THE BURDEN OF CHRONIC RESPIRATORY DISEASE IN THE WESTERN CAPE

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DEDICATION

I dedicate this work to my husband, Neil, and my son, Oliver.

Thank you for your constant love and support, and for giving me the time needed to complete this dissertation.

DECLARATION

I, Emma Claire Carkeek (CRKEMM001), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Date: 12/03/2018

ABSTRACT

Chronic respiratory disease (CRD), comprised mainly of asthma and chronic obstructive lung disease (COPD), is responsible for significant morbidity and mortality worldwide. Although asthma and COPD cannot be cured, they can be controlled using appropriate medications. Poorly controlled CRD is associated with significantly poorer quality of life and mortality for patients, an increased burden on the healthcare system, and a negative economic impact due to loss of productivity. CRD is underdiagnosed, undertreated and poorly controlled, especially in low- and middle-income countries. Improving control of CRD would result in improved quality of life for patients and a reduced burden on the healthcare system and economy. Despite the increase in burden of CRD globally, limited data are available on the burden of CRD in South Africa. Such data are essential if appropriate measures are to be put in place to address these needs.

In this mini-dissertation, I aimed to describe the symptomatic burden of disease and levels of treatment in adults with CRD attending primary healthcare facilities in the Western Cape. Additionally, I aimed to identify predictors of both the quality of life and receipt of treatment in this population.

This study was a secondary analysis of the baseline data collected during the Primary Care 101 (PC101) trial, a large pragmatic cluster randomised controlled trial conducted in 38 primary healthcare clinics in the Eden and Overberg districts of the Western Cape between 2011 and 2012. The study population for the current study was limited to the 1 157 participants enrolled in the CRD cohort of the PC101 trial.

Part A of this mini-dissertation comprises the research protocol which was submitted to, and approved by, the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee.

Part B comprises the literature review, which outlines the prevalence and increasing burden of CRD both globally and in South Africa. As demonstrated in many studies from a wide variety of countries, the literature supports that CRD is underdiagnosed,

undertreated, and has a significant impact both on affected individuals as well as healthcare systems and economies.

Part C includes the journal-ready manuscript. Findings confirm a high burden of symptoms and activity limitation, indicating a poor quality of life amongst this population. Findings also suggest undertreatment, with 40% of patients not receiving treatment for CRD despite being symptomatic. More respiratory symptoms were associated with male sex, a positive screen for depression, previous tuberculosis, previous smoking, more activity limitation and current receipt of treatment for CRD. Greater activity limitation was associated with unemployment, diabetes, a positive screen for depression, more respiratory symptoms, recent hospital admission and receiving treatment for CRD. Participants were more likely to be on treatment if they were older, more symptomatic or had greater activity limitation due to their respiratory condition. Treatment was less likely in participants who screened positive for depression, were current smokers, had increased recent clinic visits or a recent hospital admission.

In summary, we found a high burden of symptoms and activity limitation, and of undertreatment, possibly contributed to by under-recognition of respiratory disease among patients attending primary care clinics in the Western Cape. Depression, a history of previous tuberculosis and unemployment are common features in such patients. Potential interventions are to introduce a systematic approach to CRD diagnosis in primary care clinics that includes screening for depression, improving availability of essential drugs for the management of CRD, and preventive strategies such as more effective tuberculosis control, and support and pharmacotherapy to assist smokers to quit.

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ABBREVIATIONS

BOLD	Burden of obstructive lung disease
COPD	Chronic obstructive pulmonary disease
CRD	Chronic respiratory disease
DALYs	Disability adjusted life years
HIV	Human immunodeficiency virus
NCDs	Non-communicable diseases
OR	Odds ratio
PC101	Primary Care 101
PTB	Pulmonary tuberculosis
SGRQ	St George's Respiratory Questionnaire
TB	Tuberculosis
UCT	University of Cape Town
US	United States
USD	US dollar
WHO	World Health Organisation
YLDs	Years lived with disability
YLLs	Years of life lost
ZAR	South African rand

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PART A: PROTOCOL

A1. STUDY SYNOPSIS

The World Health Organisation (WHO) defines chronic respiratory disease (CRD) as 'chronic diseases of the airways and other structures of the lung', with the majority being asthma and chronic obstructive pulmonary disease (COPD).[1] CRD is responsible for significant morbidity and mortality worldwide.[2] In 2015, the estimated global prevalence of asthma was 358 million and 174 million for COPD.[3] The burden of CRD is increasing globally, with COPD increasing by 17% between 2005 and 2015, and asthma by 9.5%.[3]

Although asthma and COPD cannot be cured, they can be controlled using appropriate medications. Poorly controlled CRD is associated with significantly poorer quality of life and mortality for patients, an increased burden on the healthcare system due to increased utilisation of resources, and a negative economic impact due to loss of productivity and premature retirement from the workforce.[4,5] In general, and especially in low- and middle-income countries, CRD is underdiagnosed, undertreated and poorly controlled.[2,6,7] Improving control of CRD would result in improved quality of life for patients and a reduced burden on the healthcare system and economy.

Despite the increase in burden of CRD globally, there is a lack in data surrounding the burden of CRD in South Africa.[2,7] The WHO has developed a strategy for the prevention and control of CRD, with one of the objectives being 'better surveillance to map the magnitude of chronic respiratory diseases and analyse their determinants with particular reference to poor and disadvantaged populations, and to monitor future trends'.[8] Limited data are available on the burden of CRD in South Africa, and particularly on the availability and efficacy of measures to control them at healthcare provider level. Such data are essential if appropriate measures are to be put in place to address these needs.

The aim of this study is to describe the symptomatic burden of disease and levels of treatment in adults with CRD attending primary healthcare facilities in the Western Cape. The study also aims to identify predictors of both the quality of life and receipt of treatment in this population.

This will be a secondary analysis of data collected during the Primary Care 101 (PC101) trial, a large pragmatic cluster randomised controlled trial conducted in 38 primary healthcare clinics in the Eden and Overberg districts of the Western Cape between 2011 and 2012. The primary objective of the trial was to test the effectiveness of the PC101 programme in improving management of non-communicable diseases at a primary healthcare level. The trial recruited four patient cohorts; comprising adult clinic attendees with hypertension, diabetes, CRD and/or a positive screen for depression. Some results of the study have been reported. The current analysis and report will be restricted to the CRD cohort.

There are minimal risks associated with this study other than the risk of loss of confidentiality. To prevent this, the dataset will remain anonymous and all data will be stored in password-protected files. There will be no direct benefits for participants in this study. However, findings of this study may inform policy and improve the management of CRD in primary healthcare facilities in South Africa, and reduce the burden and severity of CRD in the community.

A2. INTRODUCTION

The World Health Organisation (WHO) defines chronic respiratory disease (CRD) as 'chronic diseases of the airways and other structures of the lung', with the majority being asthma and chronic obstructive pulmonary disease (COPD).[1] Identified risk factors for CRD include exposure to tobacco smoke, air pollution, occupational chemicals and dusts, frequent lower respiratory tract infections in childhood and previous pulmonary tuberculosis (TB).[1] Although CRD is not curable, various treatments are effective in reducing symptoms, exacerbations and complications of disease, and in improving the quality of life and survival of people affected by these conditions.[1]

Non-communicable diseases (NCDs) are the leading cause of death globally, responsible for 65% of all deaths, with the majority of these occurring in low and middle-income countries.[4] CRD is now reaching epidemic proportions in many low-income areas around the world and is responsible for a significant amount of morbidity and mortality worldwide.[2] According to The Global Burden of Disease Study in 2015, the global prevalence of CRD is estimated to be 514 million, with the majority of these cases being due to asthma (358 million) and COPD (174 million).[3] The estimated number of years lived with disability (YLDs) globally in 2015 was 30 million for CRD overall, 15 million for asthma and 12 million for COPD. This placed asthma as the eleventh leading cause of YLDs globally and ninth in South Africa, with COPD as the fourteenth leading cause globally.[3] An estimated 3.8 million people died from CRD in 2015, with 3.2 million of these deaths due to COPD and almost 400 000 due to asthma.[9] COPD is currently the tenth leading cause of years of life lost (YLLs) globally, and fourth leading cause of YLLs amongst countries with a middle socio-demographic index.[9]

The Burden of Obstructive Lung Disease (BOLD) Study, conducted in 12 international sites, reported an estimated global prevalence of COPD Stage II and higher of 10.1% (11.8% for men and 8.5% for women).[10] The WHO's World Health Survey of 2002-2004 reported a global prevalence of doctor-diagnosed and/or receipt of treatment for asthma of 4.5% in 18-45 year olds.[4] However, 8.6% of subjects surveyed reported symptoms of asthma in the preceding 12 months.

The burden of CRD in South Africa has not been well documented.[2] The South Africa Demographic and Health Survey in 2003, based on self-reporting, reported an asthma prevalence of 3.1% in men and 4.4% in women over 15 years old.[2] For emphysema/chronic bronchitis, the reported prevalence was 2.0% in men and 2.6% in women.[2] However, in the BOLD study, the Cape Town site showed an overall COPD prevalence of 23.8% and a stage 2 or higher COPD prevalence of 19.1%, significantly higher than the study's global estimate of 10.1%.[11] The Cape Town study, performed in 2005, had the highest estimated prevalence rates of COPD amongst the 12 international sites included in the study.[11,12] The WHO's World Health Survey of 2002-2004 reported that amongst the 18-45 year olds surveyed in South Africa, 10-15% reported symptoms of asthma in the preceding 12 months, compared to the global average of 8.6%.[4]

The burden of CRD is increasing globally. Between 2005 and 2015, the prevalence of CRD increased by 12%, COPD by 17% and asthma by 9.5%.[3] The past 20 years have shown an increase in NCDs in South Africa, likely due to an increase in risk factors as well as an aging population due to demographic change.[2,7] This increase has been seen in both urban and rural populations, with an increased burden amongst poorer people living in urban areas.[2,7] Due to the overwhelming prevalence of communicable diseases in South Africa such as TB and HIV, the prevention, diagnosis and management of NCDs including CRD has previously been marginalised.[2] With antiretroviral therapy now widely available, mortality from HIV has declined and the burden of NCDs has increased and is expected to continue to do so.[2] The increase in NCDs results in an increased demand for chronic disease care and places further pressure and burden on the healthcare system.[2,7] Due to the burden and suffering associated with these conditions, the WHO has identified CRD, along with cardiovascular diseases, diabetes, and cancers, as a priority issue to be targeted by national governments.[4,13]

CRD, especially in low- and middle-income countries, is underdiagnosed, undertreated and poorly controlled.[2,6,7] Although effective medications for asthma have been available for many years, asthma remains poorly controlled with excessive hospital admissions and avoidable deaths still common.[4]

CRD has a significant impact on affected individuals as well as healthcare systems and economies. Acute exacerbations of COPD are associated with worsening of respiratory symptoms and functional limitation.[5] People with frequent COPD exacerbations have significantly poorer quality of life compared to those with less frequent exacerbations, and a higher rate of lung function loss.[5] Uncontrolled asthma reduces quality of life due to both the burden of symptoms and its effect on mental and social wellbeing. Asthma may affect a persons ability to work, resulting in increased emotional and financial stress.[4] Uncontrolled CRD places an increased burden on the healthcare system due to increased utilisation of resources such as clinician and emergency visits, hospitalisations and medications.[4] People with uncontrolled disease are less likely to be able to work, resulting in loss of productivity and an increased economic burden for a country.[4]

Although asthma and COPD cannot be cured, they can be controlled using appropriate medications, with early diagnosis and initiation of treatment resulting in improved outcomes.[4] The goal of treatment is to control symptoms and improve 'future risk', that is, to prevent acute exacerbations, further worsening of health status and the development of comorbidities, and to minimise activity limitation arising from the condition.[4] Appropriate treatment of COPD has been shown to reduce the frequency of acute exacerbations and to reduce the rate of deterioration in health status.[5] Well controlled CRD results in a decrease in burden at both a personal level as well as on the healthcare system and economy.[4]

In summary, CRD results in significant morbidity and mortality and can have a major impact at both an individual and a healthcare system level. CRD is underdiagnosed, inappropriately treated and poorly controlled. Controlling CRD would result in prevention of acute exacerbations, improved quality of life for patients and a reduced burden on the healthcare system.

Despite the increase in burden, data surrounding prevalence, treatment and control of CRD in South Africa are lacking.[2,7] The WHO has developed a strategy for the prevention and control of CRD, with one of the objectives being 'better surveillance to map the magnitude of chronic respiratory diseases and analyse their determinants with particular reference to poor and disadvantaged populations, and to monitor future

trends'.[8] More data is needed to establish the burden of CRD in South Africa so that appropriate measures can be implemented to improve management and control of these conditions.

A3. PURPOSE OF THE STUDY

a) Aim of the study

The aim of this study is to describe the symptomatic burden of disease and levels of treatment in adults with CRD in two districts of the Western Cape province. The study also aims to identify predictors of both disease-specific quality of life and receipt of treatment in clinic attendees with this diagnosis.

b) Specific objectives

1. To describe quality of life and levels of treatment in adults with CRD.

2. To examine differences in patient, demographic and socioeconomic characteristics between those receiving treatment and those who are not.

3. To identify patient characteristics associated with quality of life and receipt of treatment in adults with CRD.

A4. METHODOLOGY

a) Study design

This will be a secondary analysis of data collected during the Primary Care 101 (PC101) trial, a large pragmatic cluster randomised controlled trial conducted between 2011 and 2012 in primary healthcare facilities in the Eden and Overberg Districts of the Western Cape, South Africa. The main objective of the trial was to test the effectiveness of the PC101 programme in improving management of NCDs at a

primary healthcare level. The PC101 programme aims to improve the ability of clinicians (primarily nurses) to provide quality care to patients attending these facilities through use of a customised integrated patient management tool and training programme.[6] In the PC101 trial, four adult patient cohorts were recruited and enrolled; attendees with hypertension, diabetes, CRD and/or a positive screen for depression. The current study will analyse the data from the CRD cohort only.

b) Sample size

As this was a secondary analysis, a sample size calculation was not performed. In the PC101 trial, a separate sample size was calculated for each of the four cohorts, with treatment intensification being used as the primary endpoint for the hypertension, diabetes and CRD cohorts. Sample size calculations were for two-sided tests and were powered at 85%, with calculations being increased by 20% to allow for loss to follow-up during the trial. It was also taken into account that a large amount of co-morbidity was anticipated and participants with more than one condition were eligible for more than one cohort. The calculated required cluster size for the CRD cohort was 27 participants per clinic, resulting in a total required sample size of 1 026 participants. This target was met and, following recruitment, the total number of participants in the cohort was 1 157. The full respiratory cohort will be used for this analysis.

c) Study setting

The PC101 trial was conducted in public sector primary healthcare clinics in the Eden and Overberg Districts of the Western Cape, South Africa. Together, these districts have a population of approximately 800 000 people. For clinics to be included in the study, they needed to provide services for NCDs at least 5 days a week and report more than 10 000 clinic visits per year. Of the clinics in the Eden district, 33 met these criteria. To achieve the required sample sizes, this number was supplemented with an additional 5 clinics from the adjacent Overberg district to reach a total of 38 clinics. These clinics were mainly in medium-sized towns and rural areas, and were predominantly nurse-led with doctor support ranging from daily to sessional. Respiratory services offered included diagnosis and basic treatment of common respiratory conditions, with most clinics having access to peak flow meters and X-

rays, but not to spirometry. The populations served by these clinics are generally of poor socioeconomic status with high levels of unemployment. Clinics were randomised to receive both implementation and training in the use of the PC101 patient management tool (the intervention) or to continue with routine care (the control).

d) Study population

The study population of the PC101 trial consisted of adults with hypertension, diabetes, CRD and/or a positive screen for depression, accessing healthcare at primary care level facilities in the Eden or Overberg Districts of the Western Cape.

To be included in the CRD cohort, participants needed to have one of the following:

- Self-reported asthma, chronic bronchitis or emphysema on treatment, *or*
- Cough or difficulty breathing for more than 2 weeks and not on treatment for TB in the past 3 months

They also needed to be at least 18 years of age, able to actively participate in an interviewer-administered questionnaire, likely to stay in the same area for the duration of the trial and provide written consent to participate in the study. Patients were excluded if they did not meet the eligibility criteria or were judged unable to provide informed consent.

For the purposes of this study, no further inclusion or exclusion criteria will be applied.

e) Recruitment and enrollment

Recruitment for the PC101 trial was done by trained fieldworkers from local communities. Fieldworkers approached patients in clinic waiting areas and invited them to participate in the trial. Patients were screened in a private area in the clinic and, if they fulfilled the eligibility criteria and signed the consent form, were enrolled into the trial.

For the purposes of this study, the participants recruited into the CRD cohort of the trial will be used as the study sample and no additional recruitment or enrollment will occur.

f) Research procedures and data collection methods

In the PC101 trial, a trained fieldworker conducted a baseline interview with each participant immediately after enrollment. To allow for privacy, this interview was done in a separate room in the clinic with only the fieldworker and participant present. A standardised structured questionnaire was administered by the fieldworker and conducted in the participant's language of choice (English, Afrikaans or isiXhosa). The questionnaire included questions related to basic demographics, socioeconomic status, medical history, smoking history, current state of health, severity of symptoms and levels of healthcare utilisation. To assess quality of life in the CRD cohort, the St George's Respiratory Questionnaire (SGRQ) was used and scores were calculated for both the symptoms and activity domains. As there is no tested translated isiXhosa version of the SGRQ, participants completing the interview in isiXhosa were excluded from this section of the questionnaire. Baseline anthropometric measurements were taken from each participant, including blood pressure, weight, height and waist circumference. All questionnaire responses and measurements were entered by the fieldworker into an electronic hand-held device (netbook) at the time of the interview. Fieldworkers then collected all prescription data by photocopying prescription charts for the year preceding the baseline interview. This data was reviewed by the medically qualified trial manager who was responsible for identifying medications used to treat hypertension, diabetes, CRD and depression at the time of the interview.

Participants were re-interviewed 14 months after their baseline interview. Participants were reminded of their interviews with letters and text messages. Those who missed their interviews were traced by either a phone call or home visit. Similar questions were asked and the measurements repeated. The SGRQ symptoms and activity domain questions were repeated for participants in the CRD cohort, again excluding those who chose to complete the questionnaire in isiXhosa. Responses were again entered by the fieldworker into an electronic hand-held device. Prescription charts for

the previous 14 months were collected by the fieldworkers and were again analysed by the trial manager.

Fieldworkers were supervised to ensure quality control of the data. If unusual values were entered into the electronic device, alert messages were sent to the fieldworker to check and correct these if necessary. Data was monitored by the research team to identify unusual values or trends, and all prescription data was double entered.

For this study, a secondary data analysis will be performed using the data collected from the CRD cohort in the PC101 trial. No further primary data collection will take place.

g) Data management

An anonymous dataset will be obtained from the PC101 trial manager and used for secondary data analysis. For the purposes of this study, no knowledge of participant identity will be required. The data will be stored in a Microsoft Excel password-protected file and will not be shared with anyone not directly involved in this study.

h) Data analysis

Exploratory data analysis will look at the distribution and summary statistics of each individual variable. Categorical variables will be assessed using frequency tables. Continuous variables will be assessed using histograms as well as means and standard deviations for normally distributed data, and medians and interquartile ranges for data not normally distributed.

Simple associations between each of the outcome variables and the covariates will be assessed. Scatterplots and correlation analyses will be used for continuous variables, contingency tables for categorical variables, and box plots for one continuous and one categorical variable.

Baseline characteristics will be shown for the full CRD cohort, as well as by treatment status at baseline. Differences in characteristics between participants receiving and

not receiving treatment will be tested using univariate logistic regression models. Each model will include only the participant characteristic as the explanatory variable, with the outcome being treatment status, and will be adjusted for an effect due to the cluster sampling technique used.

Multiple linear regression models will be used to identify predictors of quality of life, with quality of life measured using the SGRQ symptoms and activity domain scores. Models will initially be built using a backward selection approach, with all covariates initially being included in the model. Covariates with a p-value of ≥ 0.2 will be removed in a step-wise approach and the model repeatedly re-fitted until a final model is identified including only statistically significant covariates. Using a forward selection approach, each of the dropped covariates will then be added back into the final model one at a time to ensure no significant predictors have been omitted. Multiple logistic regression models will be used to identify predictors of treatment, built using the same approach outlined above. All models will account for the cluster sampling method used.

Stata 13.0 (Stata Corporation, College Station, Texas) will be used as the statistical software package for all analyses. A level of significance of 0.05 will be used for all statistical tests.

A5. ETHICAL CONSIDERATIONS

The PC101 trial received ethics approval from the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC REF 119/2010). This approval has been renewed annually and is currently valid until 30 July 2017. Permission for recruitment and research to occur in provincial primary healthcare facilities was granted by the Western Cape Provincial Department of Health (Reference 18/19/RP152/2010).

Permission to use the trial data for this secondary analysis has been granted by a principal investigator of the trial. This study protocol will be submitted to both the School of Public Health Departmental Research Committee and the UCT Faculty of

Health Sciences Human Research Ethics Committee for approval of secondary data analysis as described in this protocol.

a) Risks and benefits

As this is a secondary data analysis, there are minimal risks associated with this study other than the risk of loss of confidentiality. To prevent this, only an anonymous dataset will be obtained from the trial manager. All data will be stored in password-protected files and will not be shared with anyone not directly involved in the study.

There will be no direct benefits for participants in this study. However, findings of this study may highlight the burden of CRD and identify factors associated with treatment and quality of life amongst adults with CRD. Identifying these associations may inform policy change with improved management of CRD, and a reduction in the burden and severity of CRD in the community.

b) Informed consent process

In the PC101 trial, all patients approached by fieldworkers in the clinic waiting areas were given a patient leaflet to read. These were available in English, Afrikaans and isiXhosa and a copy was given in the language chosen by the patient. Patients who were interested in participating in the trial were then screened by a fieldworker in a private area of the clinic, in the language of their choice (English, Afrikaans or isiXhosa).

A detailed patient information sheet was provided for patients found to be eligible for the study. The information sheet described the purpose of the study, possible risks and benefits of participation, an overview of the study procedure and confidentiality.

Patients that were eligible for the trial were informed of what the trial would require, including a structured questionnaire and basic anthropometric measurements done at both baseline and repeated after 14 months. Consent was requested to review hospital records in the case of admission, and for identity numbers to track vital status if

necessary. Only participants that agreed and signed the consent form were included in the trial.

As this is a secondary data analysis of an anonymous dataset, no individual consent will be obtained for this study. All participants included in this study have already provided informed signed consent to participate in the PC101 trial.

c) Privacy and confidentiality

To ensure privacy in the trial, participants were screened and interviewed in a private area of the clinic with only the participant and the fieldworker present. To ensure confidentiality, a unique patient identification number was assigned to each participant in the trial and this number was used on all datasets. All netbooks were locked in the clinic when not in use and all fieldworkers and members of the research team signed a confidentiality agreement.

For this study, an anonymous dataset will be obtained from the trial manager and no knowledge of participant identity will be required. Patient consent forms will not be reviewed for this study. The data will be stored in a Microsoft Excel password-protected file and will not be shared with anyone not directly involved in the study.

A6. REIMBURSEMENT FOR PARTICIPATION

The PC101 trial provided all participants returning for the follow-up interview with a cash voucher for a local grocery store to the value of ZAR100. This amount compensated for costs incurred to attend the follow-up interview. As this study will include secondary data analysis only, there will be no further compensation or reimbursement to participants.

A7. USE OF INFORMATION & PUBLICATION

The study findings will be collated in a journal-ready manuscript and submitted as the mini-dissertation component of the author's Masters in Public Health degree. The manuscript will also be submitted to a selected journal for publication.

A8. LOGISTICS

	Apr 2017	May 2017	Jun 2017	Jul 2017	Aug 2017	Sep 2017	Oct 2017
Literature review							
Data analysis							
Results							
Discussion							
Complete write-up							
Submission							

A9. BUDGET

This study will include only secondary data analysis which will be done by the author as the mini-dissertation component of the Masters in Public Health degree. Data analysis will be conducted in the author's own time and no funding will be required.

A10. CONFLICTS OF INTEREST

None.

A11. REFERENCES

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PART B: LITERATURE REVIEW

B1: INTRODUCTION

Chronic respiratory disease (CRD) is responsible for significant morbidity and mortality worldwide, with the burden increasing globally. Although CRD cannot be cured, it can be controlled using appropriate medications. Poorly controlled CRD is associated with a poorer quality of life for patients as well as an increased burden on the healthcare system and a negative economic impact. In general, and especially in low- and middle-income countries, CRD is underdiagnosed, undertreated and poorly controlled. Improving control of CRD would result in improved quality of life for patients and a reduced burden on the healthcare system and economy.

The aim of this literature review is to describe the prevalence and burden of CRD both globally and in South Africa, as well as to describe the underdiagnosis and undertreatment associated with these conditions and the consequences of poorly controlled disease.

B2: LITERATURE SEARCH STRATEGY

The Pubmed and Google Scholar online databases were used to search for relevant literature. Multiple searches were conducted using the terms ‘chronic respiratory disease’ or ‘asthma’ or ‘COPD’ with various combinations including ‘prevalence’, ‘underdiagnosis’, ‘undertreatment’, ‘quality of life’, ‘control’, ‘consequences’, ‘impact’, ‘productivity’, and ‘economic’. The search was restricted to English language publications, with no restrictions being placed on study design or year of publication. Titles of articles were scanned by the author, and abstracts of relevant articles reviewed. Full text of the studies relevant to the aim and objectives of the literature review were retrieved and reviewed. Any further relevant studies cited in these publications that were not retrieved in the database search were also reviewed. Further to the online database searches, reports by both national and international bodies were reviewed. These included the latest World Health Organisation (WHO) and South African Department of Health reports pertaining to CRD and non-communicable diseases. A small number of other documents were reviewed as recommended by supervisors, such as unpublished theses.

B3: SUMMARY OF LITERATURE

Definition of chronic respiratory disease

The WHO defines CRD as 'chronic diseases of the airways and other structures of the lung', with the majority being asthma and chronic obstructive pulmonary disease (COPD).[1] Identified risk factors for CRD include exposure to tobacco smoke, air pollution, occupational chemicals and dusts, frequent lower respiratory tract infections in childhood and previous pulmonary tuberculosis (TB).[1] Although CRD is not curable, various treatments are effective in reducing symptoms, exacerbations and complications of disease, and in improving the quality of life and survival of people affected by these conditions.[1]

The global prevalence of chronic respiratory disease

Non-communicable diseases (NCDs) are currently the leading cause of death globally.[2,3] In 2008, 36 of the 57 million deaths globally (63%) were due to NCDs with the leading causes being cardiovascular diseases (17 million), cancers (7.6 million), chronic respiratory disease (4.2 million) and diabetes (1.3 million).[3] Most of this burden is carried by low- and middle-income countries, with 80% of NCD deaths occurring in these areas.[3]

CRD is now reaching epidemic proportions in many low-income areas around the world and are responsible for a significant amount of morbidity and mortality worldwide.[4] According to The Global Burden of Disease Study in 2015, there are an estimated 514 million cases of CRD globally, with the majority of these being asthma (358 million) and COPD (174 million).[5] The estimated number of years lived with disability (YLDs) globally in 2015 was 30 million for CRD overall, 15 million for asthma and 12 million for COPD. This placed asthma as the 11th leading cause of YLDs globally and 9th in South Africa, with COPD as the 14th leading cause globally.[5] An estimated 3.8 million people died from CRD in 2015, with 3.2 million of these deaths due to COPD and almost 400 000 due to asthma.[6] COPD is currently the 10th leading cause of years of life lost (YLLs) globally, and 4th leading cause of YLLs amongst countries with a middle socio-demographic index.[6] CRD accounted

for 97 million disability adjusted life years (DALYs) in 2015, with COPD being the 12th leading cause of global DALYs and 3rd leading cause amongst those aged 65-79 years. Asthma was the 25th leading cause of global DALYs.[7]

The Burden of Obstructive Lung Disease (BOLD) Study, published in 2007, assessed the burden of COPD in high- and low-income countries. Conducted in 12 international sites and including 8 775 participants, the study reported an estimated global prevalence of COPD Stage II and higher of 10.1% (11.8% for men and 8.5% for women).[8]

Between 2002 and 2004, the WHO's World Health Survey measured the prevalence of asthma amongst 177 496 individuals between age 18 and 45 years living in 70 countries. They reported a global prevalence of doctor-diagnosed and/or receipt of treatment for asthma of 4.5%, however, 8.6% of subjects surveyed reported symptoms of asthma in the preceding 12 months.[2] The prevalence of asthma varied widely, with the highest figures seen in Australia, Northern and Western Europe and Brazil. There is little known about the prevalence amongst the middle-aged and elderly, due to both a lack in data as well as the difficulty in distinguishing asthma from COPD in older patients.[2]

The prevalence of chronic respiratory disease in South Africa

The burden of CRD in South Africa has not been well documented.[4] The South African Demographic and Health Survey in 2003, based on self-reporting, reported an asthma prevalence of 3.1% in men and 4.4% in women over 15 years old.[4] For emphysema/chronic bronchitis, the reported prevalence was 2.0% in men and 2.6% in women.[4] However, in the BOLD study, the Cape Town site showed an overall COPD prevalence of 23.8% and a stage II or higher COPD prevalence of 19.1%, significantly higher than the study's global estimate of 10.1%.[9] The Cape Town study, performed in 2005, had the highest estimated prevalence rates of COPD amongst the 12 international sites included in the study.[9,10] The WHO's World Health Survey of 2002-2004 reported that amongst the 18-45 year olds surveyed in South Africa, 10-15% reported symptoms of asthma in the preceding 12 months, compared to the global average of 8.6%.[2] Comparison of national age-standardized mortality rates for

asthma between 2001 and 2010 show much variation, with South Africa reporting the highest mortality rate of 280 per million population.[2] The second South African National Burden of Disease Study assessed mortality trends in the country from 1997 to 2012 and reported that, in 2012, COPD was the 3rd leading cause of death amongst Caucasians, 4th amongst Coloureds and 9th amongst Indians/Asians.[11] COPD also ranked as the 8th top cause of YLLs in both the Western and Northern Cape provinces, with 3.5% of years of life lost due to COPD in the Western Cape and 2.7% in the Northern Cape.

The increasing burden of chronic respiratory disease

The burden of CRD is increasing globally. Between 2005 and 2015, the prevalence of CRD increased by 12%, with COPD by 17% and asthma by 9.5%.[5] The past 20 years have shown a substantial increase in the burden of NCDs in South Africa, particularly due to cardiovascular diseases, diabetes, COPD and cancers.[4,11,12] This is likely to be due to an increase in risk factors for these conditions as well as a growing and aging population.[4,11,12] This increase has been seen in both urban and rural populations, with a larger burden amongst poorer people living in urban areas.[4,11,12] Due to the overwhelming prevalence of communicable diseases in South Africa such as TB and HIV, the prevention, diagnosis and management of NCDs including CRD has previously been marginalised.[4] With antiretroviral therapy now widely available, mortality from HIV has declined and the burden of NCDs has increased and is expected to continue to do so.[4] The increase in NCDs results in an increased demand for chronic disease care and places further pressure and burden on the healthcare system.[4,12] This increase in burden led to the development of the South African Strategic Plan for the Prevention and Control of Non-Communicable Diseases 2013-2017, which focuses on both primary prevention as well as and management of the high burden of NCDs and their risk factors.[13] Due to the burden and suffering associated with these conditions, the WHO has also identified CRD, along with cardiovascular diseases, diabetes, and cancers, as a priority issue to be targeted by national governments.[2,14]

The underdiagnosis and undertreatment of chronic respiratory disease

Chronic respiratory disease, especially in low- and middle-income countries, is under-diagnosed, under-treated and poorly controlled.[4,12,15,16] Although effective medications for asthma have been available for many years, asthma remains poorly controlled with excessive hospital admissions and avoidable deaths still common.[2]

Underdiagnosis has been demonstrated in many studies from a wide variety of countries. The PREPOCOL Study, a cross-sectional, population-based study conducted between 2003 and 2004 and including 5 539 participants over the age of 40 years, assessed the prevalence of COPD in five Colombian cities. Of those meeting the diagnostic criteria for COPD, 87.4% were undiagnosed.[17] Following the PREPOCOL Study, Gonzalez-Garcia *et al* assessed the prevalence and diagnosis of asthma amongst the same population. They reported that 69.9% of asthma cases were undiagnosed, with this figure increasing to 79.0% in participants aged 64 years or older.[18] Following the PLATINO Study, a population-based epidemiological study assessing COPD prevalence in 5 Latin American cities in 2002, a 9-year follow-up study was conducted in the study site of Sao Paulo, Brazil. In the original study, prevalence of spirometry-confirmed COPD in Sao Paulo was reported as 15.8%, with 87.5% of these cases being undiagnosed.[19] Of those with a previous diagnosis, only 16.7% reported receiving treatment. Participants in Sao Paulo were followed up over 9 years and, of those who developed COPD during this period, 70.0% were undiagnosed.[19] Lamprecht *et al* analysed data from 4 large epidemiologic surveys assessing the prevalence of COPD, including the PREPOCOL and PLATINO studies, as well as the BOLD and EPI-SCAN studies. Underdiagnosis rates amongst those with spirometry-confirmed COPD ranged from 50.0% in Lexington, United States, to 98.3% in Ile-Ife, Nigeria, with an overall underdiagnosis rate of 81.4%.[20]

The PUMA study, a multicenter, multinational, cross-sectional study, recruited participants over the age of 40 years with risk factors for COPD attending primary healthcare facilities in Argentina, Colombia, Venezuela and Uruguay. As part of this study, Casas Herrera *et al* assessed the underdiagnosis of COPD in primary care and found that, of the 1 540 participants who completed spirometry, 20.1% met the diagnostic criteria for COPD with 77% of these cases being undiagnosed.[21] Martinez

et al conducted a cross-sectional analysis of American adults using 2 National Health and Nutritional Examination Surveys, run between 1988-1994 and 2007-2012. Amongst participants with spirometry-confirmed obstructive lung disease, 71.2% of participants in the earlier survey were undiagnosed and this figure was essentially unchanged at 72.0% in the following survey.[22]

A population-based, epidemiological study by Llordes *et al* aimed to determine the prevalence of COPD amongst an adult Spanish population with a history of smoking and to assess the accuracy of diagnosis of COPD in primary care. A total of 1 738 participants were included and findings reported that 56.7% of those with spirometry-confirmed COPD were undiagnosed.[23] Between 2003 and 2013, Colak *et al* conducted a prospective cohort study amongst the general population in Denmark to assess the prognosis of undiagnosed COPD. There was 95 288 individuals included in the study and, of those who met the criteria for COPD, 78% were undiagnosed.[24]

Hill *et al* assessed the prevalence, accuracy of prior diagnosis and the nondiagnosis of COPD amongst an at-risk population attending primary healthcare services in Ontario, Canada between 2006 and 2007. Amongst the 1 003 participants who completed spirometry, the prevalence of COPD was 20.7% with 67.3% of these cases being previously undiagnosed.[25] Using data from 8 215 adults who participated in the 2001 annual Health Survey for England, Shahab *et al* described the prevalence and extent of underdiagnosis of COPD in England. The 2011 survey specifically focused on respiratory conditions and included assessment of lung function by spirometry. Findings showed a COPD prevalence of 13.3%, with 80% of these cases being undiagnosed.[26] Even amongst those with severe or very severe COPD, levels of diagnosis were poor with 53.2% being undiagnosed. Jones *et al* conducted a retrospective cohort study using data collected from a UK general practice database between 1990 and 2009. By assessing patterns of health-care use amongst patients with confirmed COPD, they suggest that in the 5 years preceding the diagnosis of COPD, opportunities for diagnosis were missed in 85% of patients.[27]

As well as being underdiagnosed, many studies have shown CRD to be undertreated. Using data from the PUMA Study, Jardim *et al* assessed treatment of COPD in patients utilising primary health care facilities in 4 Latin American countries.

Amongst those with spirometry-confirmed COPD, including those both diagnosed and undiagnosed, only 36.6% were receiving any medication.[28] Amongst those with a previous diagnosis of COPD, this figure was 79.4%. Increased prescription of medication was associated with increased cough and dyspnoea, more severe disease, an acute exacerbation within the past year and less education. Ingebrigtsen *et al* assessed treatment amongst 5 812 patients with COPD participating in the Copenhagen General Population Study. Of those with $FEV_1 < 60\%$, only 30% of patients were prescribed treatment in the previous 12 months.[29] Treatment was more likely with increased previous respiratory tract infections, increased dyspnea, more severe disease, previous COPD-related hospital admissions and previous smoking. Patients with comorbidity were less likely to receive treatment. Make *et al* conducted a retrospective analysis of United States (US) managed care and Medicare patients with COPD to assess patterns of medication use. Eligible patients had at least one admission or two outpatient visits for COPD, with a total of 51 000 participants included. Results showed significant undertreatment, with 59.1% of those with commercial insurance and 66.0% of those with Medicare not being prescribed any medication.[30] In 2010, Sastre *et al* examined the use of medications amongst adult and adolescent patients with asthma in Europe and Canada. Although features of uncontrolled asthma such as frequent or severe symptoms, hospital admissions, emergency visits or unscheduled physician visits were commonly reported, most participants felt that their asthma was well controlled and undertreatment was high, with only 52% reporting daily use of a controller medication.[31] Enright *et al* assessed the diagnosis and treatment of asthma amongst a population aged 65 years and older in the US. Apart from the underdiagnosis and asthma-related morbidity reported in this population, undertreatment was common with only 40% of patients receiving a bronchodilator, 30% receiving an inhaled corticosteroid, and 39% receiving no medication at all.[32] These studies highlight the poor levels of treatment associated with CRD globally and suggest a need for improved treatment in order to achieve control of these conditions.

The effect of poorly controlled chronic respiratory disease

Chronic respiratory disease has a significant impact both on affected individuals as well as healthcare systems and economies. Acute exacerbations and uncontrolled

disease are associated with worsening health-related quality of life for patients, measured by assessing respiratory symptoms and functional limitation.[33–36] Miravitlles *et al* followed 336 Spanish patients with COPD over a 2-year period to evaluate the impact of acute exacerbations on their health-related quality of life. Findings suggested that frequent exacerbations were associated with significantly poorer quality of life amongst those with moderate COPD.[34] A cross-sectional survey by Jones *et al* explored the health-related quality of life in 1 817 patients with COPD accessing primary healthcare facilities in 7 European countries. They found that patients experiencing an acute exacerbation had significantly worse quality of life scores compared to those with controlled disease.[35] Nishimura *et al* examined the effect of exacerbations on the health status and pulmonary function of patients in Japan with COPD over a 6-month period. Although they did not show a significant effect on pulmonary function, those who experienced an exacerbation during the study period showed both a statistically and clinically significant decline in health status, with more frequent exacerbations causing more decline than less frequent exacerbations.[33] Zamzam *et al* assessed the quality of life and its relationship with severity of disease amongst COPD patients in Egypt in 2011, with results showing increased severity of disease to be associated with poorer health-related quality of life.[36] These studies demonstrate the importance in prevention of exacerbations to reduce deterioration in patient health status and quality of life. Treatment costs associated with CRD can be significant for patients, and the need to pay for medical consultations and treatment may result in patients not being able to afford other basic needs such as food, accommodation and education. The WHO estimates that by having to pay for health services, 100 million people are pushed into poverty every year.[3]

In many low- and middle-income countries, CRD is often managed at secondary or tertiary care level with patients presenting to these facilities with more severe or complicated disease, resulting in an increased financial burden to the healthcare system.[3] Poor control of CRD also places an increased burden on the healthcare system due to increased utilisation of resources such as clinician and emergency visits, hospitalisations and medications.[2]

People with uncontrolled disease are less likely to be able to work, resulting in loss of productivity, increased emotional and financial stress and an increased economic burden for a country.[2] Taponen *et al* conducted a cross-sectional survey in Finland to assess factors associated with employment amongst 2 613 adults with asthma, and found that more frequent asthma symptoms were associated with higher levels of unemployment and work disability.[37] In a national register-based study, Lokke *et al* assessed the economic consequences of COPD in Denmark between 1998 and 2010. They compared healthcare utilisation, procedures, medication, unemployment benefits and social transfer payments between 131 811 patients with COPD, and the same number of matched controls. Findings showed that patients with COPD had significantly higher rates of healthcare utilisation, medication use and higher socioeconomic costs.[38] COPD was also associated with significantly lower employment rates, and lower income rates amongst those employed compared with those without COPD. These associations became stronger with more advanced disease. A systematic review by Chaker *et al* assessed the global impact of NCDs on macro-economic productivity, measured in DALYs, productivity costs and labour market participation.[39] They suggest productivity losses due to COPD of 88 million USD per year in the US and 1.47 billion USD in Japan. Patients with COPD were at higher risk of reduced labor market participation, with almost 500 000 working days lost per year in the US due to their disease. They were more likely to work less hours and had a higher chance of unemployment, absenteeism and presenteeism (poorer work performance).[39]

The benefit of control of chronic respiratory disease

Although asthma and COPD cannot be cured, they can be controlled using appropriate medications, with early diagnosis and initiation of treatment resulting in improved outcomes.[2] The goal of treatment is to control symptoms, to prevent acute exacerbations, further worsening of health status and the development of comorbidities, and to minimise activity limitation arising from the condition.[2] Appropriate treatment of COPD has been shown to reduce the frequency of acute exacerbations and to reduce the rate of deterioration in health status.[33] Well controlled CRD results in a decrease in burden at both a personal level as well as on the healthcare system and economy.[2]

B4: CONCLUSIONS

Despite the increase in burden, data surrounding prevalence, treatment and control of CRD in South Africa are lacking.[4,12] The WHO has developed a strategy for the prevention and control of CRD, with one of the objectives being 'better surveillance to map the magnitude of chronic respiratory diseases and analyse their determinants with particular reference to poor and disadvantaged populations, and to monitor future trends'.[40] Further research is needed to more accurately establish the prevalence of CRD in South Africa and to assess the burden and severity of these conditions locally. More data is required to assess if CRD is being underdiagnosed and undertreated, as this would have a significant impact on both the burden of disease as well as disease severity. As primary healthcare facilities are the entry point for patients into our health system and are therefore responsible for diagnosing and treating the majority of patients with CRD in South Africa, it is important that research is conducted in primary healthcare settings. Obtaining this data would assist in establishing the burden of CRD in South Africa so that appropriate measures can be implemented to improve management and control of these conditions.

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PART C: MANUSCRIPT*

*This journal manuscript meets the requirements in the Author Guidelines for the South African Medical Journal, included as an appendix in Part D of this dissertation. Spacing of text has been adapted to align with the other sections of the dissertation.

The Burden of Chronic Respiratory Disease in the Western Cape

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[†]Abstract word limit for the South African Medical Journal is 400 words.
[‡]Manuscript word limit for the South African Medical Journal is 4 000 words.

C1: ABSTRACT

Background: Chronic respiratory disease (CRD) is underdiagnosed, undertreated and poorly controlled, especially in low- and middle-income countries. Poor control is associated with poorer quality of life, increased burden on the healthcare system, and negative economic impact due to loss of productivity. Limited data are available on the burden of CRD in South Africa.

Objectives: To describe the symptomatic burden of disease and levels of treatment in adults with CRD attending primary healthcare facilities in the Western Cape, and to identify predictors of quality of life and receipt of treatment in this population.

Methods: We enrolled 1 157 patients with CRD attending 38 primary care clinics in the Western Cape, recruited as part of a randomised controlled trial. Secondary endpoints in the trial included quality of life, assessed using the St George's Respiratory Questionnaire (SGRQ), and receipt of treatment, measured using self-report. Linear regression models were used to identify predictors of quality of life and logistic regression models to identify predictors of treatment.

Results: Among patients with CRD, the mean SGRQ symptoms score, on a scale of 0 to 100, was 55.3 and activity score 69.0. Despite being symptomatic, 40% of patients were not receiving treatment for CRD. A higher (worse) SGRQ symptoms score was associated with male sex ($p<0.001$), positive screen for depression ($p=0.001$), previous tuberculosis ($p<0.001$), previous smoking ($p=0.012$), higher (worse) SGRQ activity score ($p<0.001$) and current receipt of treatment for CRD ($p<0.001$). Greater activity limitation was associated with unemployment ($p=0.027$), diabetes ($p=0.032$), positive screen for depression ($p<0.001$), higher SGRQ symptoms score ($p<0.001$), recent hospital admission ($p=0.004$) and receiving treatment for CRD ($p=0.013$). Older patients ($p=0.002$) and patients with a higher symptoms score ($p=0.007$) or greater activity limitation ($p=0.006$) were more likely, and those who screened positive for depression, ($p<0.001$), were current smokers ($p=0.040$), or had recent clinic visits ($p=0.009$) or hospital admissions ($p=0.011$) were less likely to be receiving treatment for CRDs.

Conclusion: Our results confirm a high burden of symptoms and activity limitation, and of undertreatment, possibly contributed to by under-recognition of respiratory disease among patients attending primary care clinics in the Western Cape. Depression, a history of previous tuberculosis and unemployment are common features in such patients. Potential interventions are to introduce a systematic approach to CRD diagnosis in primary care clinics that includes screening for depression, improving availability of essential drugs for the management of CRDs, and preventive strategies such as more effective tuberculosis control, and support and pharmacotherapy to assist smokers to quit.

C2: INTRODUCTION

The World Health Organisation (WHO) defines chronic respiratory disease (CRD) as 'chronic diseases of the airways and other structures of the lung', of which asthma and chronic obstructive pulmonary disease (COPD) comprises the majority.[1] CRD is responsible for significant morbidity and mortality worldwide.[2] In 2015, the estimated global prevalence of asthma was 358 million and 174 million for COPD.[3] Between 2005 and 2015, the prevalence of COPD increased by 17%, and asthma by 9.5%.[3]

Although asthma and COPD cannot be cured, they can be controlled using appropriate medications. Poorly controlled CRD is associated with significantly poorer quality of life and mortality for patients, an increased burden on the healthcare system due to increased utilisation of resources, and a negative economic impact due to loss of productivity and premature retirement from the workforce.[4],[5] CRD is underdiagnosed, undertreated and poorly controlled, especially in low- and middle-income countries.[2],[6],[7] Improving control of CRD would result in improved quality of life for patients and a reduced burden on the healthcare system and economy.

With the global increase in burden, the WHO has developed a strategy for the prevention and control of CRD, one of the objectives being 'better surveillance to map the magnitude of chronic respiratory diseases and analyse their determinants with particular reference to poor and disadvantaged populations, and to monitor future trends'.[8] Limited data are available on the burden of CRD in South Africa and particularly on the availability and efficacy of measures to control them at healthcare provider level.[2],[7] Such data are essential if appropriate measures are to be put in place to address these needs.

This study aimed to describe the symptomatic burden of disease and levels of treatment in adults with CRD attending primary healthcare facilities in the Western Cape, and to identify predictors of both the quality of life and receipt of treatment in this population.

C3: METHODS

Study population

The study population consisted of adults accessing healthcare at primary care level facilities in the Eden and Overberg Districts of the Western Cape, who were enrolled in a pragmatic cluster randomised controlled trial designed to test the effectiveness of the Primary Care 101 (PC101) programme in improving management of non-communicable diseases at a primary healthcare level.[6] The trial recruited four adult patient cohorts; attendees with hypertension, diabetes, CRD and/or a positive screen for depression. The study population for the current study was limited to participants enrolled in the CRD cohort in both the intervention and control arms of the PC101 trial. The methods of the trial have been reported elsewhere. [6]

Participants were recruited from 38 clinics in the Eden and Overberg Districts. Together, these districts have a population of approximately 800 000 with the majority of those employed working in commercial services. For clinics to be included, they needed to provide services for non-communicable diseases at least 5 days a week and to report more than 10 000 clinic visits per year. As only 33 of the 124 clinics in the Eden district met these criteria, an additional 5 clinics from adjacent sub-districts in the Overberg district were included to ensure an adequate sample size. The clinics were mainly in medium-sized towns and rural areas, and were predominantly nurse-led with doctor support ranging from daily to sessional. The populations served by these clinics are generally of poor socioeconomic status with high levels of unemployment.

Patients were eligible for recruitment if they reported being on treatment for asthma, chronic bronchitis or emphysema, or if they reported a cough or difficulty breathing for more than 2 weeks and were not on treatment for tuberculosis (TB) in the past 3 months. They also needed to be at least 18 years of age, able to actively participate in an interviewer-administered questionnaire, likely to stay in the same area for the duration of the trial and provide written consent to participate in the study. Patients

were approached in clinic waiting areas and, those that were eligible and provided informed consent, were enrolled into the trial.

Data collection

Immediately after enrollment, a trained fieldworker conducted a baseline interview with each participant, using a standardised structured questionnaire which was completed in the participant's language of choice (English, Afrikaans or isiXhosa). Questions related to basic demographics, socioeconomic status, medical history, smoking history, current state of health, severity of symptoms and levels of healthcare utilisation. Baseline anthropometric measurements were taken, including blood pressure, weight, height and waist circumference. The fieldworker entered all questionnaire responses and measurements into an electronic hand-held device at the time of the interview. Fieldworkers then collected all prescription data by photocopying prescription charts for the year preceding the interview. A medically qualified trial manager reviewed this data and was responsible for identifying medications used to treat CRD at the time of the interview.

The St George's Respiratory Questionnaire (SGRQ), designed to measure respiratory disease-specific health status in patients with asthma and COPD, was used to assess quality of life.[9] This is a widely accepted tool with validated translations in many languages including South African English and Afrikaans. It contains three domains; including a 'symptoms' domain that assesses frequency of symptoms in order to capture the patient's perception of their current respiratory problems, and an 'activity' domain that interrogates the impact of respiratory disease on daily physical activity. For each domain, a score between 0 and 100 is calculated, with higher scores representing worse health status, and a difference in score of 4 units or more being regarded as clinically significant.[10],[11] The third domain; 'impacts' was not included and thus the usual metric of SGRQ total score was not calculated. As there is no validated translation of this questionnaire in isiXhosa, participants who completed the interview in isiXhosa (8.5%) did not complete a SGRQ questionnaire.

Receipt of treatment was measured using self-report, with participants being classified as receiving treatment if they reported taking medications for asthma, chronic bronchitis or emphysema.

Statistical analysis

Statistical analyses were performed to identify participant characteristics associated with quality of life and receipt of treatment.

Differences in characteristics between participants receiving and not receiving treatment were tested using univariate logistic regression models. Each model included only the participant characteristic as the explanatory variable, with the outcome being treatment status, and was adjusted for an effect due to the cluster sampling technique used.

Multiple linear regression models were used to identify predictors of quality of life - respiratory symptoms and activity limitation. These were measured using the SGRQ symptoms and activity domain scores respectively. A backward selection approach was used, with all covariates initially being included in the model. Covariates with a p-value of ≥ 0.2 were then removed in a step-wise approach and the model repeatedly re-fitted until a final model was identified including only statistically significant covariates. Using a forward selection approach, each of the dropped covariates was then individually added back into the final model to ensure no significant predictors were omitted. The analysis was repeated excluding clinical covariates, which may have masked the effects of more upstream covariates. Analysis was first performed on the full cohort and then stratified according to treatment status.

Multiple logistic regression models were used to identify predictors of treatment, built using the same approach outlined above and repeated excluding clinical covariates. A sensitivity analysis was also performed excluding participants who reported receiving treatment but whose prescription charts showed no evidence of treatment.

All models were adjusted for the cluster sampling method used in the trial design, but not for trial arm as only baseline data were analysed. A level of significance of 0.05 was used for all analyses. Stata 13.0 (Stata Corporation, College Station, Texas) was used as the statistical software package for all analyses.

Ethics approval

Approval for this study was granted by the University of Cape Town (UCT) Faculty of Health Sciences Human Research Ethics Committee (HREC REF 492/2017). The PC101 trial was approved by the UCT Faculty of Health Sciences Human Research Ethics Committee (HREC REF 119/2010), with permission for recruitment and research in provincial primary healthcare facilities granted by the Western Cape Provincial Department of Health (Reference 18/19/RP152/2010).

C4: RESULTS

A total of 1 157 participants were included in the analysis. Participant **baseline characteristics** and the **differences between those receiving and those not receiving treatment** are shown in Table 1. The majority of participants were female (70.8%) and Afrikaans-speaking (83.4%), with a mean age of 51.2 years. The majority had not completed secondary school education (59.6%), were unemployed (79.6%) and receiving a welfare grant (59.9%), and reported a median monthly income of ZAR 1 140. Forty-four per cent were obese and comorbidity was common with 66.6% reporting a previous diagnosis of hypertension, 41.3% reporting a previous diagnosis of cardiovascular disease and 64.8% screened positive for depression at the time of interview. Most were either previous (25.5%) or current (39.9%) smokers and 18.3% reported previous TB. The mean SGRQ score for the symptoms domain was 55.3, and for the activity domain, 69.0.

Forty per cent (458 participants) were not on treatment for CRD, despite being symptomatic. On univariate analysis (Table 1), participants receiving treatment were *more likely* to be older ($p<0.001$), unemployed ($p=0.001$), receiving a grant

(p=0.010), obese (p=0.005) and to have a history of TB (p=0.039). Treatment was also more likely with increased symptoms (p<0.001) and activity limitation (p<0.001), as well as higher levels of smoking amongst previous and current smokers (p=0.003). Participants were *less likely* to be on treatment if they were more educated (p=0.041), had received a previous diagnosis of depression (p=0.011) or screened positive for depression at the time of interview (p<0.001). Although 60% of participants reported receipt of treatment, review of prescription charts showed that only 51% had been prescribed medications for CRD (Table 2). Amongst all participants, only 48% had been prescribed a selective β2-agonist and 34% an inhaled corticosteroid.

Results of **linear regression analysis to identify predictors of respiratory symptoms** are shown in Table 3A. More symptoms were associated with male sex (p<0.001), a positive depression screen (p=0.001), previous TB (p<0.001), being a previous smoker (p=0.012), a higher SGRQ activity domain score (p<0.001) and receiving treatment for CRD (p<0.001). Diabetes was associated with fewer symptoms (p=0.017). When clinical characteristics were removed from the model, results were similar with strengthened associations seen between respiratory symptoms and depression, previous TB and smoking history. However, the association between symptoms and diabetes became insignificant. Similar results were reported when analysis was stratified according to treatment status, but the association between symptoms and smoking status became insignificant (Tables 3B and 3C). Amongst participants not receiving treatment, the association with diabetes and previous TB also became insignificant.

Results of **linear regression analysis to identify predictors of activity limitation** are shown in Table 4A. Greater limitation was positively associated with unemployment (p=0.027), diabetes (p=0.032), a positive depression screen (p<0.001), higher SGRQ symptoms scores (p<0.001), being admitted to hospital in the previous 3 months (p=0.004) and receipt of treatment for CRD (p=0.013). Male sex was associated with less activity limitation (p=0.011). When clinical characteristics were removed from the model, strengthened associations were seen with unemployment and depression. Greater limitation was also associated with cardiovascular disease (p=0.038) and previous TB (p=0.046). However, the association with sex and diabetes

became insignificant. When analysis was stratified according to treatment status, greater limitation remained more likely amongst participants with symptoms of depression and higher SGRQ symptoms scores (Tables 4B and 4C).

Results of **logistic regression analysis to identify predictors of receiving any treatment** for CRD are shown in Table 5. Participants were more likely to be on treatment if they were older (OR=1.02; p=0.002), more symptomatic (OR=1.01; p=0.007) or had higher levels of activity limitation due to their respiratory condition (OR=1.01; p=0.006). Treatment was less likely in participants who screened positive for depression (OR=0.42; p<0.001), were current smokers (OR=0.68; p=0.040), had > 3 clinic visits in the previous 3 months (OR=0.63; p=0.009) or had been admitted to hospital in the previous 3 months (OR=0.46; p=0.011). When clinical variables were removed from the model, the associations with age and a positive depression screen remained similar. However, treatment was also more likely in participants who were unemployed (OR=1.48; p=0.026), obese (OR=1.54; p<0.001) or had previous TB (OR=1.77; p=0.004), and less likely in those who were isiXhosa- versus Afrikaans-speaking (OR=0.64; p=0.025). A sensitivity analysis excluding the 126 people who reported receiving treatment but whose prescription charts provided no evidence of treatment showed similar results, however the association between treatment and smoking status became insignificant.

Table 1. Participants' baseline characteristics

Characteristics	All participants N=1 157	On treatment N=699	Not on treatment N=458	*p*-value*
Age (years), mean (SD)	51.2 (12.6)	52.7 (11.7)	48.8 (13.5)	<0.001
Sex, %				0.554
Female	70.8	71.5	69.7	
Language, %				0.274
Afrikaans	83.4	85.4	80.4	
isiXhosa	8.5	6.3	11.8	
English	8.1	8.3	7.9	
Highest education, %†				0. 041
None	9.6	11.0	7.3	
Primary	50.0	51.0	48.4	
Secondary	39.1	36.8	42.5	
Tertiary	1.4	1.1	1.7	
Unemployed, %†	79.6	83.0	74.3	0.001
Receiving welfare grant, %†	59.9	64.0	53.5	0.010
Total monthly income (ZAR), median (IQR)	1 140 (0 - 1140) n=1 151	1 140 (0 - 1140) n=695	1 080 (0 - 1140) n=456	0.239
History of hypertension, %†	66.6	68.7	63.3	0.170
History of diabetes, %†	28.2	29.9	25.5	0.257
History of depression, %†	31.5	27.9	37.1	0.011
Positive depression screen‡, %	64.8	60.7	71.2	<0.001
Known cardiovascular disease§, %	41.3	43.1	38.7	0.375
Obese¶, %†	44.0	47.5	38.6	0.005
Previous tuberculosis, %†	18.3	20.4	15.1	0.039
On antiretroviral therapy, %†	3.4	2.7	4.4	0.074
Smoking status, %†				0.326
Never smoker	34.6	33.9	35.8	
Previous smoker	25.5	29.4	19.6	
Current smoker	39.9	36.8	44.7	
Smoking pack-year history‖, mean (SD)	12.0 (13.4) n=581	13.2 (14.7) n=353	10.2 (11.0) n=228	0.003
SGRQ symptom score**, mean (SD)	55.3 (25.2) n=833	58.5 (25.2) n=534	49.7 (24.3) n=299	<0.001
SGRQ activity score**, mean (SD)	69.0 (26.0) n=1 054	72.8 (24.6) n=651	62.7 (27.0) n=403	<0.001

SD = standard deviation; ZAR = South African rands; IQR = interquartile range; BMI = body mass index; SGRQ = St George's Respiratory Questionnaire

*p-values from logistic regression models adjusted for cluster sampling method

†Percentage of available data. Lowest n for these parameters was 1036.

‡Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

§History of angina, heart attack or stroke

¶ BMI ≥ 30kg/m^2

‖For current and previous smokers

**Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. The SGRQ symptom and activity scores therefore apply to Afrikaans and English speakers only.

Table 2. Treatment amongst all participants (according to prescription charts)

Medication prescribed	**N=1 157**
None, *n* (%)	567 (49.0)
Selective beta-agonist, *n* (%)	558 (48.2)
Inhaled corticosteroids, *n* (%)	388 (33.5)
Theophylline, *n* (%)	121 (10.5)
Ipratropium bromide, *n* (%)	91 (7.9)

Table 3A. Predictors of respiratory symptoms (all participants)

Outcome	SGRQ symptom score: Full model (N=698)			SGRQ symptom score: Limited model (N=813)			SGRQ symptom score: Excluding clinical covariates* (N=821)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	0.08	-0.09 – 0.24	0.353						
Sex (male vs female)	5.54	1.80 – 9.28	0.005	5.42	2.58 – 8.25	< 0.001	4.34	1.21 – 7.47	0.008
Language									
Afrikaans (reference)	Ref								
isiXhosa†									
English	-1.71	-10.10 – 6.68	0.682						
Highest education			0.698‡						
None (reference)	Ref								
Primary	-1.83	-7.06 – 3.40	0.482						
Secondary	-1.94	-6.66 – 2.78	0.411						
Tertiary	3.33	-11.87 – 18.53	0.660						
Unemployed	1.51	-3.77 – 6.79	0.566						
Receiving welfare grant	-4.81	-7.90 – -1.71	0.003						
Total monthly income (ZAR)	1.39	-0.72 – 3.50	0.189						
History of hypertension	-2.48	-5.68 – 0.72	0.125						
History of diabetes	-3.50	-7.32 – 0.32	0.071	-4.28	-7.76 – -0.79	0.017			
History of depression	1.95	-2.02 – 5.92	0.327						
Positive depression screen§	6.98	3.21 – 10.74	0.001	6.29	2.93 – 9.66	0.001	11.92	7.93 – 15.92	< 0.001
Known cardiovascular disease¶	2.40	-1.33 – 6.14	0.201						
Obese‖	0.70	-3.07 – 4.46	0.710						
Previous tuberculosis	7.44	3.47 – 11.42	0.001	7.59	4.53 – 10.64	< 0.001	10.40	6.58 – 14.21	< 0.001
On antiretroviral therapy	1.53	-7.87 – 10.92	0.744						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	5.42	0.87 – 9.97	0.021	4.84	1.11 – 8.57	0.012	7.03	2.47 – 11.59	0.003
Current smoker	4.65	0.05 – 9.26	0.048	3.35	-0.47 – 7.18	0.084	3.67	-0.59 – 7.93	0.089
SGRQ activity score	0.47	0.39 – 0.55	<0.001	0.47	0.40 – 0.53	< 0.001	Excluded from analysis		
Clinic visits**	-0.37	-3.57 – 2.84	0.818						
Hospital admissions††	3.90	-3.24 – 11.04	0.275						
On CRD treatment	8.00	4.11 – 11.88	<0.001	7.17	3.92 – 10.42	< 0.001	Excluded from analysis		

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

*Model adjusted for all covariates in full model, excluding SGRQ activity score, clinic visits, hospital admissions and treatment status.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI $\geq 30 kg/m^2$

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

Table 3B. Predictors of respiratory symptoms amongst participants on treatment

Outcome	SGRQ symptom score: Full model (N=448)			SGRQ symptom score: Limited model (N=530)			SGRQ symptom score: Excluding clinical covariates* (N=527)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	0.02	-0.21 – 0.25	0.860						
Sex (male vs female)	5.31	1.18 – 9.44	0.013	4.94	1.33 – 8.56	0.009			
Language									
Afrikaans (reference)	Ref								
isiXhosa†									
English	-5.39	-14.93 – 4.15	0.259						
Highest education			0.531‡						
None (reference)	Ref								
Primary	-3.94	-10.10 – 2.23	0.203						
Secondary	-3.64	-9.76 – 2.48	0.235						
Tertiary	4.63	-14.96 – 24.23	0.635						
Unemployed	1.22	-5.51 – 7.95	0.716						
Receiving welfare grant	-4.19	-9.91 – 1.53	0.147						
Total monthly income (ZAR)	-0.76	-3.98 – 2.45	0.633						
History of hypertension	-3.62	-7.49 – 0.23	0.065				-5.33	-9.99 – -0.67	0.026
History of diabetes	-4.37	-9.48 – 0.75	0.092	-4.99	-9.54 – -0.44	0.033			
History of depression	3.40	-2.03 – 8.83	0.212						
Positive depression screen§	8.18	3.63 – 12.73	0.001	7.08	2.82 – 11.34	0.002	12.89	8.13 – 17.64	< 0.001
Known cardiovascular disease¶	1.94	-2.51 – 6.39	0.383						
Obese‖	-0.25	-4.65 – 4.14	0.907						
Previous tuberculosis	8.68	3.69 – 13.67	0.001	10.38	6.19 – 14.57	< 0.001	10.18	4.88 – 15.48	< 0.001
On antiretroviral therapy	3.68	-6.56 – 13.91	0.471						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	2.71	-2.67 – 8.09	0.314				5.56	0.01 – 11.12	0.049
Current smoker	2.04	-3.01 – 7.10	0.418				4.66	-0.26 – 9.57	0.063
SGRQ activity score	0.51	0.42 – 0.59	<0.001	0.50	0.41 – 0.59	< 0.001	Excluded from analysis		
Clinic visits**	-0.82	-5.22 – 3.58	0.707						
Hospital admissions††	4.82	-4.75 – 14.39	0.314						
On CRD treatment	8.54	2.96 – 14.12	0.004	7.10	2.00 – 12.20	0.008	Excluded from analysis		

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

*Model adjusted for all covariates in full model, excluding SGRQ activity score, clinic visits, hospital admissions and treatment status.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI ≥ 30kg/m^2

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

Table 3C. Predictors of respiratory symptoms amongst participants not on treatment

Outcome	SGRQ symptom score: Full model (N=250)			SGRQ symptom score: Limited model (N=295)			SGRQ symptom score: Excluding clinical covariates* (N=294)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	0.13	-0.11 – 0.37	0.276						
Sex (male vs female)	5.80	-1.68 – 13.27	0.125	7.44	1.39 – 13.50	0.017			
Language									
Afrikaans (reference)	Ref								
isiXhosa†									
English	6.64	-3.95 – 17.23	0.212						
Highest education			0.972‡						
None (reference)	Ref								
Primary	3.24	-11.56 – 18.03	0.660						
Secondary	1.69	-13.10 – 16.48	0.818						
Tertiary	4.81	-13.32 – 22.93	0.594						
Unemployed	-0.59	-8.62 – 7.45	0.883						
Receiving welfare grant	-3.12	-8.39 – 2.16	0.239						
Total monthly income (ZAR)	3.53	1.10 – 5.96	0.006						
History of hypertension	-0.16	-6.29 – 5.97	0.959						
History of diabetes	-2.49	-7.89 – 2.91	0.355						
History of depression	-0.55	-6.60 – 5.49	0.853						
Positive depression screen§	4.99	-0.39 – 10.36	0.068	5.00	0.43 – 9.56	0.033	12.94	8.45 – 17.44	< 0.001
Known cardiovascular disease¶	2.51	-3.55 – 8.58	0.407						
Obese‖	0.75	-5.47 – 6.97	0.808						
Previous tuberculosis	5.81	-0.98 – 12.59	0.091				10.08	4.14 – 16.02	0.001
On antiretroviral therapy	-1.54	-20.11 – 17.03	0.868						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	10.16	-0.37 – 20.69	0.058				9.77	1.78 – 17.76	0.018
Current smoker	8.76	0.66 – 16.85	0.035				5.43	-2.02 – 12.89	0.148
SGRQ activity score	0.42	0.33 – 0.52	<0.001	0.43	0.35 – 0.51	< 0.001	Excluded from analysis		
Clinic visits**	1.52	-3.16 – 6.19	0.515						
Hospital admissions††	1.66	-8.46 – 11.78	0.742						
On CRD treatment	15.41	-4.30 – 35.11	0.122	13.72	0.05 – 27.39	0.049	Excluded from analysis		

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

*Model adjusted for all covariates in full model, excluding SGRQ activity score, clinic visits, hospital admissions and treatment status.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI ≥ 30kg/m^2

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

Table 4A. Predictors of activity limitation (all participants)

Outcome	SGRQ activity score: Full model (N=698)			SGRQ activity score: Limited model (N=824)			SGRQ activity score: Excluding clinical covariates[*] (N=1053)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	-0.08	-0.28 – 0.11	0.395						
Sex (male vs female)	-4.08	-8.45 – 0.29	0.067	-4.70	-8.28 – -1.12	0.011			
Language									
Afrikaans (reference)	Ref								
isiXhosa[†]									
English	-2.51	-9.15 – 4.14	0.450						
Highest education			0.333[‡]						
None (reference)	Ref								
Primary	0.28	-5.51 – 6.06	0.923						
Secondary	-1.28	-6.80 – 4.23	0.640						
Tertiary	-7.04	-19.59 – 5.51	0.263						
Unemployed	5.46	-0.05 – 10.96	0.052	4.53	0.55 – 8.50	0.027	6.85	2.68 – 11.03	0.002
Receiving welfare grant	-0.33	-4.18 – 3.52	0.863						
Total monthly income (ZAR)	-0.19	-2.27 – 1.89	0.855						
History of hypertension	-0.45	-4.32 – 3.42	0.815						
History of diabetes	3.73	-0.90 – 8.37	0.111	4.29	0.38 – 8.20	0.032			
History of depression	-1.37	-5.50 – 2.77	0.508						
Positive depression screen[§]	7.93	3.47 – 12.40	0.001	7.61	4.28 – 10.94	< 0.001	11.80	8.28 – 15.31	< 0.001
Known cardiovascular disease[¶]	3.01	-1.20 – 7.23	0.156				5.41	0.33 – 10.49	0.038
Obese[‖]	2.57	-1.28 – 6.43	0.184						
Previous tuberculosis	0.01	-5.64 – 5.67	0.996				4.78	0.09 – 9.46	0.046
On antiretroviral therapy	6.60	-5.80 – 19.01	0.288						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	-2.41	-6.41 – 1.58	0.229						
Current smoker	-1.42	-5.61 – 2.77	0.497						
SGRQ symptom score	0.50	0.42 – 0.58	<0.001	0.49	0.41 – 0.57	< 0.001	Excluded from analysis		
Clinic visits[**]	-0.73	-4.82 – 3.36	0.720						
Hospital admissions[††]	4.93	-1.93 – 11.79	0.154	7.83	2.61 – 13.05	0.004	Excluded from analysis		
On CRD treatment	4.16	-0.58 – 7.73	0.024	4.60	1.04 – 8.16	0.013	Excluded from analysis		

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

[*]Model adjusted for all covariates in full model, excluding SGRQ symptom score, clinic visits, hospital admissions and treatment status.

[†]Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

[‡]Test for trend

[§]Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

[¶]History of angina, heart attack or stroke

[‖]BMI $\geq 30 kg/m^2$

[**]More than 3 versus ≤ 3 clinic visits in the previous 3 months

[††]Admitted to hospital in the previous 3 months (yes vs no)

Table 4B. Predictors of activity limitation amongst participants on treatment

Outcome	SGRQ activity score: Full model (N=448)			SGRQ activity score: Limited model (N=533)			SGRQ activity score: Excluding clinical covariates* (N=650)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	-0.09	-0.34 – 0.16	0.484						
Sex (male vs female)	-3.73	-10.38 – 2.91	0.262	-5.76	-10.76 – -0.76	0.025			
Language									
Afrikaans (reference)	Ref								
isiXhosa†									
English	-0.75	-9.31 – 7.81	0.861						
Highest education			0.845‡						
None (reference)	Ref								
Primary	3.88	-2.01 – 9.77	0.190						
Secondary	2.77	-4.09 – 9.63	0.418						
Tertiary	-5.62	-23.74 – 12.49	0.533						
Unemployed	5.40	-1.98 – 12.78	0.147	5.67	0.44 – 10.90	0.034	7.56	1.82 – 13.30	0.011
Receiving welfare grant	0.33	-4.23 – 4.88	0.885						
Total monthly income (ZAR)	0.04	-2.95 – 3.04	0.978						
History of hypertension	1.01	-3.58 – 5.61	0.657						
History of diabetes	3.32	-1.45 – 8.10	0.167						
History of depression	-2.74	-8.52 – 3.04	0.343						
Positive depression screen§	5.99	-0.03 – 12.02	0.051	5.80	0.78 – 10.82	0.025	11.55	6.73 – 16.36	< 0.001
Previous cardiovascular disease¶	2.37	-3.26 – 8.00	0.399						
Obese‖	2.81	-1.33 – 6.96	0.177						
Previous tuberculosis	-3.58	-9.83 – 2.66	0.253						
On antiretroviral therapy	7.65	-1.95 – 17.24	0.115						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	-2.24	-6.63 – 2.15	0.307						
Current smoker	-0.23	-5.00 – 4.53	0.922						
SGRQ symptom score	0.50	0.41 – 0.60	<0.001	0.48	0.38 – 0.58	< 0.001	Excluded from analysis		
Clinic visits**	-2.02	-6.79 – 2.74	0.395						
Hospital admissions††	1.00	-9.49 – 11.50	0.847						
On CRD treatment	1.72	-4.61 – 8.06	0.585						

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

*Model adjusted for all covariates in full model, excluding SGRQ symptom score, clinic visits, hospital admissions and treatment status.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI $\geq 30 kg/m^2$

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

Table 4C. Predictors of activity limitation amongst participants not on treatment

Outcome	SGRQ activity score: Full model (N=250)			SGRQ activity score: Limited model (N=299)			SGRQ activity score: Excluding clinical covariates* (N=396)		
Explanatory variable	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**	**Coef.**	**95% CI**	**p-value**
Age (years)	-0.05	-0.33 – 0.23	0.730						
Sex (male vs female)	-2.41	-10.19 – 5.37	0.534						
Language									
Afrikaans (reference)	Ref								
isiXhosa†									
English	-7.02	-18.48 – 4.43	0.222						
Highest education			0.136‡						
None (reference)	Ref								
Primary	-8.95	-23.28 – 5.37	0.213						
Secondary	-10.64	-24.93 – 3.65	0.140						
Tertiary	-13.80	-29.92 – 2.31	0.091						
Unemployed	5.41	-5.78 – 16.59	0.334						
Receiving welfare grant	-1.42	-8.97 – 6.13	0.705						
Total monthly income (ZAR)	-0.85	-4.39 – 2.70	0.631						
History of hypertension	-3.08	-10.18 – 4.01	0.384						
History of diabetes	6.06	-1.67 – 13.79	0.121	8.28	2.00 – 14.55	0.011			
History of depression	0.79	-4.68 – 6.27	0.770						
Positive depression screen§	12.41	4.95 – 19.88	0.002	11.58	6.06 – 17.10	< 0.001	17.56	11.92 – 23.19	< 0.001
Previous cardiovascular disease¶	3.52	-1.87 – 8.92	0.194				8.18	2.47 – 13.90	0.006
Obese‖	4.12	-2.96 – 11.21	0.246						
Previous tuberculosis	7.50	-0.80 – 15.80	0.075	7.73	2.36 – 13.11	0.006	11.65	5.84 – 17.46	< 0.001
On antiretroviral therapy	2.86	-18.30 – 24.01	0.786						
Smoking status									
Never smoker (reference)	Ref								
Previous smoker	-3.22	-11.91 – 5.48	0.458				6.81	0.01 – 13.61	0.050
Current smoker	-3.61	-10.56 – 3.34	0.299				2.73	-2.21 – 7.67	0.269
SGRQ symptom score	0.50	0.35 – 0.64	<0.001	0.46	0.33 – 0.60	< 0.001	Excluded from analysis		
Clinic visits**	1.10	-4.93 – 7.12	0.715						
Hospital admissions††	11.17	2.48 – 19.85	0.013	11.33	3.51 – 19.16	0.006	Excluded from analysis		
On CRD treatment	-7.61	-28.20 – 12.98	0.459						

SGRQ = St George's Respiratory Questionnaire; Coef = coefficient; CI = confidence interval; BMI = body mass index; ZAR = South African rands; CRD = chronic respiratory disease

*Model adjusted for all covariates in full model, excluding SGRQ symptom score, clinic visits, hospital admissions and treatment status.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI $\geq 30 kg/m^2$

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

Table 5. Predictors of treatment

Outcome	Treatment: full model (N=704)			Treatment: limited model (N=820)			Treatment: Excluding clinical covariates* (N=1066)		
Explanatory variable	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years)	1.02	1.00 – 1.04	0.016	1.02	1.01 – 1.04	0.002	1.02	1.01 – 1.04	0.001
Sex (male vs female)	0.68	0.45 – 1.05	0.081						
Language									
Afrikaans (reference)	1.00								
isiXhosa†							0.64	0.44 – 0.94	0.025
English	1.05	0.58 – 1.90	0.879				0.87	0.42 – 1.78	0.696
Highest education			0.931‡						
None (reference)	1.00								
Primary	0.67	0.39 – 1.16	0.154						
Secondary	0.80	0.40 – 1.61	0.538						
Tertiary	0.97	0.20 – 4.76	0.974						
Unemployed	1.04	0.51 – 2.09	0.917				1.48	1.05 – 2.09	0.026
Receiving welfare grant	1.37	0.84 – 2.23	0.210						
Total monthly income (ZAR)	0.92	0.66 – 1.27	0.609						
History of hypertension	0.74	0.49 – 1.11	0.141						
History of diabetes	0.93	0.57 – 1.49	0.750						
History of depression	0.75	0.49 – 1.14	0.178						
Positive depression screen§	0.44	0.29 – 0.66	<0.001	0.42	0.28 – 0.63	<0.001	0.64	0.48 – 0.85	0.002
Known cardiovascular disease¶	1.08	0.65 – 1.79	0.756						
Obese‖	1.34	0.90 – 1.99	0.148				1.54	1.22 – 1.95	< 0.001
Previous tuberculosis	1.34	0.83 – 2.18	0.234				1.77	1.20 – 2.63	0.004
On antiretroviral therapy	0.67	0.25 – 1.80	0.423						
Smoking status									
Never smoker (reference)	1.00			1.00					
Previous smoker	1.27	0.74 – 2.18	0.384	1.12	0.67 – 1.87	0.659			
Current smoker	0.73	0.50 – 1.06	0.102	0.68	0.47 – 0.98	0.040			
SGRQ symptom score	1.01	1.00 – 1.02	0.012	1.01	1.00 – 1.02	0.007	Excluded from analysis		
SGRQ activity score	1.01	1.00 – 1.02	0.006	1.01	1.00 – 1.02	0.006	Excluded from analysis		
Clinic visits**	0.68	0.48 – 0.94	0.022	0.63	0.45 – 0.89	0.009	Excluded from analysis		
Hospital admissions††	0.39	0.19 – 0.79	0.010	0.46	0.25 – 0.84	0.011	Excluded from analysis		

OR = odds ratio; CI = confidence interval; BMI = body mass index; ZAR = South African rands; SGRQ = St George's Respiratory Questionnaire

*Model adjusted for all covariates in full model, excluding SGRQ symptom score, SGRQ activity score, clinic visits and hospital admissions.

†Participants completing the interview in isiXhosa were excluded from the SGRQ due to no tested translated isiXhosa version of the questionnaire. Analyses including SGRQ are therefore restricted to English and Afrikaans speakers only.

‡Test for trend

§Score of ten or more on the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10)

¶History of angina, heart attack or stroke

‖BMI $\geq 30 kg/m^2$

**More than 3 versus ≤ 3 clinic visits in the previous 3 months

††Admitted to hospital in the previous 3 months (yes vs no)

C5: DISCUSSION

Our study describes the symptomatic burden of disease and levels of treatment, and identifies predictors of both the quality of life and receipt of treatment in adults with CRD attending primary healthcare facilities in the Western Cape. This population showed a significant burden of disease, demonstrated by high mean SGRQ scores. According to the SGRQ Manual, healthy individuals without respiratory disease can be expected to have a mean total score of 6, with scores of 12, 9 and 2 for the symptoms, activity and impacts domains respectively.[9] Ferrer *et al* assessed normative values for a general population in Spain and reported similar mean scores for healthy individuals.[12] Various studies have assessed health-related quality of life amongst patients with CRD and have correlated SGRQ total and/or domain scores with severity of disease based on lung function test results.[13]–[18] To limit the length of interviews, we did not assess the SGRQ impacts domain and calculate SGRQ total scores. However, it can assumed that these would be slightly lower than the symptoms and activity scores as this is a consistent finding across many studies.[9],[12]–[15],[17] Comparison of our findings indicates that the high SGRQ scores seen in our study population correlate with severe to very severe, uncontrolled disease.

We found discordance between results of the two SGRQ domains measured; consistently more activity limitation than symptom levels, a feature reported in other studies. As in this study, most report higher activity scores especially amongst females and patients with severe, uncontrolled disease.[9],[12]–[15],[17] This may reflect the fact that this was a working class population where physical activity is demanded both at home and, for those who are employed, in the workplace.

Despite this high burden and severity of disease in our population, it appears that CRD was underdiagnosed and undertreated. These findings are consistent with reports from other countries that show high levels of underdiagnosis ranging from 56.7% to 78%.[19]–[27] In the Cape Town site of the BOLD study, 81.4% of COPD cases confirmed by spirometry were undiagnosed.[19] Similarly, undertreatment of both conditions is common, with results from these and other studies ranging from 39% and 70%.[28]–[31] Surprisingly, patients with more frequent recent healthcare utilisation were less likely to be on treatment. A likely explanation is that these clinic visits and

hospital admissions were for reasons other than respiratory disease, a theory supported by the high levels of comorbidity in this cohort. This indicates missed opportunities for diagnosis and treatment of CRD in both clinic and hospital settings, consistent with a retrospective analysis of patients with COPD in the UK which showed that in the 5 years preceding the diagnosis of COPD, opportunities for diagnosis were missed in 85% of cases.[32] Comorbidity has also been found to be a significant predictor of lack of treatment amongst patients undertreated for COPD.[28]

Language, **age** and **obesity** were significant predictors of receiving treatment. isiXhosa-speaking patients were less likely to be on treatment than Afrikaans-speaking patients, possibly due to their lower socioeconomic status or level of education, or due to a language barrier in clinics where Afrikaans was the usual language of communication. Previous studies have shown an association between obesity and poorer health-related quality of life in patients with CRD[33]–[35], but surprisingly we found no such association. **Although females** reported significantly more activity limitation, **males** reported more severe symptoms. Since lung function tests were not performed, we cannot assess whether the higher symptoms score in males was due to more severe disease, but with preserved activity, or whether they over-reported symptoms.

The association between **unemployment** and higher levels of activity limitation is unsurprising as, in a working-class population, limitation of activity is likely to result in inability to perform physical work duties, resulting in increased unemployment levels. Unemployment was also associated with increased treatment, likely due to the higher burden of disease in this group and the fact that those not working have more opportunity to seek medical attention. These findings are consistent with previous studies which have shown unemployment rates and work disability to be higher amongst patients with CRD compared to those without, and higher amongst patients with more severe respiratory symptoms versus those with controlled disease.[36]–[39] Tottenborg *et al* found that unemployed patients with COPD were more likely to be poorly adherent to medication compared to employed patients, suggesting a bidirectional association between unemployment and reduced quality of life.[40]

Patients wth diabetes had significantly greater activity limitation but less severe symptoms. As the SGRQ symptoms score is more respiratory in nature, i.e. captures symptoms of respiratory impairment, the difference in these findings suggests that the activity limitation in diabetics is non-respiratory and more likely due to comorbid disease. Similarly, the association between **cardiovascular disease** and greater activity limitation is likely to be non-respiratory in nature.

A positive screen for depression was associated with both more severe respiratory symptoms and activity limitation. Previous studies have found that CRD increases the risk of depression[41],[42], but, as we could not establish temporality, we cannot conclude whether depression led to greater impairment in quality of life or vice versa. Nonetheless, there is a strong association which remains significant when analysis is stratified according to treatment status. Despite this association, patients with depression were half as likely to receive CRD treatment, indicative of a significantly high burden of CRD amongst this sub-population, with unmet treatment needs. Our findings are in keeping with other studies which have found that amongst patients with CRD, those with depression have less knowledge about their condition, poorer health-related quality of life, more frequent exacerbations and respiratory-related hospital admissions and an increased risk of mortality compared to those without.[41],[43]–[46] Treatment of depression has also been shown to decrease the risk of emergency department visits and hospitalisations due to COPD.[47]

As **smoking** is a well-recognised contributor to respiratory diseases, we were not surprised that ex-smokers in our study had more severe symptoms than never-smokers. Current smokers were less likely to be on treatment compared to never-smokers, suggesting that clinicians may possibly view cessation of smoking as the first treatment step or that they may be more reluctant to prescribe treatment to patients who continue to smoke. Van Eerd *et al* explored physicians' attitudes and practices towards smokers with COPD. They found that physicians' treatment of smokers was influenced by their inexperience in managing smoking cessation, and that continued smoking caused physicians frustration, resulting in negative attitudes towards smokers and a reluctance to prescribe effective treatment.[48]

Previous **tuberculosis** was predictive of more severe symptoms and activity limitation. Various studies have shown pulmonary tuberculosis (PTB) to be an important risk factor for COPD.[49]–[54] Patients with previous PTB have been found to have earlier development and progression of COPD, as well as poorer bronchodilator response indicating more irreversible disease.[55]–[57] Amongst patients with COPD and previous PTB, more extensive parenchymal involvement has also been associated with a higher risk of exacerbations.[57] Although both Allwood *et al* and Lee *et al* found significantly poorer spirometry results amongst those with previous PTB, in contrast to our study, neither found a difference in symptoms, SGRQ scores, exacerbations or hospitalisations between these groups.[56],[58] Unlike smokers, our study found that patients with previous PTB were more likely to receive CRD treatment than those without. This may be because they are already within the healthcare system and therefore more likely to be diagnosed. Alternatively it may support the hypothesis that healthcare worker practice and prejudice contributes towards smokers being less likely to receive treatment compared to non-smokers.

Strengths of our study include the large sample size and wide range of demographic and socioeconomic characteristics assessed that potentially impact upon CRD and their management. However, our study also has **limitations**. Firstly, patients were recruited and analysed using self-report of treatment rather than review of prescription charts and may therefore have missed patients who were previously diagnosed but were no longer on treatment or not symptomatic at the time of recruitment. However, issues like missing prescription charts, duplicate clinic folders or attendance at more than one clinic are limitations of the alternative method. Eighteen percent of participants recruited by self-report had no evidence of treatment in their prescription charts. However, sensitivity analysis showed similar results when this sub-group was excluded. A second limitation is that the method did not distinguish asthma from COPD and other less common respiratory conditions. The reasons for this approach were that i) trial interventions to confirm diagnoses would have influenced the pragmatic nature of the study design, ii) treatments available for these diseases in primary healthcare clinics are similar and iii) distinguishing asthma from COPD in patients over 40 years is difficult, with up to 20% having features of both. Nonetheless, the study provides a perspective on the burden of CRD in general, and the impact of various patient characteristics including smoking, TB and other

comorbidities. Thirdly, using the presence of prolonged cough or difficulty breathing to recruit patients may have resulted in selection bias as these symptoms may, uncommonly, be cardiac in origin. Although self-reported cardiovascular disease was adjusted for, this did not include diagnosed or undiagnosed cardiac failure. A fourth limitation is the homogeneity of the population in terms of language and socioeconomic status, therefore limiting observations about the impact of these factors in more diverse populations. Lastly, the SGRQ was not completed by isiXhosa-speaking participants. Thus, analyses of predictors of quality of life were limited to English and Afrikaans speakers.

C6: CONCLUSION

Despite these limitations, our study adds to the limited knowledge of the burden of CRD in South Africa, with implications for both clinicians and policymakers. Findings indicate a high burden of disease in this population where manual labour is common and symptoms therefore more limiting. In keeping with global reports, there is major underdiagnosis and undertreatment of CRD in the study population. However a difference from global experience is the very high clinical burden in terms of symptoms and activity limitation, depression, previous TB and of unemployment. We suggest that missed opportunities for diagnosis and treatment in both clinic and hospital settings indicate a need for improved screening for CRD amongst patients with respiratory symptoms, especially those with identified risk factors or comorbid conditions. Our results suggest underdiagnosis of depression; improved mental health screening amongst patients with CRD may result in both improved mental health and control of respiratory disease. The lack of treatment prescribed to smokers indicates a need to explore whether healthcare workers are equipped or reluctant to support behaviour change such as smoking cessation and/or provide treatment to smokers who are unable or unwilling to quit. Health authorities need to prioritise early recognition and treatment for TB to reduce the future burden of COPD, especially in areas with a high burden of disease such as the Western Cape. By addressing the above needs, earlier diagnosis and treatment of CRD may be achieved, resulting in improved quality of life and mental health of patients, greater productivity in the workforce and a reduced burden on the healthcare system.

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C8: AUTHOR CONTRIBUTIONS

The author conducted all statistical analyses and wrote the manuscript.

C9: FUNDING

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C10: CONFLICTS OF INTEREST

None.

C11: REFERENCES

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PART D: APPENDICES

Appendix A1. PC101 trial ethics approval from UCT HREC (original)

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6626 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

01 February 2011

HREC REF: 119/2010

Prof D Levitt
Chronic Diseases Initiative in Africa
J47, OMB

Dear Prof Levitt

PROJECT TITLE: ***Development and evaluation tools to manage chronic non-communicable diseases***

Thank you for submitting your new study and response to the Faculty of Health Sciences Human Research Ethics Committee.

Date of meeting: 28 January 2011

Decision: Approval was granted at a full HREC meeting held on the 28 January 2011. Approval is granted for a further 12 months until 28 January 2012.

Voting for approval was as follows: Approved 9 of the 12 core or nominated alternate members present; Not approved 0; Abstentions 0.

The full committee determined that this study posed no greater than minimal risk to participants and that future reviews of this study could be expedited. (Point # 9 OHRP Guidance, August 11, 2003).

Voting for approval was as follows: Approved 9 of the 12 core or nominated alternate members present; Not approved 0; Abstentions 0.

Approval includes:

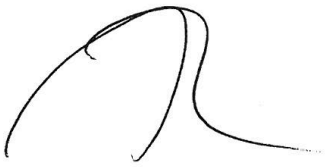
- Proposal March 2010 Revised December 2010.
- Patient Information and Consent Forms

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

Please quote the REC. REF in all your correspondence.

lemjedi

Yours sincerely



PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix A2. PC101 trial ethics approval from UCT HREC (current)

HUMAN RESEARCH ETHICS COMMITTEE
15 JUL 2016
HEALTH SCIENCES FACULTY

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637, IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/07/2017
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	19/7/2016

Comments to PI from the HREC

Letter dated 14/7/2016; received 15/7/2016 with Pat Jay

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	14/7/2016		
HREC REF Number	119/2010	Current Ethics Approval was granted until	30/01/2016
Protocol title	Development and Evaluation Of Tools To Manage Chronic Non-Communicable Diseases		
Protocol number (if applicable)	NHLBI-HV-09-12 IRB 00001938 Federal Wide Assurance Number: FWA00001637		
Are there any sub-studies linked to this study?	☐ Yes √☐ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Naomi Levitt		
Department / Office, Internal Mail Address	Department of Medicine, Faculty of Health Science University of Cape Town Private Bag X3		

1.1 Does this protocol receive US Federal funding?	√☐ Yes	☐ No

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix A3. PC101 trial ethics approval from PGWC

DEPARTMENT of HEALTH
Provincial Government of the Western Cape

COMPONENT

claudabr@pgwc.gov.za
tel: +27 21 483 9907; fax: +27 21 483 9895
1st Floor, Southern Life Centre, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za

REFERENCE: 18/19/RP152/2010
ENQUIRIES: Dr N Peer

Chronic Diseases Initiative in Africa
Department of Medicine
Faculty of Health Sciences
University of Cape Town
Private Bag X3
Observatory
7935

Fax: (021) 406 6513

For attention: Prof D Levitt

Effectiveness of an integrated care guideline training programme on the processes and outcomes of non-communicable chronic diseases primary care in South Africa: A pragmatic cluster randomised controlled trial

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 Dr R Crous (044) 803 2708 to assist you with access to the facilities:

Crags Clinic
Kranshoek Clinic
Kwanokathula Clinic
New Horizon Clinic
Plettenberg Bay CDC
Haarlem Clinic
Uniondale (Lyonsville) Clinic
Thembalethu CDC
Blanco Clinic
Conville CDC
George Civic Centre
Lawaaikamp Clinic
Pacaltsdorp Clinic
Parkdene Clinic

The Afrikaans or Xhosa version of this document is available on request.

page 1 of 3

Rosemoor Clinic
Riversdale Clinic
Albertinia Clinic
Heidelberg Clinic
Calitzdorp (Bergsig)
Ladismith (Nissenville) Clinic
Zoar Clinic
Hornlee Clinic
Keurhoek Clinic
Khayelethu Clinic
Knysna Town Clinic
Sedgefield Clinic
Wit Lokasie Clinic
Alma Clinic
D'Almeida Clinic
Eyethu Clinic
Great Brak River Clinic
Bongolethu Clinic
Bridgeton CDC
De Rust (Blommenek) Clinic
Dysseldrop Clinic
Oudtshoorn Clinic
Toekomsrus Clinic

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 report within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (healthres@pgwc.gov.za).
3. The reference number above should be quoted in all future correspondence.

We look forward to hearing from you.

Yours sincerely

DR J CUPIDO
DEPUTY-DIRECTOR GENERAL
DISTRICT HEALTH SERVICES AND PROGRAMMES
DATE: 14-12-2010.

CC: **DR R CROUS** **DIRECTOR: EDEN DISTRICT**

The Afrikaans or Xhosa version of this document is available on request.

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Appendix A4. PC101 trial summary

<table>
<tr><th colspan="2">Primary Care 101 Trial Summary
January 2014</th></tr>
<tr><td>Title</td><td>Effectiveness of an integrated care guideline training program on the processes and outcomes of non-communicable chronic diseases in primary care in South Africa: a pragmatic cluster randomized controlled trial</td></tr>
<tr><td>Disease/ condition/ study domain</td><td>Primary care management of:
diabetes
hypertension
chronic respiratory disease
depression</td></tr>
<tr><td>Purpose of the study</td><td>To evaluate the effectiveness of an integrated guideline-based training programme for primary healthcare nurses and doctors (Primary Care 101) on processes and outcomes of non-communicable chronic diseases, compared with current training and support for chronic diseases.</td></tr>
<tr><td>Design/ methodology</td><td>Pragmatic, two-arm, cluster randomized controlled trial</td></tr>
<tr><td>Ethics approval</td><td>University of Cape Town Human Research Ethics Committee and the Western Cape Provincial Department of Health</td></tr>
<tr><td>Participants – inclusion criteria</td><td><u>Clinics:</u>
38 nurse-led primary care clinics in the Eden district of the Western Cape province, South Africa (all clinics service around or more than 10 000 attendances per year)
<u>Patients:</u>
Age ≥ 18 years and
Planning to reside in the area for the next year and
Written consent to participate in the study and
Capable of actively engaging in an interviewer-administered questionnaire at the time of recruitment and 14 months later
Four cohorts are defined. Patients may fulfil inclusion criteria for more than one cohort. Inclusion criteria based on target chronic disease:

<table><tr><th>Target condition</th><th>Inclusion criteria</th></tr><tr><td>Hypertension</td><td>Self-reported hypertension on medication</td></tr><tr><td>Diabetes</td><td>Self-reported diabetes on medication</td></tr><tr><td>Chronic respiratory disease (CRD)</td><td>Self-reported asthma/ COPD/ chronic bronchitis/ emphysema on medication OR Cough and/or difficult breathing >2 weeks (not on TB treatment in the past 3 months)</td></tr><tr><td>Depression</td><td>CES-D 10 (Centre for Epidemiologic Studies Depression Scale) score of 10 or more</td></tr></table></td></tr>
<tr><td>Participants – exclusion criteria</td><td><u>Clinics:</u>
Clinics with less than 9000 attendances in the year preceding</td></tr>
</table>

<table>
<tr><td></td><td>randomization
• Satellite and mobile clinics
• Clinics providing exclusive antiretroviral treatment services
<u>Patients:</u>
• Inability to meet the above criteria</td></tr>
<tr><td>Anticipated start date</td><td>Baseline data collection: March 2011
Training: May 2011</td></tr>
<tr><td>Anticipated end date</td><td>June 2014</td></tr>
<tr><td>Target number of participants</td><td><u>Clinics:</u> 38
<u>Patients:</u> Estimated 4598
All calculations are for two-sided tests and are powered at 85%.
Sample sizes have been inflated by 20% to allow for loss to follow up at 1 year.

<table><tr><th>Chronic disease</th><th>Cluster size</th><th>Int</th><th>Con</th><th>ICC</th></tr><tr><td>Hypertension</td><td>60</td><td>0.36</td><td>0.25</td><td>0.04</td></tr><tr><td>Diabetes</td><td>60</td><td>0.36</td><td>0.25</td><td>0.04</td></tr><tr><td>CRD</td><td>27</td><td>0.25</td><td>0.15</td><td>0.02</td></tr><tr><td>Depression</td><td>60</td><td>0.10</td><td>0.04</td><td>0.04</td></tr></table></td></tr>
<tr><td>Interventions</td><td><u>Intervention group:</u>
Primary Care 101:
• Integrated care guideline
• Training of existing PALSA PLUS trainers as outreach trainers for expanded guideline (one 5 day training)
• Outreach training of all primary care staff in intervention clinics (estimated 6 sessions per clinic)
• Expanded prescribing provisions for professional nurses (PN) trained in Primary Care 101 at intervention clinics for the duration of the trial.
• PALSA PLUS maintenance training to continue in intervention group
<u>Control group:</u>
PALSA PLUS training and guideline</td></tr>
<tr><td>Primary outcome measures</td><td>Based on target chronic condition.
<table><tr><th>Chronic disease</th><th>Primary outcome</th></tr><tr><td>Hypertension</td><td>Treatment intensification:
Increase in dose of antihypertensive medication or
Addition of new antihypertensive or
Addition of aspirin or
Addition/ increase in dose of statin</td></tr><tr><td>Diabetes</td><td>Treatment intensification:
Increase in dose of oral hypoglycaemic/ insulin or
Addition of new oral hypoglycaemic / insulin or
Addition/ increase in dose of ACE inhibitor or
Addition of aspirin or</td></tr></table></td></tr>
</table>

<table>
<tr><td></td><td><table>
<tr><td></td><td>Addition/ increase in dose of statin</td></tr>
<tr><td>Chronic respiratory disease</td><td>Treatment intensification:
Addition of beta-agonist or
Addition of ipratropium bromide or
Addition of oral theophylline or
Addition/ increase in dose of inhaled corticosteroid</td></tr>
<tr><td>Depression</td><td>Case detection:
Started on antidepressant medication or
Referred for counselling or
Referred to psychiatric services</td></tr>
</table></td></tr>
<tr><td>Secondary outcome measures</td><td><u>Process outcomes:</u>
1. Breakdown of treatment intensification by components
2. Appropriate screening for complications:
Proportion reporting dilated eye exam
Proportion reporting foot exam
3. Smoking endpoints:
Proportion receiving smoking cessation advice
Readiness to quit smoking
Proportion who quit
Number of units smoked per day
<u>Intermediate outcomes</u>
4. Systolic BP
5. HbA1C
6. Waist circumference
7. BMI
<u>Health outcomes</u>
8. Health related quality of life (EuroQol 5D, St Georges Respiratory Questionnaire, WHO Disability Assessment Schedule II)
9. Mortality
<u>Economic:</u>
10. Income and changes due to illness
11. Clinic visits
12. Admissions
13. Inpatient days</td></tr>
</table>

Appendix A5. PC101 trial patient information sheet and consent form

Patient information sheet

Rec no IRB 00001938
Version Number: Revised 28 March 2011

We invite you to participate in a study. Before you agree to take part you need to understand what it involves.

Purpose of study

The purpose of the study is to evaluate a nurse training programme. Some clinics in the Eden district will receive the programme, which includes providing the nurses with, and training them in the use of a new guideline. Other clinics will continue with the usual care. We want to evaluate whether the new programme improves the treatment patients receive compared with usual care. We will also be looking at a new way to predict someone's risk of developing a heart attack or stroke over the next 10 years.

What are the possible benefits of participating in this study?

The information that we obtain from the study will help us understand whether changing the way training is delivered results in improvements of care for people with chronic diseases and what costs are involved for patients (e.g. transport, GP visits etc.)

What are the possible drawbacks or discomforts in participating in this study?

We may ask you to have a blood sample taken. This will be the only discomfort in this study. Risk of infection will be minimized by using sterile procedures, and all blood samples will be taken by suitably qualified persons.

We estimate that the questionnaire will take approximately 20 to 40 minutes. We may want to interview you once more in about 14 months time. The second interview should be quicker than the first.

Do I have to participate in this study?

Your participation in this study is voluntary. Should you agree to participate, we will ask you to sign the attached form. You are free to withdraw from the study at any stage and this will in no way affect the care you receive at the clinic.

What will happen to me if I participate?

We will ask you some questions using a structured questionnaire and may record any medication you might be taking. We will then measure your height, weight, and the width around your waist and hip using a tape measure with your clothes on. We will also measure your blood pressure and may take a blood sample from your arm. We will take 15 ml of blood (3 teaspoons). The blood will be used to measure the level of fat in the blood and a test to see how high your blood sugar level is. The needle may cause you a little discomfort, but it will be taken in the way blood is usually taken from you when you attend the clinic. If any serious abnormal findings are identified we will inform the staff at the clinic who can then treat you appropriately.

We may want to see you again in about 14 months time. Then we will ask you some more questions like we will today and may also ask you for another blood sample to repeat the same tests. After the second time we see you we will provide you with a gift voucher to the value of R100 that you will be able to use in a shop near you, as a token of our appreciation in this important study.

We are also asking your permission to review your hospitalisation records, should you be hospitalised during the course of the study. We will also ask you for your South African identity number if available. This will allow linkage with a research copy of the Department of Home Affair's databases to track your vital status. This research copy is securely stored by the Medical Research Council, and is used to complete research on the burden of diseases in South Africa. No identifiable information concerning your person will be made available to persons outside of the

study, and even the researchers who will analyse the data will use datasets from which your identifiers will be removed.

Will the information remain confidential?

Should you agree to take part in the study all your records will be seen by the researchers only. Your information will not be seen by any other persons or parties not involved in this study.

Contact details of the study staff:

If you have any questions you can contact the following study staff members:

Name : Serena Van Haght Telephone number:

If you have any complaints regarding this research study you may contact the University of Cape Town, Faculty of Health Science, Human Research Ethics Committee at (021 406-6492).

Consent:

I,.....

(Name of participant in block letters)

have read and understood all the information given to me about my participation in this study and I have been given the opportunity to discuss it and ask questions. I voluntarily agree to take part in this study and understand that I will receive a copy of this consent form.

....

Signature of Participant Date

I have explained the nature and purpose of the study to the participant named above.

....

Signature of Principal Investigator or delegate Date

.....

Printed name of Principal Investigator or delegate

Appendix A6. PC101 trial eligibility screen and baseline questionnaire

Eligibility Screen

1	What is your home language	English	Afrikaans	IsiXhosa

2	Date of interview:
3	Clinic:
4	Interviewer Code:

We are conducting a study to evaluate care and risk factors for common chronic diseases, including diabetes, hypertension, chest conditions and depression, and we are looking for people with certain criteria to take part. I would like to start by asking you a few questions to see whether you qualify to take part in our study.

5	What is your name	First name	Surname
6	What is your date of birth	*if ≥18 goto 7*	*if <18 goto 25*
7	Enter sex	Male	Female
8	Are you planning to stay in the area for the next year	Yes*: goto 9*	No*: goto 18*
9	Are you taking medicine for high blood pressure (hypertension)	*Yes: goto 10*	*No: goto 10*
10	Are you taking medicine for diabetes ('sugar')	*Yes: goto 11*	*No: goto 11*
11	Are you taking medicine for asthma or chronic bronchitis or emphysema	*Yes: goto 13*	*No: goto 12A*
12A	Do you have cough or difficult breathing which has lasted for more than 2 weeks	*Yes: goto 12B*	*No goto 13*
12B	Have you been on treatment for TB in the past 3 months *[Yes to 12A and No to 12B = yes for question 12]*	*Yes: goto 13*	*No: goto 13*

13 We would like to know how your general well-being has been over the past week.
I am going to read a list of some of the ways you may have felt or behaved during the last week. Using the showcard, please indicate how often you have felt this way during the **past week**.

Interviewer mark one option on each line

During the past week...	Rarely or none of the time (less than 1 day)	Some or little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
I was bothered by things that usually don't bother me	0	1	2	3
I had trouble keeping my mind on what I was doing	0	1	2	3
I felt depressed	0	1	2	3
I felt that everything I did was an effort	0	1	2	3
I felt hopeful about the future	0	1	2	3
I felt fearful	0	1	2	3
My sleep was restless	0	1	2	3
I was happy	0	1	2	3
I felt lonely	0	1	2	3
I could not "get going"	0	1	2	3

TOTAL SCORE:

Eligible for trial if one or more of the following:	***Yes: eligible for trial: goto 14***	***No: not eligible for trial: goto 18***
• ***YES to question 9 (hypertension cohort)*** • ***YES to question 10 (diabetes cohort)*** • ***YES to question 11 (respiratory cohort)*** • ***YES to question 12A AND NO to question 12B (respiratory cohort)*** • ***Score of 10 or more for question 13 (depression cohort)***		
*Interviewer to fill in **enrolment log** (paper chart) to keep a record of how many patients in each of the 4 cohorts (hypertension, diabetes, chronic respiratory disease and depression risk score ≥10) the clinic has recruited.*		

14	***[eligible for trial, now see if eligible for validation study as well with questions 14-17]*** *Computer to draw age from previous question*	*If ≥35 goto 15.*	*If <35 goto 22*
15	Has a doctor or nurse ever told you that you have or have had any of the following: *15A* a heart attack — *yes* / *no* *15B* a stroke — *yes* / *no* *15C* angina (chest pains with exertion/activity) — *yes* / *no*	*If YES to any of the three (15A, 15B or 15C) then eligible for trial only: goto 22*	*If NO to all three (15A, 15B and 15C) then goto 16*
16	Do you have a South African identity (ID) number	*Yes: goto 17*	*No: eligible for trial only: goto 22*
17	Would you be able to give me your ID number today	*Yes: eligible for trial and validation: do **not** enter ID number at this stage: goto 23*	*No: eligible for trial only: goto 22*

18	***[not eligible for trial, now assess whether eligible for validation study with questions 18-21]*** *Computer to draw age from previous question*	*If ≥35 goto 19*	*If <35 goto 25*
19	Has a doctor or nurse ever told you that you have or have had any of the following: 19A a heart attack — yes / no 19B a stroke — yes / no 19C angina (chest pains with exertion/activity) — yes / no	*If YES to any of the three (19A, 19B or 19C) then not eligible for trial or study: goto 25*	*If NO to all three (19A, 19B and 19C) goto 20*
20	Do you have a South African identity (ID) number	*Yes: goto 21*	*No: not eligible for trial or validation study: goto 25*
21	Would you be able to give me your ID number today	*Yes: eligible for validation study only: do **not** enter ID number at this stage: goto 24*	*No: not eligible for trial or validation study: goto 25*

22	***[Eligible for trial only]****:* You qualify for our study and we would like you to take part. I will go through the written information with you and if you would like to take part then we will ask you to sign the form saying you are willing to participate. I will then go through the questionnaire with you, check your measurements (blood pressure, weight, height, waist circumference and hip measurement), and we may want to take a blood sample*. [HbA1c]* *[Interviewer to go through the patient information and consent form. A study number will then be allocated]*
23	***[Eligible for trial and validation]: -> AS2*** You qualify for our study and we would like you to take part. I will go through the written information with you and if you would like to take part then we will ask you to sign the form saying you are willing to participate. I will then go through the questionnaire with you, check your measurements (blood pressure, weight, height, waist circumference and hip measurement), and we may want to take a blood sample [HbA1c, lipids] *[Interviewer to go through the patient information and consent form. A study number will then be allocated]*
24	*[**Eligible for validation only***: *-> AS3* You qualify for our shorter questionnaire and we would like you to take part. I will go through the written information with you and if you would like to take part then we will ask you to sign the form saying you are willing to participate. I will then go through the questionnaire with you, check your measurements (blood pressure, weight, height, waist circumference and hip measurement), and we may want to take a blood sample *[HbA1c, lipids]* *[Interviewer to go through the patient information and consent form. A study number will then be allocated]*
25	***[Not eligible for trial or validation study]*** We are looking for people with certain criteria or illnesses to take part in the study. You do not have the criteria we are looking for so we will not be able to include you in the study. Your usual care will not be affected by not taking part in our study. We would like to thank you very much for answering the questions and for your time today and we wish you well. *[Interviewer to document that the eligibility screen was done and that the patient is **not eligible for trial or validation** study. No further action required.]*

Questionnaire 1:

[Conducted immediately after the eligibility screen for patients eligible to take part in the trial and validation study, or just the trial.]

I am now going to go through the questionnaire with you. We will need to take three blood pressure readings during the course of the interview, at least two minutes apart. *[interviewer to take first blood pressure reading now].* I would like to start by asking you a few questions about your past illnesses: *1* Has a doctor or nurse ever told you that you have or have had any of the following			
1A	high blood pressure (hypertension)	*Yes*	*No*
1B	heart attack	*Yes*	*No*
1C	stroke	*Yes*	*No*
1D	angina (chest pains with exertion/activity)	*Yes*	*No*
1E	depression	*Yes*	*No*
1F	TB	*Yes*	*No*
1G	diabetes ('sugar')	*Yes*	*No*

2	I am now going to ask you some questions about smoking		
2A	Do you currently smoke cigarettes daily	*Yes: goto 2B*	*No: goto 2E*
2B	How old were you when you first started smoking daily	Age in years	Don't remember/not sure
2C	On average, how many cigarettes do you smoke each day	*Enter number*	
2D	Have you had advice from a health worker to stop smoking in the past year	*Yes: goto 2J*	*No: goto 2J*

2E	In the past, did you ever smoke daily	*Yes: goto 2F*	*No: goto 2J*
2F	How old were you when you first started smoking daily	Age in years	Don't remember/not sure
2G	How old were you when you stopped smoking daily	Age in years	Don't remember/not sure
2H	On average, how many cigarettes did you smoke each day	*Enter number and goto 2J*	

2J	Are you currently a smoker. Choose one of the following options	Yes, I currently smoke *Goto 2K*	No, I quit within the last 6 months *Goto 3*	No, I quit more than 6 months ago *Goto 3*	No, I have never smoked *Goto 3*
2K	In the last year, how many times have you quit smoking for at least 24 hours	*Enter number:* *Goto 2L*			
2L	Are you seriously thinking of quitting smoking. Choose one of the following options	Yes, within the next 30 days	Yes, within the next 6 months	No, not thinking of quitting	

3	I would like to ask about your current state of health. Please indicate which of the following statements best describe your health state TODAY (choose one option per group)

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	❑

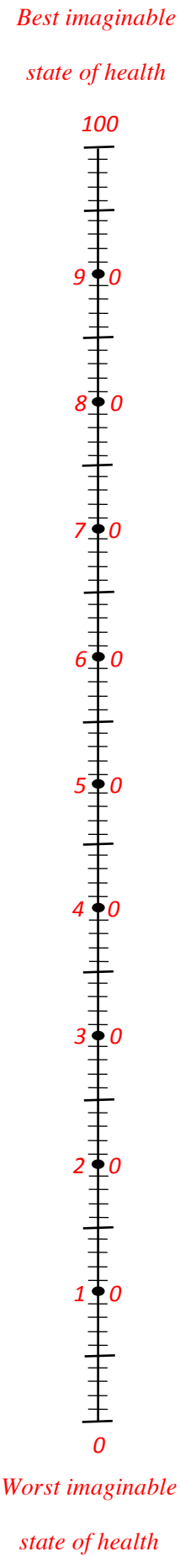
Anxiety/Depression

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



4	*[Modified St Georges Questionnaire for chronic respiratory disease patients only]* I would now like to ask you some more detailed questions about your cough or breathing problem

Questions about how much chest trouble you have had over the past 3 months. Please tick one box for each question:					
Over the past 3 months, I have coughed:	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
Over the past 3 months, I have brought up phlegm (sputum):	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
Over the past 3 months, I have had shortness of breath:	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
Over the past 3 months, I have had attacks of wheezing:	Most days a week	Several days a week	A few days a month	Only with chest infections	Not at all
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

How long did the worst attack of chest trouble last? (Go to next question 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

Over 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

If you have a wheeze, is it worse in the morning? Please tick one:	yes	no

Questions about what activities usually make you feel breathless <u>these days</u>. Please tick in 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 the level		
Walking up a flight of stairs		
Walking up hills		
Playing sports or games		

These are questions about how your activities might be affected by your breathing. Please tick in 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, carrying 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 the garden, jog or walk at 8 kilometers per 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		

5	I am now going to ask you some questions about the health care you have received and the medicines you were given in the last year					
5A	Has a health worker examined the back of your eyes in the last year *[show picture of ophthalmoscope eye exam]*			*yes*	*no*	
5B	Has a health worker examined your feet in the last year with any of the following *[showcard picture of foot, tuning fork, pin, cotton wool]*			*yes*	*no*	
5C	Have you received counselling from any of the following people in the last year (counseling is not just receiving advice on how to take medication. It means talking with someone in a way that helps you to find solutions to your problems, or receive emotional support)					
	Doctor at a clinic/outpatients			*Yes*	*No*	
	Doctor at a general practice			*Yes*	*No*	
	Nurse			*Yes*	*No*	
	Mental health nurse			*Yes*	*No*	
	Clinic counsellor			*Yes*	*No*	
	Social worker			*Yes*	*No*	
	Psychiatrist or psychologist			*Yes*	*No*	
	Religious counsellor, traditional healer or faith healer			*Yes*	*No*	
5G	Have you had a 'flu vaccine in the last year		*Yes*	*No*		
5H	Has a health worker given you advice in the last year about weight management		*Yes*	*No*		
5I	How often do you exercise	Rarely/	1 to 3 times	1 time per	2 to 4	5 to 6	daily

	vigorously enough to work up a sweat. Choose one of the following options:	never	per month	week	times per week	times per week	
5J	Are you taking any medicine regularly that was prescribed by a doctor or nurse			*Yes: goto 5K*	*No: goto 5L*		
5K	I am now going to look at your file to see what medicines have been prescribed over the last year						
5L	Are you currently taking any medicine for TB			*yes*	*no*		
5M	Are you currently taking any ARVs (antiretrovirals)			*yes*	*no*		
5N	How often do you miss your medication, either forgetting to take it or deciding not to			Never/very rarely	sometimes	often	
5O	I am now going to take your second blood pressure reading						

6 We would like to understand how much time and money your illness costs you. In order to do this we need to ask some questions about your use of health care services, your employment status and income. We would like to remind you that all the information you give us is confidential.						
6A Have you had a chest x-ray over the last 3 months	*Yes goto 6B*				*No goto 6C*	
6B Please state how many chest x-rays you have had over the last 3 months	*Enter number*					
6C Have you had blood tests over the last 3 months	*Yes*			*No*		
6D How do you usually travel to this clinic (choose one of the following options)	Walk *goto 6H*	Taxi: *goto 6F*	Private motor vehicle (such as car) *Goto 6E*	Bus *goto 6F*	Patient transport/ ambulance *goto 6F*	Other (specify) *goto 6F*
6E What was the distance travelled to the clinic (in km one way) then goto 6H	*Enter distance in km one way*					
6F Do you usually pay a transport fare	*Yes:Goto 6G*			*No: goto 6H*		
6G How much do you pay for a return fare	*Enter amount in rands*					
6H Please detail other costs usually associated with your visit	Accommodation *(enter amount in rands)*			Food *(enter amount in rands)*		
6I Aside from today, have you visited this clinic in the last 3 months	*Yes: goto 6J*			*No goto 6K*		
6J How many times have you visited this clinic in the last 3 months (excluding today)	*Enter number of visits*					
6K Have you visited any other health care provider in the last 3 months	*Yes: goto 6L*			*No: goto 6M*		

6I	Please indicate which of the following health care providers you have visited in the last 3 months. I will also ask you some more details about those visits.		
i) Another clinic ii) Hospital (outpatient visits only) iii) General Practitioner iv) Private Pharmacy v) Traditional healer/ herbalist vi) Other (please state)			
For each option selected, the following details will be asked:			
a)	Number of visits in the last 3 months		
b)	Did you pay a fee on your last visit	Yes	no
c)	*If yes:* What was the fee in rands	R	

d)	What transport did you use to get to your last visit	i)walk	li)taxi	iii)car	iv)bus	v) patient transport/ ambulance	vi)other
e)	Did you pay a transport fare on your last visit				Yes		no
f)	*If yes:* What was the return fare in rands				R		
g)	If you used your own car, what was the distance travelled (in kilometers one way)						
h)	Please detail other costs associated with your last visit				i)accommodation		ii)food

6M Have you been admitted to hospital in the last 3 months	*Yes: goto 6N*	*No: goto 6U*
6N How many times have you been admitted to hospital in the last 3 months	*Enter number:*	
6O How many nights in total have you spent in hospital over the last 3 months:	*Enter number:*	
6P What is the total amount you have had to pay for your admissions over the last 3 months (your out-of-pocket expenses)	*Enter amount in rands:*	

6Q For the most recent admission to hospital please provide the following details:

How did you travel to the hospital (choose one of the following options):	Walk: *goto 6U*	Taxi: *goto 6S*	Private motor vehicle (such as car) *Goto 6R*	Bus: *goto 6S*	Patient transport/ ambulance *goto 6S*	Other (specify): *goto 6S*

6R What was the distance travelled to the hospital (in km one way) *then goto 6U*	*Enter distance in km one way:*	
6S Did you pay a transport fare	*Yes:Goto 6T*	*No: goto 6U*
6T How much did you pay for a return fare	*Enter amount in rands*	

6U Which of the following best describes your employment status? Choose *one* :	
Employed	How much did you earn last month (excluding grant income)
	How many days were you unable to work because of illness in the last 3 months (including health care visits)
	How much income have you lost in the last 3 months as a result of not being able to work because of any illness
Self-employed	How much did you earn last month (excluding grant income)
	How many days were you unable to work because of illness in the last 3 months (including health care visits)
	How much income have you lost in the last 3 months as a result of not being able to work because of any illness
Student/learner	How many days have you been unable to attend school/college because of illness in the last 3 months (including health care visits)
Unemployed and looking for work	
Unemployed and not looking for work	

6V Are you getting a pension or grant (eg disability or child care grant)	*Yes: goto 6W*	*No: goto 6X*
6W What was your total grant income in the last month	*Enter amount in rands*	
6X Have you lost your job or resigned because of illness during the past year	*Yes: goto 6Y*	*No: goto 7*
6Y Before you lost your job or resigned, how much did you earn in the last month you worked (excluding grant income)	*Enter amount in rands*	

6Z Since losing your job or resigning, have you got another job	*Yes: goto 8*	*No: goto 8*
8 I am now going to take your third blood pressure reading, height, weight, waist circumference and hip measurement.		
9 If a blood test is required: When did you last have anything to eat or drink, other than water	Date:	Time:
10 It is important for our study that we interview you once more, in 14 months time. I will schedule that appointment for you now and we will send you SMS reminders from 3 months before the appointment. I will provide you with a contact number. Please let us know if your cell phone number changes or if you need to reschedule the appointment. In order to make it as easy as possible to contact you if necessary, I would be grateful if you could provide as many of the following contact details as possible:		

Home address	
Telephone number at home	
Cell phone number	
Work address	
Work telephone number	
Alternative number (friend, relative, neighbour)	
Clinic folder number	
Re-enter clinic folder number	
Name of hospital patient attends	
Hospital folder number if available	
ID number	
Re-enter ID number	

We would like to thank you very much for your time today. We look forward to seeing you next year.

Questionnaire for patients eligible for Validation Study only:

I am now going to go through the questionnaire with you. We will need to take three blood pressure readings during the course of the interview, at least two minutes apart. *[interviewer to take first blood pressure reading now].*

1. Has a doctor or nurse ever told you that you have or have had diabetes ('sugar')	*Yes*	*No*

2.: Are you taking any medicine regularly that was prescribed by a doctor or nurse for high blood pressure (hypertension) *fieldworker to confirm from prescription charts*	*Yes*	*No*

3. Are you taking any medicine regularly that was prescribed by a doctor or nurse for cholesterol *fieldworker to confirm from prescription charts*	*Yes*	*No*

4. I am now going to look at your file to see what medicines have been prescribed for hypertension and cholesterol

[interviewer to take second blood pressure reading if ≥2 minutes since first reading]

5. Do you currently smoke cigarettes daily	*Yes:*	*No:*

6. How often do you exercise vigorously enough to work up a sweat. Choose one of the following options:	*Rarely/ never*	*1 to 3 times per month*	*1 time per week*	*2 to 4 times per week*	*5 to 6 times per week*	*daily*

7. In case we need to contact you, I would be grateful if you could provide as many of the following contact details as possible:	
Home address	
Telephone number at home	
Cell phone number	
Work address	
Work telephone number	
Alternative number (friend, relative, neighbour)	
Clinic folder number	
Re-enter clinic folder number	
Name of hospital patient attends	
Hospital folder number if available	
ID number	
Re-enter ID number	

8. I am now going to take your third blood pressure reading, height, weight, waist circumference and hip measurement. You will require a blood test. You will not require a blood test		
9 .If a blood test is required: When did you last have anything to eat or drink, other than water	*Date:*	*Time:*

We would like to thank you very much for your time today. We will not need to interview you again and we wish you well.

Appendix A7. PC101 trial follow-up questionnaire

Thank you for returning for your Chronic Disease Study follow-up interview.

1	I would like to start by checking which language you would like to use for the interview:	i) English	ii) Afrikaans	iii) IsiXhosa

2	Date of interview:
3	Clinic:
4	Interviewer Code:

We have checked our records and we are not able to find a complete consent form for you. Please could we ask that you sign the same form again now. *Patient information sheet and consent form here*

5	I would like to ask about your current state of health. Please indicate which of the following statements best describe your health state TODAY (choose one option per group) *EQ5D here*

6	I am now going to take your first blood pressure reading

7A	We would like to know in more detail about how you felt, not just today, but over the past week. I am going to read a list of some of the ways you may have felt or behaved. Using the showcard, please indicate how often you have felt this way during the past week. *Interviewer mark one option on each line. CESD10 here.*

7B	Has the thought of ending your life been on your mind	Yes	No

8A	I would now like to ask you some more detailed questions about your cough or breathing problem that you reported at our first interview *(Questions 8A-8F for respiratory cohort patients only) SGRQ for English and Afrikaans here*

8B	Since our interview about a year ago, have you had to visit a doctor or nurse because your chest was bad, but not including routine check-ups and visits just to collect medicines.	Yes: go to 8C	No: go to 8F
8C	Number of clinic or general practice (GP) visits for a bad chest	Enter number:	
8D	Number of hospital casualty or emergency visits for a bad chest	Enter number:	
8E	Number of hospital admissions for a bad chest (when you have spent at least one night in casualty, emergency ward, or hospital):	Enter number:	
8F	Since our interview about a year ago, how many times have you had to take short courses of steroids (4-8 small white pills a day) for your chest problem	Enter number:	

9	I am now going to ask you some questions about smoking

9A	Are you currently a smoker. Choose one of the following options	i)Yes, I currently smoke	ii)No, I quit within the last 6 months	iii)No, I quit more than 6 months ago	iv)No, I have never smoked *Go to 10*

		Go to 9B	*Go to 10*	*Go to 10*	
9B	On average, how many cigarettes do you smoke each day	*Enter number*			
9C	Since our interview about a year ago, how many times have you quit smoking for at least 24 hours	*Enter number:*			
9D	Are you seriously thinking of quitting smoking. Choose one of the following options	i)Yes, within the next 30 days	ii)Yes, within the next 6 months	iii)No, not thinking of quitting	
9E	Since our interview about a year ago, has a health worker advised you to stop smoking?		Yes	No	

10	I would like to ask you a few questions about your health and the healthcare you have received. Since our interview about a year ago, has a health worker given you a new diagnosis of any of the following:			
10A	high blood pressure (hypertension)	Yes	No	
10B	diabetes ('sugar')	Yes	No	
10C	Asthma, chronic bronchitis or emphysema	Yes	No	
10D	TB	Yes: *go to 10E*	No*: go to 10F*	
10E	When did you start treatment for TB	*Drop down options for month and year, or not yet started*		
10F	Depression	*Yes*	*No*	
10G	Has a health worker examined the back of your eyes since our interview about a year ago *[fieldworker to show picture of ophthalmoscope eye exam]*		Yes	No
10H	Has a health worker examined your feet with any of the following since our interview about a year ago *[fieldworker to show picture of foot, tuning fork, pin, cotton wool]*		Yes	No
10I	Have you had a 'flu vaccine since our interview about a year ago	Yes	No	

10J	Have you had a chest x-ray since our interview about a year ago	Yes *go to 10K*	No *go to 10L*
10K	Please state how many chest x-rays you have had since our interview about a year ago	*Enter number*	
10L	Have you had blood tests since our interview about a year ago	Yes	No
10M	Has a health worker given you advice about weight management since our interview about a year ago	Yes	No
10N	Have you received counselling from any of the following since our interview about a year ago (counseling is not just receiving advice on how to take medication. It means talking with someone in a way that helps you to find solutions to your problems, or receive emotional support)		

i)	Doctor at a clinic/outpatients	Yes	No
ii)	Doctor at a general practice	Yes	No
iii)	Nurse	Yes	No
iv)	Mental health nurse	Yes	No
v)	Clinic counsellor	Yes	No
vi)	Social worker	Yes	No
vii)	Psychiatrist or psychologist	Yes	No
viii)	Religious counsellor, traditional healer or faith healer	Yes	No

11	I am now going to take your second blood pressure reading

12	We now want to ask you a few questions about how your health may affect the things you do: *WHODAS2 here*

13	We would like to understand how much time and money your illness costs you. In order to do this we need to ask some questions about your use of health care services, your employment status and income. We would like to remind you that all the information you give us is confidential.						
13A	How do you usually travel to this clinic (choose one of the following options)	i)Walk *go to 13E*	ii)Taxi *go to 13C*	iii)Private motor vehicle (such as car) *go to 13B*	iv)Bus *go to 13C*	v)Patient transport/ ambulance *go to 13C*	vi)Other (specify) *go to 13C*
13B	What was the distance travelled to the clinic (in km one way)				*Enter distance in km one way then go to 13E*		
13C	Do you usually pay a transport fare			Yes*: go to 13D*	No*: go to 13E*		
13D	How much do you pay for a return fare				*Enter amount in rands*		
13E	Please detail other costs usually associated with your visit			i)Accommodation *(enter amount in rands)*	ii)Food *(enter amount in rands)*		
13F	Aside from today, have you visited this clinic in the last 3 months			Yes: *go to 13G*	No*: go to 13H*		
13G	How many times have you visited this clinic in the last 3 months (excluding today)			*Enter number of visits*			
13H	Have you visited any other health care provider in the last 3 months			Yes: *go to 13I*	No*: go to 13J*		

13I	Please indicate which of the following health care providers you have visited in the last 3 months. I will also ask you some more details about those visits.							
i) Another clinic ii) Hospital (outpatient visits only) iii) General Practitioner iv) Private Pharmacy v) Traditional healer/ herbalist vi) Other (please state)								
For each option selected, the following details will be asked:								
a)	Number of visits in the last 3 months							
b)	Did you pay a fee on your last visit				yes			no
c)	What was the fee in rands				R			
d)	What transport did you use to get to your last visit	i)walk	li)taxi	iii)car	iv)bus	v) patient transport/ ambulance		vi)other
e)	Did you pay a transport fare on your last visit				yes			no
f)	What was the return fare in rands				R			
g)	If you used your own car, what was the distance travelled (in kilometers one way)							
h)	Please detail other costs associated with your last visit				i)accommodation			ii)food

13J	Have you been admitted to hospital in the last 3 months	Yes: *go to 13K*	No: *go to 13R*
13K	How many times have you been admitted to hospital in the last 3 months	*Enter number:*	
13L	How many nights in total have you spent in hospital over the last 3 months:	*Enter number:*	
13M	What is the total amount you have had to pay for your admissions over the last 3 months (your out-of-pocket expenses)	*Enter amount in rands:*	

For the most recent admission to hospital please provide the following details:

13N	How did you travel to the hospital (choose one of the following options):	i)Walk: *go to 13R*	ii)Taxi: *go to 13P*	iii)Private motor vehicle (such	iv)Bus: *go to 13P*	v)Patient transport/ ambulance	vi)Other (specify): *go to 13P*

				as car) *go to 13O*		*go to 13P*	
13O	What was the distance travelled to the hospital (in km one way)	*Enter distance in km one way then go to 13R*					
13P	Did you pay a transport fare	Yes*: go to 13Q*	No*: go to 13R*				
13Q	How much did you pay for a return fare	*Enter amount in rands*					

13R Which of the following best describes your employment status. Choose *one* :		
i)	Employed	a) How much did you earn last month (excluding grant income)
		b) How many days were you unable to work because of illness in the last 3 months (including health care visits)
		c) How much income have you lost in the last 3 months as a result of not being able to work because of any illness
ii)	Self-employed	a) How much did you earn last month (excluding grant income)
		b) How many days were you unable to work because of illness in the last 3 months (including health care visits)
		c) How much income have you lost in the last 3 months as a result of not being able to work because of any illness
iii)	Student/learner	a) How many days have you been unable to attend school/college because of illness in the last 3 months (including health care visits)
iv)	Unemployed and looking for work	
v)	Unemployed and not looking for work	

13S	What is the highest level of education you have achieved	i)Never went to school	ii)Grade 1-7 (primary school)	iii)Grade 8-12 (high school)	iv)Tertiary/diploma	
13T	Are you getting a pension or grant (eg disability or child care grant)	Yes: *go to 13U*	No*: go to 13V*			
13U	What was your total grant income in the last month	*Enter amount in rands*				
13V	Have you lost your job or resigned because of illness since our interview about a year ago	Yes*: go to 13W*	No*: go to 13Y*			
13W	Before you lost your job or resigned, how much did you earn in the last month you worked (excluding grant income)	*Enter amount in rands*				
13X	Since losing your job or resigning, have you got another job	Yes	No			
13Y	Have you moved house since our interview about a year ago:	Yes: *go to 13ZZ*	No: *go to 10Z*			
13Z	How many rooms does your house have (excluding bathroom and kitchen)					
13ZZ	How many people are living with you in your house					
13ZZZ	Has the number of people living with you in your house changed since our interview about a year ago	Yes	No			

14	I am now going to take your third blood pressure reading, height, weight, and waist measurement.

15	I am now going to ask you a few questions about medication you might be taking. This is very important information for understanding the care you are receiving.		
15A	Are you currently taking any medicine regularly that was prescribed by a doctor or nurse	Yes: *go to 15B*	No*: go to 15F*
15B	Where do you collect your regular medication	i)At this clinic	ii)At another site: *enter name of site*
15C	Are you currently taking any ARVs (antiretrovirals)	yes	no

For patients in the hypertension cohort only:	None	Some	Most	All the	Not	Don't

		of the time	of the time	of the time	time	applicable	know
15D	How often do you forget to take your high blood pressure medicine						
15E	How often do you decide not to take your high blood pressure medicine						
15F	How often do you eat salty food						
15G	How often do you miss scheduled appointments						
15H	How often do you run out of high blood pressure pills						
15I	How often do you skip your high blood pressure medicine 1-3 days before you go to the clinic						
15J	How often do you miss taking your high blood pressure pills when you feel better						
15K	How often do you miss taking your high blood pressure pills when you feel sick						
15L	How often do you take someone else's high blood pressure pills						
15M	How often do you miss taking your high blood pressure pills when you care less						

16	I would be grateful if you could confirm the following details	
16A	Full clinic folder number (including letters and numbers)	
16B	Re-enter clinic folder number	
16C	Colour or letter on folder for chronic medication if available	
16D	Name of hospital patient attends	
16E	Hospital folder number if available	
16F	ID number *only if ID number was missing or not valid at baseline*	
16G	Re-enter ID number	

17	Before we finish I would like to confirm what medication has been prescribed since our interview about a year ago.

18	We would like to thank you for taking part in this study and as a token of our appreciation, we would like to give you a voucher of R100 to use at a store close to where you live. We thank you for your time and wish you well.

Appendix C1. Letter of approval from UCT Human Research Ethics Committee

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

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 404 7682 • **Facsimile** [021] 406 6411
Email: nosi.tsama@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

31 July 2017

HREC REF: 492/2017

Prof L Myer
Public Health & Family Medicine
Falmouth Building

Dear Prof Myer

PROJECT TITLE: THE BURDEN OF CHRONIC RESPIRATORY DISEASE IN THE WESTERN CAPE (MASTERS CANDIDATE - DR E CARKEEK) SUB-STUDY LINKED TO 119/2010

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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 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 following student will be involved in this study: Emma Carkeek.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Please quote the HREC REF in all your correspondence.

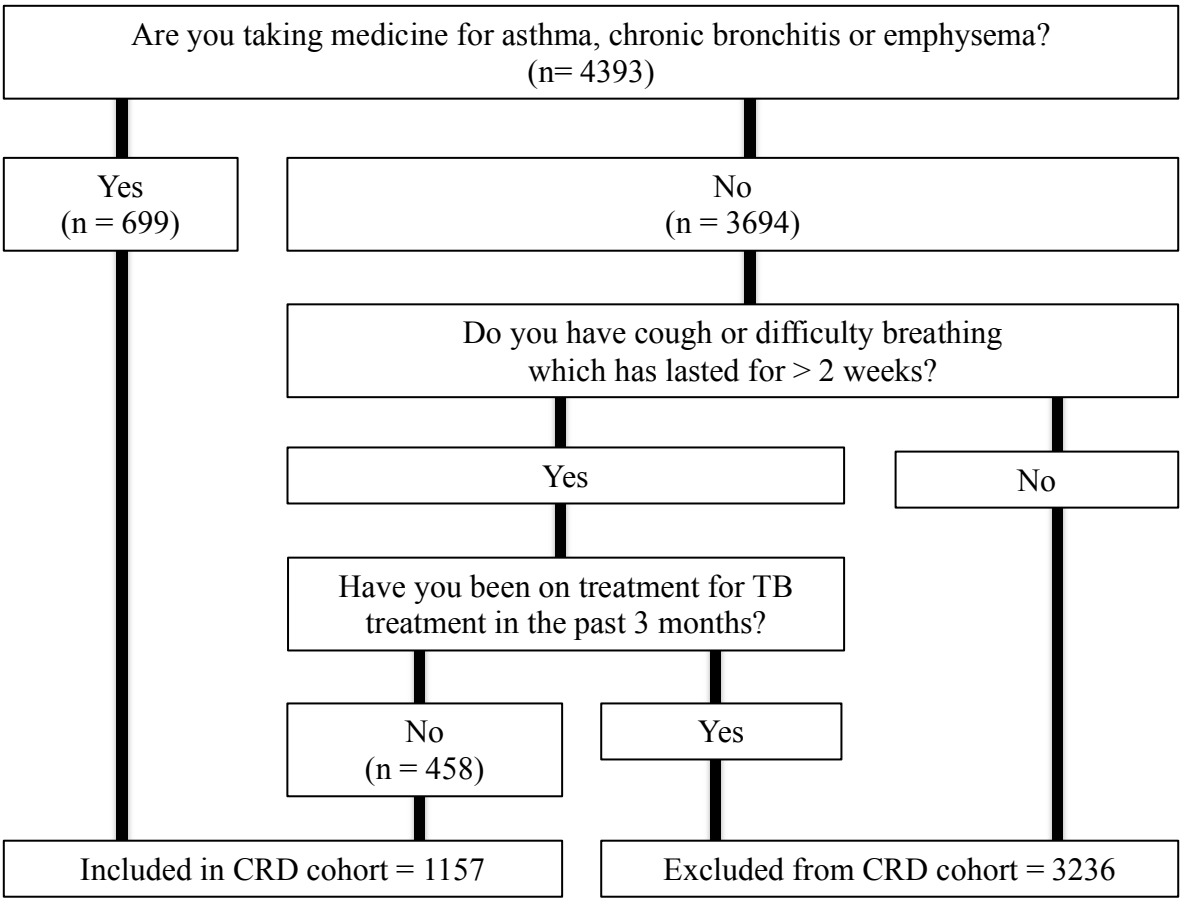
Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

Appendix C2. Flow diagram showing participant selection



Appendix C3. Author Guidelines for the South African Medical Journal

Available at: http://www.samj.org.za/index.php/samj/about/submissions#authorGuidelines

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript. To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website: www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journa*l are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 000 (ex vat) for each research article published. The charge applies only to Research articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.

Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research:

principles, processes and structures to ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchers have been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Protection of rights to privacy

Patient
Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals
Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The Author Agreement form should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images
If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn

the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, *full* affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:
- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.
**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.
- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:
    - Human Gene Mapping Workshop (HGMW): genetic notations and symbols
    - HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
    - OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
    - Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type
- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research
Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The

conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.
Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
    - Background: why the study is being done and how it relates to other published work.
    - Objectives: what the study intends to find out
    - Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
    - Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
    - Conclusion: must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.
The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion
Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions
This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:
Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:
Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:
Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must not be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.

- First and last page, in full, should be given e.g.: 1215-1217 not 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182
- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references
    - Government Gazettes:
      National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
      In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
    - Provincial Gazettes:
      Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
    - Acts:
      South Africa. National Health Act No. 61 of 2003.
    - Regulations to an Act:
      South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
    - Bills:
      South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
    - Green/white papers:
      South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
    - Case law:
      Rex v Jopp and Another 1949 (4) SA 11 (N)
      Rex v Jopp and Another: Name of the parties concerned
      1949: Date of decision (or when the case was heard)
      (4): Volume number

SA: SA Law Reports
11: Page or section number
(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.
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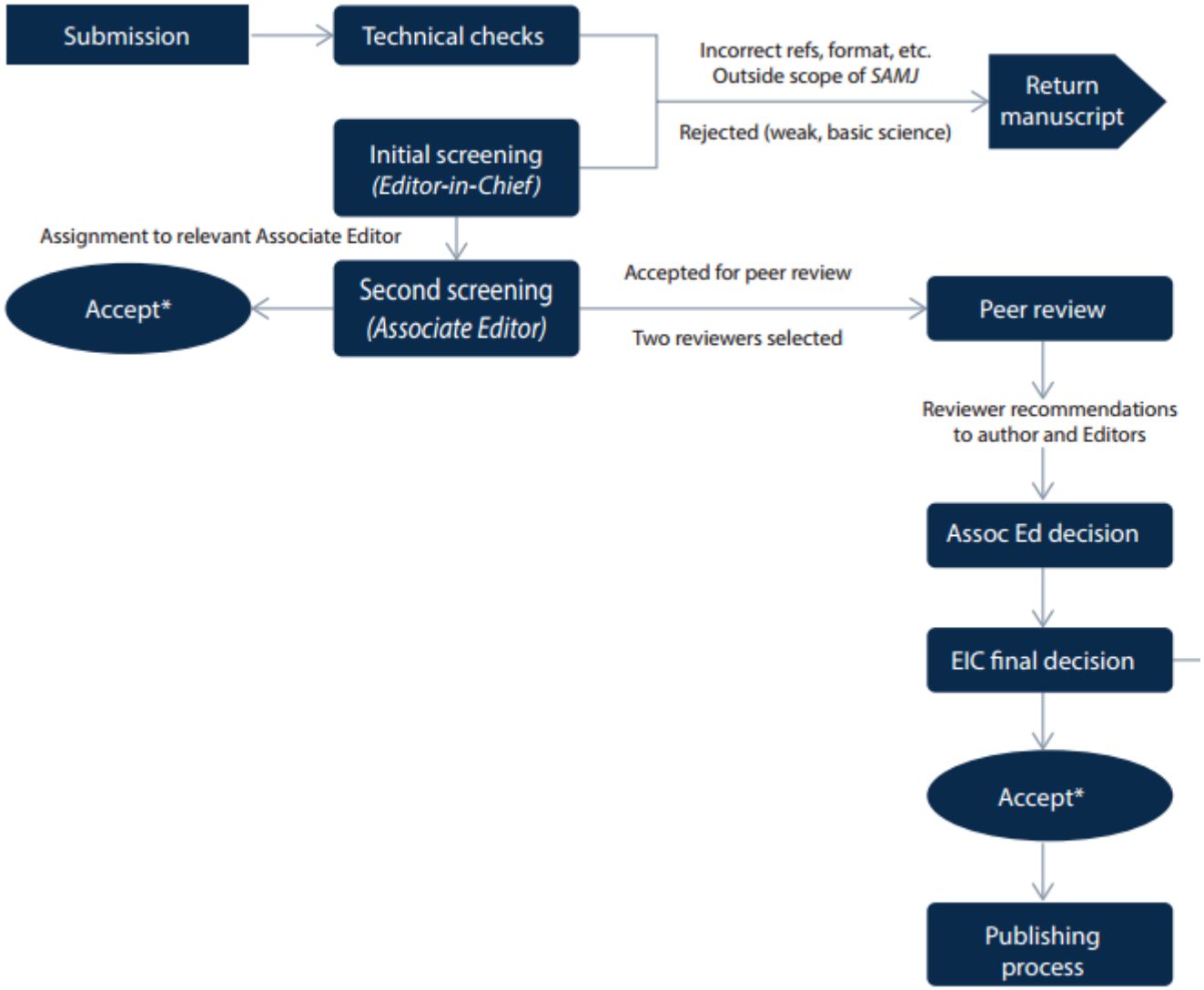

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