DD	MM	YY
Date of diagnosis			
When did you start your TB treatment?			
When are you due to complete your TB treatment?			
	YES	NO	
Have you been taking your medication regularly since diagnosed?			
If NO, how many times did you default?			
TB Regiment:			
1st line			
2nd line			
Drug susceptibility			

HIV INFORMATION			
HIV status (mark applicable with an **X**)	positive	negative	unknown
Date of diagnosis	DD	MM	YY
ART status (mark applicable with an X)	Current	Previous	Never
If on ART (mark applicable with and X)	1st line	2nd line	
Last Viral Load		date	
Last CD4 count		date	

Appendix D: SGRQ South Africa – English 3 months

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
☐	☐	☐	☐	☐

P.W. Jones, PhD FRCP
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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 is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick (✓) these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write down any other important activities that your chest trouble may stop you doing:

.....

.....

.....

.....

Please tick (✓) only one box which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please check to see that you have answered all the questions.

EQ - 5D

Health Questionnaire

(South African English version)

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some 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 with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

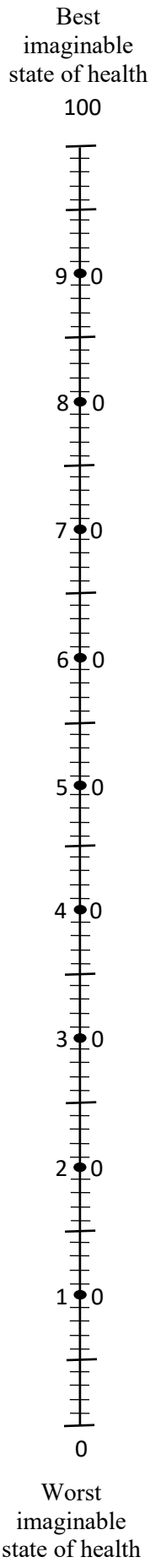
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale, in your opinion, how good or bad your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

1. Have you experienced serious illness?

	Yes	No
yourself	❑	❑
in your family	❑	❑
while caring for others	❑	❑

PLEASE TICK APPROPRIATE BOXES

2. What is your age in years? ☐

	Male	Female
3. Are you:	❑	❑

PLEASE TICK APPROPRIATE BOX

4. Are you:

a current smoker	❑
an ex-smoker	❑
a person who has never smoked	❑

PLEASE TICK APPROPRIATE BOX

5. Do you now, or did you ever, work in health services or social welfare?

Yes	No
❑	❑

PLEASE TICK APPROPRIATE BOX

If so, in what capacity?.....

6. Which of the following best describes your main activity?

in employment or self-employment	❑
retired	❑
housework	❑
student	❑
seeking work	❑
other (please specify)	❑ .....

PLEASE TICK APPROPRIATE BOX

7. Did your education continue after the minimum school leaving age (15 years / grade 9 / standard 7)?

Yes	No
❑	❑

PLEASE TICK APPROPRIATE BOX

	Yes	No
8. Do you have a degree or a diploma?	❑	❑

PLEASE TICK APPROPRIATE BOX

9. If you know your postal code, would you please write it here ☐

EQ - 5D

Iphepha lemibuzo ngezempilo

(Inguqulelo yesiXhosa saseMzantsi Afrika)

(Xhosa version)

(best available)

Beka uphawu kwibhokisi ibenye kwiqela ngalinye echaza imeko yempilo yakho namhlanje, kwezi bhokisi zilandelayo.

Musa ukuphawula ngaphezulu kwebhokisi enye kwiqela ngalinye.

Ukuhamba

Andinangxaki zokuhamba ❑

Ndinazo ingxakana zokuhamba ❑

Ndingumlwelwe obopheleleke ebhedini ❑

Ukuzinonophela isiqu

Andinangxaki zokuzinonophela ❑

Ndinazo ingxakana zokuhlamba okanye ukuzinxibisa ❑

Andikwazi ukuzihlamba okanye ukuzinxibisa ❑

Izinto zesiqhelo (Umsebenzi, Ukufunda izifundo

Umsebenzi wasekhaya*,* Usapho, Ezolonwabo*)*

Andinangxaki nokuzenzela izinto zesiqhelo ❑

Ndinazo iingxakana zokuzenzela izinto zesiqhelo ❑

Andikwazi kuzenzela izinto zesiqhelo ❑

Iintlungu / Ukungaziva kakuhle

Andinazintlungu okanye ukungaziva kakuhle ❑

Ndinentlungwana okanye ukungaziva kakuhle okungephi ❑

Ndinentlungu ezigqithileyo okanye ukungaziva kakuhle okugqithileyo ❑

Ukuxhalaba / Ukudakumba

Andinaxhala okanye andidakumbanga ❑

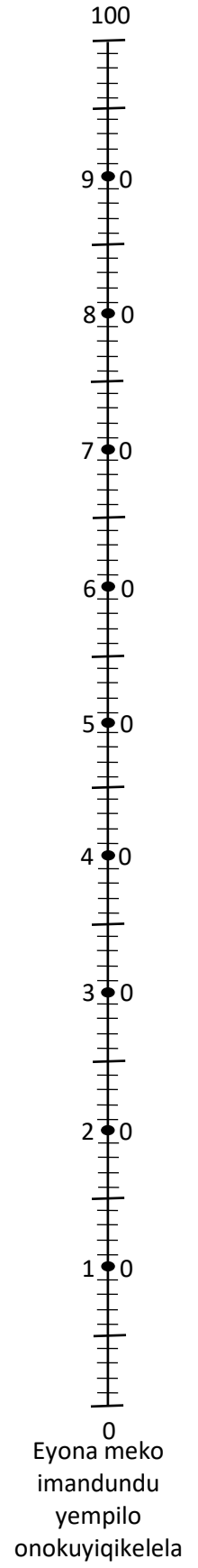
Ndibuxhalaba okanye ndibudakumba ❑

Ndixhalabe gqitha okanye ndidakumbe gqitha ❑

Ukunceda abantu ukuze baxele okokuba imeko yabo yempilo intle okanye imandundu na sizobe isikali (esifana nethemometha). Eyona meko entle yempilo iphawulwe ngo-100, eyona meko imandundu iphawulwe ngo-0.

Singathanda ubonise kwesi sikali ngokoluvo lwakho ukuba impilo yakho intle okanye imandundu kangakanani namhlanje.
Nceda wenze oku ngokuzoba umgca osuka ebhokisini engezantsi ukuya kulo ndawo esikalini ibonisa ukuba imeko yempilo yakho intle okanye imbi kangakanani namhlanje.

Imeko yempilo yakho namhlanje



Njemgoko kunganyanzelekanga ukuba ubhale igama lakho, kodwa ke kuyakunsinceda siqonde ngcono iimpemdulo ukuba sinolwazana lwemvelaphi kulowo nalowo umntu njengoko zichatshazelwe kule mibuzo ilandelayo

1. Ukhe wabanamava okugula kakhulu na?

	Ewe	Hayi
Wena	❑	❑
Kusapho lwakho	❑	❑
Xa ukhathalele abanye	❑	❑

Phawula iibhokisana ezifanelekileyo

2. Mingaphi iminyaka yakho?

3. U-

Yindoda	Libhinqa
❑	❑

Phawula ibhokisana efanelekileyo

4.

Uyatshaya	❑
Wawutshaya	❑
Ungumntu ongazange atshaye	❑

Phawula ibhokisana efanelekileyo

5. Usebenza, okanye ukhe wasebenza kwiinkonzo zezempilo okanye ezentlalontle?

Ewe	Hayi
❑	❑

Phawula ibhokisana efanelekileyo

Ubusenzani? .....

6. Koku kulandelayo kokuphi okuchaza ngcono okwenzayo?

Uyaphangela okanye uyazisebenzela	❑
Udla umhlalaphantsi	❑
Umsebenzi wasekhaya	❑
Umfundi	❑
Ufuna umsebenzi	❑
Okunye (Chaza)	❑

Phawula ibhokisana efanelekileyo

7. Leliphi ibanga ofikelele kulo esikolweni?……..

8. Unesidanga okanye i-diploma

Ewe	Hayi
❑	❑

Phawula ibhokisana efanelekileyo

9. Ukuba uyayazi ikhowudi yeposi yakho nceda uyibhale apha

Appendix G: Guidelines for Spirometry Procedure

Taken from Miller *et al.* (2005)
TABLE 4

Procedures for recording forced vital capacity
Check the spirometer calibration
Explain the test
Prepare the subject
Ask about smoking, recent illness, medication use, etc.
Measure weight and height without shoes
Wash hands
Instruct and demonstrate the test to the subject, to include
Correct posture with head slightly elevated
Inhale rapidly and completely
Position of the mouthpiece (open circuit)
Exhale with maximal force
Perform manoeuvre (closed circuit method)
Have subject assume the correct posture
Attach nose clip, place mouthpiece in mouth and close lips around the mouthpiece
Inhale completely and rapidly with a pause of, 1 second at TLC
Exhale maximally until no more air can be expelled while maintaining an upright posture
Repeat instructions as necessary, coaching vigorously
Repeat for a minimum of three manoeuvres; no more than eight are usually required
Check test repeatability and perform more manoeuvres as necessary
Perform manoeuvre (open circuit method)
Have subject assume the correct posture
Attach nose clip
Inhale completely and rapidly with a pause of, 1 second at TLC
Place mouthpiece in mouth and close lips around the mouthpiece
Exhale maximally until no more air can be expelled while maintaining an upright posture
Repeat instructions as necessary, coaching vigorously
Repeat for a minimum of three manoeuvres; no more than eight are usually required
Check test repeatability and perform more manoeuvres as necessary

Appendix H: Standard Operating Procedure (SOP) for the Execution of the Six-Minute Walk Test (6MWT)

1. Purpose:

1.1. The purpose of this document is to describe the process of the six-minute walk test (6MWT).

2. Responsibilities:

2.1. This SOP applies to Medical officers, Research Nurses and/or any staff member involved in conducting the 6MWT.

3. General Information:

3.1. All participants taking part in study one (prevalence study) will perform a 6MWT at baseline.

3.2. Participants should wear comfortable clothes and – if possible – shoes appropriate for walking.

3.3. Contra-indications for the 6MWT are:

- Current respiratory infection other than TB
- Myocardial infarction or unstable angina pectoris less than one month ago
- Severe dyspnoea

4. Abbreviations and/or Definitions:

4.1. SOP- Standard Operating Procedure

4.2. 6MWT – six-minute walk test

5. Equipments and/or materials:

5.1. Countdown timer

5.2. Clipboard with worksheet

5.3. Pulse oxymeter on spirometer

5.4. Cones

5.5. Modified Borg scale for dyspnoea

6. Procedure:

6.1. The participant should sit at rest on a location close to the starting position for at least 10 minutes before the test starts.

6.2. Record baseline heart rate and oxygen saturation.

6.3. Record baseline dyspnoea and overall fatigue using the Modified Borg scale.

6.4. Instruct the participant as follows:

" The purpose of this test is to walk as far as possible for 6 minutes. You will walk back and forth between these two cones. Six minutes is a long time to walk, so you will be exerting yourself. You might get out of breath or become exhausted. You are permitted to slow down, to stop, or to rest if necessary; resume walking as soon as you are able. You will be walking back and forth between those two cones. Try to turn briskly at the cones and continue back the other way without hesitation. I will show you now."

Demonstrate by walking one lap yourself.

"Are you ready? I will use this sheet to keep track of the number of laps you walk. Remember, the purpose is to walk as far as possible for 6 minutes, but do not run or jog."

6.5. Set the timer at 6 minutes.

6.6. Position the participant near the starting line. Participants are allowed their usual walking aids during the test. Start the timer as soon as the participant starts to walk.

6.7. Tick each lap on the 6MWT work sheet each time the participant crosses the start line.

6.8. During the test, do not encourage the participant, other than described below:

After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."
When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."
When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."
When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."
When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this: "You can rest if you would like; then continue walking whenever you feel able."

When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

6.9. When the patient rests, do not stop the timer.

6.10. When the timer reaches zero, say: "Stop". Walk over to the patient and mark the spot where they stopped with the third cone. Sit the participant down.

6.11. Record post-test heart rate and oxygen saturation immediately afterwards.

6.12. Record post-test dyspnoea and overall fatigue using the Modified Borg scale.

6.13. Count the number of laps and measure and record the additional distance covered; calculate the total distance by multiplying the number of laps by 40 and adding up the additional distance.

6.14. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), discontinue the walk, and note on the worksheet the distance covered (see above), the time stopped, and the reason for stopping prematurely. Record post-test heart rate, oxygen saturation, dyspnoea and overall fatigue score as mentioned above.

6.15. Reasons for immediately stopping the 6MWT are:

- chest pain
- intolerable dyspnoea
- leg cramps
- staggering
- excessive sweating
- pale or ashen appearance

7. References:

7.1. Laboratories, A.T.S.C.o.P.S.f.C.P.F., *ATS statement: guidelines for the six-minute walk test.* Am J Respir Crit Care Med, 2002. **166**(1): p. 111–7.

7.2. Holland et al 2014.

EQ - 5D

Gesondheidsvraelys

Afrikaanse weergawe
(Afrikaans version)

Dui asseblief aan watter stellings u eie gesondheidstoestand vandag die beste beskryf deur ’n regmerkie in een blokkie by elkeen van die onderstaande groepe te maak.

Beweeglikheid

Ek het geen probleme om rond te loop nie ❑

Ek het sommige probleme om rond te loop ❑

Ek is beperk tot die bed ❑

Selfversorging

Ek het geen probleme om myself te versorg nie ❑

Ek het sommige probleme om myself te was of aan te trek ❑

Ek is nie in staat om myself te was of aan te trek nie ❑

Gewone Aktiwiteite (bv. werk, studeer, huiswerk, familie- of ontspanningsaktiwiteite)

Ek het geen probleme om my gewone aktiwiteite uit te voer nie ❑

Ek het sommige probleme om my gewone aktiwiteite uit te voer ❑

Ek is nie in staat om my gewone aktiwiteite uit te voer nie ❑

Pyn/ Ongemak

Ek het geen pyn of ongemak nie ❑

Ek het matige pyn of ongemak ❑

Ek het uiterste pyn of ongemak ❑

Angstigheid/ Neerslagtigheid

Ek is nie angstig of neerslagtig nie ❑

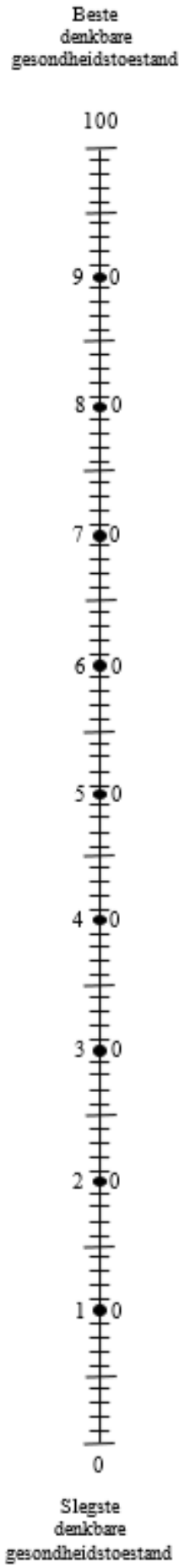
Ek is matig angstig of neerslagtig ❑

Ek is uiters angstig of neerslagtig ❑

Om mense te help om te sê hoe goed of sleg hul gesondheidstoestand is, het ons ’n skaal (baie soos ’n termometer) geteken waarop die beste gesondheidstoestand wat u u kan verbeel, gemerk is met 100 en die slegste gesondheidstoestand wat u u kan verbeel, gemerk is met 0.

Ons wil graag hê dat u op hierdie skaal aandui hoe goed of sleg u eie gesondheid vandag na u mening is. Doen dit asseblief deur ’n streep te trek vanaf die blokkie hieronder (waar dit sê: “u eie gesondheidstoestand vandag”) tot by enige punt op die skaal wat aandui hoe goed of sleg u gesondheidstoestand vandag is.

U eie gesondheids-toestand vandag



Omdat alle antwoorde naamloos is, sal dit ons help om u antwoorde beter te verstaan indien ons ’n bietjie agtergrondinligting oor almal het, soos in die volgende vrae gedek.

1. Het u ernstige siekte ondervind?	Ja	Nee	
in uself	❑	❑	MERK
in u familie	❑	❑	ASSEBLIEF
in die versorging van andere	❑	❑	TOEPASLIKE
2. Wat is u ouderdom in jare?			
3. Is u:	Manlik	Vroulik	MERK
	❑	❑	ASSEBLIEF
			TOEPASLIKE
4. Is u:			
’n huidige roker	❑		MERK
’n voormalige roker	❑		ASSEBLIEF
iemand wat nog nooit gerook het nie	❑		TOEPASLIKE
5. Werk u nou, of het u ooit in die gesondheids- of maatskaplike dienste gewerk?	Ja ❑	Nee ❑	MERK ASSEBLIEF TOEPASLIKE
Indien wel, in watter hoedanigheid? …….			
6. Watter van die volgende beskryf u hoofaktiwiteit die beste?			
in diens wees of vir uself werk	❑		
afgetree	❑		MERK
huiswerk	❑		ASSEBLIEF
student	❑		TOEPASLIKE
soek werk	❑		
ander (spesifiseer asseblief)	❑……..		
7. Het u onderwys voortgegaan na die minimum skoolverlatersouderdom (15 jaar oud / Graad 9 / Standerd 7)?	Ja ❑	Nee ❑	MERK ASSEBLIEF TOEPASLIKE
8. Het u ’n graad of ’n diploma?	Ja	Nee	MERK
	❑	❑	ASSEBLIEF
			TOEPASLIKE
9. Indien u u poskode ken, sal u dit asseblief hier neerskryf			

Appendix J: CXR Scoring Form

Assessment of lung function, functional capacity and quality of life in first time, drug sensitive pulmonary tuberculosis patients.

Date (dd/mmm/yyyy) of reading	___ ___	___ ___ ___	___ ___ ___ ___
Study personnel initials (leave (___) blank if no 3rd initial)	___ ___ (___)	Study ID Number	

1. Chest X-ray quality review			
1.1 Chest X-ray ID number			
1.2 Date of X-ray (dd/mmm/yyyy)	___ ___/___ ___ ___/___ ___ ___ ___		
1.3 Film Quality (tick)	**optimal**	**suboptimal**	**unreadable**
If suboptimal or unreadable, please discuss with radiographer and/or repeat			
1.4 Comments (circle in right hand columns if applicable) 1. penetration 2. rotation 3. inspiratory attempt (diaphragm should be intersected by the 5th - 7th ant ribs in mid-clavicular line)		1. under-penetrated 2. rotated towards the right 3. poor inspiratory attempt	1. over-penetration 2. rotated towards the left 3. hyper-inflated

2. Total percentage of affected lung per zone

- Please indicate the predominant infiltrate in the zone as **N** for **Nodular** or **H** for **Homogeneous; remember to x total percentage by 0.5 if N**
- Please indicate if a **pleural effusion** is obscuring greater than a costophrenic angle of a lung zone by entering **PE and DO NOT SCORE THAT ZONE**, and note that grand total will need to be adjusted accordingly e.g. /500 if one zone was not scored due to PE

	Right (%)	N/H	**Left (%)**	N/H
2.1 Upper Zone				
2.2 Middle Zone				
2.3 Lower Zone				

3. Grand Total: affected lung (/600 if all zones are included)	
4. Grand Total: percentage of affected lung	_____%
5. Estimated percentage unaffected lung	_____%

6. Cavities		
6.1 Are there any cavities ≥1cm in diameter visible?	YES ☐ NO ☐ (skip to end)	
6.2 If yes please add 40 to Grand Total: percentage of affected lung and indicate new total in right column	_____%	
6.3 Location (state number of cavities in zone)	**Right** ☐ upper ☐ middle ☐ lower	**Left** ☐ upper ☐ middle ☐ lower
6.4 Size of cavity in cm (diameter)	**Location**	**Size**

8. Pleural effusion
Any pleural effusion will be documented, using the following grading system: • *1+ = costrophrenic angle* • *2+ = up until 1/3 of the lung* • *3+ = greater than 1/3 of the lung*
Is there any pleural effusion visible? ☐ Yes ☐ No
If 'yes', please indicate grade ☐ 1+ ☐ 2+ ☐ 3+ and side ☐ right ☐ left ☐ both

7. Lymph nodes
The presence of lymph nodes will only be scored if the diameter is > 10mm *The following scoring system will be used:* • *1+ = lnn present in one location* • *2+ = lnn present in two locations* • *3+ = lnn present in more than two locations*
Are there any enlarged lymph nodes visible? ☐ Yes ☐ No
If 'yes', please indicate grade ☐ 1+ ☐ 2+ ☐ 3+
If 'yes' please indicate location: ☐ right hilar ☐ left left hilar ☐ right mediastinal ☐ left mediastinal ☐ other

9. Tracheal deviation
Tracheal deviation present? ☐ Yes ☐ No
If 'yes' please indicate to which side it is deviated? ☐ Right ☐Left

10. Pleural calcification
Pleural calcification present? ☐ Yes ☐ No
If 'yes', please indicate hemi-side (tick both if bilateral): ☐ right ☐ left ☐ both

11. Apical cap
Apical cap present? ☐ Yes ☐ No
If 'yes', please indicate hemi-side (tick both if bilateral): ☐ right ☐ left ☐ both

12. Reviewer details	
Initials _____ Date _____	
13. Consensus score	
Total percentage score reviewer 1	
Total percentage score reviewer 2	
Average total percentage score	
Cavities ☐ Yes ☐ No if 'yes', add 40	
Final consensus score	

Appendix K: HREC Approval Letter – Study 1

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 November 2015

HREC REF: 725/2015

Prof S Amosun
Health & Rehab Sciences
Division of Physiotherapy
F-45
OMB

Dear Prof Amosun

PROJECT TITLE: THE ASSESSMENT OF LUNG FUNCTION ABNORMALITY IN ADULT PATIENTS WITH TUBERCULOSIS IN A HIGH HIV PREVALENT SETTING AND THE IMPACT OF A PULMONARY REHABILITATION INTERVENTION TO IMPROVE FUNCTIONAL OUTCOMES (PhD-candidate-S Manie)

Thank you for your response letter addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has formally approved the above-mentioned study.

Approval is granted for one year until the 30th November 2016.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the following student: - Shamila Manie is also involved in this project.

Please quote the HREC reference no in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

Hrec/ref:725/2015

Appendix L: Approval Letter from WC_2017RP33_156 – Study 2

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 6857: fax: +27 21 483 9895
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_2017RP33_156
ENQUIRIES: Ms Charlene Roderick

University of Cape Town

Anzio Road

Observtory

Cape Town

7925

For attention: Mrs Shamila Manie, Prof Seyi Ladele Amosun, Prof Graeme Meintjies, Prof Brian Allwood

Re: Assessment of lung function abnormalities in adult patients with tuberculosis in a high HIV-prevalent setting and the impact of a pulmonary rehabilitation intervention to improve functional outcomes.

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research. Please contact following people to assist you with any further enquiries in accessing the following sites:

Khayelitsha (Site B) CHC	**Mr David Binza**	**021 360 5207**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**annexure 9**) within six months of

completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).

4. The reference number above should be quoted in all future correspondence.

Yours sincerely

DR A HAWKRIDGE

DIRECTOR: HEALTH IMPACT ASSESSMENT

DATE: 18 | 8 | 2017.

CC: **M PHILLIPS** **DIRECTOR: KESS**

Appendix M: MIR Interpretation and Quality Control Grade

MIR
MEDICAL INTERNATIONAL RESEARCH

update October 2018

ABOUT MIR™ SPIROMETRY INTERPRETATION AND QUALITY CONTROL GRADE

Spirometry is a test which requires active cooperation from the patient. To assist the healthcare professional in performing a correct Spirometry test, MIR™developed a proprietary algorithm based on ATS/ERS latest recommendations. The results of this algorithm are the Automatic Interpretation of the Spirometry Session and the definition of the Quality grade of the Spiromery Session. Interpretation and Quality grade are available on all MIR™ spirometers and softwares.

About the Interpretation

Automatic Interpretation refers to Forced Vital Capacity (FVC), and is represented by a colored traffic light indicator associated to a specific message. The messages can include the following:

a) Normal spirometry
b) Slight obstruction/restriction
c) Moderate obstruction/restriction
d) Moderately severe obstruction/restriction
e) Severe obstruction/restriction
f) Very severe obstruction/restriction
g) The final interpretation level is "restriction + obstruction", where the indicator light indicates the worst parameter between restriction and obstruction.

Severity Classification of an Obstruction is based on FEV1 value, compared to predicted.

Severy Classification of a Restriction is based on the highest value between FVC/EVC/IVC, compared to predicted.

About the Quality Control Grade

After each FVC or VC test, the Quality Control Grade of the Session is also calculated, based on a scale from A to F grades. For each spirometry session, a minimum of 3 to a maximum of 8 attempts shall be performed. The quality control system uses letters as described below:

MIR Head Office via del Maggiolino, 125 - 00155 Roma (ITALY)
T. +39 06 22 754 777 - F. +39 06 22 754 785 - E. mir@spirometry.com
www.spirometry.com
www.oximetry.com

1st case: PRE test

A = at the end of two acceptable attempts, the variation of the two highest FEV1 values and the two highest FEV6 values are less than or equal to 100 mL.

B = at the end of two acceptable attempts, the variation of the two highest FEV1 values is between 101 and 150 mL

C = at the end of two acceptable attempts, the variation of the two highest FEV1 values is between 151 and 200 mL

D = only one attempts was acceptable or there is more than one acceptable attempts but the variation of the two highest FEV1 values is greater than 200 mL

F = no acceptable attempts.

2nd case: POST bronchodilator test

A = two acceptable tests, the variation of the two highest FEV1 values is less than or equal to 100 mL.

B = two acceptable tests, the variation of the two highest FEV1 values is between 100 and 200 mL. C = two acceptable tests, the variation of the two highest FEV1 values is greater than 200 mL.

D = one acceptable test

F = no acceptable test

So as you can see, the grading system is based primarily on the reproducibility of acceptable tests. **"Acceptable"** is also an ATS/ERS medical term and acceptable test in general are:

- A good start of exhalation
- Free from artifacts
- No cough during first second of exhalation (for FEV 1)
- No glottis closure or abrupt termination (for FVC)
- No early termination or cutoff (for FVC)
- Maximal effort provided throughout the maneuver
- No obstructed mouthpiece

While using MIR™ equipment, basically you can consider a test "acceptable" when there are no error messages in winspiroPRO™ for a specific attempt, such as:

- blow out longer
- do not hesitate
- expire all the air
- etc.

Acceptability Criteria is calculated by the MIR™ Spirometer when used in stand-alone mode, or by winspiroPRO™ when the spirometer is connected to the software for real time test.
Acceptability Criteria will change from time to time according to the latest spirometry guidelines.
So to avoid any discrepancy when a test is performed on the Spirometer in stand-alone mode first and then imported in winspiroPRO™, the rule is that winspiroPRO™ will always import also the same Acceptability Criteria used by the Spirometer in stand-alone mode, prevent using its own in this specific situations.

Appendix N: Spearman's Correlation for SGRQ and Lung Parameters (Study 1)

	U-LFT		**A-LFT**		**combined**	
	Spearman's Correlation coefficient	**p-value**	**Spearman's Correlation coefficient**	**p-value**	**Spearman's Correlation coefficient**	**p-value**
FEV_1 vs SGRQ	-0.4109	0.0012	-0.1712	0.0269	-0.2517	0.0001
FEV_1 % predicted vs SGRQ	-0.2903	0.0257	-0.1479	0.0564	-0.1851	0.0052
FEV_1/FVC vs SGRQ	-0.3614	0.0049	-0.0949	0.2225	-0.1176	0.0778
FEV_1/FVC % predicted vs SGRQ	-0.3671	0.0042	-0.1375	0.0764	-0.1553	0.0195

Appendix O: Search Strategy Used

Pulmonary tuberculosis OR pulmonary TB *(using the abbreviation as an alternative retrieved more)*

AND

Pulmonary rehabilitation OR physiotherapy OR physical therapy OR exercise OR exercise tolerance OR exercise therapy

It was not necessary to include the MeSH terms for exercise or exercise therapy as the keyword search for those terms map to the MeSH and therefore includes MeSH in its search.

Appendix P: ACSM New Pre-Participation Health Screening Questionnaire

Exercise pre-participation Health screening questionnaire for exercise professionals
Assess your client health needs by marking all the TRUE statements

STEP 1	**Tick √**
Symptoms: **Does the client (participant) experience:**	
• Chest discomfort with exertion (with working)	
• Unreasonable breathlessness	
• Dizziness, fainting, blackouts	
• Ankle swelling	
• Unpleasant awareness of a forceful, rapid or irregular heart rate	
• Burning or cramping sensations in your lower legs when walking short distances	
If you **did mark any** of the statements under the symptoms, **STOP**, your client (participant) should seek medical clearance before engaging in or resuming exercise. Your client (participant) needs to use a facility with a medically qualified staff If you **DID NOT** mark any symptoms, continue to steps 2 and 3	
STEP 2	
CURRENT ACTIVITY **Does your client (participant) perform planned, structured physical activity at least 30 min at moderate intensity on at least 3 days per week for at least the last 3 months?** **YES** ☐ **NO** ☐ **Continue to step 3**	
STEP 3	
MEDICAL CONDITIONS Has your client (participant)had or do they currently have:	
• A heart attack	
• Heart surgery, cardiac catheterization or coronary angioplasty	
• Pacemaker/implantable cardiac defibrillator/rhythm disturbance	
• Heart valve disease	
• Heart failure	
• Heart transplantation	
• Congenital heart disease	
• diabetes	
• Renal (kidney) disease	
EVALUATING STEP 2 & 3:	**TICK √**
• If you did not mark any of the statements in step 3, medical clearance is not necessary.	
• If you marked STEP 2 YES and marked any of STEP 3, your client (participant) may continue to exercise at light to moderate intensity without medical clearance. Medical clearance recommended before engaging in vigorous exercise	
• If you marked STEP 2 NO and marked any of the statements in STEP 3, medical clearance is recommended. Your client may need to use a facility with a medically qualified staff.	

Appendix Q: Pilot Study Feedback Questionnaire for Study 3 (Intervention)

1. What part of the exercise programme did you enjoy the most?
2. Which exercises did you find too difficult to do?
3. Were the exercises tempo energetic enough?
4. Was the space and time provided for the exercises enough?
5. What would you change in the exercise programme?

Appendix R: Enrolment Information Sheet and Informed Consent

Good day

My name is Shamila Manie. I am a student at the University of Cape Town. As part of my studies I must do some research. This letter is to tell you about what I am doing and how you can possibly help me.

I am trying to find out if people that are being treated for TB (sometimes they have HIV as well) might feel better if they **take part in an exercise programme**

Why are we doing the study?

We know people with TB can have a problem with how well their lungs work. Normally you get pills to make the TB better. I want to see if taking the pills and doing some exercises to make the lungs and body stronger will make you feel better. It doesn't matter if you are only taking pills for TB; or if you have other things that you take pills for, like HIV.

What kind of people can join the study?

We are looking for people with TB in their lungs and changes we can see on your chest X-ray as well as being safe to participate in an exercise class. As you have already been screened for the above, we would like you to consider joining our research study.

What do I have to do?

First, we will explain all about the study. Then we will ask for you to sign to say that you would like to join. You do not have to say yes. If you wish to think about it and talk to your family first before saying yes, that is fine. If you say yes now, or at a later stage, you can still change your mind without having to say why. If you do say yes:

- We will ask all about you. We want to know about your sickness; how you are feeling and about what you can do for yourself at home and at work.
- We will look in your folder at the clinic to see if you come to your appointments
- We will do some activities with you. You must blow into a machine fast and hard. We will help you by explaining what to do and tell you when you are doing it nicely. You might have to do this a few times. This helps us know how your lungs work. If you need a rest you can tell us. We will explain what the machine says about how your lungs are working.
- Next you will take steps up and down (like climbing stairs) for six minutes. We want to see if it makes you out of breath.

What happens next?

We will tell you if you have been included in the exercise programme or not. **The way this works is that we have numbers generated by a computer programme and then the computer decides whether you will be in the exercise programme or not. We don't know who will be in the exercise programme or who won't be. This is to make sure that everyone has an equal chance to get into the exercise programme and nobody is favoured above the other.** We cannot say if you will get exercise now, but if you don't, you will get a booklet about TB and how to live a healthy life with TB. After the end of the study you will get a chance to do the exercise programme if it is seen to be helpful. So, everyone who wants to do exercises will be able to do them, just half will do them now and half will go on a waiting list and do them later.

If I get into the exercise group what happens then?

You will come to the clinic and we will show you the exercises and help you do them. There are two classes a week. Each class lasts for one hour. You do a warm-up and cool-down exercises as well as exercises to make your body and chest stronger. After six weeks, we do the blowing test, stepping test and another chest X-ray. We will also ask about how you are feeling using the same forms we did the first time. You finish the classes after another six weeks. So, you will be doing the exercises for three months. Then we will check you again at six and twelve months. **It is important that you continue to take your medication while you in the study even if you are feeling better. If you do stop taking your medication for more than a week then you will no longer be able to continue with the exercise sessions.**

If you do not get into the classes straightaway, we will give you advice and a booklet about things you can do at home. **You will also be invited to come to educational sessions at the clinic that will educate you on things like eating healthy foods and why stopping smoking is important to your health**. Once the first group has finished you **will be given the chance to participate in exercise sessions if it is proven to be helpful.**

Is there any harm if I agree?

We start by talking about your sickness. You might feel shy or upset telling us about this. If so we can get a counsellor to talk to you. The activities like blowing and stepping might make you feel a bit dizzy or short of breath for a few minutes.

When you do any new exercises, it is normal to feel a bit stiff and sore for a few days. You need to tell us if there is any problem because of the exercises. We think they will help because we know that exercise is good for you. The people working on this study are all physiotherapists – this means they understand how the body works and how exercises help the body to work well.

Might I get better if I agree?

If you agree you will get information about TB and exercise. When you do the exercise classes we know exercise is healthier than not doing exercise. **We expect you to feel better on your TB treatment. We however do not know whether the exercise programme will add any additional benefit and that is why we are testing it in this study**.

Do I have to pay? Will you pay me?

You do not have to pay to join the exercise classes. If you agree to join, we will give you R150 to thank you for your time and to pay towards your transport costs. Everyone who comes for the blowing test, stepping test and chest X-ray will get R150 to say thank you. If we ask you to join the exercise classes rather than go on the waiting list, we will pay you R100 each time you come to class.

Is there anything else I can do if I don't want to join?

You must carry on with all the pills the doctor gave you. While you won't get the exercise classes, we will give you information about the kind of exercises you can do at home which might help you.

Voluntary participation

You will be taking part in this study out of your own free will and do not have to join if asked if you don't want to.

Right to withdraw from study

Even if you do agree to join the study, you have the right to withdraw from the study at any point, and for any reason. This reason does not need to be explained to the researchers. You will still receive your normal treatment at the clinic if you do not wish to continue in this study.

Confidentiality

Your identity will remain a strictly confidential. A number will be placed on each consent form and after the consent is obtained, the individual identity of a person will no longer be referred to. Instead, the participants will be referred to by a number. It will not be possible for researchers to link personal responses to individual identities when using this method.
All data will be processed using password protected computer files and only researchers will have access to the data. Upon finishing the study, data will be stored in a password-protected folder.

Compensation/treatment in the event of injury

If patients experience any dizziness or shortness of breath, researchers are trained in teaching breathing techniques to alleviate symptoms. **This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study. The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006 (or latest version), which are based on the Association of the British Pharmaceutical Industry Guidelines. The insurer will pay without you having to prove that the research was responsible for your bodily injury. You may ask the study doctor for a copy of these guidelines.**

The insurer will not pay for harm if, during the study, you:

- **Use medicines or other substances that are not allowed**
- **Do not follow the study doctor's instructions**
- **Do not tell the study doctor that you have a bad side effect from the study medicine**
- **Do not take reasonable care of yourself and your study medicine**

If you are harmed and the insurer pays for the necessary medical costs, usually you will be asked to accept that insurance payment as full settlement of the claim for medical costs. However, accepting this offer of insurance cover does not mean you give up your right to make a separate claim for other losses based on negligence, in a South African court.

It is important to follow the study doctor's instructions and to report straightaway if you have a side effect from the study medicine.

What will you do with the results of the research?

Results of the study will be made available to the facility manager of your clinic from which you were recruited. It is also likely that results of this exercise class will be written up and published in a medical magazine. If you wish to be contacted in order to be informed of the results of the study, you may contact the researcher or give your contact numbers so that they can contact you.

Who can I contact for further information?

Participants may contact the following persons for more information regarding the research:

Mrs. Shamila Manie (primary investigator/researcher)
Address: F56 Old Main Building, Groote Schuur Hospital, Observatory 7925
Contact numbers: Tel: +27 (0) 21 406 6428; Mobile: 083 225 1736;
Fax: +27 (0) 21 406 6323/0866111883
Email address: shamila.manie@uct.ac.za
Or
Prof. Dele Amosun (primary supervisor):
Address: F45 Old Main Building, Groote Schuur Hospital, Observatory 7925
Contact numbers: Tel: +27 (0) 21 406 6428 Fax: +27 (0) 21 406 6323/0866111883
Email address: seyi.amosun@uct.ac.za
Or

Prof. Graeme Meintjes (co-supervisor):
Email address: Graeme.meintjes@uct.ac.za

Or

Associate Prof. Brian Allwood (co-supervisor)
Email address: brianallwood@gmail.com

You may also contact the Human Research Ethics Committee (HREC) if you have any questions regarding your rights as a research participant.
Address: Room E52-24, Old Main Building, Groote Schuur Hospital, Observatory, 7925.
Telephone: 021 406 6338 Fax: 021 406 6411
Email: shuretta.thomas@uct.ac.za
Website: www. Health.uct.ac.za/research/humanethics/forms

CONSENT FORM

Declaration by participant

By signing below, I _____ agree to take part in this research study entitled: Assessment of lung function abnormalities in adult patients with tuberculosis in a high HIV-prevalent setting and the impact of a pulmonary rehabilitation intervention to improve functional outcomes.

I declare that:

	Tick (√)
I have read/had read to me this consent form and the Information Sheet and had the opportunity to ask any questions I may have.	
I agree to participate in this research study. The decision I have made is completely my own. I agree for my results to be used for research purposes and that the results may be published.	
I know that I can withdraw from the study at any time without having to give any reason.	
I know there a 50% is a chance I can start my exercise programme now, but also a 50% chance I will only start it later.	
I understand I can't choose when my exercise programme starts	
I know all the details about me, including medical information, will be kept private. Even if the results of the study are published I understand that I will not be identifiable.	
I understand what I am required to do in terms of the tests and the exercise programmes and I am willing to join the study for a period of up to one year, even though the exercise programme is for a shorter time than this. During this time, I will receive follow up visits and phone calls to monitor my progress.	
I understand that the risks involved in this study are minimal and similar to those encountered in daily living.	
I have been informed that I may possibly benefit from doing the exercise programmes. I do not have to pay for the exercise programmes. I will be reimbursed for travel and time for my participation.	

_____ _____
Participant's name (please print) and signature Date

_____ _____
Witness name (please print and sign) Date

Declaration by investigator

I *(name)* …… declare that:

- I explained the information in this document to ……..
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above
- I did/did not use a interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*

Signed at (*place*) ..... on (*date*) ……..…….. 20...

…… ……

Signature of investigator **Signature of witness**

Declaration by interpreter

I *(name)* …… declare that:

- I assisted the investigator (*name*) ……. to explain the information in this document to (*name of participant*) …….. using the language medium of Afrikaans/Xhosa.
- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all his/her question satisfactorily answered.

Signed at (*place*) ..... on (*date*) ……..……..

…… ……

Signature of interpreter **Signature of witness**

Should you wish to be contacted in order to be informed of the results of the study, please provide your contact number/email address: _____

Usuku Oluhle

Igama lam ndingu Shamila Manie. Ndingumfundi kwi- Dyunivesiti yase Kapa. Kwinxalenye yezifundo zam kumele ndenze uphando. Lencwadi ingokuxelela ngomsebenzi endiwenzayo nangokuba wena ungandincedisa kanjani na.

Ndizama ukukhangela ukuba abantu abanyangelwa isifo-sephepha (maxa-wambi babe bephila kunye nentsholongwane kagawulayo (HIV) kwangaxeshalinye) kungenzeka bazivengcono na xa benokuthi bazibandakanye okanye bathathe inxaxheba kwinkqubo yokuzilolonga.

Kutheni sisenza oluphando nje?

Siyayazi ukuba abantu abanesifo-sephepha(TB) banganengxaki nohlobo imiphunga yabo esebenza ngayo. Ngokwesiqhelo uye ufumane iipilisi/amayeza ukwenza isifo-sephepha sibengcono. Ndifuna ukujonga ukuba xa uthe wathatha iipilisi kwaye umana uzilolonga ukwenza womelelelise imiphunga kwanomzimba kungakwenza uzive ngcono na. Akukhathaliseki okokuba usebenzisa iipilisi zodwa zesifo-sakho sephepha na okanye uthatha namanye amayeza ezinye izifo ezifana nentsholongwane kagawulayo (HIV).

Ngabaphi abantu esibafunayo ukuba bazibandakanye noluphando?

Sikhangela abantu abanesifo-sephepha kwimiphunga yabo nokuba lukhona na utshintsho esinokulibona kuxilongo lwakho lwesifuba , kwaye kwangaxeshanye sijonge ukuba ukhuselekile na ukuthatha inxaxheba kuleklasi yemithambo. Nanjengoko sele uvavanyelwe ezizinto zingasentla, singathanda okokuba uthathe inxaxheba koluphando lwethu.

Ingaba kumele ndenzentoni na?

Okukuqala, sakucacisela ngophando. Okulandelayo sakukucela ukuba utyikitye usinike imvume yokuba ungathanda ukuthatha inxaxheba koluphando. Awunyanzelekanga ukuba uthi uvume. Ukuba uyafuna ukhe uziphe ixesha ucinge ngalomba okanye uxhumane nomnye wamalungu osapho mayelana nalomba phambi kokuba wenze isigqibo sokuba uyavuma, oko kuvumelekile. Ukuba uthi ewe ngoku, okanye emveni kwethuba, uvumelekile ukuba ungazitshintsha ingqondo kwaye akunyanzelekanga ukuba usicacisele ukuba uzitshintshele ntoni. Ukuba uthi ewe:

- Sakubuza konke ngokumalungana nawe. Sifuna ukwazi mayelana nesigulo sakho; ukuba uzivanjani kwakhona ukuba yintoni okwazi ukuzenzela yona ngokunokwakho ekhaya nase emsebenzini.
- Sakuthi sijonge amaphepha akho asekliniki(folder) sikhangele ukuba uyaziwahamba na amadinga akho asekliniki; ngokwezotyelelo kumtholampilo uyawafezekisa na.
- Sakwenza imidlalwana kunye nawe. Kuyakufuneka ukuba uvuthele ematshinini ngamandla kwaye ngokukhawuleza. Sakukuncedisa ngokuthi sikucacisele ukuba kufuneka wenze ntoni kwaye ukwenza nini oko kakuhlenje. Uzakwenza oku amaxeshana ambalwa. Oku kusinceda ekubenibasazi ukuba imiphunga yakho isebenza kanjani na. Ukuba ufuna ukuphumla ungasixelela. Sizakuchazela ukuba umatshini uthini ngohlobo imiphunga yakho esebenza njanina.
- Okulandelayo, sizakucela ukuba wehle usenzuka izitepisi kangangemizuzu emithandathu. Sifuna ukubona ukuba uphelelwe ngumphefumlo na.

Yintoni ezakulandela ngoku?

Sizakuxelela ukuba ufakiwe okanye awufakwanga kulenkqubo yokuzilolonga. Uhlobo lenkqubo esebenza ngayo yile: Sakubanenombolo ezikhethwe yikhompyutha (computer) emva koko, le khompyutha izokuthatha isigqibo sokuba uzakuyingenela na lenkqubo okanye awuzoyingenela. Thina asiyazi ukuba ngubani na ozokukhethwa ukuba athathe inxaxheba kulenkqubo yokuzilolonga. Okanye engekho kuyo. Oku kukuqinisekisa ukuba wonke ubani unamathuba alinganayo, ukuba angenele lenkqubo yokuzilolonga kwaye ngalendlela sifuna ukuqinisekisa ukuba akekho umntu okhethwa ukodlula omnye umntu. Angekhe sitsho ukuba lenkqubo yemithando uzakuyingenela ngoku, kodwa ukuba akuyingeneli, uzakufumana incwadana emayelana nesifo-sephepha kwaye nokuthi ungaphila njanina ubomi obungcono uphilisana nesifo-sephepha (TB).
Emveni kokuba uphando luphelile uzakufumana ithuba lokwenza lenkqubo yemithambo ukuba iyeyabonakala iluncedo. Ngoko ke, wonke ubani ofuna ukuzilolonga uzobe ekwazi ukwenzanjalo, okuyingxenye kungaqala ukuba kwenze ngoku, ize enye ingxenye ibe ilinda ukufakelwa kuluhlu lwabantu abazakulinda-abazakubuya benze kamva.

Ke ukuba ndiyangena koluluhlu lwezemithambo kuzakwenzeka ntoni kengoko?
Uyakucelwa ukuba uze ekliniki kwaye ke sizakubonisa imithambo kwaye sikuncede ukukubonisa ukuba yenziwa kanjani na. Kuneklasi ezimbini ngeveki. Iklasi nganye ithatha iyure enye. Uyazifudumeza kuqala-kwaye uzipholise kwaye kwangaxeshanye uzilolonge ukwenzela umzimba nesifuba sakho somelele. Emveni kweeveki ezintandathu, sizakwenza oluvavanyo lukuvuthela, uvavanyo lokunyuka kwakunye novavanyo lwesifuba-lukagesi. Sakukubuza kwakhona ukuba uziva njanina ukusebenzisa ezindlela zinye ebesiqalengazo ekuqaleni. Uyakuyigqiba kwakhona eziklasi emveni kwezinye iiveki ezintandathu. Ngoko ke, uzakube uzilolonga kangangesithuba seenyanga ezintathu. Kwakhona sizakukujonga kwakhona kwisithuba seenyanga ezintandathu nakwi nyanga yeshumi elinesibini. **Kubalulekile okokuba ube uyaqhubekeka nonyango lwakho lokuthatha amayeza, logama ukuphando nangoku uziva-ngcono wena. Ukuba uyema ukuthatha amayeza akho ngaphezulu-kweveki ngoko ke uyakube ungavunyelwa ukuba uphinde wamkelwe uphinde uqhubekeke neziseshoni zemithambo.**

Ukuba awufumani klasi ngoko-nangoko, sakunikeza ingcebiso kwakunye nencwadana emalungana nezinto onokuzenza ngexesha usendlini. Uzokumenywa ukuba uze kwiinkqubo zemfundo ekliniki, ezinkqubo zizokufundisa ngezinto ezifana nokutya okusempilweni nokuba kutheni kubalulekile ukuba uyeke utshaya icuba mpilweni yakho. Emva kokuba iqela lokuqala ligqibile, uzokunikwa ithuba lokuba uthathe inxaxheba kwiinkqubo yozilolonga ukuba ifumaniseke iluncedo.

Ingaba ukhona umonzakalo/ na ukuba ndithe ndavuma ukuthatha inxaxheba koluphando?
Siqala ngokuba sithethe ngesigulo sakho. Ungaziva uneentloni okanye uphatheke kakubi ukusixelela ngawe oku. Ukuba kunjalo singakufunela umcebisi ngakwicala lentetho-ntuthuzelo athethe nawe. Imidlalwana efana nokuvuthela kwaye wenyuke ingakwenza uzive unesiyezi maxa wambi uzive ngokungathi unesiyezi okanye ukuvaleka xa uphefumla/kangangesithuba semizuzwana.

Xa uqala ukuzilolonga, kuqhelekile ukuba uzive umzimba ubuhlungu kangangesithuba seentsukwana. Kufuneka usixelele xa ufumana nayiphi na ingxaki ngenxa yokuzilolonga. Sicinga oko kuyaksinceda ngenxeni yokuba sisazi okokuba ukuzilolonga kukulungele. Abasebenzi abaphangelela oluphango bonke baqeqeshiwe kwezemithambo-lonto ithetha ukuba bayayiqonda ukuba umzimba usebenzanjani na kwaye okukuzilolonga kuncedisana kanjanina nomzimba ukuze usebenze kakuhle.

Ingaba ithethukuthi ndakuziva ngcono xa ndivuma?
Ukuba uyavuma uyakufumana ingcaciso mayelana nesifo sephepha kwakunye nemithambo. Xa usenza eziklasi zokuzilolonga siyazi ukuba ukuzilolonga kusempilweni ukudlula ungazilolongi kwantlobo. Silindele ukuba uzive ngcono kunyangolwakho lwesifo-sephepha. Kwakhona asazi nokuba lenkqubo yemithambo iyakuthi yongeze nalo naluphi na uhlobo lwenzuzo kwaye kukho yiyo lonto sisenza oluvavanyo koluphando

Kumele ndibhatale? Okanye nina nakundibhatala?

Akumelanga kuhlawula ukuzibandakanya neziklasi. Ukuba uyavuma ukuzibandakanya, sakunikeza ikhulu elinanamashumi amahlanu eerandi (R150) ukukubulela ngexesha lakho kwakhona ukubhatalelela iindleko zakho zokukhwela. Wonke umntu oza kuba ezokwenza uvavanyo lokuvuthela, uvavanyelo lokwenyuka usehla kwakunye nokuxilongwa isifuba, bonke abo bayakufumana ikhulu elinamashumi amahlanu eerandi (R150)ngokwelizwi lombulelo. Ukuba siyakucela ukuba uzibandakanye neziklasi zemithambo kunokuba ubekuluhlu lwabantu abazakulinda, sakubhatala iKhulu leerandi (R100) maxa onke usiza eklasini.

Ingaba ikhona enye into endinokuyenza xa ndingafuni ukuzibandakanya?

Kwakufuneka okokuba uqhubekeke nazo zonke iipilisi/amayeza akho owanikwe ngu-Gqirha. Logama ungazukuzifumana iiklasi zemithambo, sakunika ingcaciso mayelana nohlobo lwemithambo onokuyenza ekhaya ekunokwenzeka ikuncede.

Ukuthatha inxaxheba ngokuzithandela

Uyakuthatha inxaxheba apha koluphando ngokuzikhethela/ ukuzithandela, kwaye akhobani uyakukucenga okanye akugunyazise kwaye akunyanzeleki ukuba uzibandakanye xa ungafuni.

Ilungelo lokurhoxa kuphando

Nasekubeni bokuba uvuma ukuzibandakanya nophando, unalo ilungelo lokurhoxa kuphando nangaluphi na ixesha ufuna, ungadanga ube unikeze sizathu. Akunyanzelekanga ukuba ucacise sizathu kubaphandi. Uzoqhubeka ufumana unyango kwakho oluqhelekileyo apha ekliniki naxa ungasaziva ufuna ukuqhubekeka noluphando.

Imfihlelo:

Ubume bakho bokungaziwa bakuhlala buyimfihlo. Inombolo liyakuthi ibekwe kwifomu yesivumelwano nganye okanye ifomu yesivumo ngasinye, emveni kokuba ifomu yesivumelwano siyifumene, ubuni bomntu ngamnye awuzukwaziwa ngabo. Endaweni yoko abathathi-nxaxheba bayakwaziwa ngokwenombolo. Ngoko ke akusoze kubelula kubaphandi ukuba bayamanise impeendulo zabantu okanye ubani xa kusetyenziswa oluhlobo.
Zonke inkcukacha zizokugcinwa kwaye zisetyenziswe kwifaiyile zekhompyutha ekhuselekileyo, kwaye ngabaphandi bodwa abazokufikelela kuyo. Xa kugqityiwe ngoluphando, ezinkcukacha zakugcinwa ngokwefolida yophando ekhuselekileyo.

Ukubhatala/ Isinxephezelo kwakunye nonyango kwiimeko apho kukho umenzakalo okanye ukugruzuka.

Ukuba abathathi-nxaxheba bathi bafumane nakuphi na ukuziva ngokungathi banesiyesi, maxa wambi ibengathi nentloko le iyajikeleza okanye ukuziva uminxeka ibengathi nomphefumlo lo uphela okanye uyavaleka nokunqam-nqamka kwawo, abaphandi baqeqeshiwe kulemiba yezokuphefumla ukusiphuphula ezimpawu-nezombonakalo. Lenkqubo yoluphando ikhuselwe ngokokhuseleko lwe-inshorensi ipolisi ethathwe yi-Dyunivesiti yase-Kapa ukuba uthe wabe ufumana umenzakalo ngokwasemzimbeni ngenxeni yokuba uthatha inxaxheba koluphando. Umntu lowo uthatha imiqathango ngokugunyaziswe luphando: uyakuthi abhatalele zonke iindleko ngokugunyaziswa luhlobo ebekumele ukuba unyangwa ngalo ngokwasemzimbeni ngokomenzakalo lowo, ngokunxulumene nendlela eyiyo yelo Mzantsi-Afrika, ejongene nohlobo kwanendlela eyiyo yokusebenza ngohlobo olululo kwanemiqathango emiselweyo ka-2006 (ngokumiselwe kutshanje) ngokujoliswe kwi- Ndibaniswelwano yama Britani yeenkampani ezinkulu zezonyango nemiqathango. Umhawuli ogunyazisiweyo ngokophando uyakubhatala ngaphandle kokuba ubenesiqinisekiso sokuba uphando lulo olubangele umonzakalo kuwe ngokwasemzimbeni. Ungabuza uGqirha

wophando okanye ucele uGqirha wophando iphetshana ngokwalemigqaliselo okanye imiqathango. Umhlawuli ogunyazisiweyo ngokophando akawuhlawulela umonzakalo, okanye umqruzuko ukuba ngexesha lophando wena uye wa:

- Sebenzisa amayeza okanye imithi okanye wathatha amachiza angavumelekanga okanye angagunyaziswanga.
- Okanye awulandelanga imiqathango ka-Gqirha.
- Okanye awumxelelanga uGqirha wophando ukuba wena ufumana imiphumela emibi kumayeza okanye iipiisi zophando.
- Okanye akukhange uthathe unakekelo oluqiqiweyo wena ngokunokwakho ngokunxulumene namayeza akho ophando.

Ukuba uye wonzakala kwaye umhlawuli wabhatalela iindleko zezonyango eziyimfuneko, ngokwesiqhelo uyakucelwa ukuba wamkele ukuba umhlawuli ogunyazisiweyo ngokophando uzenzile iintlawulo ezigcweleyo zebango ngokwentlawulo zeendleko zempilo. Nangona, ukwamkela esisinunuso se-inshorensi ikukhavarishayo lonto ayiyithethi ukuba unikezela ngamalungelo akho okwenza ibango lakho labucala ngokwezinye izinto othe wabe uphulukene nazo ngenxeni yokungakhathali, ngokwenkundla yelo-Mzantsi Afrika. Kubalulekile ukulandela imiqathango kaGqirha wophando kwaye kuchazwe ngokonangoko ukuba unemiphumela emibi oyifumanayo ngokunxulumene namayeza ophando.

Nizakwenzantoni ngeziphumo zoluphando?

Iziphumo zophando ziyakufumaneka okanye zibhengezwe ngokomphathi wekliniki uberwetyeshekuwo. Kuyabonakala futhi okokuba iziphumo zalemithambo ngokweziklasi iyakuthi ibhalwe kwaye ithiwe pahaa/ ibhengezwe kwimagazini yezempilo. Ukuba uyafuna kuxhunyanwe nawe ngenjongo zokuba waziswe ngeziphumo zoluphando, ungaxhumana nomphandi okanye unikeze inombolo yakho kamakhala emkhukwini ukuze bakwazi ukuxhumana nawe.

Ngubani endinokuxhumana naye mayelana nengcaciso ephangaleleyo?
Abathathi-nxaxheba bangathi baxhumane nababantu balandelayo mayelana nengcaciso ephangaleleyo:

Mrs. Shamila Manie (primary investigator/researcher)
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Nkskz. Shamila Manie (Umphandi-Ongezantsi)

Okanye

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Okanye

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Okanye ungathi uxhumane Nabantu abajongene Nezemithetho mayelana nokuziphatha kwabezophando okanye lekomiti (HREC) ukuba unayo nayiphi na imibuzo ngokunxulumene namalungelo akho njengomthathi-nxaxheba.

Kuledilesi Ingezantsi.
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Website: www. Health.uct.ac.za/research/humanethics/forms

PARTICIPANT NO: _____	**PRP STUDY**	**HRECREF: 323/2017**
PARTICIPANT INITIALS: _____	**SITE: KHAYELITSHA SITE B/ MICHAEL MAPONGWANA**	

CONSENT FORM
Ifomu Yesivumelwano

Izindululo- ngokomthathi-nxaxheba

Ngokutyikitya apha ngezantsi Ndingu_____Ndiyavuma ukuthatha-Inxaxheba koluphando lusihloko sithi: Ukuphononongwa kwendlela imiphunga esebenzanyo engatshongokhona kubantu abadala abazizigulana ezinesifo-sephepha apho izinga lentsholongwane yesandulela-ngculazi lixhomile ngokwendlela zokuphila nangohlobo ezichaphazela imiphunga nokuqondiswa kongenelele lokuphucula lokusenza kweziphumo zayo.

Ndiyandululula ukuba: **Tick (√)**

1.	Ndiyifundile okanye ndafundelwa ifomu yesivumelwano kwakunye nephetshana lengcaciso kwaye ndafumana nethuba lokubuza nayiphina imibuzo ebendinayo.	
2.	Ndiyavuma ukuthatha inxaxheba koluphando. Isigqibo endisenzileyo sisesi sesam phaqa phecelezi esam. Ndiyavuma ukuba iziphumo zam ukuba zingasetyenziswa ngenxeni enxulumana nophando. Kwaye kwakhona ukuba iziphumo zingapapashwa.	
3.	Ndiyazi ukuba ndingarhoxa koluphando nangaliphina ixesha ngaphandle kokuba ndinikeze nasiphina isizathu.	
4.	Ndiyazi ukuba kukho amathuba angangeshumi elinesihlanu eepesenti wokuba ndingaqalisa kulenkqubo yozilolonga ngoku, kodwa kwangaxeshanye akwakhona namanye amathuba angangamashumi amahlanu eepesenti wokuba ndingaqalisha kamva nje.	
5.	Ndiyazi okukuba andizokwasi ukuzikhethela ukuba lenkqubo yozilolonga iqalenini.	
6.	Ndiyazi zonke iinkcukacha ngam, nkqu kwakunye nenkcukacha zam ngokwezempilo, zakugcinwa ziyimfihlelo/kwaye ngokusekhusini. Nditsho nokuba iziphumo zophando zingapapashwa okanye zibhengezwe ndiyayiqonda into yokuba andingekhe ndaziwe.	
7.	Ndiyayiqonda into ekumele ndiyenze ngokumayelana neemvavanyo kwaye nalenkqubo yozilolonga kwaye ndizimisele ukuzibandakanya noluphando kangangexesha lonyaka omnye, nasekubeni ukuba lenkqubo yozilolonga yeyethutyana elifutshane kunalena. Malungana nelixesha, ndakufumana utyelelo ngokokuhanjelwa kwaye iingcingo zemfono-mfono ziyakwenziwa ukulandelela ukujonga inkqubela phambili yam.	
8.	Ndiyayiqonda kungabakho izichenge koluphando nangona zincinci kwaye zifana nezo sithi sizifumane ngexesha lokuphila kwethu kubomi bemihlangemihla.	
9.	Ndichazelwe ukuba ndingahle ndifumane indzuzo ngokwenza lenkqubo yozilolonga. Akumelanga ndihlawule ngokwalenkqubo yozilolonga. Kwaye ndakuthi ndibuyekezwe ngexesha lam nangokusebenzisa imali yam xa bendikhwele isithuthi.	

_____ _____
Igama lomthathi-nxaxheba (aliprinte) kwakunye nesigitshala Umhla

_____ _____
Igama (nceda uliprinte kwaye utyikitye nesiginitshala) Umhla

PARTICIPANT NO: _____	**PRP STUDY**	**HRECREF: 323/2017**
PARTICIPANT INITIALS: _____	**SITE: KHAYELITSHA SITE B/ MICHAEL MAPONGWANA**	

Declaration by investigator

Izindululo-zomphandi

Mna (igama)…….. Ndenza isindululo sokuba:

- Ndiyininikile ingcaciso nolwazi olukoluxwebhu ku_____
- Ndimkhuthazile yena umfana /okanye intombi ngokukuko waqonda zonke iinkalo zophando, njengokuba zichaziwe apha ngasentla.
- Akhange ndimsebenzise umntu otolikayo. (Ukuba umntu otolikayo usetyenzisiwe ngoko ke lomntu utolikayo makasayine ifomu yesindululo ngezantsi.

Tyikitya (indawo) _____ **Ngomhla we**_____20__.

_____ _____

Isignitshara Yomphandi **Isignitshara Yengqina**

Isindululo Somtoliki

Mna (igama)…….. Ndifaka isindululo sokuba:

- Siyanikhuthaza / ngokwesini sobuduna nesikhomokazi ukuba nibuze imibuzo kwaye nithathe ixesha elaneleyo ukuphendula imibuzo leyo.
- Ndihambisa inyaniso engangxengwanga ngokwesihloko endisinikiweyo.
- Ndonelisekile ngokuba umthathi-nxaxheba uyakuqonda oku ngokugcweleyo ingxam yalefomu yesivumelwano salomqulu kwaye wanalo lonke ngokwesini sesiduna nesikhomokazi kwihlobo lemibuzo ethe yaphenduleka ngokwendlela eyiyo.

Ityikitywe (indawo)_____ (Ngomhla) we_____

_____. _____

Isignitshara Yetoliki **Isignitshara Yengqina**

Ukuba unganomnqweno wokuba kuxhunyanywe nawe ngeendlela zokuba waziswe ngemiphumela yoluphando, nceda usazise ngokuba usinikeze inombolo kamakhalemkhukhwini wakho okanye idilesi yakho ye-emaili._____

Appendix S: Modified Clinical Research Form (CRF) for Study 3

Folder no. **Height:** **Weight:**

DEMOGRAPHIC DATA

Address:

Date of Birth:
DD MM YR

Contact no.:
Alternate contact no.:

Gender Male Female

MEDICAL HISTORY

Do you have or has the doctor ever said you have one of the following diseases: **Tick all that apply:**

Hypertension
Diabetes Type 1
Diabetes Type 2
Angina/***heart disease***
Any other medical condition not listed above?

_____

SOCIO-ECONOMIC INFORMATION:

Tell me about the house you live in: **Tick all that apply:**

1. Brick house
2. Shack /backyard dwelling
3. Electricity
4. Amenities inside the dwelling (running water, flushing toilet)
5. Amenities outside the dwelling (running water, flushing toilet)
6. Bucket toilet outside of house

How many people on average sleep in your house per night, in the last month?

Tick all that apply:

Do you cook in your home using:
Wood/coal/dung
Paraffin
Gas
Electricity

If yes to the 1st two, for how many years?

What level of schooling did you complete? **Tick (√) one only:**

1. Primary school (or less than Std. 5/Gr. 7)*
2. High school (or less than Std. 10/ Gr. 12)*
3. Diploma course
4. University degree
5. None

note which grade completed

Employment **Tick (√) one box only**

10. Employed full time
11. Employed part-time
12. Self-employed
13. Currently unemployed, looking for work
14. Not working because of poor health
15. Full time house person
16. Full time student
17. Pensioner
18. Other

Is your workplace very dusty? Or does your work entail a lot of dust?

What kind of work do you do?

How long have you been doing this current job?

SMOKING HISTORY

Do you smoke/use: **Tick (√) all that apply**

	Current	Ex-smoker	Never	No. of yrs
8. Tobacco products (cigarettes, cigars, pipe)				
9. Recreational drug user (TIK, dagga, mandrax)				

Age or year you started smoking
Age or year you stopped smoking
How many cigarettes etc. do you smoke a day
*Pack year calculation

TB INFORMATION

	DD	MM	YY
Date of diagnosis			
When did you start your TB treatment?			
When are you due to complete your TB treatment?			

	1	2	3 or >
No. of previous TB episodes? Tick			

Year of previous TB episodes.

HIV INFORMATION			
HIV status (mark applicable with an **X**)	positive	negative	unknown
Date of diagnosis	DD	MM	YY
ART status (mark applicable with an X)	Current	Previous	Never
Last Viral Load		date	
Last CD4 count		date	

Appendix T: Screening for Eligibility Information and Consent Form

Good day

My name is Shamila Manie. I am a student at the University of Cape Town. As part of my studies I must do some research. This letter is to tell you about what I am doing and how you can possibly help me.

I am trying to find out if people that are being treated for TB (sometimes they have HIV as well) might feel better if they **have some exercise classes**

Why are we doing the study?

We know people with TB can have a problem with how well their lungs work. Normally you get pills to make the TB better. I want to see if taking the pills and doing some exercises to make the lungs and body stronger will make you feel better. It doesn't matter if you are only taking pills for TB; or if you have other things that you take pills for, like HIV or diabetes.

What kind of people can join the study?

We are approaching people like you who have been told that they have TB in their lungs only. It doesn't matter if you had TB in your lungs before. But before I can ask you to think about joining my study I have to know where in your lungs you have TB and if it will be safe for you to join and participate in **exercise classes /exercise programme.**

What does screening for eligibility mean?

It means that we want to make sure that your TB is only in your lungs by taking a chest x-ray (a picture of your lungs) and that before we ask you to think of joining us in our study we want to be sure that it will be safe for you to do so.

That is why we are asking your permission to take a chest x-ray which you've probably had done before so you know it is not sore. **The chest x-ray will be taken at Ubuntu Site B clinic, so you won't have to wait in a queue to have it taken**. Also we want to ask you a few questions about your general health to make sure that it would be safe for you to **participate in exercise classes** if you were given the opportunity to do so as part of our study. **Some of the questions regarding your health you may not know or be sure of the answers exactly and so we would need to look at your medical folder.**

What happens next?

If you agree, a chest x-ray will be taken to see if and how your lungs have been affected. We will assist you in filling out a form that tells us if it is safe for you to do lots of exercise.

If the chest x-ray shows you have at least one area in your lung that has been affected by the TB and that the questions you answered says that you are safe to do exercises, then we will ask you to think about joining our study where you may or may not participate in exercise classes to see if it could help patients feel and get better.

Do I have to pay for the chest x-rays? Will you pay me?

You do not have to pay for the chest x-rays. You will also not have to wait in a long line to have it taken as we have our own x-ray machine. It will take less than 5 minutes of your time and we will be able to tell you what it says immediately. If you agree to join, we will give you R100 to thank you for your time and to pay towards your transport costs even if we do not ask you to consider joining our research study.

Voluntary participation

You will be taking part in this study out of your own free will and do not have to join if asked if you don't want to.

Right to withdraw from study

Even if you do agree to join the study, you have the right to withdraw from the study at any point, and for any reason. This reason does not need to be explained to the researchers. You will still receive your normal treatment at the clinic if you are not invited to join the study or if you do not wish to continue in this study.

How will I benefit from agreeing to be screened?

You already know that you have TB, but having the chest x-ray will show you if your lungs have been affected a lot or only a little. The questions that we ask you regarding your health will also help you to know if you have any possible heart problems that you may not have been aware of. Having a x-ray taken does expose you to some radiation but this is very little and therefore there is very little risk of any negative side effects.

Confidentiality

Your identity will remain strictly confidential. A number will be placed on each consent form and after the consent is obtained, the individual identity of a person will no longer be referred to. Instead, the participants will be referred to by a number. It will not be possible for researchers to link personal responses to individual identities when using this method.

All data will be processed using password protected computer files and only researchers will have access to the data. Upon finishing the study, data will be stored in a password-protected folder.

CONSENT FORM

Declaration by participant

By signing below, I _____ **have agreed** to be screened for eligibility to take part in this research study entitled: **Assessment of lung function abnormalities in adult patients with tuberculosis in a high HIV-prevalent setting and the impact of a pulmonary rehabilitation intervention to improve functional outcomes**.

I declare that:

		Tick (√)
1.	I have read/had read to me this Information Sheet and consent form and had the opportunity to ask any questions I may have.	
2.	I agree to be screened for possible participation in this research study. The decision I have made is completely my own.	
3.	I know that if my chest x-ray shows that I have at least one are affected and that I am safe to participate in an exercise class I will be asked to join the research study. **If I so wished to join the research study there is a 50% chance I can start an exercise programme now, but also a 50% chance I will only be able to start it later if the exercise class has shown to be helpful.**	
4.	I understand that if my chest x-ray does not show any area affected then I will not be asked to join the study but will still receive reimbursement for my time and travel cost.	
5.	**To the best of my knowledge I do not have asthma, heart disease or any other lung disease other than TB and that I have not had any recent severe chest trauma (last three months), or recent history of pneumonia (one month prior to screening)**	
6.	**I have been explained as to why information from my medical folder may be needed and give permission for it to be used.**	
7.	I know all the details about me, including medical information obtained from my medical folder, will be kept private. Even if the results of the study are published, I understand that I will not be identifiable.	
8.	I understand that the risks involved having a chest x-ray as part of the screening process is minimal.	
9.	I have been informed that I may be asked to join the study and that I may possibly benefit from doing the exercise programme. I do not have to pay for the exercise programme. I will be reimbursed for travel and time for my participation.	

_____ _____

Participant's name (please print) and signature Date

_____ _____

Witness name (please print and sign) Date

Appendix T_1: Screening for Eligibility Information and Consent Form

Imini Entle

Igama lam ndinguShamila Manie. Ndingumfundi kwi-Dyunivesiti yaseKapa. Kwinxalenye yezifundo zam kufuneka ndenze uphando. Lencwadi ingokuxelela ukuba ndenza ntoni na kwaye wena ungandinceda njani na.

Ndizama ukufumanisa ukuba abantu abanyangelwa isifo sephepha (maxawambi babe bephila kunye nentsholongwane kagawulayo (HIV) kwaxeshanye) kungenzeka bazive ngcono xangabe benokungenela iiklasi yozilolonga.

Kutheni sisenza oluphando nje?

Siyazi ukuba abantu abanesifo sephepha banganengxaki kangangohlobo imiphunga yabo esebenza ngayo. Ngokwesiqhelo ufumana iipilisi/amayeza ukwenza isifo sephepha sibengcono. Ndifuna ukujonga ukuba ukuthatha iipilisi kwakunye nokuzilolonga ukwenza imiphunga kwakunye nomzimba, womelele oko kungakwenza uzive ngcono na. Akukhathaliseki nokuba uthatha iipilisi zesifo sephepha na okanye unazo ezinye izinto othathela zona iipilisi, njenge sentsholongwane kagawulayo (HIV) okanye isifo seswekile.

Ngabantu abanjani abanokungenela oluphando?

Sikhangela abantu abantu abafana nawe abachazelweyo ukuba banesifo sephepha emiphungeni yabo qha.Akukhathaliseki nokuba wakhe wanaso isifo sephepha na kwilixa elingaphambili. Kodwa phambi kokuba ndibe ndingakubuza ukuba ucinge ngokuzibandakanya nokungenela oluphando kumele ndazi ukuba isifo sephepha sindawoni kanye kwimiphunga yakho na,kwaye ndibone ukuba kukhuselekile na ukuba uthathe inxaxheba kule klasi/kulenkqubo yokuzilolonga.

Ithetha ukuthini into yokuvavanyelwa ukuba ululungelena uphando?

Lento ithetha ukuthi sifuna ukuqiniseka ukuba ngenene nangenyaniso isifo sakho sephepha ingaba sisemiphungeni qha na ngokuthi senze uxilongo lwesifuba (umfanekiso wemiphunga) yakho. Kwaye kwakhona phambi kokuba sikubuze, ukuba ucinge ngokungenela oluphando sifuna ukuqinisekisa ukuba kuyakukhuseleka kuwe ukwenza oko.

Kungoko ke sicela imvume kuwe ukuba wenze uxilongo lukagesi lwesifuba ekunokuba sele ulwenzile kwixesha langaphambile. Ngoko ke uyazi ukuba akukho buhlungu. Oluxilongo lukagesi lwesifuba luzakwenzelwa apha kumtholampilo ngokuba yi-Ubuntu apha eSite-B, Ngoko ke awuzukulinda mgceni xa uzakwenza oluxilongo. Kwakhona sifuna ukubuza imibuzo embalwa mayelana nemeko yakho yezempilo ukuze siqinisekise okokuba kukhuselekile kuwe ukuthatha inxaxheba kuleklasi yezemithambo ukubangaba ubulifumene ithuba lokwenzanjalo njengenxalenye yophando lwethu. Eminye imibuzo ngokunxulumene nempilo yakho, ubungekhe wazi okanye uqiniseke ngeempendulo ezithenqo, ngoko ke kuzakufuneka sijonge ifolida yakho yezempilo.

Kuzakwenzeka ntoni okulandelayo?

Ukuba uyavuma, uxilongo lukagesi lwesifuba luzakwenziwa ukujonga ukuba kwaye imiphunga yakho iphazamiseke kangakanani na. Kwaye sizakuncedisa ukuzalisa uxwebhu oluzakusichazela ukuba kulungile na ukuba wenze imithambo eminintsi. Ukuba uxilongo lukagesi lwesifuba lubonisa ukuba une ndawana enye ubuncinane emphungeni wakho, ethe yabe ichaphazelekile sisifo sephepha kwaye nemibuzo oyiphendulileyo ithi ngokwenene ukulungele ukwenza lenkqubo yokuzilolonga, ngoko ke sizakucela ukuba ucinge ngokungenela oluphando lwethu apho uzakuthi okanye ungathabathi nxaxheba kweziklasi zemithambo, ukwenzela sijonge ukuba kunokunceda na izigulane ukuziva babengcono.

Kumele ndihlawule ukwenza uxilongo lukagesi lwesifuba? Okanye nakundibhatala?
Awumelanga kuhlawula ukwenza uxilongo lukagesi lwesifuba. Kwakhona awuzulinda migceni-mide ukwenziwa oluxilongo, kuba sinomatshini wethu. Oku kuzothatha imizuzu engaphantsi kwesihlanu lwexesha lakho, kwaye sakukuxelela ngoko nangoko ukuba iziphumo zithini na. Ukuba uyavuma ukuzibandakanya, Sakuthi sikunike Ikhulu Leerandi ukukubulela ngexesha lakho, kwakhona ukubhatalela iindleko zakho zothutho nangona uye wakhetha ukungazibandakanyi nophando lwethu.

Ukuthatha inxaxheba ngokuzithandela
Uzakuthatha inxaxheba koluphando ngokuzikhethela okanye ukuzithandela kwaye awunyanzelekanga ukuzibandakanya nathi xa ungafuni.

Ilungelo lakho lokurhoxa kuphando
Nangona uthe wavuma ukungenela uphando, unalo ilungelo lokurhoxa nangaliphina ixesha. Awunyanzelekanga unike isizathu kwabaphandi. Uzoqhubekeka ufumana unyango lwakho oluqhelekileyo ekliniki xa uthe wamenywa ukuba uzibandakanye koluphando, lonto ayizokutshintsha nokuba awufuni ukuqhubeka uzibandakanya koluphando.

Ukuba ndithe ndabendiyavuma ukuzivavanya, ndakuzuzantoni?
Nanjengoko sele usazi ukuba unesifo sephepha, kodwa ukwenza uxilongo lukagesi wesifuba, oko kuyakubonakalisa ukuba imiphunga yakho, ichaphazelekile kakhulu okanye kancinci. Imibuzo isikubuza yona ngokunxulumene nempilo yakho nawe izakunceda ekubeni ukuba wazi ukuba usengxakini yokubanengxaki yentliziyo mhlawumbe obungayazi. Ngoko ke ukwenza uxilongo lukagesi lwesifuba lungakwenza uchaphazeleke ngokwamaza athi abhebhetheke/ pilisi/igazi elithiwayo/uxilongo lukagesi/ okanye ukuchazelwa ukuba unesosifo kodwa lento yenzeka kancinci kakhulu kwaye kwakhona umonzakakalo omncinci kakhulu wemiphumela engekhoyo kwa-ubakho.

Imfihlelo
Ubuni bakho bugcinwa buyimfihlelo. Ukusuka apho inombolo iyakusetyenziswa ibekwe kwi-fomu yesivumelwano nganye, emveni kokuba isivumelwano sisifumene, ubuni bomntu ngamnye abuzukusetyenziswa, endaweni yoko, abathathi-nxaxheba bayakwaziwa ngenombolo. Akuzubalula kubaphandi ukuba bayamanise iimpendulo zomntu nobuni bayenabani na xa sisebenzisa oluhlobo. Zonke iingcombolo neenkcukacha xa zisetyenziswa kuzakusetyenziswa inombolo ekhuselekileyo ye-folida okanye icwecwe lengcaciso yesigune kwakhona ngabaphandi bodwa abayakufikelela kumthombo wolwazi nengcaciso yezigulana. Xa uphando sele lusondele emaphethelweni, ulwazi lwakugcinwa ngokwenombolo ekhusekileyo yefolida leyo yogcino lwemfihlelo zezigulana.

SCREENING CONSENT FORM
Izindululo ngoko Mthathi-nxaxheba

Ngoko Tyikitya ngezantsi Mna……Ndiyavuma ukuba ndivavanyelwe ukuba ndikulungele na ukuthatha inxaxheba koluphando Lusihloko: uphononongo lwemiphunga nendlela imiphunga esebenza ngayo engeyiyo kubantu abadala abanesifo-sephepha kwindawo apho izinga lentsholongwane yesandulela-ngculazi lixhomileyo kakhulu kwiindawo apho sisebenza kuzo nohlobo apho isifo-sephepha semiphunga singolulekwakhona kwaye kubekho ungenelelo lokuphucula eziziphumo zalemeko.

<u>Mna ndiyagunyazisa ukuba:</u>

		Tick (√)
1.	Ndiyavuma ukuba lengcaciso ekumqulwana wephetshana lengcaciso ndiyifundile kwaye nefomu yesivumelwano kwaye ndafumana nethuba lokubuza imibuzo ebendinayo.	
2.	Ndiyavuma okokuba ndingahlolwa kujongwe ukulungela kwam oluphando. Isigqibo endisenzileyo sesam buqu kwaye khange ndintlokothiswe ngaso.	
3.	Ndiyazi ukuba uxilongo lwam lukagesi lwesifuba lubonakalisa ukuba ndinawo kancinci amathuba okuba omnye wemiphunga yam abe uyachaphazeleka ukuba ndazi ndikhuselekile ukuthatha inxaxheba, kwiklasi yozilolonga ndakucelwa ukuba ndingenele uphando. Ukubangaba ndinqwenela ukuzibandakanya nophando, kukho amathuba angangamashumi amahlanu eepesenti amathuba okuba ndingaqala lenkqubo yokuzilonga ngoku, kodwa kwakhona amanye amathuba amashumi amahlanu eepesenti okuba ndingaqalisa kamva nalenkqubo yeklasi yokuzilolonga ibonakalise ukuba ingaluncedo.	
4.	Ndiyayiqonda ukuba uxilongo lukagesi wesifuba alubonakalisi nayiphi na indawo echaphazelekileyo ngoko ke anduzucelwa ukuba ndibeyinxalenye yoluphando kodwa ke ndakuthi ndibuyekezwe ngexesha lam nangendleko zam zokukhwela.	
5.	Ngokolwazi lwam lonke andinayo ingxaki yesifuba-ukuminxana kwesifuba, isifo sentliziyo okanye naso nasiphi na isifo semiphunga ngaphandle kwesifo-sephepha kwaye kwakhona kwaye kwakhona ukothusa okumaxhaphetshu kokuvaleka kwesifuba kutshanje (kwiinyanga ezintathu-ezidlulileyo) okanye imbali ngokwesifo semiphunga kwinyanga enye phambi kokuba ndivavanywe koluphando.	
6.	Ndicaciselwe ukuba kutheni ingcaciso kwi-folida yam yezempilo apho inofunekakhona kwakhona ndinikeze imvume ukuba ingasetyenziswa.	
7.	Ndiyazi ukuba zonke iingcombolo ngam, kubandakanya nengcaciso yam yolwazi lwam ngokunxulumene nemeko yam yezempilo oluthe lwabe lufun yenwe kwifolida yam yezempilo, lwakugcinwa luyimfihlo. Nasekubeni upapasho loluphando luthe lwabhengezwa. Ndiyayiqonda into yokuba sozendichazwe, kwaye ndakuhlala ndingaziwa.	
8.	Ndiyayiqonda ukuba umonzakalo obandakanywayo apha xa ndivavanyelwa ugesi wesifuba njengenxalenye yophando mncinci kakhulu.	
9.	Ndichazelwe ukuba ndingacelwa ukuba ndizibandakanye nophando kwaye kwakhona ndingathi ndizuze ngokuthathi nxaxheba kulenkqubo yemithambo. Anduzukuyibhatalela lenkqubo yemithambo. Ndiyakubuyekezwa ngexesha lam kwanokuthathi nxaxheba.	

_____ _____
Igama lomthathi-nxaxheba printa kwakunye nesiginitshara Umhla.

_____ _____
Igama-Lengqina (Nceda uprinte kwaye usayine) Umhla.

Appendix U: TB Pamphlet Western Cape

TUBERCULOSIS - KNOW THE FACTS

What is TB?

TB is an infection. It is caused by a germ called Mycobacterium tuberculosis. TB mainly affects the lungs, but can be found in any part of the body. TB is both preventable and curable.

How is TB spread?

- TB germs are spread from person to person.
- When a person with TB coughs, sneezes or spits, the TB germs get into the air.
- The germs stay in the air for a long time if there is no fresh air flowing through.
- Anyone who is in this space will breathe in the TB germs.
- Not everyone who breathes in the TB germs will get TB.

How does TB make you ill?

If your immune system is weakened, the TB germs that you have breathed in grow and you can become ill with TB.

Many things can weaken your immune system, including:

- HIV
- Lack of proper food
- Drinking too much alcohol
- Stress
- Cancer
- Diabetes Children have a weaker immune system and are also more likely to get TB.

The TB germs damage the lung and may cause holes in the lungs. This can make you cough, feel tired and have difficulty with breathing. You may sometimes cough up blood.

What would make you think that you have TB?

If you have any of these symptoms, you could have TB:

- A cough for longer than two weeks
- Night sweats (sheets wet with sweat)
- Chest pains
- Coughing up blood
- Loss of appetite
- Weight loss
- Feeling tired and weak.

TB in other parts of the body may cause pain in that area and weight loss.

If you have a cough for more than 2 weeks or any of these symptoms, please visit your nearest clinic as soon as possible for a free TB test.

How is TB diagnosed?

If you have these symptoms, we will test your sputum for TB

- We will give you 2 jars to cough into.
- Your sputum will be sent to the laboratory for testing.
- You will need to return in a few days for the results.
- We will also do a culture test if you had TB before. This result will only be back in about 6 weeks.

In children we use skin tests and chest x-rays to diagnose TB.

If you come to the clinic for a TB test, please return on the date you have been given for your TB test result.

What will happen if you have TB? If you are diagnosed with TB, you will receive TB treatment. TB treatment should be started as soon as possible.

TB is curable if you take all your TB treatment. Many important people like President Nelson Mandela and Archbishop Desmond Tutu had TB and were cured.

Taking TB Treatment

If this is the first time that you have TB, you will need to take treatment for 6 months. If you had TB before you will need to take treatment for 8 months.

- The tablets must be taken once daily from Monday to Sunday.
- If you had TB before you will also receive daily injections at the clinic from Monday to Friday for 2 months.

You can choose the place that is most convenient for you to take your tablets during the week:

- At the clinic
- From a community DOT supporter.
- At your workplace
- With support from a treatment partner

You will need to take tablets at home over the weekend.

Why is it important to complete the full course of treatment?

You need to complete the full course of treatment to kill all the TB germs and to be cured.
If you stop TB treatment too soon or don't take all your treatment:

- The germs start growing and you can get sick again
- You can develop drug resistant TB (MDR or XDR TB) which is difficult to treat
- You can die
- You can spread TB to those around you
- You may need to start the course of treatment all over again

How do TB and HIV go together?

HIV weakens the immune system and increases the chance of you getting TB.

TB treatment is the same whether you have HIV or not. If you have HIV you need other treatment as well as your TB treatment:

- Cotrimoxazole (Bactrim) tablets to lower your chances of getting other infections.
- A vitamin supplement (Pyridoxine).
- You will need antiretroviral treatment if your CD4 count is below 200.

We strongly recommend an HIV test for all our TB clients, so that we can provide all the care you need.

How can you help prevent the spread of TB?

- Cover your mouth and nose with your hand or your sleeve when you cough or sneeze.
- Do not spit on the ground.
- Open all windows and doors at home to allow the fresh air to flow through.
- If you think someone may have TB, make sure they go to the clinic for a TB test.

If you have TB, complete your full course of treatment. Ask your family to help you to complete the treatment. Help others with TB to complete their treatment.

Special care for children Young children (under 5 years of age) are at high risk of picking up TB from adults with TB.
Take all children under 5 years of age who have been in close contact with an adult with TB to the clinic. The clinic nurse will check if the child has TB. TB treatment will be provided if the child is found to have TB.

If the child does not have TB, the nurse will provide medicines to prevent TB.

Western Cape Government
Health
BETTER TOGETHER.

Appendix V: Intervention Exercise Programme

DESCRIPTION OF ACTIVITY	NO. OF REPS/DURATION
1. Breathing exercise Diaphragmatic breathing with upper limb flexion	1 min
2. March on the spot: Marching on the spot for 2 minutes while pumping your arms up and down in time with your steps. Keep elbows bent and fists soft	For 2 minutes
3. Heel digs: Place alternate heels to the front, keeping the front foot pointing up. Punch out with each heel dig. Keep the supporting leg slightly bent.	60 reps in 1 min
4. Knee lifts: Stand up straight, bring up knees to touch the opposite hand. Keep your tummy (abs) tight and back straight. Make sure that you keep supporting leg slightly bent.	30 reps for in 30 seconds (1 min)
5. Shoulder rolls While marching on the spot roll your shoulders forward 5 times and backwards 5 times. Let your arms hang loose by your sides.	2 sets of 10 reps (1 min)
6. Knee bends/squats Stand with feet shoulder-with apart and your hands stretched out. Lower yourself no more than 10cm by bending your knees.	10 reps (1 min)
7. Buttocks Kicks Standing up straight, kick your heel to your buttocks while walking forward and backwards.	1 minute
UPPER LIMB ACTIVITIES	
1. Jumping jacks	For 1 minute
2. Bicep curls *with resistance bands Standing tall with feet hip-width apart, place the resistance band under one foot, or two for more of a challenge. Keep your stomach flat and squeeze your bum. Hold the band with arms straight and by your sides, and palms facing out. Slowly bend from the elbow, raising your fists to your shoulders, keeping your elbows tucked in. Slowly lower the band down and repeat.	2 sets of 10 reps (1 min)
3. **Lateral raises *with resistance bands** Stand tall with feet hip-width apart. Place the resistance band under both feet. Keep your stomach flat and squeeze your bum.	2 sets of 10 reps

DESCRIPTION OF ACTIVITY	NO. OF REPS/DURATION
Hold the band in each hand, palms facing in, and arms straight by your sides. Slowly raise both arms, keeping them straight, up to shoulder height, taking care not to lift your shoulders. Slowly lower and repeat.	
4. **Triceps extension with resistance bands** – grab one end of the resistance band with your hand and then step on the other end of the band with your foot. Pull the band up over your shoulders and so that your elbows are pointed forward. Extend your arms upward until they are in a straight line and then bring back down to your shoulders.	2 sets of 10 reps
5. ¾ Press-up Place your hands underneath your shoulders with your arms fully extended, palms flat and fingers facing forward. Rest your knees on the floor. Bend at your elbows, lowering your chest down, no lower than 2 inches from the floor. Push back up and repeat.	2 sets of 10 reps
6. Rocket jumps Start position: stand with feet hip width apart, legs bent and hands on your thighs. Jump up, driving your hands straight above your head and extending your entire body. Land softly, reposition your feet and repeat. For more of a challenge, start in a lower squat position and hold a weight or a bottle of water in both hands at the centre of your chest.	2 sets of 10 * with 30 sec recovery march on the spot
LOWER LIMB ACTIVITIES	
7. Squats Stand with your feet shoulder-width apart and your hands down by your sides or stretched out in front for extra balance. Lower yourself by bending your knees until they are nearly at a right angle, with your thighs parallel to the floor. Keep your back straight and don't let your knees extend over your toes.	2 sets of 10 * with 30 sec recovery march on the spot
8. Lunges **Starting position**:-Stand in split stance with right leg forward and left leg back. **Action**-Slowly bend the knees, lowering into a lunge until both legs are nearly at right angles. Keeping the weight on the heels, push back into starting position.	2 sets of 10 reps
9. Back raises Lie down on your back and place your hands by your temples or extended out in front for more of a challenge. Keeping your legs together and feet on the ground, raise your shoulders off the floor	2 sets of 10 reps

DESCRIPTION OF ACTIVITY	NO. OF REPS/DURATION
no more than 3 inches and slowly lower down. Keep a long neck and look down as you perform the exercise.	
10.Stomach crunches Lie down on your back, knees bent and hands behind your ears. Keeping your lower back pressed into the floor, raise your shoulder blades no more than 3 inches off the floor and slowly lower down. Don't tuck your neck into your chest as you rise and don't use your hands to pull your neck up.	2 sets of 10
11.Step –up Using step, step up and off step for 1 minute. Followed by stepping up and off step from the side, while swinging both arms forward and backwards.	2 minutes with 30 sec recovery walking on the spot
12.Side-lying leg raise (buttocks and back) Lie on your right-hand side with your right knee bent at 90 degrees, and your left leg straight and in line with your back. Press your left fingers into the top of your buttock to keep your left hip slightly tilting forward. Raise your left leg as far as you can without letting your hips tilt back. Slowly lower to the starting position. Perform 8 to 10 times and repeat on the other side.	Perform *5 to 10 times and repeat on the other side. *at start of programme
13. One leg kick backs Place yourself on your hands and knees, with your knees under your hips and your hands under your shoulders. Keeping your right leg bent at 90 degrees, raise it behind you as high as you can, squeezing your buttocks. Lower to the starting position.	Repeat 8 to 10 times with each leg.
14. "Air cycling" Lie on your back with your hands on your temples- don't lift your head. Bend you legs towards you and raise them as if you were cycling.	Start with 30 sec and increase in increments of 10 seconds in week 3, 6 and 9
COOL DOWN (5 MIN)	
15. Stretches of large muscle groups: **Start in long sitting** -try to touch toes - Biceps stretch - Neck stretches- flexion/extension/rot and side flexion with participant providing self-stretch at end of movement **In standing:**	Hold each position for 20sec and repeat for left and right where applicable

DESCRIPTION OF ACTIVITY	NO. OF REPS/DURATION
-Gastrocnemius/calf stretches - quadriceps stretch	
16. **Deep breathing exercises** with arm movements -from neutral to full flexion with inspiration and return to neutral on expiration	X 5 times

Appendix W: Rate of Perceived Exertion with Modified Borg Scale

The Modified Borg scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (maximal)

At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: “Please grade your level of shortness of breath using this scale.” Then ask this: “Please grade your level of fatigue using this scale.”

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

Appendix X: HREC Approval Letter – Study 3

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

24 July 2017

HREC REF: 323/2017

Prof S Amosun
Department of Health & Rehab Sciences
F-45
OMB

Dear Prof Amosun

PROJECT TITLE: THE ASSESSMENT OF LUNG FUNCTION ABNORMALITY IN ADULT PATIENTS WITH TUBERCULOSIS IN A HIGH HIV PREVALENT SETTING AND THE IMPACT OF A PULMONARY REHABILITATION INTERVENTION TO IMPROVE FUNCTIONAL OUTCOMES (PhD-candidate-S Manie) sub-study linked to 725/2015

Thank you for your response letter dated 10 July 2017, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student, S Manie will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC; the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 323/2017

Appendix Y: PACTR Approved – S Manie Tuberculosis Prospective

27 June 2017

To Whom It May Concern:

RE: Impact of a pulmonary rehabilitation intervention to improve lung function and functional outcomes of TB patients in a high HIV-prevalent setting.

As project manager for the Pan African Clinical Trial Registry (www.pactr.org) database, it is my pleasure to inform you that your application to our registry has been accepted. Your unique identification number for the registry is **PACTR201706002153458**

Please be advised that you are responsible for updating your trial, or for informing us of changes to your trial.

Additionally, please provide us with copies of your ethical clearance letters as we must have these on file (via email, post or fax) at your earliest convenience if you have not already done so.

Please do not hesitate to contact us at +27 21 938 0835 or email epienaar@mrc.ac.za should you have any questions.

Yours faithfully,

Elizabeth D Pienaar
www.pactr.org Project Manager
+27 021 938 0835

THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL
Cochrane South Africa | PO Box 19070, Tygerberg, 7505
Tel: +27 (0)21 938 0438 | Email: cochrane@mrc.co.za | Web: www.southafrica.cochrane.org

Appendix Z: Good Clinical Practice GCP Certificate 2017

Good Clinical Practice Certificate 2017

This is to certify that

SHAMILA MANIE

REGISTRATION NUMBER: PT 0062200

Successfully completed the following *Level 2* course

The above-mentioned practitioner qualifies for 21 CEUs of which 8 are Ethics CEUs

Good Clinical Practice: Beginners' Course

GCP Beg/2017

Facilitator: Dr. HD Geldenhuys

Date: 06 & 07 April 2017

CREDE
Clinical Research Education and Development

Teaching Clinical Research to All

Accredited by SMLTSA appointed by the PBMT HPCSA: MT-17/002

"This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors."

This certificate is valid for 3 years.

Appendix AA: Additional Data

Analysis of step count at various assessment points in relation to number of previous TB episodes and Lung function

Steps		**Control group**			**Intervention group**		
Baseline	**No. of previous TB episodes**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	0	15	94	68-142	12	132,5	76-155
	1	8	61,5	33-124	5	117	60-128
	2	4	75	57-93,5	9	115	88-142
	3	0			1	141	141
	Total	27	79	42-134	27	117	84-154
6 weeks	**No. of previous TB episodes**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	0	11	128	72-181	10	185,5	120-200
	1	7	68	56-142	2	207,5	162-253
	2	3	68	68-155	7	150	92-169
	3	0			1	289	289
	Total	21	99	68-143	20	168,5	115,5-199
12 weeks	**No. of previous TB episodes**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	0	10	146	112-173	8	170,5	139-226
	1	7	120	104-150	2	109	163-201,7
	2	4	119,5	86-172	6	167	116-189
	3	0			1	211	211
	Total	21	128	109-166	17	167	147-215

Comparison of means for number of steps by number of previous TB episodes at various timepoints comparing IG and CG

No. of previous TB episodes	**Baseline p-value**	**6-weeks p- value**	**12- weeks p-value**
0	0.4440	0.1055	0.1378
1	0.4165	0.0124	0.0452
2	0.1625	0.2579	0.3170
3			

Analysis of step count at in relation to Lung function classification

Steps		Control group			Intervention group		
Baseline	**Lung Function**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	Normal lung function	14	78,5	42-142	11	115	62-161
	obstructive disease	5	72	68-78	9	123	110-142
	Total	19	78	42-130	20	120	86-157,5
6 weeks	**Lung Function**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	Normal lung function	16	113	68-143	16	185,5	155-201
	obstructive disease	4	70	58-119	4	115,5	101,5-141
	Total	20	90	68-143	20	168,5	115,5-199
12 weeks	**Lung Function**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
	Normal lung function	14	129	170	13	167	154-215
	obstructive disease	6	137	166	4	177	134-209
	Total	20	129	168	17	167	147-215

Comparison of means for number of steps by lung function at various timepoints comparing IG and CG			
Lung function	Baseline p value	6 weeks p value	12 weeks p value
Normal lung function	0.2800	0.0014	0.0240
Obstructive disease	0.0348	0.3202	0.2181

Association between lung function and SGRQ						
Lung Function	Odds Ratio	Std. Err.	z	P>z	[95% Conf. Interval]	
Symptoms score	1,006	0,010	0,59	0,552	0,987	1,025
Activity score	1,002	0,012	0,17	0,865	0,978	1,026
Impacts score	0,965	0,036	-0,97	0,333	0,897	1,037
Total score	0,997	0,022	-0,12	0,904	0,956	1,041