UNIVERSITY OF CAPE TOWN

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The quality and variation of spirometry reads for testing lung function in children in sub Saharan Africa

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PART 0: PREAMBLE

THE QUALITY AND VARIATION OF SPIROMETRY READS FOR TESTING LUNG FUNCTION IN CHILDREN IN SUB SAHARAN AFRICA

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13 February, 2019

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DECLARATION

I, Dumsile Maduna (MDNDUM002), hereby declare that the work in this mini dissertation is based on my original work (except where acknowledgements indicate otherwise) and has not, in whole or in part, been submitted towards another degree at this or any other university.

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Date: 13 February 2019

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Theses Abstract

Background: Lung function assessments have become the cornerstone of understanding the ever-increasing burden of non-communicable respiratory conditions worldwide. The introduction of pulmonary function testing (PFT) has made maximal expiratory flow/volume (MEFV) measurements the basis of lung function assessments and spirometry the most widely used diagnostic tool for lung function testing. The effectiveness of spirometry to distinguish between normal and abnormal lung function has been realised in adults; however, there is an observed history of misinterpretation in children. The quality of measurements remains a major concern in children and good quality measurements are critical in the diagnosis of any health condition as well as understanding the burden of abnormal lung function in children in low and middle-income countries (LMICs).

Objective: This study describes the quality and variation of spirometry reads for evaluating lung function in children in a Malawian population.

Methods: This study was conducted according to a protocol developed and granted ethical approval by the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town (HREC REF 669/2018). The protocol describes the parent study data collection, project analysis plans and ethical and other considerations. Current literature on lung function using spirometry was systematically reviewed and synthesised. The literature review included primary studies and review articles that included spirometry measurement in children from settings in Africa and other low- and middle- income countries. The descriptive study involves secondary analysis of data contributed by the Children Lung Health study, a cross-sectional survey conducted in

Malawi. Spirometry measurements from 802 healthy children aged 6-8 years, inexperienced in performing MEFV manoeuvres, are evaluated. Data in the primary study were collected by means of a structured questionnaire which included items on socio-demographic characteristics and spirometry was performed according to the American Thoracic Society and European Respiratory Society (ATS/ERS) guidelines using an Easy on-PC spirometer in the participant's home. The ATS/ERS standards for adults and the modified recommendations for children were applied to evaluate quality. Descriptive statistics were used to describe the quality of spirometry indices and univariable logistic regression to identify and describe variables that are predictors of quality.

Results: The findings of the study were that many children (34**%)** failed to reach the complete ATS/ERS quality standards. The end-of-test criteria (forced expiratory time) was the most difficult to meet for children and if this is not met (i.e. exhalation is not complete), the forced vital capacity (FVC) will be underestimated leading to it being misinterpreted. More than 30**%** of the children failed to meet the repeatability criteria when the relative differences for FVC and forced expiratory volume in the first second (FEV1) was used, yet they are the most appropriate in paediatric practice as compared to absolute differences. Young children were more likely to produce poor quality spirometry as compared to older children.

Conclusion: Young children may perform acceptable spirometry according to the modified ATS/ERS recommendations; however, the quality remains suboptimal. Further modification of the already lowered quality standards, seems to be the viable option, but the implications of this clinically has not been evaluated. Other alternatives need to be

explored for this group.

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Abbreviations

ALHS Adult Lung Health Study

ATS American Thoracic Society

BEV Back Extrapolated Volume

BMI Body Mass Index

BOLD Burden of Lung Disease

CAPS Cooking and Pneumonia Study

CLHS Child Lung Health Study

COMREC College of Medicine Research Ethics Committee

COPD Chronic Obstructive Pulmonary Disease

CRD Chronic Respiratory Diseases

DALYs Disability Adjusted Life Years

DFVC Absolute difference between two highest FVC

DFEV1 Absolute difference between two highest FEV1

DFVC% Relative difference between two highest FVC

DFEV1% Relative difference between two highest FEV1

EOTV End of Test Volume

ERS European Respiratory Society

FEF Forced expiratory flow

FET Forced Expiratory Time

FEV1 Forced expiratory volume in the first second

FVC Forced Vital Capacity

GBD Global Burden of Disease

GLFI Global Lung Function Initiative

HIV/TB Human Immunodeficiency Virus/ Tuberculosis

HREC Human Research Ethics Committee

ISAAC International Study for Asthma and Allergies Control

LMICs Low and Middle Income Countries

LSTM Liverpool School of Tropical Medicine

MEFV Maximal Expiratory Flow Volume

NCD Non-Communicable Diseases

NHANES National Health and Nutrition Examination Survey

PEFT Peak Expiratory Flow Time

PFT Pulmonary Function Test

QC Quality Control

SALPALDIA Swiss Study on Air Pollution and Lung Diseases in Adults

SOP Standard Operation Procedures

SSA sub Saharan Africa

UCT University of Cape Town

WHO World Health Organisation

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PART A: PROTOCOL

Background

Non-communicable diseases (NCDs) are a growing public health concern globally due to a rapidly increasing burden which may soon overtake the burden of infectious diseases (Global Health Estimates, 2016 and GBD, 2013). Chronic lung diseases such as COPD and asthma are one of the major contributors to the burden of NCDs in sub-Saharan Africa (Ahmed, Robinson and Mortimer, 2017). African countries, like many other low and middle-income countries (LMIC), are likely to be significantly affected by chronic lung diseases due to prevailing conditions favouring disease in these settings such as high rates of tuberculosis and biomass fuel use (Sana et al, 2018).

However, the limited data available in published literature for Africa (Finney et al, 2013) limits the knowledge about the status quo of chronic lung disease in the continent. Most work assumes a high prevalence of respiratory disease due to the degree of exposure and risk in these areas, for example, due to biomass fuel dependence and high HIV/TB prevalence (Meghji et al, 2016). The burden of chronic lung disease is often measured by self-reported correlates of compromised lung function (e.g. breathlessness) or by clinical measurement. The most common clinical measure of lung function is by spirometry (Miller et al, 2005).

Spirometry is a non-invasive evaluation of lung function. A spirometry evaluation involves the participant inhaling and exhaling into a device (spirometer), which measures lung volumes. Low lung volume may be due to reduced vital capacity where a participant, although having achieved maximal inhalation, the amount of air blown out is reduced (Rylance, 2018). This means that participants may have started off with full

lungs, however their lungs could be smaller than average causing a condition called restriction or restrictive lung disease (Miller et al, 2005). On the other hand, the air passages on the lungs could also be narrowed leading to a reduced early expiration or a situation where a participant may take longer than normal to fully exhale. This is referred to as obstruction or obstructive lung disease. The measure of the lungs to inspire to full capacity and forcefully expire at a given point in time can be used to score or rank individuals into different lung function categories e.g. normal or obstructed. The use of spirometry to measure lung volumes over time can be converted into a measure of abnormal lung function, which can then be used to estimate burden.

Measuring lung function is fundamental in understanding the burden of chronic lung disease in African populations. Recent studies measuring lung function by spirometry have found a substantial burden of abnormal lung function, especially restriction, in sub-Saharan populations (Meghji et al, 2016) and lower than expected forced vital capacity (FVC) (Obaseki et al, 2017). However, the scarcity of data is to likely provide inaccurate estimates (either over or underestimation) of the extent of disease and the amount of long term damage caused by chronic lung disease (Ahmed, Robinson and Mortimer, 2017). Although progress is being made, the diagnosis of lung function abnormalities is poor when compared to other NCDs, yet it is essential in informing decision making for disease management and planning of health services.

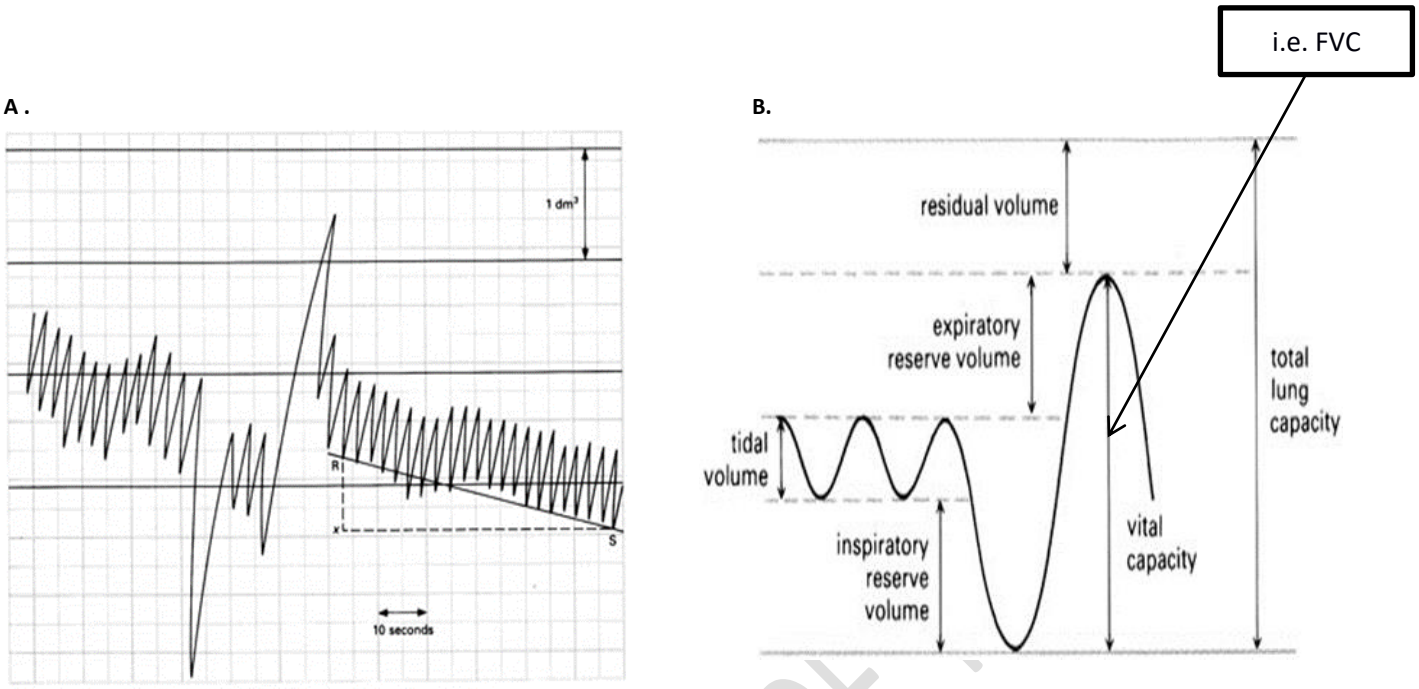

Figure 1 A & B Standard traces showing how to read off residual volume, tidal volume, expiratory reserve volume, inspiratory reserve volume, vital capacity and total lung capacity. (Source: Nuffield foundation, 2011, used with by permission).

The most important estimates of lung function measured by spirometry are FVC (Figure 1 B) and FEV1. FVC measures the amount of air starting from the point of full inhalation to the end of a forceful expiration, which is as complete as possible. The first second of the FVC manoeuvre is the FEV1 (Miller et al, 2005). Together these estimates are used to calculate a FEV1/FVC ratio which gives insight into the clinical disorders commonly termed obstruction and restriction. Because height, age, and weight are known to directly affect lung volumes, FVC and FEV1 are usually represented as standardized z-scores. Although the spirometer provides other measurements, they are rarely interpreted or analysed in clinical studies, but they can be used for quality control. Additional measures available include back extrapolated volume (BEV) and end of test volume (EOTV). These two measures are utilized to classify a spirometry manoeuvre as "acceptable" or not. There are few epidemiological studies in the literature that

investigate the association of BEV and EOTV with other measures of lung function, or the association between BEV/EOTV with FVC and FEV1. Another spirometry outcome of interest is the forced expiratory time (FET) which accounts for the minimal expiratory time which is normally less for children when compared to adults.

In general, a good diagnostic test is characterized by high specificity and sensitivity, which for this procedure is known to depend both on the individual being tested and upon the manufacturers and technicians using this instrument (Miller et al, 2005). The quality of spirometry measurements is of paramount importance in correctly diagnosing poor lung function. Poor quality BEV and EOTV renders a manoeuvre unacceptable for a FVC and FEV1 measurement. The BEV can be used to identify individuals who do not start off with a forceful exhalation, whilst the EOTV identifies those individuals who have not completely exhaled (Miller et al, 2005).

Using poor-quality manoeuvres may lead to incorrect diagnosis and lowers the sensitivity and specificity of spirometry as a diagnostic tool. Though there is evidence that the quality of spirometry varies within and between manoeuvres as well individuals (Meghji et al, 2016), the possible associations between poor quality spirometry and poor lung health have not been well described. Available literature shows evidence that suggests a relationship between poor quality spirometry and poor lung function (Enright et al, 2011), but information is limited. Individual characteristics that have been found to be associated with spirometry abnormalities include sex, age, BMI, education, smoking, occupation, biomass exposure, TB/HIV status, and various blood-based biomarkers (Meghji et al, 2017). These factors have been identified as independent predictors of the quality of spirometry, in meeting the requirements by the ATS/ERS 2005 spirometry

standards (Enright et al, 2011).

Classification of spirometry measures into clinically meaningful diagnosis e.g. restrictive disease relies on the use of reference values. Reference values are a range of normal values for populations used to base lung function measurements and these vary between populations and countries (Miller et al, 2005). The variability in normal values, and the use of reference values themselves, impacts the reliability of test results, particularly when reducing spirometry measurements to a binary classification.

There are varying perspectives on the use of spirometry reference values, and the definition of normal values for healthy lung function, specifically around the use of different normal values for different populations. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommended that reference range development be drawn and based on populations being studied i.e. samples with similar ethnicity/race (Kiefer et al, 2016).

This study seeks to describe the variation in the quality of spirometry reads when measuring lung function in typical LMIC settings. It will contribute knowledge on suboptimal spirometry and the description of the variation in the sub Saharan Africa study population. This will highlight the difficulty in measuring lung function especially when children with poor lung function cannot produce good quality traces (Rylance, 2017).

Findings of this study will provide a broad understanding of how poor-quality traces are associated with each other or other variables existing in the population that influence spirometry reads. This study will also contribute to the discussion of the utility of sub-

quality spirometry clinically and its effects in achieving acceptable measurements for lung function diagnosis. Understanding of the variations, patterns and association will inform decision making on prevention and control measures.

2. Study aims and objectives

The objective of the study is to describe the quality and variation of spirometry reads for evaluating lung function in children in a Malawian population.

Objectives

1. Describe the quality of spirometry and estimate the frequency of poor quality traces in children using BEV and EOTV measurement criteria for manoeuvre acceptability in children
2. Assess the interpretive changes of BEV and EOTV when the quality rules are relaxed or made more stringent
3. Compare spirometry quality across selected variables such as age, sex, height, weight, size of lung, effort/strength of person, personal characteristics/underlying clinical conditions in the quality of traces in children aged 6-8 years.
4. Compare observed quality with published guidelines for spirometry quality assessment

3. Study design

This descriptive study involved secondary data analysis from contributed data that has been de-identified and anonymized at source.

The following is a brief description of the original study design. The data originated from the Children Lung Health study (CLHS), a cross-sectional survey, conducted in Malawi. The CLHS is titled "*Child lung health and exposure to household air pollution in rural Malawi"* and was approved by the College of Medicine Research Ethics Committee (COMREC) p.07/16/1994 in Malawi and LSTM Research Ethics Committee (REC) 16-040. This study protocol sought ethical approval from the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town.

All data was anonymized and could not be traced to the original participants. Data had already been collected and analysed except with regards to the variables this study seeks to focus on. This study describes the use of spirometry as a reference standard for testing lung function and clinical diagnosis in children. Spirometry reads were analysed to evaluate its quality and variations in the sub-Saharan Africa population with focus on BEV and EOTV as well as the quality control (QC) criterion which uses the difference between FEV1 or FVC between traces as percentage for children.

4. Characteristics of study population

Data was already extracted and de-identified. It included measures from the following groups:

The CLHS study was conducted among the same Chikwawa communities that participated in Cooking and Pneumonia Study (CAPS). Children who were included in

the CLHS were from households that had participated in the Cooking and Pneumonia Study (CAPS) especially the ALHS and Carbon monoxide exposure sub-studies. Assenting children were recruited from each of the 50 village level clusters in Chikwawa, in households with at least one child aged 6-8 years.

Exclusion criteria: Children were excluded if they were currently on treatment for tuberculosis or if they currently suffer from acute respiratory infection (cough < 1week, with fever +/- increased work of breathing) and or show a contraindication to spirometry (chest or abdominal pain, haemoptysis).

Sample size

Datasets of children that participated in the CLHS was purposively used. All individuals had performed spirometry for lung function measurements in the study. The CLHS recruited 802 children between 6-8 years of age. The sample size was determined to allow estimates of non-communicable lung disease with a precision (95% CI) of ±2.6 to ±3.8% and a prevalence of 10-25% was assumed (Rylance et al, 2017). Study sample provided sufficient power (>80%) to estimate moderate to large associations under multivariable regression models. Below is the calculation for sample size:

$$n = \frac{p(1-p)z^2}{d^2}$$

p is the anticipated population proportion, ***d*** is the precision required on either side of the proportion and ***z*** **= 1.96.**

the Anticipated population proportion (p) was 25%; for the 95% CI: z = 1.96) and Desired precision (d) was 3.85%

n = (0.25(1-0.25)1.96^2)/0.038 = 499 children were required for the study to achieve at least 80% power.

Research procedures and data collection methods

Research Procedures

Secondary data analysis was done by the researcher from datasets already collected by the CLHS in Malawi. Data was provided in de-identified, anonymized digital format. Researchers carried out data cleaning, data manipulation and data analysis to answer the question of this study, described in analysis methods below.

Data Collection Methods

This study used secondary data that was already collected. The following procedures were followed when collecting data in the study being used:

The CLHS study collected data on children during home visits after consent was given. A questionnaire was also administered in Chichewa or English by study staff and it included questions from the international study of asthma and allergies in children (ISAAC) and burden of lung disease (BOLD) studies (Asher et al, 1995 and Buist et al, 2005). Questions asked were related to the frequency of symptoms such as breathlessness, cough, asthma, phlegm, eczema rhinitis, and for detailed information about hospital admissions, HIV/TB diagnoses, and any treatments received.

Spirometry was also conducted by trained study personnel in the participant's home using an ndd (new diagnostic design) Easy on-PC spirometer and followed the ATS/ERS guidelines (Miller et al, 2005). Each child had their spirometry taken before and after 4 puffs of Salbutamol inhaler via a large volume spacer, where they blew into

the machine 8 times to obtain the FVC and FEV1.

5. Data Management and Analysis

Data safety and monitoring

There was no need for data safety and monitoring as no participants were being enrolled and no new data was collected. The original studies were low risk observational studies carried out under ethical approval.

Data analysis

This was a descriptive analysis of secondary data. Data have already been collected. All statistical data analysis was performed using Stata version 14.2 statistical software (Stata Statistical Software: R.14; StataCorp LLC, College Station, TX) and R software.

The characteristics of the study population were explored using descriptive statistics and univariable analysis. Summary statistics were calculated for continuous variables and histograms were used to show distributions of numerical data. Frequency tables were used to summarize categorical variables. Scatter plots were used to explore associations between two continuous variables. Box plots explored the associations between continuous and categorical variables. Contingency tables and Chi squared test was used to identify associations between two categorical variables.

The prevalence (95% confidence intervals) of poor quality traces (abnormal BEV and EOTV) was estimated and regression analysis used to identify variables associated with poor quality traces. The associations of suboptimal spirometry were described on selected variables (table 1).

To determine the relationship and its strength between spirometry parameters with outcomes (primary outcome, quality and secondary outcome, acceptance), binary logistic regression was performed with the statistical significance set at alpha = 0.05. For the primary outcome, quality, each grade (A, B, C, D and F) was analysed as an independently and categorized as Yes or No. Clinical factors affecting spirometry parameters were identified from literature. The BEV and EOTV of each individual accepted manoeuvre was described and the variability within manoeuvre identified. These parameters were also compared with the other two manoeuvres of an individual (between manoeuvre variability).

Table 1 List of variables for data analysis

	Variable	**Type**
Demographic Information	Gender	Binary
	Age	Continuous
	Height	Continuous
	Weight	Continuous
	Ethnicity	Nominal
Tests	Test date	Discreet
	Test stage	Ordinal
Spirometry Parameters	FEV1	Continuous
	FVC	Continuous
	FEV6	Continuous
	FEV_FVC	Continuous
	FET	Continuous
	BEV	Continuous
	EOTV	Continuous
Outcomes	Quality	Ordinal (A, B, C, D & F)
	Acceptance	Binary (Yes/No)

Study measures

Important variables that were analysed included the BEV, FET, EOTV (variables for acceptability) and FVC, FEV1, FVC/FEV1 (variables for repeatability). Variables of the relative and absolute differences of the FVC and FEV1 were the DFVC, DFVC%, DFEV1 and DFEV1% (See supplementary table 7 page 83 for definitions). Variables considered as predictors of quality were clinical factors such as the age, gender, weight and height.

6. Ethical considerations

This was an analysis of secondary data and so comprised no direct risk to study participants. No participants were enrolled for this analysis, no new data was collected.

The study contributing data was carried out under ethically approval and conducted in Malawi in children. The CLHS study titled, “Child lung health and exposure to household air pollution in rural Malawi”, by Rylance et al (2017) was approved by the College of Medicine Research Ethics Committee (COMREC) p.07/16/1994 in Malawi and Liverpool School of Tropical Medicine Research Ethics Committee (LSTM REC) 16-040 (Appendix B and C).

Ethical approval for this study was sought with the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town.

Informed consent process

All children participants in the CLHS study provided assent with parental or proxies’ e.g.

main carer consent. All study materials, including consent forms, were provided in Chichewa, the local language. Trained study field workers administered informed consent during home visits.

A written information sheet, using the University of Malawi, College of Medicine template was used before consent to participate was obtained and this was read out to all participants in English or Chichewa to accommodate those who could not read. Written informed consent was obtained from all participants and those who were unable to sign the consent form made a mark, witnessed by a person independent to the study.

Description of risks and benefits

This was an analysis of de-identified secondary data, and as such there were no direct risks to the individuals from whom data was used. The source data studies were low risk observational surveys that represented very low direct risk to study participants. Individuals were not identifiable as all personal identifiers were removed.

There are no direct benefits to study participants, as data collection was already finished. However, the findings of this study may provide better insight and understanding of the importance of good quality spirometry measurements for improved diagnosis of lung function in children. Prompt and proper diagnosis of lung function is necessary for proper management of disease, which would improve the quality of life of the populations. This would also reduce the burden of lung disease hence reducing economic costs associated with these diseases. Understanding the variation of spirometry in children could be a base for further research on other possible diagnostic tools for those groups who fails to provide good quality spirometry.

Privacy and confidentiality

Data in the proposed study was electronically kept in the researcher's laptop and supervisor's desktop which are protected by passwords. An encrypted, password protected external hard drive was used for back up. All data was provided without personal identifiers. This information is only accessible to the supervisor and researcher.

Findings from this study may be shared through publication in peer reviewed journals and the UCT library.

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PART B: Structured Literature Review

1. Introduction

1.1. Background and objectives of literature review

The rise of chronic respiratory diseases (CRDs) presents a new challenge to the ever-increasing burden of non-communicable diseases (NCDs) (Wang et al, 2015 and De-Graft Aikins et al, 2010). According to statistics from the World Health Organization (WHO), NCDs account for at least 63% of global deaths of which 3.9 million deaths are reported to be linked to CRDs (Wang et al, 2015 and De-Graft Aikins et al., 2010). CRDs are the fourth leading cause of NCDs deaths worldwide (GBD, 2013), with interstitial lung disease and pulmonary sarcoidosis, displaying a substantial increase of 51·5% in overall mortality rates between 2005 and 2015, to 121 800 deaths. The age-standardized rates, also increased by 14·1% (Wang et al, 2015). Moreover, respiratory disease has been projected to presents the highest global statistics in the following decades (WHO, 2013 and De-Graft Aikins et al., 2010). In addition, respiratory diseases affect the global economy causing an estimated 4.7% of global disability-adjusted life years (DALYs), with two thirds resulting from chronic obstructive pulmonary disease (COPD) and one fifth due to asthma (Wang et al, 2015).

In children globally, respiratory disorders account for considerable morbidity and mortality. They are the reason behind most children hospitalizations and hospital visits (Jat, 2013). In as much as morbidity and mortality caused by NCDs occurs mainly in adulthood, initial exposures to associated risk factors present early in life. Children often die because of treatable NCDs, and this will be the case if comprehensive care which involves health promotion and disease prevention and control not provided (WHO, 2013). The most challenging aspect of this situation is that governments in many

countries have not given CRDs as much attention as they require.

Information on CRDs is very limited despite the high burden of NCDs in low and middle-income countries (LMICs) where CRDs are common in all age groups (Bousquet et al, 2003). In sub- Saharan Africa (SSA), information regarding the estimates of prevalence, natural history, and associated mortality and morbidity of diseases is lacking due to scarcity of data (Beran et al, 2015; Bousquet et al., 2003 and Meghji et al, 2016). The limited available information strongly suggests that a high burden of CRDs (Finney, 2013 and Buist, 2007) is to be expected in this region due to high exposures to risk factors of respiratory pathology (Stocks, 2013). Common risk exposures associated with abnormal lung function are: air pollution; tobacco smoking; and respiratory infections (Bousquet et al, 2003).

A recent study that was conducted in a Malawian population found that more than 40% of the adult population had abnormal lung function (spirometry restrictions), attributed to high biomass exposures and high HIV prevalence (Meghji et al, 2016). Other ecological and prospective studies have also shown a relationship between restrictive lung disease and low respiratory volume, which is the main cause of mortality (Burney et al, 2011 and 2014).

However, without quantifiable research on the burden of lung diseases measured by lung function, CRDs cannot be understood, and planning of interventions may be misguided. Bousquet et al (2003), suggested the need for research (Starfield, 2001) to evaluate the burden and magnitude of the diseases, trace the history of disease correlates, discover and suggest outcomes and alternatives to account for associates, and investigate possible discussions and interventions.

Measuring lung function is one way to estimate the burden of disease among populations. To better understand lung function, it can be linked back to the general concept of lung development from the early years of life to adulthood.

The objectives of this literature review are to: 1) provide an overview of the lung disease burden as measured by lung function in sub Saharan Africa; 2) review studies investigating spirometry in children; 3) describe variations in spirometry reads and factors associated with the quality of spirometry in children; and 4) review epidemiological studies investigating the quality and interpretation of spirometry in measuring lung function.

1.2. **Literature search strategy**

Literature was searched through Google Scholar and Pubmed electronic search tools for systematic reviews, peer-reviewed articles and guidelines published up until January 2019. Epidemiological studies on lung function testing using spirometry were included in this review. Available studies conducted in Low and Middle-Income countries, international studies, including all study designs were used in the review. Also, relevant articles suggested by these search engines and relevant literature from reference lists of articles examined were considered. Search terms were used in combination and alone (see APPENDIX B).

PubMED: (http://www.ncbi.nlm.nih.gov/pubmed/) and, Google Scholar: (https://google-scholar.uct.ac.za/).

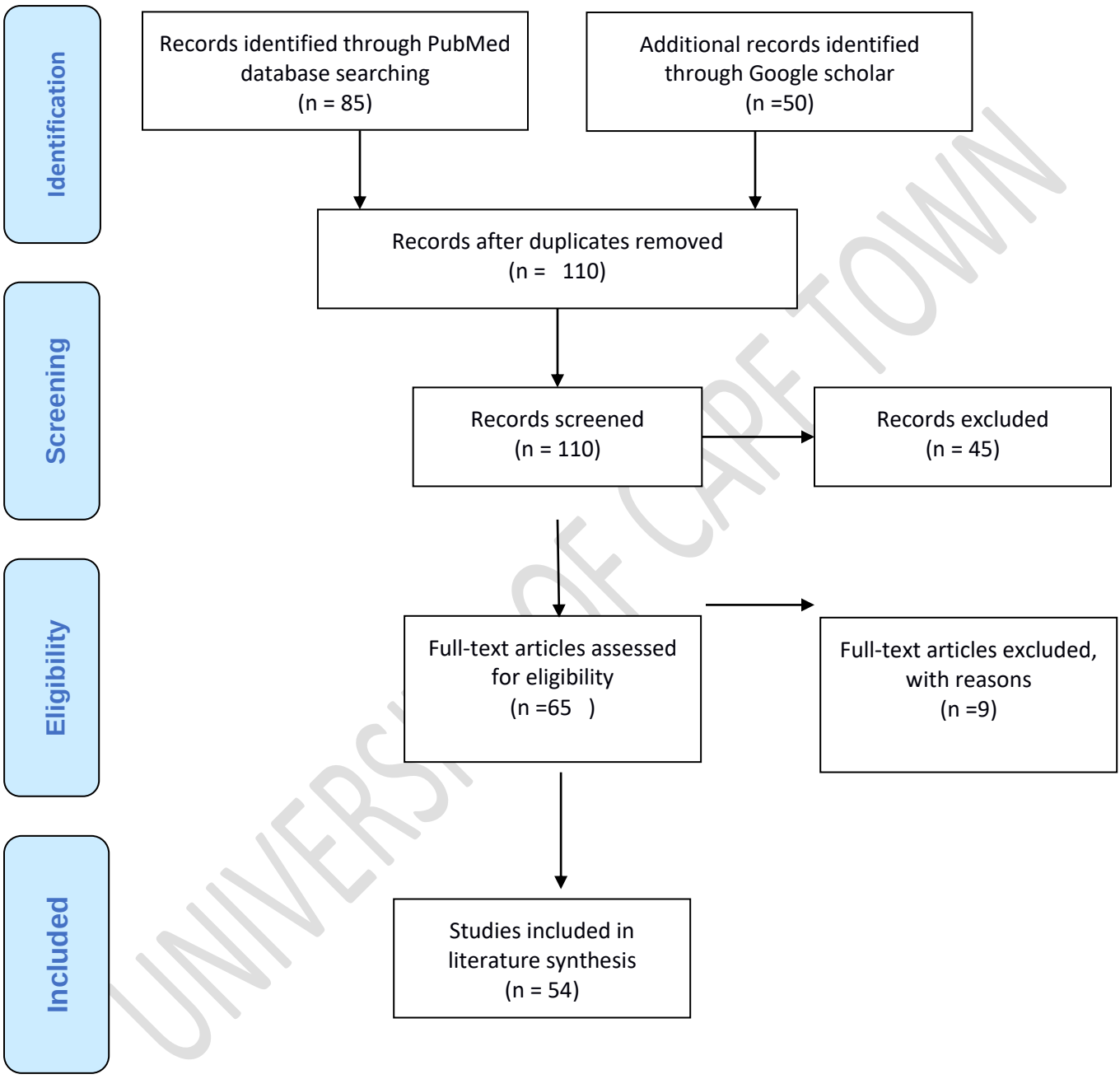

Figure 2 Literature search flow diagram

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit **www.prisma-statement.org.**

2. **Lung development and Function**

A better understanding of the respiratory physiology in children is important in the investigation of lung function (Jat, 2013). Lungs generally follow several distinct developmental stages, and these include: the embryonic stage; the pseudo glandular, canalicular, saccular, and alveolar stage; and the extended stage of equilibrated lung development (Maritz et al, 2005). The pulmonary alveoli and the airways that are connected to them, grows and matures later in the fetal life or even after birth (Maritz et al, 2005). These are the center for gas exchange in humans and are prone to placental insufficiency, premature birth and infections due to their developmental timing (Maritz et al, 2005). Compromises occurring during these critical phases of lung development can permanently alter the structure and function of the lungs, resulting in long-term adverse effect of the respiratory health of the foetus, infant and later in life (Maritz et al, 2005).

In children, lung function develops alongside child's growth due to their dynamic and rapid growth phase. Lung volume and airway size increases rapidly in early childhood when growth is also rapid (Jat, 2013). Lung function peaks in early adulthood, and then begins to decline steadily with age (Becklake et al, 1993 and Hibbert et al, 1995).

The development of lungs, like any other organ, is greatly affected by conditions of the pre-and postnatal environments (Maritz et al, 2005). Exposure to determinants of poor lung growth and function, according to findings of epidemiological research, may make lungs ineffective gas exchangers and could increase the risk of respiratory symptoms, illness and disease in adolescence and adulthood (Jackson, 2000). Important pre-natal conditions include limited nutrients and lack of oxygen and exposure to nicotine via maternal tobacco smoking (Maritz et al, 2005). Lung function can also be influenced by

prematurity, ethnicity, weight, age, sex and other environmental factors (Jat, 2013) causing variability within and between the population.

3. Lung Function Testing

Maximal expiratory flow/volume (MEFV) measurements have become the cornerstone of pulmonary function testing (PFT) since its introduction in 1947 (Arets et al, 2001). In children, however, lung volumes and air flow measurements are not used as frequently. PFTs are now an invaluable and widely used tool in assessing, diagnosing and monitoring respiratory conditions in adults and children (Arets et al, 2001). In children, however, lung volumes and air flow measurements are not used as frequently as in adults, due to the common obstructive nature of lung function disorders in children compared to restrictive lung diseases. The choice of PFT in children largely depends on the developmental stage of the child. Age has a huge influence on the feasibility, assessment and interpretation of PFT, which varies among young and older children (van den WIJNGAART et al, 2015).

Beydon et al (2007) proposed that an ideal PFT would be applicable to all ages, be easy to perform, not harmful, be repeatable, and highly sensitive to growth changes, and be able to distinguish between normal and abnormal lung function, and be well received by all parties involved. For lung function, nowadays, the most common diagnostic instrument used is spirometry (Giner et al, 2014). This is regarded as the gold standard for lung function measurements in many settings globally and in LMICs (van den WIJNGAART et al, 2015).

3.1. Spirometry in measuring lung function

Spirometry is a useful, safe, non-invasive investigation tool for diagnosing, managing, and monitoring lung function and a number of respiratory conditions (Jat, 2013), through measuring lung dysfunction (Giner et al, 2014). It is used clinically to distinguish between normal and abnormal function of lungs. This instrument measures lung capacity whereby low lung volume, which is the inability to inhale fully, is considered sub-optimal lung function. This condition is called restrictive lung disease (Miller et al, 2005). A lung condition can also be obstructive when the lungs fail to fully exhale air. The ability of the lungs to inspire to full capacity and forcefully expire at a given point in time is recorded by the spirometer and then translated and used as an indication of a healthy or ill lung. Measurements are based on the spirometry estimates which are clinically interpreted to aid in the diagnosis of lung function. They also provide a useful diagnostic tool for many other respiratory diseases in children such as cystic fibrosis, asthma, and congenital or acquired airway malformations (Jat, 2013).

3.2. Indications of lung function spirometry in children

Spirometry testing has been commonly used for monitoring respiratory conditions in adults but has been historically underused or incorrectly interpreted by paediatricians treating children with respiratory disease (Jat, 2013). In young children, the test has always been considered ineffective as this age group would not voluntarily produce breathing manoeuvres whereas adults would. However, currently the use of better equipment that is computerized with updated regional reference values, provision of incentives, and presence of modified acceptability and repeatability criteria, has made it feasible to carry out reliable spirometry in children (Aurora et al, 2004; Masekela et al,

2013; Nystad et al, 2002; and Veras et al, 2011).

Spirometry has been successful as a diagnostic test in symptomatic children such as children with persistent wheezing (Constant et al, 2011); or for monitoring purposes, for example in children with asthma and cystic fibrosis (Holt et al., 2006 and Dundas et al, 2006). It has been considered an important component in reviewing asthma control and cystic fibrosis disease progression. It is also frequently used in measuring lung function for many pulmonary diseases including haematological disorders and chest deformities. In some instances, it has been helpful in ascertaining preoperative lung function (Chong, 2011) or screening of schoolchildren for respiratory diseases (Constant et al, 2011). There are reservations, however, regarding the correlation between clinical severity and spirometry measurements which could possibly be a source of misdiagnosis (Schneider et al, 2011 and Langhan, 2009). Therefore, spirometry is not considered a stand-alone clinical diagnosis.

3.3. Spirometry test procedure

The procedure for conducting a spirometry test in children aged >6 years is no different than in adults in terms of equipment and process (Jat, 2013). The success of spirometry tests can be measured by the quality of the information obtained from the test which does not only rely on the instrument but the competence from all parties involved (Giner et al, 2014). There are three essential elements that should be emphasized when conducting the test in children. The first element is the ability of the person performing the test to detect errors and to interpret the results of the test (Jat, 2013). Technicians and all health professionals that are involved with lung testing must be thoroughly trained on paediatric spirometry (Giner et al, 2014 and Masekela et al, 2013).

Secondly, the instrument itself must be appropriately selected and prepared as this would affect the quality of measurements (Miller et al, 2005). The accuracy of the instrument mostly depends on the manufacturer and selected equipment should fulfil the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations for spirometry (Jat, 2013). There are a variety of spirometry devices that are available on the market.

Lastly, the test procedure should be well understood by the child through clear, friendly explanation (Jat, 2013). Older children usually do not have a problem producing good measurements; however the younger age-groups require attention and support (Giner et al, 2014). Incentives are also often used in this age group to ensure optimum performance. It is the responsibility of the individual doing the procedure to ensure that proper procedures are being followed to ensure precise spirometry reads and manoeuvre measurements. Good quality measurements are necessary to be able to use a spirometer to correctly distinguish between normal and abnormally functioning lungs.

3.4. Selection of the appropriate test manoeuvre

The most important parameters of lung function measured by a spirometer are the forced volume capacity (FVC) and the Forced Expiratory Volume (FEV1). FVC measures the amount of air starting from full inspiration to a forceful expiration, which is as complete as possible, and the volume expired during the first second (s) of the FVC manoeuvre is the FEV1 (Miller et al, 2005). These are objective and less prone to bias (Jat, 2013), thus are reliable measures to correctly detect lung abnormality.

Together these estimates are used to calculate a FVC/FEV1 ratio which gives insight

into the clinical lung function disorder present i.e. obstruction or restriction. FVC and FEV1 are usually represented in most studies as z-scores to account for height, age, and weight (Miller et al, 2005), which are factors known to directly affect lung volumes and influence the spirometry outcomes. Other parameters are measured but rarely interpreted or analysed in clinical studies using spirometry. Additional measures available include the back extrapolated volume (BEV) and end of test volume (EOTV) which are necessary for FCV and FEV1 manoeuvre acceptability.

An acceptable manoeuvre is characterized by three distinct phases (Miller et al, 2005) and (Enright et al, 2011). First phase is the maximal inspiration/inhalation *"takes a deep breath"*. This is the phase where a subject inhales rapidly and completely from functional residual capacity to total lung capacity meaning from normal breathing to the maximum point of inhaling. This is followed by "blast" expiration, without or with minimal hesitation. This means that the client must forcefully "blast" out the inhaled air from the lungs, reaching *a "sharp"* (high) peak flow during the first tenth of a second and a high average flow during the first second of the manoeuvre (FEV1). The last phase is the continued complete exhalation to the EOT *(maximal exhalation effort)*. In this phase the client continues exhaling until all the air from the lungs has been fully exhaled.
Each of these phases, is characterized by the differing amount of effort required (Enright et al, 2011). However, these requirements are often not easily met in certain instances i.e. measuring FVC becomes a challenge in elderly people where the prevalence of airflow issues tends to be high. Therefore, a vital capacity (VC) is recommended for patients with signs of dizziness to avoid syncope. A VC allows for reduced effort or maximal forced expiration (Miller et al, 2005).

4. Spirometry Quality

4.1. Acceptability and repeatability of spirometry

The acceptability and repeatability of spirometry tests is a useful indicator of spirometry quality and this is necessary for results that are used for lung function diagnosis. In the United States, for instance, the current ATS/ERS standards base acceptability and repeatability of a test (Miller et al, 2005) on the technologists' ability to achieve the set goals in 90% of tested adult participants. This requires that technologists are well trained and spirometry test are hospital-based (Enright et al, 2004).

Manoeuvre acceptability is defined by the BEV at the beginning of the test and the EOTV at the end of the test (Miller et al, 2005). These parameters should be satisfactory for a good trace measurement (table 1). During manoeuvres, technicians or clinical personnel, monitor the trace while continuously encouraging clients to give to their full capacity. Children have proven to have challenges meeting the quality criteria, set for adults, and modifications are mentioned in the ATS/ERS statement on PFT in preschool children (Beydon et al, 2007). A BEV of <80mL or 12.5% of the FVC is considered acceptable for children that are less than 10 years old (Jat, 2013). Arets et al, 2001, proposed new acceptability and repeatability criteria for spirometry to accommodate children which include the BEV <0.12 L for children under 15 years old and <0.15 L for older children above the age of 15 years; and FET >1s and >2 s for children <8 and >8 years old.

EOT criteria is especially difficult to meet by very young children when compared to

other acceptability criteria (Miller et al, 2005) necessitating the development of new EOT criteria specific for paediatrics (Desmond et al, 1997). Instead of the plateau at the end of test, for satisfactory expiration, a flow-volume curve that is rapidly rising to the peak flow and descends smoothly is accepted (Jat, 2013). This is in contrast to Miller et al (2005) statement that manoeuvres that don't meet the EOT criteria do not qualify for selection of the 3 acceptable manoeuvres. For subjects who terminate manoeuvres early, FEV1 may be used or reported depending on the length of exhalation.

Manoeuvre reproducibility is defined by the FVC or FEV1. The ATS proposed the absolute difference in FVC or FEV1 (DFVC or DFEV1), as a criterion of reproducibility (American Thoracic Society, 1987) whilst the ERS mention the use of the relative difference criterion (Quanjer et al, 1993). A study conducted by Arets et al in children experienced in MEFV found that the DFVC or DFEV1 was easily met by the most children. The criterion in their findings however, was age-dependent and was not applicable to all ages. They, therefore, recommended the relative criteria (%DFVC or %DFEV1) as appropriate in paediatric practice since they were made to control for changes in the absolute magnitudes of measurements with pulmonary development (Arets et al, 2001).

Table 1 Acceptability and repeatability criteria for spirometry manoeuvres in children. Adapted from Miller et al., 2005

Spirometry Acceptability Criteria
1. Good start: • The inhalation is good • BEV of <5% of FVC or <100mL if FVC <1000mL, whichever is greater (For children of 6-12 years of age)
2. Satisfactory exhalation: • Expiratory Time (ET) of 3 seconds • EOTV is when a plateau in the volume-time curve is reached or if child cannot or should not continue to exhale.
Repeatability criteria
A maximum of three acceptable traces are required: • The 2 largest values of FVC must be within 150mL of each other or within 5% FVC or <100mL if FVC <1000mL • The 2 largest values of FEV1 must be within 5% FVC or <100mL if FVC <1000Ml
Other criteria for good quality traces
Manoeuvres should: Be without coughs through the first second (s) of exhalation • Have no early cut off or termination • Have maximal efforts throughout • Have no leaks

- Have no obstruction of mouthpiece
- Have no glottis closure influencing measurement

4.2. Quality Assessment and Variability

A spirometer is designed with an inherent quality evaluation system which assigns grades to manoeuvres from A, B, C, D, E and F (table 2). Each grade is a measure of quality and is defined by a set of requirements that needs to be satisfied for a test to qualify to be in that category. Acceptability represents each measure's ability to meet stipulated thresholds for that measure, according to quality standards such as the ATS/ERS 2005.

Table 2. Spirometry quality grading system. Reproduced from Culver et al (2017)

Grade:	Criteria:
A	≥3 acceptable tests with repeatability within 0.150 L (for age 2–6, 0.100 L), or
B	≥2 acceptable tests with repeatability within 0.150 L (for age 2–6, 0.100 L), or
C	≥2 acceptable tests with repeatability within 0.200 L (for age 2–6, 0.150 L), or
D	≥2 acceptable tests with repeatability within 0.250 L (for age 2–6, 0.200 L), or
E	1 acceptable test
F	No acceptable tests

4.2.1. Within-manoeuvre sources of measurement errors and variability

Issues preventing the meeting of the ATS/ERS 2005 recommendations include the failure to achieve maximal effort and this has a direct influence on the quality of the trace, causing measurement errors. Poor efforts may occur during any (or all) of the manoeuvre phases (Enright et al, 2011).

The most common problem is sub-optimal effort during inhalation which could be easily identified by comparing multiple manoeuvres wherein unique FEV1 and FVC are created that are not reproducible. This problem is often a result of poor interaction between the subject and the technologist (Enright et al, 2011). A submaximal inhalation falsely reduces PEF, FEV and FVC (all of the results, except for the ratios).

Also, in each trace two common issues can be identified; a hesitant start and a slow start or poor exhalation effort (Enright et al, 2011). The former often result to a high BEV start which renders the manoeuvre unacceptable according to the ATS guidelines as it creates measurement errors in the FEV1 especially. A slow start or poor exhalation effort causes long peak expiratory flow time (PEFT) another source of error (Enright et al, 2011). A submaximal blast during the second phase wrongly underestimates the PEF, affecting the FEV1, and increases the FVC measures.

Premature terminations or manoeuvres that “quit too soon” cause a false reduction of the true FVC and can be identified by a high EOTV (Enright et al, 2011). Premature finishes are usually flows ending at above 10% of peak flow (Jat, 2013). For example, adults are expected to achieve an FET >6s, including an “obvious plateau” in the volume-time curve as per the ATS/ERS 2005 recommendations (Enright et al, 2011).

Another study found that expiratory time (TE) was a source of another common error, the frequent manoeuvre lasting <6s. This was found mostly in younger subjects where 5.1% of all performed manoeuvres, causing the most defects (Giner et al, 2014).

4.2.2. External sources of measurement errors and variability

The potential for systematic errors and increased random errors in studies involving

different spirometry technicians or teams is very high (Künzli et al, 1995). Measurement errors such as systematic measurement errors between technicians within a team or between teams are an important concern requiring attention (Künzli et al, 1995). If not taken into consideration systematic errors in lung function testing could bias the results by either underestimating or over-estimating spirometry outcomes. High random measurement variability leads to false negative conclusions by obscuring the effects of the exposure (Künzli et al, 1995).

Separate quality control studies, involving 23 experienced technicians and eight teams, were conducted for the (Swiss study on air pollution and lung diseases in adults (SAPALDIA) to test for technician, team, device and within-subject variability-related measurement errors (Künzli et al, 1995). These studies were focused on both systematic and random measurement errors. They were aimed at finding out if there was any systematic measurement bias across technicians within each team or across eight teams (Künzli et al, 1995). These studies also sought to determine if there was evidence for systematic errors across the eight SAPALDIA pulmonary function devices (one device per team) and to describe ways in which within-subject variability measured with different technicians or devices compare to the expected biological within-subject variability, given only one technician and one device (American Thoracic Society, 1991). Findings from these studies found that there were no systematic errors due to technician, team or device (Künzli et al, 1995).

Technician effect studies showed no team effect. However, these studies were limited by power, potential interactions between subjects and technicians in the fieldwork, and recruiting unhealthy subjects which could have increased total variability (Künzli et al,

1995). On the other hand, Giner et al, (2014), suggests that individual technologists conducting the test are the main source of variability in spirometry test quality. Masekela et al., (2013) emphasizes on the importance of dedication and competence of lung function technologist for successful spirometry. However, Enright et al, 2011 argues that no matter how competent technicians could be in doing the procedure in terms of training and other efforts to improve test success, there will always be at least 10% failure rate.

However, further investigation showed evidence of important internal error sources (device-related), which could not be easily detected even by trained technicians (Künzli et al, 1995). These unrecognizable technical problems could be hardware and software errors found in modern device and could introduce errors on any day, with any device. This makes the instrument, another good source of variability (Giner et al, 2014). Spirometry measurements may vary with models of spirometers. There is therefore a great need for quality control in spirometry to ensure valid and reliable results

4.2.3. Subject-related sources of measurement errors and variability

Individual clients' characteristics could be a good source of measurement errors and may influence the success or failure of the test (He et al, 2014). Most often they are associated with inability to reach stipulated quality standards (Giner et al, 2014). The burden of lung disease (BOLD) study found that factors that influence a spirometry test quality includes younger age, female children, higher education, lack of dyspnoea, higher pre- bronchodilator FEV1, poor bronchodilator response, and study site. However, these predictors of quality accounted for only 10% of the overall variability in test quality (Giner et al, 2014). Chhabra (2015), He et al, (2014) and Arigliani et al,

2016, stated that in addition to anthropometric measures other factors that may also influence spirometry measurements includes; environmental, genetic, socio-economic, technical and the inherent biological determinants of lung function (Becklake, 1986). Some of these factors cannot be adequately quantified and accounted for (Chhabra, 2015).

Spirometry errors are directly associated with sex and are frequently seen in females (Giner et al, 2014 and Liu et al, 2009). Gender is one of the major sources of variation in lung function (Cotes, 1979). FVC and FEV1 have been found to be higher by 10% to 15% in males when compared to females of the same age and heights. This is the case even with the PEF rate, which is also high in males than in females. However, the FEV1/FVC ratio and the expiratory flow rates are slightly higher in females. These support the development of separate equations for males and females (Chhabra, 2015).

For age, older patients are more prone to perform good quality spirometry. Poor performance is usually due to deteriorated lung condition which is common in this population. Surprisingly though, younger patients are usually the most spirometry-naïve subjects and tends to have more errors (Giner et al, 2014). Chhabra, (2015) and Chhabra et al, (2016), stated that age is a well-known source of lung function variation. There is a linear relationship between child growth and lung development. The rapid physiological changes of a child from birth to adulthood, directly influences the change in FVC and FEV1, which follows the growth pattern. The FVC and FEV1 increases up until it reaches a plateau at the age of 20 years and begin to decline steadily after 40 years, as the elastic coil is lost and closing volume increases (Chhabra, 2015).

Additionally, height has been found to explain the maximum variability. This is due to the

positive relationship that height has with spirometry variables (Chhabra, 2015 and Chhabra et al, 2016).

On another note, studies that directly compared pulmonary function in children from different ethnic groups confirmed the presence of ethnic differences in lung function in children (Rossiter et al, 1974; Korotzer et al, 2000; Jacobs et al, 1992 and Arigliani et al, 2016), suggesting that the causes of these differences could be genetic (Strippoli et al, 2013 and Arigliani et al, 2016). Ethnic differences were seen mostly for FVC and FEV1 and were not significant for FEV1/FVC ratio and flow rates (Chhabra, 2015).

Patients' characteristics that contributed to good quality measurements with fewer errors included previous experience with spirometry (Enright et al, 2011). The learning effect in some studies enhanced performance and reduced errors in patients who had previously performed spirometry (Enright et al, 2011).

Other than patients' characteristics, underlying conditions, such as patients showing respiratory symptoms, airway obstruction, or bronchodilator responsiveness, are more likely to fail quality goals, especially the EOTV (Enright et al, 2011). It is not easy to avoid unexplained variability and this leads inaccurate results and contributes to the loss of certainty of estimates (Chhabra, 2015).

Künzli et al (1995) stated that the primary goal to prevent systematic effects and reduce random measurement errors is to enforce quality on all levels of data collection. Other most effective tools include using available lung function testing standards or guidelines (Gardner et al, 1986), ensuring training to individuals conducting the tests, quality control and regular supervision (Künzli et al, 1995). They proposed that manufacturers

should ensure that software versions are adaptable to enhance the technicians' effort in obtaining accurate unbiased assessment. When conducting research studies, the reliability and accuracy of device hardware and software should not be assumed by researchers but tested to ensure proper functioning in the field. Also, there should be comparison tests in place even before the study commences (Künzli et al, 1995).

5. Interpretation of Spirometry

The availability of appropriate reference data determines the reliability of interpretations of spirometry results (Stanojevic, Wade and Stocks, 2010). Reference data is useful in distinguishing between normal and abnormal lung function as well as in assessing the severity and nature of functional impairment (Stanojevic, Wade and Stocks, 2010).

5.1. Normal Lung Function

Generally, the definition of normality of lung function is another controversy due to its subjectivity**.** Normal lung function is mostly assumed based on data from a “healthy population” wherein spirometry values ranges were obtained (Stanojevic et al., 2010 and Chhabra et al, 2016). This range of values is deemed to represent “normal” on the bases that it represents most individuals’ values. A normal range is one in which 95% of the range of values from the “healthy population” falls. Those with values outside of this normal range are said to have abnormal lung function and are often referred for further investigation. Since these values are derived from adult data, it becomes a challenge with children. Another question lies within the definition of a “healthy population”, especially as these lung function ranges are a reference on which all spirometry measurements and outputs are based.

Interpreting spirometry is a huge challenge embedded in the selection of appropriate reference values or misinterpretations where inappropriate equations were used. The increasing number of new and old published reference equations makes it more difficult to choose the appropriate ones (Stanojevic, Wade and Stocks, 2010 AND Chhabra et al, 2016). Inappropriate reference equations are a source of errors such as misdiagnosis and over or under diagnosis of disease, and their financial and human costs are very high.

5.2. Reference values

The use of different reference equations when measuring lung function is also another important source of variability in the interpretation of spirometry reads (He et al, 2014). This was more common before the Global Lung Function Initiative (GLI, 2012) developed multi-ethnic, all-age reference equations for spirometry which are now the new gold standard and have been adopted by many respiratory societies (Stanojevic et al, 2014). These become very useful in interpreting and presenting spirometry outcomes, especially the FEV1 and FVC incorporating multi-ethnic groups and all age groups.

The GLI-2012 reference equations were developed to try and bridge the gap and address the implications of variable equations between populations and age groups which have been common for a long time. These were investigated in pre-school children in three countries in Sub-Saharan Africa (Angola, D. R. Congo and Madagascar), and were found to be appropriate (Arigliani et al, 2016).

Reference equations provide a range of normal values which are compatible with normal lung function incorporating gender, age, ethnicity and body size of individuals

being investigated (Stanojevic, 2008). The use of different reference equations has led to elusive and extreme differences in findings reported by studies, based on the reference equations used (Quanjer, 2008). This highlights the importance of implementing updated and appropriate reference values for understanding the apparent lung function status of populations.

Most commonly, different reference standards were used for children and adults including gender and age specific equations. However, these have been shown to have limitations with varying clinical impact. Some equations overestimate lung function (FEV1 and predicted FVC) e.g. the Knudson equations, by producing low predicted values (Stanojevic et al, 2014). These limitations were mostly observed in children as realised in the Wang–Hankinson equations derived from the National Health and Nutrition Examination Survey (NHANES) III data. There is also evidence of the under diagnosis or under reporting of asthma in children in LMICs in the literature (Olaniyan et al, 2019 and Mohammad et al, 2017). Another loophole with reference values, especially age specific ranges, was that the transition from early childhood to adolescence to adulthood showed outstanding differences that have the potential to lead to substantial misinterpretation. This would mean that a patient with disease would be more likely to have results that are in the normal range due to incorrect data (false negative/false re-assurance).

The GLI-2012, therefore addressed these challenges by starting at 3 years of age. Such equations were aimed to improve interpretation of spirometry in paediatric practice as well as to enable appropriate assessment and disease management (Stanojevic et al, 2014). Universal reference equations are also crucial in improving comparability within

and between research studies. This would also address the implications caused by using spirometry cut-offs that exist between studies which forms the basis for participant selection (i.e. 90% predicted FEV1).

5.3. Steps for interpreting spirometry

Interpretation of children's lung functions' using adult criteria is a challenge and another major cause of errors in interpretation for this population. Abnormal lung function in children, for instance, is defined by applying the fixed adult predicted FEV1 cut-offs of 80% or 0.7 FEV1/FVC, which may cause misdiagnosis. Generally, the over reliance on fixed thresholds to define normal or abnormal lung function, magnifies misinterpretation problems regardless of well recognized age-related variations ((Stanojevic, Wade and Stocks, 2010).

Jat, (2013) summarized the interpretation of spirometry results in four steps: the 1st step is the assessment of acceptability and repeatability of spirometry followed by the identification of test patterns (Normal, Obstructive, Restrictive, or Mixed), the grading of patterns for severity and lastly the diagnoses, treatment or further investigation of identified conditions.

5.3.1. Assessment of acceptability and repeatability of tests

Spirograms are used to assess test acceptability and repeatability. These are the flow-volume curves which evaluate the BEV and volume-time curves which assess the EOT. The shape of the flow-volume curve is also useful in detecting errors and artefacts in the spirometry procedure which must be done first to ensure acceptability. They should comply with ATS/ERS standards (table 1).

5.3.2. Spirometry pattern and identification

The results of a spirometry test may suggest the following ventilation patterns: normal; obstructive; restrictive; or mixed pattern (Quanjer et al, 1993 and Barreiro, 2004) (table 3). Identification of abnormalities is through the analysis of the shapes of the flow-volume curves and volume-time curves and comparing the values of test parameters to their z-scores which account for sex, age, height, weight, and ethnicity.

A flow-volume curve that is sharply rising to a peak and descending at a 45° angle represents normal lung function (Aurora et al, 2004).. Mild to moderate airway obstruction is indicated by a concave curve whilst severe obstruction has an extended end like a rat's tail. A normal volume-time curve is also characterized by a sharp rise followed shortly by a plateau. Moderate to severe airway obstruction is indicated by a slow gradual rise with no definite plateau reached (Aurora et al, 2004). A restrictive pattern is shown by a small flow-volume curve whilst extra thoracic obstruction is shown by a flat FVC flow-volume curve without a peak. In younger children the convex shape of the flow-volume curve, which becomes more linear as the child grows, is due to the rapid emptying of the larger airways than the result in smaller lung volumes (Aurora et al, 2004).

Table 3 Spirometry pattern and identification. Adapted from Jat, 2013

Four types of ventilation patterns	**Characteristics and Indications**
Normal spirometry	- FVC: >80% of predicted or above the lower limit of normal - FEV1: >80% of predicted or above the lower limit of normal - FEV1/FVC is suggestive of normal function.
The obstructive pattern	- Decreased FEV1 <80% of predicted or below the lower limit of normal - Decreased FEV1/FVC - Normal FVC (in severe obstruction). - Mid expiratory flow (FEF25-75%) below 60% of predicted (small airway patency/ airway obstruction) (Lebecque et a, 1993; Valletta et al, 1997 and Simon et al, 2010)
The restrictive pattern	- Predominantly decreased FVC - Normal or decreased FEV1 - Normal or increased FEV1/FVC
The mixed pattern	- A decreased value of all three parameters (i.e. FEV1, FVC, and FEV1/FVC). - Normal expiratory flow but decreased inspiratory flow is suggestive of collapsible extra-thoracic airway obstruction (e.g. laryngeal paralysis) - Decreased maximal expiratory flow with normal inspiratory

	flow suggests collapsible major intrathoracic airway obstruction. - If both inspiratory and expiratory flows are decreased, a fixed intrathoracic or extra-thoracic airway obstruction is likely (Pellegrino et al, 2005)

5.3.3. Grading the severity of pattern identified

Spirometry results have been found to correlate with asthma severity, requiring oral steroids, emergency department visits, and hospitalizations (Fuhlbrigge et al, 2006) in preschool children (Vilozn et al, 2005). The FEV1 (% predicted) together with other clinical features of an individual, classifies the severity asthma into mild, moderate, and severe persistent asthma (Stout et al, 2006) (table 4).

Table 4 Grading severity of spirometry patterns in cases of asthma. Reproduced from Stout et al (2006)

Severity	**FEV1 (% predicted)**
Mild obstruction	FEV1 <100% to 80%
moderate obstruction	FEV1 <80% to 50%
severe airway obstruction	FEV1 <50% to 30%
very severe obstruction	FEV1 <30%

5.3.4. Diagnosis, linkage to care or further assessment

Spirometry alone does not provide aetiology or diagnosis of disease and should not be viewed in isolation of clinical evaluations, which should preferably be performed prior to spirometry. Instead, spirometry provides a pattern of ventilation and physiological pulmonary abnormalities, which aid diagnosis (Jat, 2013). These can be normal,

obstructive, restrictive, or mixed. In children, a typical example of the obstructive condition is asthma. Interstitial lung disease, pneumonia and pleural effusion show a restrictive pattern. Conditions such as cystic fibrosis may have either an obstructive, restrictive, or mixed spirometry pattern (Jat, 2013).

Results from both the clinical assessments and spirometry measurements are therefore used to provide a basis for diagnosis of disease. Patients diagnosed with these conditions may then be linked to care as necessary, i.e. referred for treatment, or subjected to further investigations of disease in advanced respiratory laboratories (Jat, 2013).

6. Conclusion

Spirometry is a useful tool for lung function investigation, yet quality remains a major concern in children. Despite, the modification of quality standards, the availability of better spirometers which have age-specific reference standards, intensive trainings and experience on paediatrics spirometry, the use of incentives to aid performance, young children still fails to meet good quality spirometry standards. Mostly they produce acceptable manoeuvres and maximal expiratory flow/volume curves that are useful for interpretation; the reliability of measurements cannot be guaranteed in children. In most cases these measurements are based on low quality standards. Other alternatives, with less quality implications could be explored for young children.

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PART C: Journal Ready Manuscript

This article has been prepared for the purposes of submission to the Journal, Paediatrics. The Instructions to Authors document has been attached (Appendix E). The author adhered to all the instructions set out by the Journal including the Times New Roman font and spacing, however, for the purpose of this thesis, some tables are included in the text. For the purpose of adhering to the MPH rules, the author has assumed sole authorship of this thesis. The supervisor and collaborators were acknowledged appropriately otherwise.

Title of Manuscript: The Quality and Variation of Spirometry Reads for Measuring Lung Function in Children in sub Saharan Africa

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Short title: Children spirometry in sub Saharan Africa

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Abbreviations:

ALHS	Adult Lung Health Study
ATS	American Thoracic Society
BEV	Back Extrapolated Volume
CAPS	Cooking and Pneumonia Study
CLHS	Child Lung Health Study
COMREC	College of Medicine Research Ethics Committee
DFEV1	Absolute difference between two highest FEV1
DFEV1%	Relative difference between two highest FEV1
DFVC	Absolute difference between two highest FVC
DFVC%	Relative difference between two highest FVC
EOTV	End of Test Volume
ERS	European Respiratory Society
FEV1	Forced expiratory volume in the first second
FET	Forced Expiratory Time
FVC	Forced Vital Capacity
HREC	Human Research Ethics Committee
ISAAC	International Study for Asthma and Allergies Control
LSTM	Liverpool School of Tropical Medicine
SOP	Standard Operation Procedures

Table of Contents Summary: Through secondary data analysis of the Child Lung Health Study, this study describes the quality and variations of spirometry measurements in children.

What's Known on This Subject: Although spirometry is a widely used diagnostic tool for measuring lung function in many primary health care settings, the quality and variation of spirometry measurement in children have not been evaluated in sub Saharan Africa.

What This Study Adds: This study describes and evaluates the quality and variation of spirometry reads for evaluating lung function in children aged 6-8 years, in a Malawian population.

Contributors' Statement

Miss Dumsile Maduna conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. She approved the final manuscript as submitted and agrees to be accountable for all aspects of the work.

Manuscript Abstract

BACKGROUND AND OBJECTIVE: Despite spirometry being the most commonly used diagnostic test for lung function, the quality of measurements have not been evaluated in sub-Saharan Africa. The objective of this study was to describe the quality and variation of spirometry reads in children, in a Malawian population.

METHODS: This descriptive study involved secondary analysis of data contributed by the Children Lung Health study (CLHS), a cross-sectional survey, conducted in Malawi. Spirometry measurements from 802 children, aged 6-8 years were studied. The Acceptability criteria; start-of-test (backward extrapolated volume (BEV)), end-of-test (forced expiratory time (FET) and EOTV (end-of-test volume) and Reproducibility criteria (absolute and relative difference (percentage difference between best and second-best FVC and forced expiratory volume in one second (FEV1) (DFVC, DFVC %, DFEV1 and DFEV1 %)) were applied to these manoeuvres. Statistical analysis was mainly descriptive statistics and logistic regression.

RESULTS: The BEV was <0.15 L in 99% of the children and varied with height and weight. FET was >6 s in 3% and 5% of the younger and older age group respectively. The EOTV was <0.05 L in 85% of the children. Both FET and EOTV were significantly associated with younger, but taller children. The DFVC <200 mL criterion was met by 95% of the children; DFVC% <5% by 66%; DFEV1 <200 mL by 97%; DFEV1% <5% by 64% of the children.

CONCLUSION: The failure for young children to meet all acceptable quality standards for spirometry proves a limitation of the measurement device and supports a re-evaluation of standards or technical amendments.

1. Introduction

Lung function investigations have become the centre of knowledge used to understand the growing burden of non-communicable pulmonary diseases globally (Murray et al, 2012). Chronic respiratory diseases, such as chronic obstructive pulmonary disease, asthma, pneumonia, and other lung diseases, are an emerging public health concern in low and middle-income countries (Ahmed, Robinson and Mortimer, 2017). Proper and timely diagnosis of these conditions is critical for health care systems in countries highly affected by chronic lung diseases, especially in Africa (Buist et al, 2017). In children, asthma, which compromises lung function in adolescence and subsequently adulthood (Phelan et al, 2002), is a major chronic respiratory disease (Asher and Pearce, 2014) with high burden in Africa. Diagnosis of lung diseases should not rely only on clinical symptom assessments but should be confirmed by airflow limitation (Reddel et al, 2015), which is commonly measured by spirometry.

Spirometry is a non-invasive method of lung function measurement, which is often used to distinguish between normal and abnormal lung function (Miller et al, 2005 and Levy et al, 2009). Spirometry measures lung capacity and is typically interpreted as normal, restrictive or obstructive. A recent study conducted in Malawi found a high prevalence of restrictive spirometry in adults, which is of great concern due to the relationship of restrictive spirometry with increased mortality (Meghji et al, 2016). However, there is very little research on measuring lung function in children in the sub Saharan Africa. Therefore, little is known about the burden of chronic lung diseases in children.

The most important parameters of lung function measured by a spirometer are the Forced Vital

Capacity (FVC) and Forced Expiratory Volume (FEV1) (Barreiro and Perillo, 2004). FVC measures the volume of air starting from a point of full inspiration to a forceful expiration which is as completely as possible and the first second of the FVC manoeuvre is the FEV1 (Miller et al, 2005). Together these estimates are used to calculate a FVC/FEV1 ratio which gives insight into the clinical disorder present i.e. obstruction or restriction. FVC and FEV1 are represented in most studies as z-scores to account for height, age, weight which are known to directly affect lung volume, and hence spirometry measures. Other parameters are measured but are rarely interpreted or analysed in clinical studies using spirometry. Additional measures available include the back extrapolated volume (BEV) and end of test volume (EOTV) which are used to classify an FCV and FEV1 manoeuvre as acceptable. Spirometry relies on the quality of these measurements to provide meaningful result.

The Department of Health (2004), and Commission for Healthcare Audit and Inspection (2009), and the Respiratory Alliance (2003), stated that high quality, reliable, diagnostic spirometry are critical elements underpinning improvements in quality of care and recognition of lung function conditions. The quality of spirometry measurements plays a major role in detecting lung function abnormalities, providing appropriate interventions, and planning health services. Therefore, accurate and reliable measurements are crucial in pulmonary function interpretation and documentation (Tan et al, 2014). In recent years, maximal expiratory flow/volume measurements have become the cornerstone of lung function testing, making spirometry the most common diagnostic and follow-up tool for children with respiratory conditions (Arets et al, 2001).

The American Thoracic Society (ATS) and European Respiratory Society (ERS) describe the

quality of spirometry through criteria for acceptability and repeatability (Miller et al, 2005 and Pallegrino et al, 2005). Emphasis is placed on the start of the test (BEV), the EOTV, and the forced expiratory time (FET) as important determinants of test quality (Miller et al, 2005). These, if not taken into consideration, could be major sources of error and mismeasurement. Children have always been recognized as having the greatest challenge in meeting spirometry quality standards, which were originally designed for adults (Arets et al, 2001). However, this is changing due to improved technology of the test instrument which takes age into account, modified quality criteria, and improved trainings of health practitioners involved in spirometry. One study that evaluated the applicability of the ATS/ERS criteria for spirometry in school-age children (aged 5–19 years) found the end of test to be the most challenging criteria for most children, whilst younger children struggle to produce maximum effort at the start of the test (Arets et al, 2001). Other studies argue that meeting the criteria is age-dependent and older children have no problem meeting them. Some studies emphasize on technicians' ability in obtaining maximal effort in children (Jat, 2013).

This study describes the use of spirometry as a reference standard for testing lung function and clinical diagnosis in children aged 6 -8 years old in the sub-Saharan African population. The aims of the analysis were to evaluate the quality and variation of spirometry reads in children. Also, variables associated with quality (and variation) of spirometry (reads) were identified.

2. Patients and Methods

2.1. Study design and population

This study was a secondary analysis of data collected as part of the Child Lung Health Study

(CLHS). The CLHS was a cross sectional survey assessing the prevalence and determinants of non-communicable lung disease in children aged 6-8 years, by measuring lung function and household-level particulate exposure (Rylance et al, 2017). The age range chosen reflected the younger age group (6 -7 years) included in the worldwide international study for asthma and allergies in children (ISAAC) trial (Rylance et al, 2017). Data used for the present study were collected from December 2016 to September 2017 in village-level clusters in Chikwawa that participated in the Cooking and Pneumonia Study (CAPS), Malawi (Havens, 2017).

2.2. Ethics and consent

All participants assented to be part of the study and adults who participated in the Adult Lung Health Study (ALHS) and carbon monoxide exposure components of CAPS gave written informed consent for children aged 6 -8 years who were recruited from their households during home visits (Rylance et al, 2017). Anthropometric measurements were taken from eligible individuals and spirometry was conducted pre- and post-bronchodilator treatment by trained and certified staff. The CLHS study entitled, "Child lung health and exposure to household air pollution in rural Malawi", by Rylance et al, 2017 was approved by the College of Medicine Research Ethics Committee (COMREC) p.07/16/1994 in Malawi and LSTM Research Ethics Committee (REC) 16-040. Ethical approval for this study was given by the Faculty of Health Sciences Human Research Ethics Committee, University of Cape Town (HREC REF 669/2018).

2.3. Data collection

Spirometry was performed according to the ATS/ERS guidelines (Miller et al, 2005) using an Easy on-PC spirometer (new diagnostic design, ndd) in the participant's home. Study staff received training in paediatric spirometry from experienced researchers and Spirometry Training

Services Africa (Rylance et al, 2017). Spirometry was performed before and after four puffs (total 400 micrograms) of a Salbutamol inhaler via a large volume spacer (Rylance et al, 2017). The child would blow into the machine a maximum of eight times, to record the maximum lung volume (FVC) and FEV1.

Lung function quality assurance was achieved through full training of study staff on performing paediatric spirometry tests before the study commenced (Rylance et al, 2017). Standard operating procedures (SOP) were developed to aid study staff in achieving a quality output and reduce variability of results. Study equipment was calibrated and maintained according to the manufacturer's instructions. Spirometry traces were reviewed by two clinicians independently for adherence to within-manoeuvre and between-manoeuvre quality criteria. Study field workers were supervised by senior team members to ensure standard operation procedures (SOPs) were adhered to and to identify any additional training needs (Rylance et al, 2017). Test sessions were evaluated automatically by the Easy on-PC spirometer, which graded quality into five categories (A, B, C, D and F) and a minimum of three acceptable manoeuvres were obtained for each child.

2.4. Statistical analysis

Descriptive statistics were calculated for both the pre- and post-bronchodilator time points to: describe the characteristics of the study population; and summarize the spirometry indices for individual manoeuvres. Frequency tables were used to summarize the primary outcome, quality and secondary outcome, acceptance. Histograms were used to show distributions of numerical data (discreet or continuous). Scatter plots were used to display bi-variate data and show the strength of the relationship between spirometry indices and anthropometric variables. Box plots were used to graphically show selected descriptive measures for indices and quality outcomes.

Contingency tables and Chi squared test were used to identify associations between quality and acceptance outcomes. Study measures included the BEV, FET, EOTV (variables for acceptability) and FVC, FEV1, FVC/FEV1 (variables for repeatability). For the relative and absolute differences (DFVC and DFEV1) were used. (See supplementary table 7 pg 83 for definitions). Predictors of quality were Age, gender, weight and height.

Univariable analysis (binary logistic regression) was performed to: determine the relationship and its strength between spirometry indices with primary outcome, quality and secondary outcome, acceptance; to determine the associations between spirometry parameters and clinical factors considered as predictors of quality; and to identify variables associated with poor quality traces. Each quality grade (A, B, C, D and F) was analysed independently and categorized as Yes or No. Proportions using contingency tables and Chi squared test were used to estimate the prevalence (95% confidence intervals) of poor quality traces (suboptimal BEV, FET and EOTV). All tests were two-tailed in nature and were performed using Stata version 14.2 statistical software (Stata Statistical Software: R.14; StataCorp LLC, College Station, TX) and R software. A p value < 0.05 was considered statistical significant.

3. Results

3.1. Participation and demographics

The analysis of the pre- and post-bronchodilator spirometry data included data from all 802 participants from village-level clusters of Chikwawa in Malawi. Participants were African children (99.9%); 48% were males; 47% below 7-years-old (young children) and 53% above 7-years-old (older children); mean age was 7.1 ($\pm$0.8) years; mean height was 1.2m ($\pm$ 0.1) and the mean weight was 19.9 ($\pm$2.8) kg/m2 (Table 1). A total of 12% of the children did not perform

post-bronchodilator spirometry. These were mostly young children with a mean age of 7.0 (±0.8) years); who were short, with a mean height of 1.2m (± 0.1) and were females (51.0%).

Table 1 Baseline characteristics of the 802 children cohort at Pre and Post-bronchodilator time points. Values given as frequency (per cent) unless otherwise specified

	Total	**Pre-BD**	**Post-BD**	**Subject without Post-BD**
Study subjects (n)	802 (100%)	802(100%)	706 (100%)	96(100%)
Gender:				
Males	387 (48.3%)	387 (48.3%)	340(48.2%)	47(49.0%)
Females	415 (51.8%)	415 (51.8%)	366 (51.8%)	49(51.0%)
Ethnicity :				
African	801(99.9%)	801 (99.9%)	706 (100%)	96(100%)
Asian	1 (0.1%)	1(0.1%)	0 (0.0%)	N/A
Age categories:				
<7 (Young)	374 (46.6%)	374 (46.6%)	319 (45.2%)	41(42.7%)
>7 (Older)	428 (53.4%)	428 (53.4%)	387 (54.8%)	55(57.3%)
Anthropometry (mean, SD)				
Age, yrs.	7.1 ± (0.8)	7.14 ± (0.8)	7.16 ± (0.8)	7.0± (0.8)
Height, cm	1.2 ± (0.1)	1.16 ± (0.1)	1.2 ± (0.1)	1.1 ± (0.1)
Weight, Kg	19.9 ± (2.8)	19.8 ± (2.8)	19.9 ± (2.8)	19.2± (2.7)

3.2. Quality assessment and Variability by the Easy on-PC spirometer

The Easy on-PC spirometer automatically evaluated test sessions according to quality grades (A, B, C, D, and F) (Enright et al, 2011). Out of the 1508 test sessions conducted showed that 65% for pre-bronchodilator test sessions and 71% of post-bronchodilator tests sessions had adequate quality (Grades A, B and C); 12% in both time points had D quality; 23 % and 17% had F quality in pre-bronchodilator and post- bronchodilator sessions respectively. Quality grades A and F were associated with older age, male gender and taller height (Table 2(a)).

Table 2 (a) Risk factors associated with spirometry quality grades (A, B, C, D and F) in both the pre-and post-bronchodilator test sessions

	Pre-BD		**Post-BD**	
Risk factor	**Crude**		**Crude**	
Grade A	**OR**	**95% C. I**	**OR**	**95% C. I**
Age	**1.65**	**1.37-1.99**	**1.22**	**1.01-1.49**
Gender: Male	**0.64**	**0.49-0.85**	0.76	0.57-1.03
Height	**89.46**	**8.96-893.01**	6.97	0.60-80.88
Weight	1.05	1.00-1.10	1.03	0.98-1.09
Grade B				
Age	0.76	0.54-1.07	0.76	0.53-1.11
Gender: Male	1.27	0.77-2.10	1.32	0.76-2.29
Height	0.02	0.00-1.46	0.03	0.00-2.69
Weight	0.93	0.85-1.02	0.93	0.84-1.03
Grade C				
Age	1.02	0.72-1.45	1.34	0.94-1.92
Gender: Male	0.89	0.52-1.53	1.18	0.67-2.07
Height	0.39	0.00-30.94	25.38	0.26-2507.93
Weight	1.01	0.92-1.12	1.06	0.96-1.16
Grade D				
Age	0.77	0.58-1.02	0.83	0.62-1.13
Gender: Male	1.30	0.85-1.99	0.83	0.52-1.31
Height	0.66	0.02-20.48	0.05	0.00-2.29
Weight	1.02	0.94-1.09	0.94	0.86-1.02
Grade F				
Age	**0.63**	**0.50-0.79**	0.78	0.60-1.02
Gender: Male	**1.50**	**1.07-2.09**	1.49	1.00-2.22
Height	**0.02**	**0.00-0.24**	0.37	0.01-9.68
Weight	0.95	0.89-1.01	1.00	0.93-1.07
Narrative: statistically significant figures are written in bold.				

The Easy on-PC spirometer further evaluated test sessions by acceptance outcomes (whether manoeuvre was accepted or not). This study found that 77% of children had acceptable 1st manoeuvres, yet only 71% and 56% had acceptable second and third manoeuvres respectively. 23% of children had an unacceptable 1st manoeuvre and these also failed the second and the 3rd subsequent manoeuvres. However, 7% of children with an accepted first manoeuvre failed both the 2nd and the 3rd subsequent manoeuvres. Figure 1 shows the distribution of children through

the different manoeuvres by the acceptance outcomes. Acceptance of manoeuvres was associated with age, gender, height and weight (Table 3 (b)).

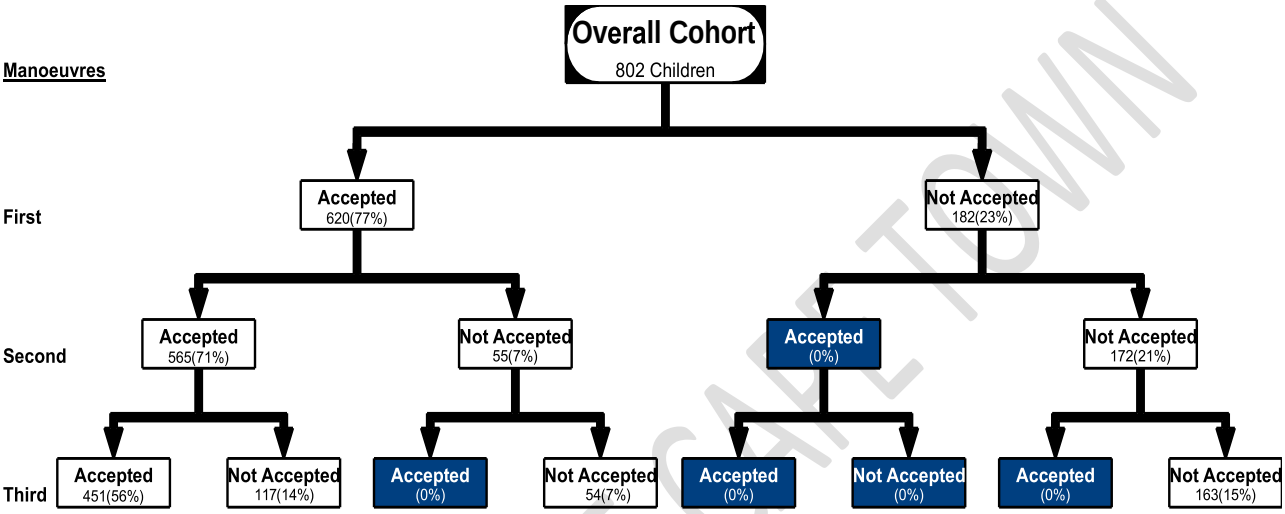

Figure 1 Flow chart showing the distribution of children in the different manoeuvres by acceptance outcomes. Boxes represent acceptance outcomes and rows represent manoeuvres. Highlighted boxes mean there were no children with that outcome

Table 2 (b) Risk factors associated with manoeuvre acceptance in both the pre and post bronchodilator test sessions

	Pre-BD		**Post-BD**	
Risk factor	**Crude**		**Crude**	
Manoeuvre 1	**OR**	**95% C. I**	**OR**	**95% C. I**
Age	**1.58**	**1.26-1.99**	1.27	1.00-1.66
Gender: Male	**0.67**	**0.48-0.93**	0.67	0.45-1.00
Height	**65.33**	**4.14-1029.76**	2.70	0.10-70.59
Weight	1.05	0.99-1.12	1.00	0.93-1.07
Manoeuvre 2				
Age	**1.76**	**1.42-2.19**	**1.39**	**1.09-1.78**
Gender: Male	**0.65**	**0.48-0.89**	0.75	0.53-1.08
Height	**92.13**	**7.00-1212.71**	10.17	0.52-197.99
Weight	**1.40**	**0.62-3.17**	1.04	0.97-1.11
Manoeuvre 3				
Age	**1.83**	**1.50-2.23**	**1.39**	**1.12-1.72**
Gender: Male	**0.64**	**0.48-0.85**	**0.71**	**0.51-0.97**
Height	**99.13**	**9.02-1089.39**	**15.35**	**1.08-218.60**
Weight	1.05	1.00-1.11	1.05	1.00-1.12
Definition of abbreviation; BD stands for bronchodilator				

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3.3. Quality assessment and Variability by the ATS acceptability and repeatability criteria

The ATS criteria for acceptability in children are BEV <100 ml, FET > 3 seconds and EOTV <50 ml; and for repeatability, variation in FEV1 (<200ml), FVC (< 200 ml) (Pellegrino et al, 1994). Tables 3 (a) and 4 shows the mean, and SD for pre- and post-bronchodilator spirometry variables for all children according to the ATS/ERS criteria of acceptability and repeatability.

Table 3 Spirometry quality indices for the ATS/ERS criteria of acceptability (BEV, FET, EOTV), for each manoeuvre in the pre and post–bronchodilator spirometry tests

	Pre-BD		**Post-BD**	
	Mean	**SD (+)**	**Mean**	**SD (+)**
Manoeuvre 1				
BEV, L	0.05	0.05	0.05	0.02
FET, sec	3.57	1.65	3.78	1.40
EOTV, L	0.04	0.10	0.02	0.08
Manoeuvre 2				
BEV, L	0.04	0.04	0.05	0.02
FET, sec	3.59	1.75	3.69	1.41
EOTV, L	0.05	0.11	0.02	0.08
Manoeuvre 3				
BEV, L	0.04	0.04	0.05	0.04
FET, sec	3.42	1.76	3.63	1.34
EOTV, L	0.05	0.11	0.03	0.09

Table 4 Spirometry indices for the ATS/ERS criteria of repeatability by manoeuvre of the pre- and post–bronchodilator test sessions in the Child Lung Health Study. Data is presented as means and percentages

		Pre-BD			**Post-BD**			
	Mean	**Pred**	**Pred%**	**LLN**	**Mean**	**Pred**	**Pred%**	**LLN**
Manoeuvre 1								
FVC	1.12	1.39	80.57	1.11	1.14	1.40	81.43	1.12
FEV1	0.99	1.26	78.57	1.00	1.01	1.26	80.16	1.01
FEV1/FVC	0.89	0.91	97.80	0.79	0.89	0.91	97.80	0.79
FEF2575	1.36	1.67	81.4	1.05	1.49	1.68	88.69	1.05
Manoeuvre 2								
FVC	1.08	1.39	77.70	1.11	1.09	1.40	77.86	1.12
FEV1	0.95	1.26	75.40	1.00	0.97	1.26	76.98	1.01
FEV1/FVC	0.88	0.91	96.70	0.79	0.89	0.91	97.80	0.79
FEF2575	1.30	1.67	77.84	1.05	1.43	1.68	85.12	1.05
Manoeuvre 3								
FVC	1.07	1.39	76.98	1.11	1.07	1.40	76.43	1.12
FEV1	0.92	1.26	73.02	1.00	0.95	1.26	75.40	1.01
FEV1/FVC	0.88	0.91	96.70	0.79	0.89	0.91	97.80	0.79
FEF2575	1.26	1.67	75.45	1.05	1.40	1.68	83.33	1.05

Definition of abbreviation: LLN stands for Lower Limit Normal.

Quality results for the ATS criteria of acceptability (BEV, FET and EOTV), and repeatability (FEV1 and FVC) using the absolute and relative differences for the pre and post–bronchodilator spirometry test sessions are presented in Tables 5. Quality assessments were conducted for different thresholds of the ATS criteria. This study found that more than 95% of all the children met the criteria for acceptability and above 85% children met the repeatability criteria when it is relaxed. Acceptability variables were taken from the “best manoeuvre” and repeatability variables were the differences between the highest and second highest manoeuvres.

The acceptability of manoeuvres for the children was mostly dependent on FET other than BEV and EOTV when the "best manoeuvre” was analysed. Only FET was associated with acceptability of manoeuvres for the children, OR 1.63 (95% CI: 1.44, 1.83). The BEV showed no association and the EOTV was too small for analysis.

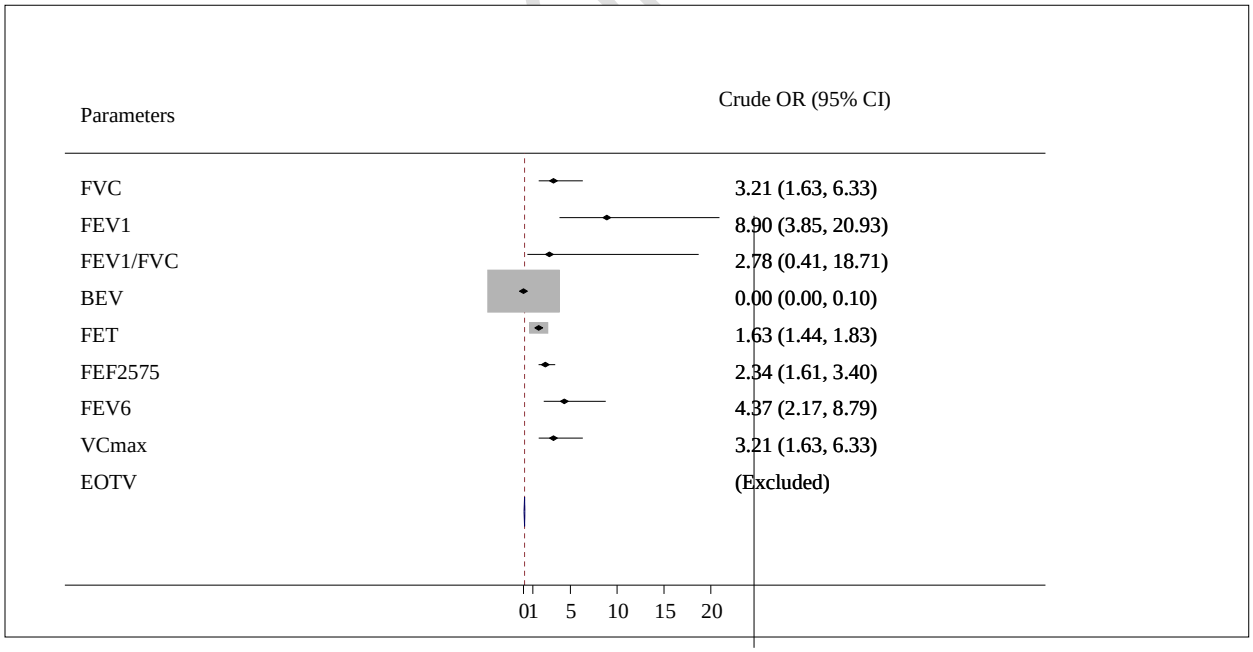

Figure 3 Odds ratios (OR) and 95% Confidence Interval (C.I.) of "best manoeuvre” indices and acceptability

Table 5 Proportion of children with manoeuvres that met the American Thoracic Society and European Respiratory Society acceptability and reproducibility criteria; Results are in frequencies and Percentages.

	Stringent	**Relaxed**
Acceptability Criteria		
BEV		
Young <=7-yrs-old	371(99.2%)	371(99.2%)
Older >7-yrs-old	425(99.3%)	425(99.3%)
BEV%FVC		
Young <=7-yrs-old	300 (80.2%)	
Older >7-yrs-old	361 (84.4%)	
FET		
Young <=7-yrs-old	11(2.9%)	208(56.6%)
Older >7-yrs-old	20(4.7%)	321(75.0%)
EOTV		
Young <=7-yrs-old	296(79.1%)	
Older >7-yrs-old	387(90.4%)	
Reproducibility Criteria		
DFVC		
Young <=7-yrs-old	348(93.1%)	311(83.2%)
Older >7-yrs-old	412(96.3%)	367(85.8%)
DFVC%		
Young <=7-yrs-old	236(63.1%)	
Older >7-yrs-old	297(69.4%)	
DFEV1		
Young <=7-yrs-old	365(97.6%)	326(87.2%)
Older >7-yrs-old	415(97.0%)	375(87.6%)
DFEV%		
Young <=7-yrs-old	232(62.0%)	
Older >7-yrs-old	282(65.9%)	
Stringent are criteria for adults: BEV<0.15L BEV%FVC<5% FET > 6s EOTV<0.05L DFVC<200ml DFVC%<5% DFEV1<200ml DFEV1%<5%	Relaxed are modified criteria for children: BEV<0.10L FET>3s DFEV<100ml DEFV1<100ml	

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The acceptability criteria for start-of-test showed that the BEV% FVC was <5% in 82% of all children. At least 80% of the young age group (7-yrs-old and below) were able to reach this criterion and 84% of the older children (above 7-yrs-old) (Tables 5). The mean best BEV%FVC was 4 (±3%), range (1-60). There was no evidence of association between BEV% FVC and age, gender, height and

weight (Table 6). The BEV was <0.15 L in 99% of the children in both the younger age group and the older age group (Table 5). The mean best BEV was 0.05 (±0.05) L, range (0.01–1.12). There was a significant association of the BEV with height (Table 6).

The acceptability criteria for end-of-test, show that the maximal FET was >6 s in 4**%** of all the children. 3% children in the younger age group and 5% in the older age group met this criterion (Table 5). The mean FET was 3.57 (±1.65) s, range (0.28–13.49). The FET was significantly related (positively) to height and negatively related to age (younger children) (Table 6). When FET was tested using the >3s criteria, 56% of the younger children, and 75% of the older children met this criterion. The EOTV was <0.05 L in 85% of the children. 79% children in the younger age group and 90% in the older age group met this criterion (Table 5). The mean best EOTV was 0.04 (±0.10) L, range (0.00–0.76). There was a weak positive relationship of the EOTV with age (younger children), and a negative relationship with height (Table 6).

The repeatability (reproducibility) criteria show that the absolute difference between the two highest FVC (DFVC), was <200 mL in 95% of the children. There were 93% children in the younger age group and 96% in the older age group that met this criterion (Table 5). The mean DFVC was 0.60 (±0.90) L, range (0–1.48). There was a weak, although significant relationship of the DFVC with only the male gender (Table 6). The relative difference between two highest FVC (DFVC%) <5% was met by 66% of children (Table 5). Mean DFVC % was 5.14 (± 6.14%), range (0–58.9). 69% of the children in the older age group reached the criterion and 63% in the younger age group. There was a weak, but significant relationship of DFVC % with height (Table 6).

The absolute difference between two highest FEV1 (DFEV1) was <200 mL in 97% of all children. 98% patients in the younger age group and 97% in the older age group met this criterion (Table 5). The mean DFEV1 was 0.05 (±0.06) L, range (0-0.65). The DFEV1 was not significantly related to all

the anthropometry measures (Table 6). The relative difference between two highest FEV1 (DFEV1%) was <5% in 64% of the children (Table 5). The mean DFEV1 % was 5 (±5%), 95% C.I. (0–46). There was also no significant relationship between DFEV1% and anthropometry measures (Table 6).

Table 6 Association between anthropometry measures and indices from the "best manoeuvre" and manoeuvres with the highest FEV and FVC, estimated by odds ratios (OR) and 95% confidence intervals

	BEV%FVC	**BEV, L**	**FET, s**	**EOTV, L**	**DFVC**	**DFVC %**	**DFEV1**	**DFEV1 %**
Age: Older	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Young	1.00(1.00-1.01)	1.00(0.99-1.01)	**0.50(0.40-0.62)**	1.03(1.01-1.04)	1.01(0.99-1.02)	1.01(1.00-1.02)	1.00(0.99-1.01)	1.01(1.00-1.01)
Gender Female	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.00(0.99-1.00)	1.00(1.00-1.01)	1.23(1.00-1.54)	1.00(0.99-1.01)	**1.02(1.01-1.03)**	1.01(1.00-1.02)	1.01(1.00-1.02)	1.01(1.00-1.02)
Height	0.98(0.95-1.02)	**1.08(1.02-1.15)**	**326.37(53.47-1992.28)**	**0.81(0.72-0.90)**	0.95(0.86-1.05)	**0.88(0.82-0.94)**	1.06(0.99-1.13)	0.96(0.90-1.02)
Weight	1.00(1.00-1.00)	1.00(1.00-1.00)	1.14(1.09-1.18)	1.00(0.99-1.00)	1.00(1.00-1.00)	1.00(1.00-1.00)	1.00(1.00-1.00)	1.00(1.00-1.00)

4. Discussion

The results show that most children were able to perform acceptable flow/volume manoeuvres according to the ATS and ERS acceptability and reproducibility criteria. Younger children, however, proved to have a challenge meeting the acceptability criteria but not the reproducibility criteria. Good quality spirometry is still not easily achievable by children even with the presence of modified quality criteria. Literature seems to suggest lowering the already lowered quality standards in order increase the number of children meeting the standards (Arets et al, 2001; Tomalak et al, 2008), but

this may have implications clinically.

This study found that most children had acceptable 1st manoeuvres but as more manoeuvres were performed acceptance rates decreased. This is in contrast with findings by Arets et al (2001), which suggested that, several attempts could improve skills and results for inexperienced children. Inexperienced children should familiarize themselves with spirometry procedures, especially during their first test attempt to ensure adaptability and positive experience from it, which is necessary for good compliance and performance in subsequent tests (Arets et al, 2001).

Also, children with an unacceptable 1st manoeuvre also failed the second and the 3rd subsequent manoeuvres. This means that children who fail the 1st manoeuvre are most likely to also fail the following manoeuvres and it is understandable considering that the quality of all the failed 1st manoeuvres was F. Unaccepted manoeuvres were correlated with age (younger age group) and height. This shows how difficult it is to perform acceptable spirometry in young children, which is consistent to findings by a retrospective study assessing the adherence of flow-volume measurements to ATS/ERS 2005 standards in children younger than 10 years of age (Tomalak et al, 2008). The study found that children aged $\geq$6 years had lower cooperation levels, which went only up to 50%, despite specific techniques developed to aid performance (Tomalak et al, 2008). Even for the children with an accepted first manoeuvre, some failed both the 2nd and the 3rd subsequent manoeuvres, as they started off with poor quality manoeuvres (first manoeuvres were grade D).

The second set of our findings was that most of the studied children could meet the current start-of-test criteria, which is the most important phase of the manoeuvre (the maximally deep breath), requiring the most emphasis (Enright, 2003). The BEV appears to be the most appropriate start-of-test criterion because of its independence to age and height (Arets et al, 2001). Arets et al (2001) found comparable results, which showed that with the guidance of a well-trained technician, most

children can achieve this criterion. Although, they studied children with extensive experience in lung function testing, 95% children aged <15 years met the BEV<0.15 L criterion. In the present study, 99% of all children, although inexperienced, met both the BEV<0.15 L and the ERS criterion of BEV<0.10 L. Height and weight were positive, but weakly correlated with BEV and not correlated with BEV%FVC. This can be explained by the rise in FVC during the spontaneous growth of children (Arets et al, 2001).

Moreover, the end-of-test criteria still proves to be far more difficult to meet for children and if this is not met (i.e. exhalation is not complete), the FVC will be underestimated leading to it being misinterpreted (i.e. misdiagnosing of patients as suffering from lung restriction, when they actually have normal lung volumes (Enright, 2003). The FET criteria of ≥6s required by the ATS (Enright et al, 2011), was only met by a few children, yet it's necessary for volume/ time curve without an obvious plateau in the display. Arets et al (2001), found that only 9% and 13% of children <8 years and 8-11 years old respectively, met the >6s criterion. They discovered that only 36% of the adolescents (aged >15 years) met this criteria, implying that older children also fails to forcefully exhale during >6s. The current study found that only 5% of the eldest group and 3% for the younger group expired beyond 6s, which is consistent with Arets et al (2001) that this criterion is unsuitable for use in paediatric practice.

When FET was adjusted to >3s, as per the recommendations of the newest ATS/ERS for children aged > 10 years old (Beydon et al, 2007), still more children could not meet this criteria. In such cases the ATS, therefore, recommends that shorter FET be accepted in children, although these fails to be more specific (ATS, 1987 update). Tomalak et al, (2008), also found the current time of forced expiration >3 as too restrictive, and only 23.9% children in their study met this criteria. They proposed the development of specific standards for children. The EOTV was <0.05 L was 79% in the younger children and 90% for the older children.

Thirdly, when the absolute difference in FVC or FEV1, as proposed by the ATS, was taken as a criterion of reproducibility, this was easily met by most children, even the younger ones.

Repeatability criteria using absolute differences for both FVC and FEV1 were significantly influenced by sex and weight for FEV1. This contradicts with Arets et al (2001), who found that these were significantly influenced by age and height. The proportion of children decreased when relative criteria for repeatability was used. Relative criteria showed dependency upon height and weight instead of age. The ERS mentions that criteria using the relative difference (Quanjer et al, 1993) are more appropriate in paediatric practice as they are not associated with either height or age. However, results from this study showed that most criteria depended upon height and weight instead of age. The 5% difference criteria were reached by 66% and 64% of children for FVC and FEV1, respectively. The current 5% criteria, when applied in this study seemed to be less useful in childhood than the absolute criterion of 100 or 200ml, opposing findings by Arets et al (2001).

Lastly, the cross-sectional nature of this study; involving children inexperienced with lung function testing was the major limitations of this study. Spirometry and associations were also measured only at one point in time in participants homestead during the course of the study. A longitudinal design could produce more accurate results by enabling repeated measures of the outcomes and ensure enough chances for children to get experience and attain necessary skills for lung function testing. This design could also enable the investigation of other important predictors of quality which were not included in this study. The hospital setting would have been more appropriate and preferred for this study than home setting.

5. Conclusion

This study has provided evidence that children fails to reach the goals of all ATS/ERS criteria.

Although, most children do produce acceptable manoeuvres, with the modified criteria, however the quality remains poor. Literature proposes further modification of the already lowered quality standards; however, not much thought has been given to the implications of this clinically. The concern would be if it's still worthwhile to use spirometry in young children. Also, in order to determine whether experience could improve the quality of spirometry in this population, longitudinal studies involving repeated spirometry measurements are needed for lung function testing studies.

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Legends of figures from the study

Figure 1. The proportion of acceptable manoeuvres decreased as more spirometry sessions were performed in children. An analysis of manoeuvre acceptability was conducted for the 3 "best manoeuvres". Data showed that in the 1st manoeuvres, acceptability was at 77%, which declined by 6% and 21% in the 2nd and 3rd manoeuvres.

Figure 2. Spirometry quality indices were the least parameters used to determine acceptability of manoeuvres. A regression analysis was conducted to sow associations between spirometry indices and acceptability. Data showed a no association for BEV, EOTV was too small to be calculated and FET shows positive association (ORs: 0, excluded and 1.63).

SUPPLEMENTARY TABLES TO JOURNAL MANUSCRIPT

Table 7 Definitions

	Spirometry values
FVC	Forced vital capacity; the total volume of air that can be exhaled during a maximal forced expiration effort.
FEV1	Forced expiratory volume in one second; the volume of air exhaled in the first second under force after a maximal inhalation.
FEV1/ FVC ratio	The percentage of the FVC expired in one second.
FET	Forced expiratory time is the total time it takes for a patient to complete their exhalation in a FVC manoeuvre.
FEF25-75%	Forced expiratory flow over the middle one half of the FVC; the average flow from the point at which 25 per cent of the FVC has been exhaled to the point at which 75 per cent of the FVC has been exhaled.
VC	Vital capacity; the largest volume measured on complete exhalation after full inspiration.
BEV	backward extrapolated volume
EOTV	End of test volume
BEV % FVC	Backward extrapolated volume as percentage of forced vital capacity
DFVC	Absolute difference between two highest forced vital capacities
DFVC %	Percentage difference between two highest forced vital capacities
DFEV1	Absolute difference between two highest forced expiratory volumes in one second
DFEV1%	Percentage difference between two highest forced expiratory volumes in one second
Prod	Predicted values
Prod%	Predicted%=Observed/predicted*100
LLN	Lower limit of normal. Lower predicted boundary/ range usually set at 5% above which normal value lies. It is calculated from the mean predicted value and the residual standard deviation.
Manoeuvre	Refers to a trace recording on the spirometer when a client forcefully blast out air from a point of maximum inhalation to complete exhalation
Best manoeuvre	Manoeuvre with the largest FVC + FEV1 sum

Table 8 Relationships each spirometry index has on the levels of quality which is in Grades A, B, C, D and F

	Spiro Indices	**Pre**		**Post**	
Quality Grade		**Crude OR**	**95% C. I**	**Crude OR**	**95% C. I**
Grade A	**Maneuver 1**				
	FVC	**4.06**	**2.29-7.22**	1.77	0.96-3.26
	FEV1	**7.21**	**3.57-14.57**	**4.89**	**2.34-10.22**
	FEV1/FVC	0.53	0.10-2.77	**76.85**	**9.27-637.29**
	FEF2575	**1.71**	**1.26-2.31**	**2.62**	**1.92-3.58**
	FEV6	**4.85**	**2.69-8.74**	**2.24**	**1.18-4.26**
	Vaux	**4.06**	**2.29-7.22**	1.77	0.96-3.26
	BEV	0.11	0.00-3.95	**0.00**	**4.99e-08-0.02**
	FET	**1.50**	**1.35-1.66**	**1.14**	**1.02-1.28**
	EOTV	**1.17e-08**	**2.84e-11- 4.81e-06**	**0.00**	**0.00-0.08**
	Maneuver 2				
	FVC	**5.35**	**2.96- 9.64**	**2.80**	**1.46-5.37**
	FEV1	**13.43**	**6.41-28.14**	**8.80**	**4.08-18.97**
	FEV1/FVC	1.10	0.23-5.16	**249.66**	**29.60-2105.41**
	FEF2575	**2.04**	**1.50-2.79**	**3.48**	**2.50-4.84**
	FEV6	**6.40**	**3.50-11.73**	**3.16**	**1.63-6.13**
	VCmax	**5.28**	**2.93-9.53**	**2.80**	**1.46-5.37**
	BEV	0.02	0.00-6.20	0.10	0.00-51.52
	FET	**1.40**	**1.28-1.54**	**1.16**	**1.03-1.29**
	EOTV	**8.37e-10**	**1.17e-12 -5.99e-07**	**0.00**	**3.57e-06-0.03**
	Maneuver 3				
	FVC	**2.06**	**1.19-3.56**	0.96	0.51-1.84
	FEV1	**3.49**	**1.75-6.93**	**2.32**	**1.10-4.90**
	FEV1/FVC	0.73	0.17-3.03	**77.89**	**11.35-534.70**
	FEF2575	**1.41**	**1.05-1.89**	**2.44**	**1.78-3.34**
	FEV6	**2.51**	**1.41-4.45**	1.02	0.53-1.94
	VCmax	**2.03**	**1.17-3.52**	0.99	0.52-1.89
	BEV	**2.52e-06**	**3.23e-09 - 0.00**	**1.73e-08**	**2.17e-11-0.00**
	FET	**1.39**	**1.27-1.52**	**1.20**	**1.07-1.34**
	EOTV	**2.74e-08**	**2.19e-10-3.42e-06**	**7.65e-07**	**2.65e-09-0.00**
	Maneuver1	**OR**	**95% C. I**	**OR**	**95% C. I**
	FVC	0.44	0.16-1.22	0.34	0.11-1.11
	FEV1	0.60	0.18-1.98	0.34	0.09-1.26
	FEV1/FVC	18.17	0.56-591.35	1.81	0.04-75.85
	FEF2575	1.22	0.72-2.07	0.71	0.42-1.22
	FEV6	0.46	0.17-1.28	0.35	0.11-1.14
	VCmax	0.44	0.16-1.22	0.34	0.11-1.11
	BEV	0.00	2.88e-09 - 840.75	0.09	6.08e-07 - 13662.08
	FET	0.89	0.76-1.05	0.94	0.77-1.15
	EOTV	0.13	0.00-4.80	0.00	9.16e-08 - 88.39
	Maneuver2				

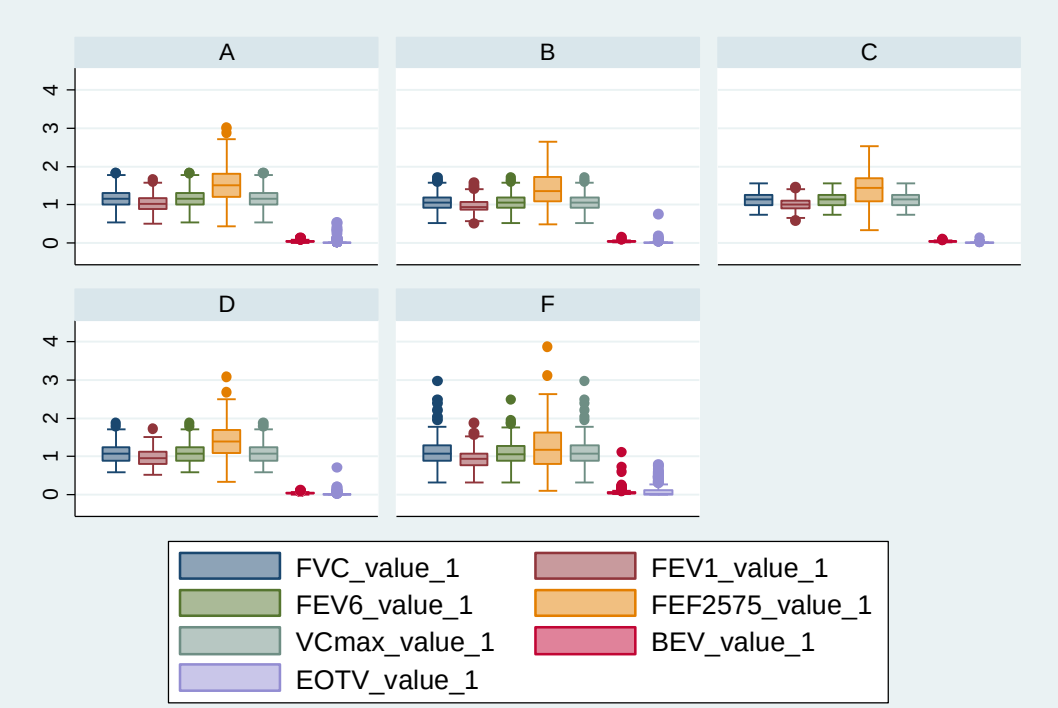
Grade B	FVC	0.52	0.19-1.41	0.36	0.11-1.18
	FEV1	0.67	0.20-2.24	0.37	0.10-1.39
	FEV1/FVC	7.16	0.32-157.76	1.40	0.04-50.92
	FEF2575	1.20	0.70-2.04	0.77	0.45-1.33
	FEV6	0.55	0.20-1.50	0.37	0.11-1.21
	VCmax	0.52	0.19-1.42	0.36	0.11-1.18
	BEV	0.32	0.00 - 1430.94	6.18e-06	9.86e-13-38.71
	FET	0.97	0.84-1.12	0.88	0.72-1.08
	EOTV	0.01	0.00-1.14	0.06	0.00-30.76
	Maneuver3				
	FVC	2.16	0.85-5.52	2.58	0.79-8.41
	FEV1	**4.83**	**1.46-16.03**	2.89	0.74-11.22
	FEV1/FVC	11.72	0.57-240.76	0.94	0.03-26.92
	FEF2575	**1.83**	**1.09-3.07**	0.96	0.56-1.64
	FEV6	2.45	0.90-6.65	2.59	0.79-8.47
	VCmax	2.18	0.86-5.57	2.61	0.80-8.52
	BEV	10.03	0.15-688.83	**664.12**	**1.69-260292.5**
	FET	**0.79**	**0.68-0.93**	0.87	0.71-1.06
	EOTV	0.82	0.08-8.16	3.68	0.33-41.73
Grade C	**Maneuver1**	**OR**	**95% C. I**	**OR**	**95% C. I**
	FVC	0.79	0.27-2.29	1.86	0.63- 5.45
	FEV1	0.70	0.19-2.54	2.90	0.76- 11.13
	FEV1/FVC	0.34	0.02-7.01	3.58	0.06- 1.99.15
	FEF2575	0.81	0.45-1.45	1.18	0.69- 2.05
	FEV6	0.84	0.28-2.47	2.24	0.68- 7.43
	VCmax	0.79	0.27-2.29	1.86	0.63- 5.45
	BEV	**2.52e-09**	**5.20e-17-0.12**	0.01	1.37e-08 – 3504.78
	FET	1.06	0.90-1.24	0.97	0.79 – 1.19
	EOTV	**1.10e-07**	**1.56e-14-0.78**	3.15e-14	1.55e-32 – 64137.71
	Maneuver2				
	FVC	**0.28**	**0.09-0.83**	0.67	0.20- 2.23
	FEV1	**0.16**	**0.04-0.61**	0.71	0.19- 2.76
	FEV1/FVC	0.32	0.02-5.24	1.28	0.03- 50.14
	FEF2575	**0.47**	**0.26-0.85**	0.72	0.41- 1.26
	FEV6	**0.29**	**0.09-0.87**	0.70	0.21- 2.34
	VCmax	**0.28**	**0.09-0.84**	0.67	0.20- 2.23
	BEV	**7.55e-15**	**2.37e-23 - 2.41e-06**	1.46e-06	1.11-13 – 19.30
	FET	0.99	0.84-1.15	1.06	0.87 – 1.28
	EOTV	0.00	4.97e-06-1.59	0.01	9.25e-07 – 74.89
	Maneuver 3				
	FVC	0.56	0.19-1.63	1.41	0.42-4.70
	FEV1	0.46	0.12-1.70	1.33	0.33-5.27
	FEV1/FVC	0.67	0.05-9.62	0.47	0.02-12.71
	FEF2575	0.71	0.40-1.25	0.81	0.46-1.40
	FEV6	0.58	0.19-1.74	1.27	0.38-4.29
	VCmax	0.56	0.19-1.64	1.25	0.37-4.23
	BEV	0.31	0.00-1116.52	20.95	0.21-2140.91

	FET	1.04	0.90-1.21	1.12	0.90-1.38
	EOTV	0.10	0.00-3.42	0.02	0.00-20.34
Grade D	**Maneuver1**	**OR**	**95% C. I**	**OR**	**95% C. I**
	FVC	0.53	0.23-1.25	0.29	0.11- 0.77
	FEV1	0.65	0.24-1.79	0.34	0.12-1.03
	FEV1/FVC	11.44	0.65- 200.26	8.11	0.28-238.84
	FEF2575	1.08	0.69-1.69	0.89	0.57-1.38
	FEV6	0.56	0.24-1.32	**0.29**	**0.11-0.78**
	VCmax	0.53	0.23-1.25	**0.29**	**0.11-0.77**
	BEV	0.00	1.05e-09 – 18.96	0.02	5.63e-07 – 468.64
	FET	0.90	0.79 – 1.03	**0.80**	**0.67- 0.95**
	EOTV	0.08	0.00- 2.12	0.12	0.00-10.40
	Maneuver2				
	FVC	0.94	0.41-2.16	**0.34**	**0.13-0.89**
	FEV1	0.39	0.14-1.08	**0.21**	**0.07-0.64**
	FEV1/FVC	**0.04**	**0.00-0.30**	0.32	0.02-5.08
	FEF2575	**0.47**	**0.29-0.75**	**0.58**	**0.37-0.91**
	FEV6	0.83	0.35-1.93	**0.29**	**0.11-0.77**
	VCmax	0.95	0.42-2.18	**0.34**	**0.13-0.89**
	BEV	0.51	0.00-277.64	213.29	0.08- 578042.6
	FET	1.04	0.92-1.17	0.90	0.76- 1.06
	EOTV	0.25	0.02-2.76	2.54	0.23-28.45
	Maneuver 3				
	FVC	1.42	0.63-3.17	0.54	0.20-1.47
	FEV1	0.77	0.28-2.14	0.40	0.13-1.26
	FEV1/FVC	0.21	0.03-1.51	0.36	0.03-5.20
	FEF2575	0.66	0.42-1.03	**0.62**	**0.39-0.98**
	FEV6	1.12	0.48-2.63	0.55	0.20-1.49
	VCmax	1.43	0.64-3.20	0.55	0.20-1.48
	BEV	9.66	0.20-473.75	15.25	0.20-1178.59
	FET	1.03	0.92-1.17	0.90	0.76-1.06
	EOTV	1.49	0.26-8.57	1.70	0.16-18.27
Grade	**Maneuver1**	**OR**	**95% C. I**	**OR**	**95% C. I**
	FVC	**0.31**	**0.16-0.62**	1.08	0.49-2.40
	FEV1	**0.11**	**0.05-0.26**	**0.14**	**0.05-0.38**
	FEV1/FVC	0.36	0.05-2.44	**0.00**	**0.00-0.00**
	FEF2575	**0.43**	**0.29-0.62**	**0.22**	**0.14-0.33**
	FEV6	**0.23**	**0.11-0.46**	0.70	0.30-1.64
	VCmax	**0.31**	**0.16-0.62**	1.08	0.49-2.40
	BEV	**10317.54**	**10.17-1.05e+07**	**1.98+08**	**113682.7 – 3.44e+1**
	FET	**0.62**	**0.55-0.69**	0.97	0.84-1.12
	EOTV	**7714152**	**152895.5- 3.89+08**	**11736.61**	**380.48 – 362038.1**
	Maneuver2				
	FVC	**0.20**	**0.10 - 0.40**	0.78	0.32-1.85
	FEV1	**0.11**	**0.05 - 0.27**	**0.14**	**0.05-0.39**
	FEV1/FVC	**8.55**	**1.09 – 66.97**	**0.00**	**0.00 – 0.01**
	FEF2575	0.70	0.49 – 1.01	**0.22**	**0.14-0.34**
	FEV6	**0.16**	**0.08 – 0.34**	0.69	0.29-1.67

F	VCmax	**0.20**	**0.10 - 0.41**	0.78	0.32-1.85
	BEV	**44519.83**	**41.33 – 4.80e+07**	1013.07	0.65- 1582052
	FET	**0.57**	**0.51 – 0.65**	0.86	0.74-1.00
	EOTV	**5520587**	**184883.3 – 1.65e+08**	**1038.99**	**66.16- 16317.61**
	Maneuver 3				
	FVC	**0.21**	**0.10-0.43**	0.85	0.34 – 2.09
	FEV1	**0.11**	**0.04-0.26**	**0.19**	**0.06 – 0.54**
	FEV1/FVC	2.34	0.37- 14.65	**0.00**	**0.00 – 0.03**
	FEF2575	**0.67**	**0.47 – 0.96**	**0.30**	**0.19 – 0.48**
	FEV6	**0.17**	**0.08-0.36**	0.80	0.32 – 1.98
	VCmax	**0.21**	**0.10 – 0.43**	0.86	0.35 – 2.11
	BEV	**160.01**	**1.48- 17319.51**	42.69	0.48 – 3762.049
	FET	**0.62**	**0.55 – 0.70**	**0.79**	**0.68 – 0.93**
	EOTV	**8587.18**	**1102.27 – 66898.1**	**2570.73**	**172.15 – 38388.68**

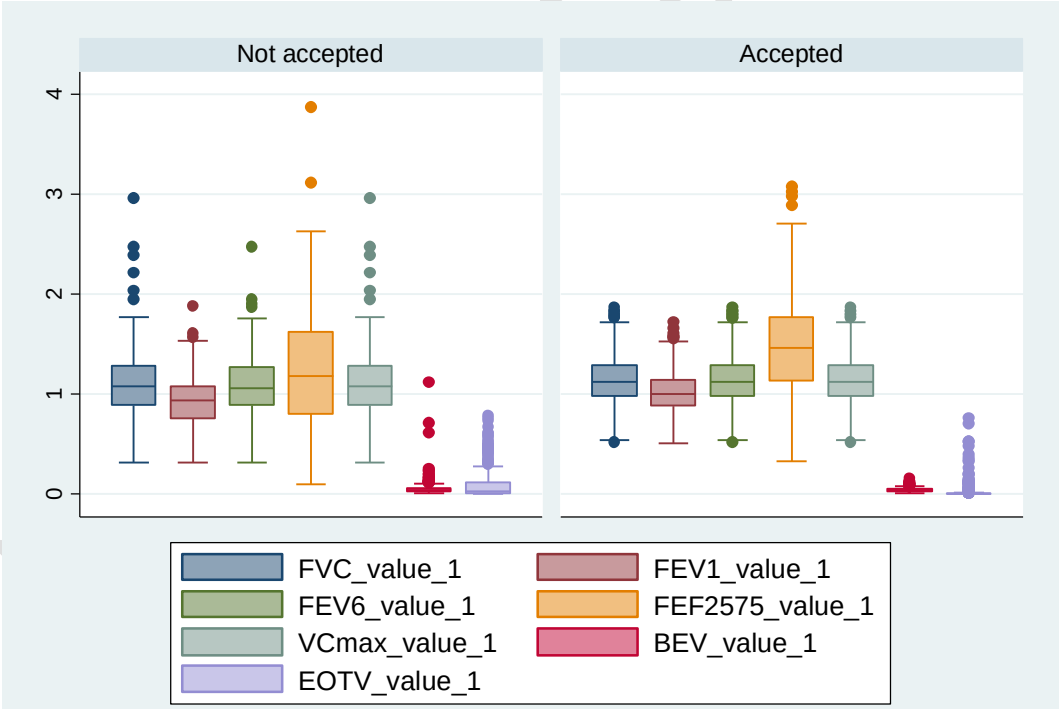
Table 9 Relationships of spirometry indices with acceptability outcomes in both the pre and post bronchodilator tests

	Pre		Post	
Risk factor	**Crude OR**	**95% C. I**	**Crude OR**	**95% C. I**
Maneuver1				
FVC	**3.21**	**1.63-6.33**	0.92	0.42-2.04
FEV1	**8.9**	**3.85-20.93**	**7.01**	**2.66-18.9**
FEV1/FVC	2.78	0.41-18.71	**2971.71**	**248.52 -35534.68**
FEF2575	**2.34**	**1.61-3.40**	**4.65**	**3.03-7.13**
FEV6	**4.37**	**2.17-8.79**	1.43	0.61-3.33
VCmax	**3.21**	**1.63-6.33**	0.92	0.42-2.04
BEV	**0.00**	**9.55e-08- 0.10**	**5.05e-09**	**2.90e-12-8.80e-06**
FET	**1.63**	**1.44-1.83**	1.03	0.89-1.19
EOTV	**1.30e-07**	**2.57e-09 -6.54e-06**	**0.00**	**2.76e-06-0.00**
Maneuver2				
FVC	**2.67**	**1.43-4.98**	1.01	0.47-2.16
FEV1	**5.03**	**2.32-10.89**	**4.38**	**1.82-10.54**
FEV1/FVC	0.52	0.09-3.00	**1144.20**	**115.64-11321.2**
FEF2575	**1.49**	**1.06-2.08**	**3.81**	**2.57-5.64**
FEV6	**3.37**	**1.77-6.41**	1.20	0.56-2.60
VCmax	**2.64**	**1.41-4.94**	1.01	0.47-2.16
BEV	**8.24e-08**	**6.11e-11-0.00**	**8.43e-06**	**4.65e-09- 0.02**
FET	**1.57**	**1.41-1.74**	**1.23**	**1.07-1.41**
EOTV	**7.78e-10**	**5.13e-12 - 1.18e-07**	**0.00**	**1.18e-07-0.00**
Maneuver3				
FVC	1.37	0.79-2.38	0.61	0.31-1.21
FEV1	1.70	0.86-3.37	1.64	0.75-3.56
FEV1/FVC	0.27	0.06-1.21	**1.55.76**	**22.02-1101.73**
FEF2575	1.04	0.77-1.39	**2.46**	**1.77-3.42**
FEV6	1.65	0.93-2.94)	0.63	0.32-1.24
VCmax	1.36	0.78-2.35)	0.60	0.31-1.19
BEV	**7.83e-10**	**5.24e-13 - 1.17e-06)**	**2.52e-10**	**2.37e-13-2.68e-07**
FET	**1.53**	**1.39-1.68**	**1.24**	**1.10-1.40**
EOTV	1.10e-09	**6.49e-12- 1.86e-07**	**2.86e-08**	**6.48e-11- 0.00**



Graph box of spiro indices by quality graades

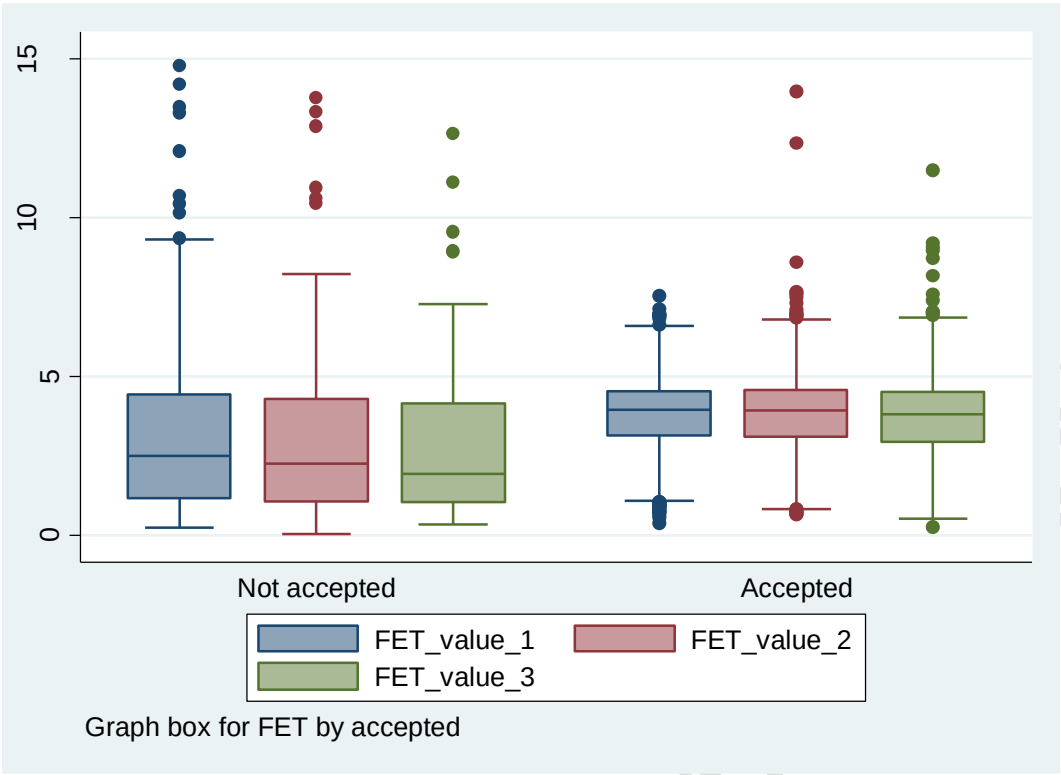
A.



Graph box for spiro indices by accepted

B.

C.



D.

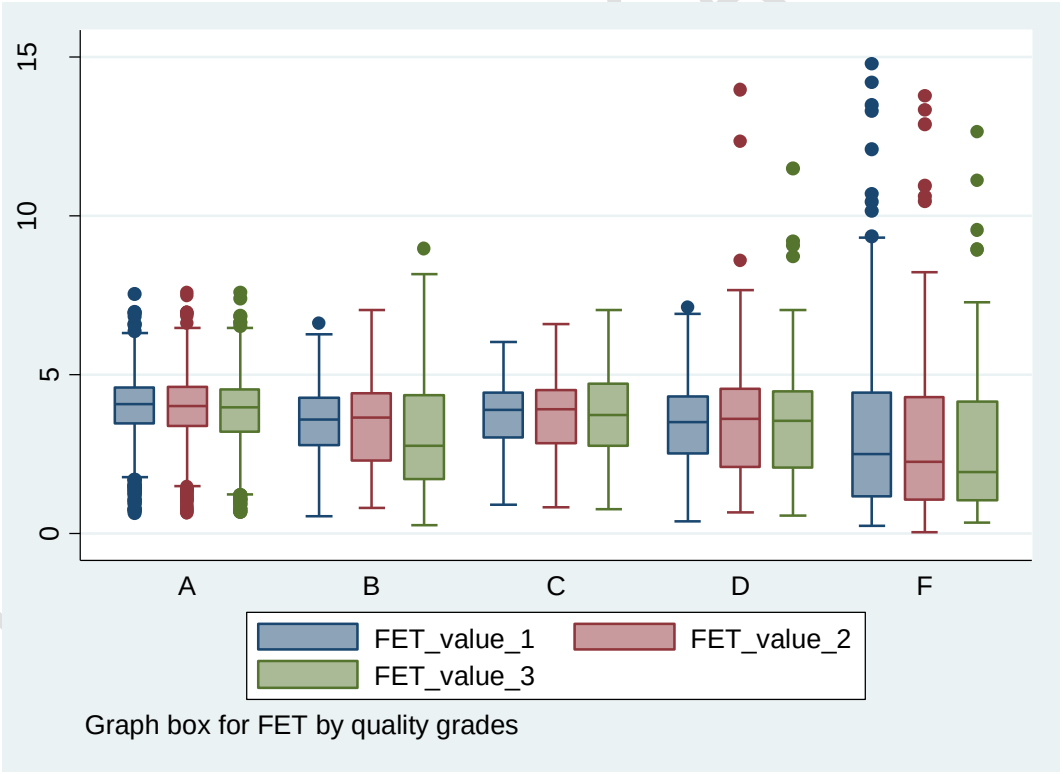
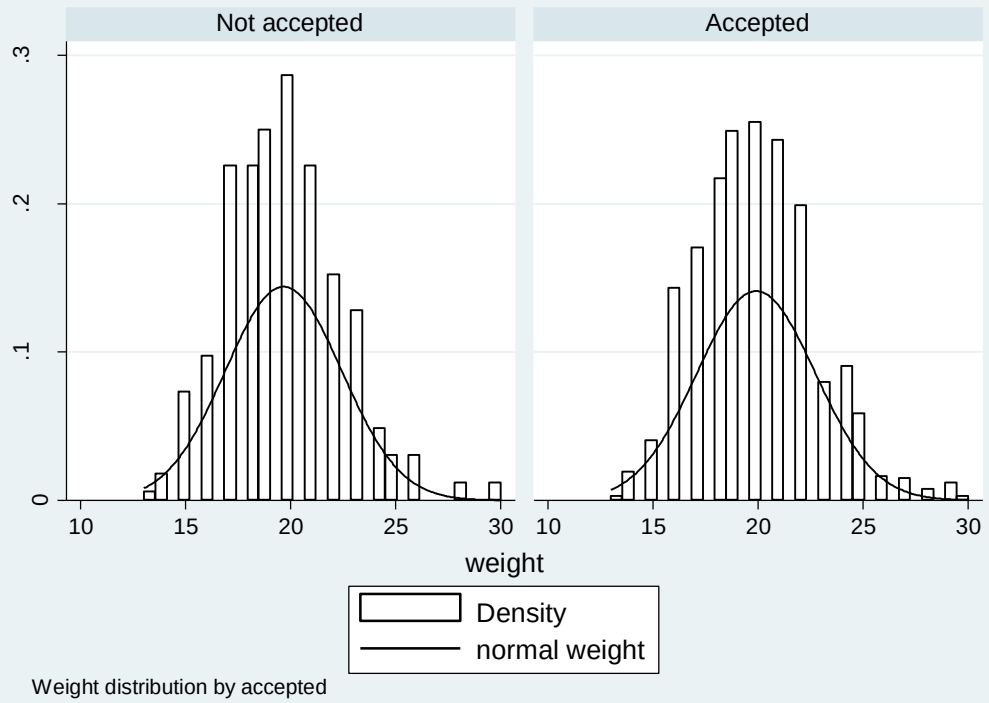


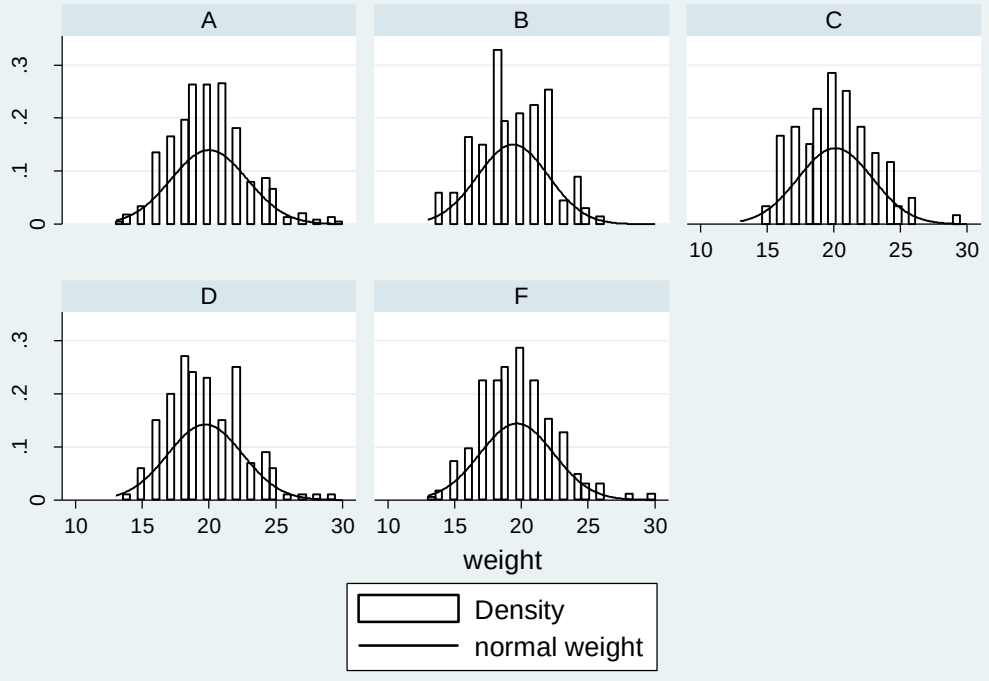
Figure 3 (A, B, C and D) Box plots showing the distribution of each spirometry index in the 1st manoeuvre by acceptance outcome and quality grades.

A.

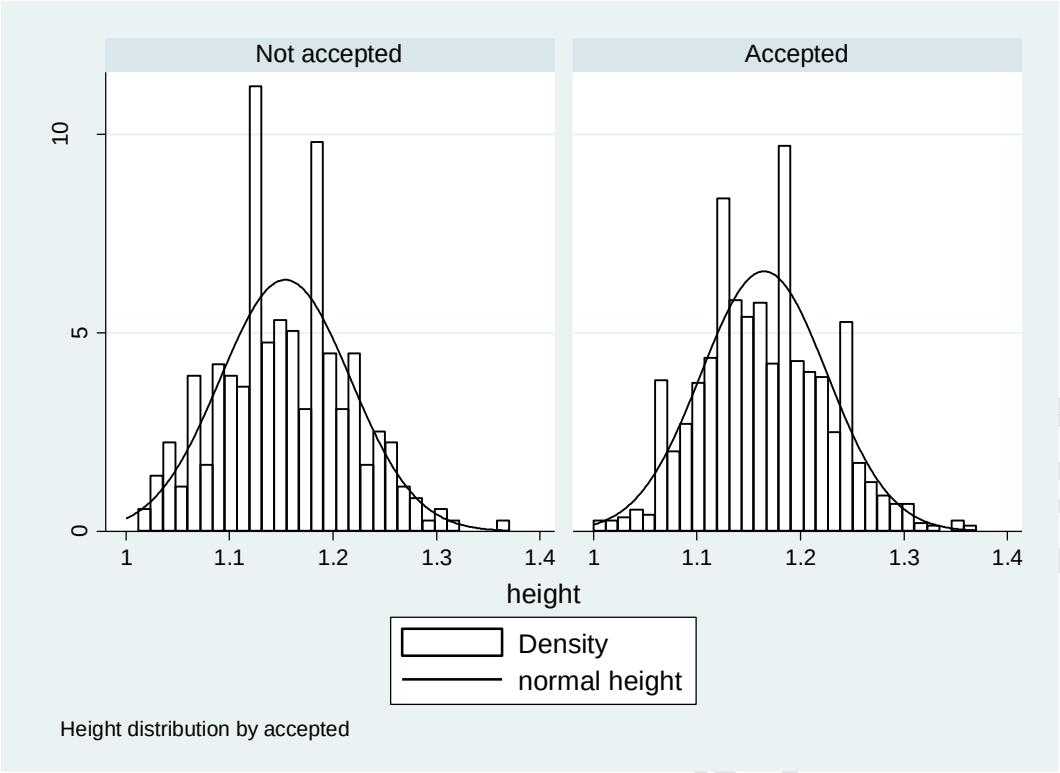


Weight distribution by accepted

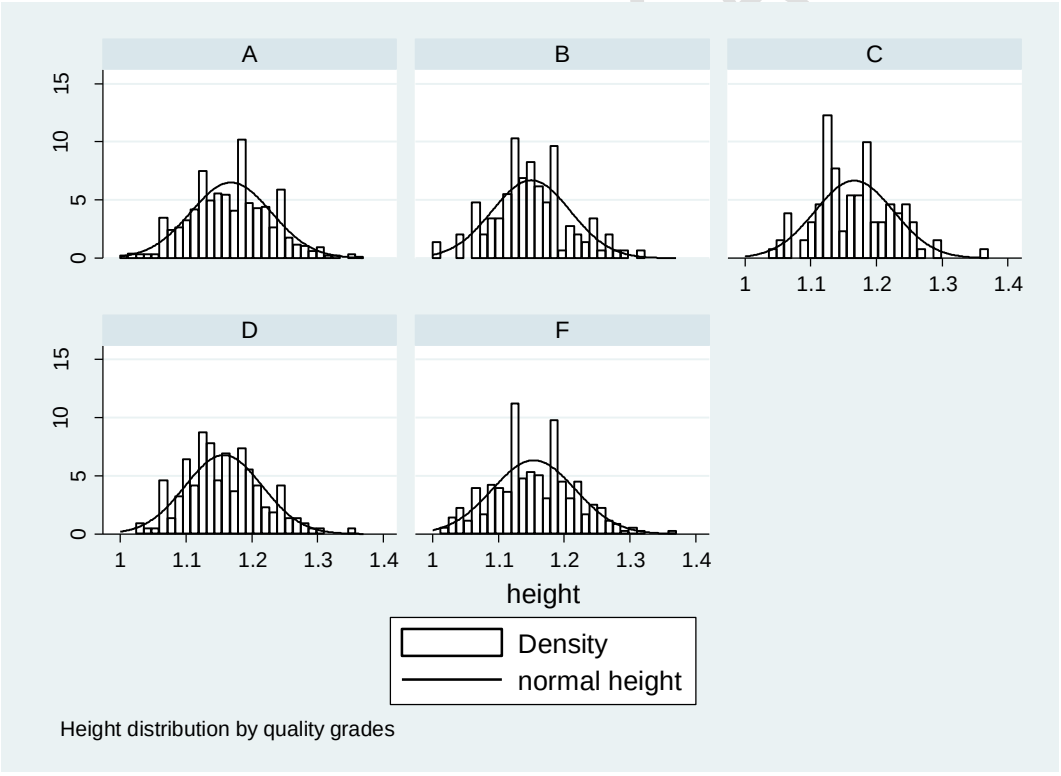
B.



Weight distribution by quality grades



C.



D.

Figure 4 (A, B, C and D) Histograms showing distribution of Age, weight and height by acceptance outcomes and quality grades

PART D: APPENDICES

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

Room E53-40 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shurelle.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 October 2018

HREC REF: 669/2018

Dr M Lesosky
Public Health & Family Medicine
Epidemiology and Biostatistics
Falmouth Building

Dear Dr Lesosky

PROJECT TITLE: THE QUALITY AND VARIATION OF SPIROMETRY READS FOR TESTING LUNG FUNCTION IN CHILDREN IN SUB SAHARAN AFRICA (Masters Candidate – Miss D. Maduna)

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

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

Approval is granted for one year until the 30 October 2019.

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)

Please quote the HREC REF in all your correspondence.

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

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

The HREC acknowledge that the student, Dumsile Maduna will also be involved in this study.

Yours sincerely

signature removed to avoid exposure online

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

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.07/16/1994 – Child lung health and exposure to household air pollution in rural Malawi (Abbreviated title: Child lung health study) version 4.0 dated 10/10/16 by Dr. S. Rylance

On 31st October 2016

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC as indicated on the next page

signature removed to avoid exposure online

Dr. C. Dzamalala- Chairperson (COMREC)

Approved by College of Medicine

(COMREC) Research and Ethics Com...

31st October 2016

Date

COLLEGE OF MEDICINE

Principal

M. H. C. Mipando MSc PhD

Our Ref.:

Your Ref.: P.07/16/1994

College of Medicine
Private Bag 360
Chichiri
Blantyre 3
Malawi
Telephone: 01 877 245
01 877 291
Fax: 01 874 700

Email: comrec@medcol.mw

20th October 2017

Dr. S. Rylance
Malawi Livepool Wellcome Trust
P.O Box 30096
BLANTYRE

Dear Dr. Rylance

RE: **P.07/16/1994** – Child lung health and exposure to household air pollution in rural Malawi (Abbreviated title: Child lung health study) version 1.0 dated 08/07/16

I write to inform you that COMREC reviewed the progress report which you submitted and it approved the continuation of the study for another 12 months with effect from 31st October 2017.

This renewal is subject to continued adherence to the College of Medicine requirements for all COMREC approved research studies.

Yours Sincerely,

signature removed to avoid exposure online

Approved by
College of Medicine
20 OCT 2017
(COMREC)
Research and Ethics Committee

Dr. L. Alfazema-Chiuzeni
COMREC CHAIRPERSON

LAC/gk

APPENDIX D **RECORD OF SEARCH STRATEGY**

Topic: the quality and variation of spirometry reads to measure lung function in children in sub Saharan Africa

Population/Problem: **children**

Intervention/Issue: **good quality spirometry**

Comparison:

Outcome/Evaluation: **lung function diagnosis**

Main concepts/keywords/synonyms: quality, variations, lung function tests, children, sub Saharan Africa

Searches were conducted in two databases to identify recent publications – PubMed and Google scholar.

Limits: Language **English**

Time frame: PubMed (**up-to-2019)** & Google scholar (2015-2019)

Abstracts of identified documents were read and full text of relevant documents was retrieved for inclusion in the review. Reference lists of retrieved documents were also searched to identify additional publications. A summary of the database searches is set out below.

Database searched	Search terms	Results	Sources used
PubMed	**Set 1**. Child [Mesh] OR Child, Preschool [Mesh} OR Child OR Children	2341515	
	Set 2. Spirometry"[Mesh]) OR (Spirometry OR Spirometry	234188	

	tests OR respiratory function tests)		
	Set 3. Quality Control"[Mesh]) OR "Quality Assurance, Health Care"[Mesh]) OR "Quality Improvement"[Mesh]) OR (Quality OR variations OR quality control OR quality improvement OR quality assurance)	1525608	
	Set 4. (lung function OR respiratory function	445681	
	Set 5. ((Deprived Countries[Text Word] OR Deprived Population[Text Word] OR Deprived Populations[Text Word] OR Developing Countries[Text Word] OR Developing Country[Text Word] OR Developing Economies[Text Word] OR Developing Economy[Text Word] OR Developing Nation[Text Word] OR Developing Nations[Text Word] OR Developing Population[Text Word] OR Developing Populations[Text Word] OR Developing World[Text Word] OR LAMI Countries[Text Word] OR LAMI Country[Text Word] OR Less Developed Countries[Text Word] OR Less Developed Country[Text Word] OR Less Developed Economies [Text Word] OR Less Developed Nation[Text Word] OR Less Developed Nations[Text Word] OR Less Developed World[Text Word] OR Lesser Developed Countries[Text Word] OR Lesser Developed Nations[Text Word] OR LMIC[Text Word] OR LMICS[Text Word] OR Low GDP[Text Word] OR Low GNP[Text Word] OR Low Gross Domestic[Text Word] OR Low Gross National[Text Word] OR Low Income Countries[Text Word] OR Low Income Country[Text Word] OR Low Income Economies [Text Word] OR Low Income Economy[Text Word] OR Low Income Nations[Text Word] OR Low Income Population[Text Word] OR Low Income Populations[Text Word] OR Lower GDP[Text Word] OR lower gross domestic[Text Word] OR Lower Income Countries[Text Word] OR Lower Income Country[Text Word] OR Lower Income Nations[Text Word] OR Lower Income Population[Text Word] OR Lower Income Populations[Text Word] OR Middle Income Countries[Text Word] OR Middle Income Country[Text Word] OR Middle Income Economies [Text Word] OR Middle Income Nation[Text Word] OR Middle Income Nations[Text Word] OR Middle Income Population[Text Word] OR Middle Income Populations[Text Word] OR Poor Countries[Text Word] OR Poor Country[Text Word] OR Poor	1373466	

	Economies [Text Word] OR Poor Economy[Text Word] OR Poor Nation[Text Word] OR Poor Nations[Text Word] OR Poor Population[Text Word] OR Poor Populations[Text Word] OR poor world[Text Word] OR Poorer Countries[Text Word] OR Poorer Economies [Text Word] OR Poorer Economy[Text Word] OR Poorer Nations[Text Word] OR Poorer Population[Text Word] OR Poorer Populations[Text Word] OR Third World[Text Word] OR Transitional Countries[Text Word] OR Transitional Country[Text Word] OR Transitional Economies[Text Word] OR Transitional Economy[Text Word] OR Under Developed Countries[Text Word] OR Under Developed Country[Text Word] OR under developed nations[Text Word] OR Under Developed World[Text Word] OR Under Served Population[Text Word] OR Under Served Populations[Text Word] OR Underdeveloped Countries[Text Word] OR Underdeveloped Country[Text Word] OR underdeveloped economies[Text Word] OR underdeveloped nations[Text Word] OR underdeveloped population[Text Word] OR Underdeveloped World[Text Word] OR Underserved Countries[Text Word] OR Underserved Nations[Text Word] OR Underserved Population[Text Word] OR Underserved Populations[Text Word])))) OR ((Afghanistan[Text Word] OR Albania[Text Word] OR Algeria[Text Word] OR American Samoa[Text Word] OR Angola[Text Word] OR Armenia[Text Word] OR Azerbaijan[Text Word] OR Bangladesh[Text Word] OR Belarus[Text Word] OR Byelarus[Text Word] OR Belorussia[Text Word] OR Belize[Text Word] OR Benin[Text Word] OR Bhutan[Text Word] OR Bolivia[Text Word] OR Bosnia[Text Word] OR Botswana[Text Word] OR Brazil[Text Word] OR Bulgaria[Text Word] OR Burma[Text Word] OR Burkina Faso[Text Word] OR Burundi[Text Word] OR Cabo Verde[Text Word] OR Cape Verde[Text Word] OR Cambodia[Text Word] OR Cameroon[Text Word] OR Central African Republic[Text Word] OR Chad[Text Word] OR China[Text Word] OR Colombia[Text Word] OR Comoros[Text Word] OR Comores[Text Word] OR Comoro[Text Word] OR Congo[Text Word] OR Costa Rica[Text Word] OR Côte d'Ivoire[Text Word] OR Cuba[Text Word] OR Djibouti[Text Word] OR Dominica[Text Word] OR Dominican Republic[Text Word] OR Ecuador[Text Word] OR Egypt[Text Word] OR El Salvador[Text		

	Word] OR Equatorial Guinea[Text Word] OR Eritrea[Text Word] OR Ethiopia[Text Word] OR Fiji[Text Word] OR Gabon[Text Word] OR Gambia[Text Word] OR Gaza[Text Word] OR Georgia[Text Word] OR Georgia Republic[Text Word] OR Ghana[Text Word] OR Grenada[Text Word] OR Grenadines[Text Word] OR Guatemala[Text Word] OR Guinea[Text Word] OR Guinea- Bissau[Text Word] OR Guyana[Text Word] OR Haiti[Text Word] OR Herzegovina[Text Word] OR Hercegovina[Text Word] OR Honduras[Text Word] OR India[Text Word] OR Indonesia[Text Word] OR Iran[Text Word] OR Iraq[Text Word] OR Jamaica[Text Word] OR Jordan[Text Word] OR Kazakhstan[Text Word] OR Kenya[Text Word] OR Kiribati[Text Word] OR Democratic People's Republic of Korea[Text Word] OR Kosovo[Text Word] OR Kyrgyz[Text Word] OR Kirghizia[Text Word] OR Kirghiz[Text Word] OR Kyrgyzstan[Text Word] OR Lao PDR[Text Word] OR Laos[Text Word] OR Lebanon[Text Word] OR Lesotho[Text Word] OR Liberia[Text Word] OR Libya[Text Word] OR Macedonia[Text Word] OR Madagascar[Text Word] OR Malawi[Text Word] OR Malay[Text Word] OR Malaya[Text Word] OR Malaysia[Text Word] OR Maldives[Text Word] OR Mali[Text Word] OR Marshall Islands[Text Word] OR Mauritania[Text Word] OR Mauritius[Text Word] OR Mexico[Text Word] OR Micronesia[Text Word] OR Moldova[Text Word] OR Mongolia[Text Word] OR Montenegro[Text Word] OR Morocco[Text Word] OR Mozambique[Text Word] OR Myanmar[Text Word] OR Namibia[Text Word] OR Nepal[Text Word] OR Nicaragua[Text Word] OR Niger[Text Word] OR Nigeria [Text Word] OR Pakistan [Text Word] OR Palau[Text Word] OR Panama[Text Word] OR Papua New Guinea[Text Word] OR Paraguay[Text Word] OR Peru [Text Word] OR Philippines[Text Word] OR Principe[Text Word] OR Romania[Text Word] OR Ruanda[Text Word] OR Rwanda[Text Word] OR Samoa[Text Word] OR Sao Tome[Text Word] OR Senegal[Text Word] OR Serbia[Text Word] OR Sierra Leone[Text Word] OR Solomon Islands[Text Word] OR Somalia[Text Word] OR South Africa[Text Word] OR South Sudan[Text Word] OR Sri Lanka[Text Word] OR St Lucia[Text Word] OR St Vincent[Text Word] OR Sudan[Text Word] OR Surinam[Text Word] OR Suriname[Text Word] OR Swaziland[Text Word] OR Syria[Text Word] OR Syrian Arab Republic[Text Word] OR		

	Tajikistan[Text Word] OR Tadzhikistan[Text Word] OR Tajikistan[Text Word] OR Tadzhik[Text Word] OR Tanzania[Text Word] OR Thailand[Text Word] OR Timor[Text Word] OR Togo[Text Word] OR Tonga[Text Word] OR Tunisia[Text Word] OR Turkey[Text Word] OR Turkmen[Text Word] OR Turkmenistan[Text Word] OR Tuvalu[Text Word] OR Uganda[Text Word] OR Ukraine[Text Word] OR Uzbek[Text Word] OR Uzbekistan[Text Word] OR Vanuatu[Text Word] OR Venezuela[Text Word] OR Vietnam[Text Word] OR West Bank[Text Word] OR Yemen[Text Word] OR Zambia[Text Word] OR Zimbabwe[Text Word]))		
	1 AND 2 AND 3 AND 4 AND 5	85	
Googlescholar	Googlescholar: "Chronic respiratory diseases" AND estimates AND children AND sub saharan Africa	31600	
	Since 2015 (chose the first 50)	12900	

Health Sciences Library, UCT

APPENDIX E Paediatrics Author Guidelines

(http://www.aappublications.org/content/pediatrics-author-guidelines#submitting)

Paediatrics Author Guidelines

Paediatrics is the official peer-reviewed journal of the American Academy of Paediatrics. Paediatrics publishes original research, clinical observations, and special feature articles in the field of paediatrics, as broadly defined. Contributions pertinent to paediatrics also include related fields such as nutrition, surgery, dentistry, public health, child health services, human genetics, basic sciences, psychology, psychiatry, education, sociology, and nursing.

Paediatrics considers unsolicited manuscripts in the following categories: reports of original research, particularly clinical research; review articles; special articles; and case reports. When preparing a manuscript for Paediatrics, authors must first determine the manuscript type and then prepare the manuscript according to the specific instructions below.

The digital edition of Paediatrics is the journal of record. Some accepted article types may also be presented in full in print, in addition to the digital edition of Paediatrics.

Contents

Introduction

- Journal Style
- Reuse of Data Sets
- Data Sharing

Manuscript Preparation

- Formatting Requirements
- Title Page
- Contributors' Statement Page
- Word Count
- Figures, Tables, and Supplementary Material

Article Type

- Regular Article

Journal Style

All aspects of the manuscript, including the formatting of tables, illustrations, and references and grammar, punctuation, usage, and scientific writing style, should be prepared according to the most current AMA Manual of Style (http://www.amamanualofstyle.com).[1]

Author Listing

All authors' names should be listed in their entirety, and should include institutional/professional affiliations and degrees held.

Authoring Groups

If you choose to include an organization, committee, team, or any other group as part of your author list, you must include the names of the individuals as part of the Acknowledgments section of your manuscript. This section should appear after the main text prior to your References section. (If your Acknowledgments include both group members and other persons/organizations that are not in that group, you should instead list the group members in a separate appendix to avoid confusion.) The terms "for" or "on behalf of" must also be used when referencing the authoring group in the by-line.

Titles

Paediatrics generally follows the guidelines of the AMA Manual of Style for titles. Titles should be concise and informative, containing the key topics of the work. Declarative sentences are discouraged as they tend to overemphasize a conclusion, as are questions, which are more appropriate for editorials and commentaries. Subtitles, if used, should expand on the title; however, the title should be able to stand on its own. It is appropriate to include the study design ("Randomized Controlled Trial"; "Prospective Cohort Study", etc.) in subtitles. The location of a study should be included only when the results are unique to that location and not generalizable. Abbreviations and acronyms should be avoided. The full title will appear on the article, the inside table of contents, and in MEDLINE. Full titles are limited to 97 characters, including spaces. Short titles must be provided as well and are limited to 55 characters, including spaces. Short titles

may appear on the cover of the journal as space permits in any given issue.

Abbreviations

List and define abbreviations on the Title Page. Unusual abbreviations should be avoided. All terms to be abbreviated in the text should also be spelled out at first mention, followed by the abbreviation in parentheses. The abbreviation may appear in the text thereafter. Abbreviations may be used in the abstract if they occur 3 or more times in the abstract. Abbreviations should be avoided in tables and figures; if used they should be redefined in footnotes.

Units of Measure

Like many US-based journals, Paediatrics uses a combination of System International (SI)[2,3] and conventional units. Please see the AMA Manual of Style for details.

Proprietary Products

Authors should use non-proprietary names of drugs or devices unless mention of a trade name is pertinent to the discussion. If a proprietary product is cited, the name and location of the manufacturer must also be included.

References

Authors are responsible for the accuracy of references. Citations should be numbered in the order in which they appear in the text. Reference style should follow that of the AMA Manual of Style, current edition. Abbreviated journal names should reflect the style of Index Medicus. Visit: http://www.nlm.nih.gov/tsd/serials/lji.html

References

1. Iverson C, Christiansen S, Flanagin A, et al. AMA Manual of Style. 10th Ed. New York, NY: Oxford University Press; 2007.
2. Lundberg GD. SI unit implementation: the next step. JAMA. 1988; 260:73-76.
3. System International conversion factors for frequently used laboratory components. JAMA. 1991; 266:45-47.

Reuse of Data Sets

If a manuscript uses the same or similar data contained in previously published articles, the authors must state this in the cover letter (and provide citations to the related or possibly duplicative materials).

If a separate manuscript by the same authors using the same data set is under review or accepted but not yet published in another journal, the authors must state this in the cover

letter and provide enough information to assure that the manuscript submitted to Paediatrics is not duplicative.

Data Sharing

The International Committee of Medical Journal Editors (ICMJE) requires ICMJE journals to include data sharing statements in articles that report results of clinical trials.

Data sharing statements must include:

- Whether DE identified participant data (including data dictionaries) will be shared
- The data that will be shared
- Whether additional documents will be made available
- The start and end dates of data availability
- Access criteria
- How the data will be made available

The data sharing statement must be included on the title page of your manuscript and entered into the section provided in the manuscript management system.

If you will not be sharing your data, insert the following statement on your title page and in the manuscript submission system.

Data Sharing Statement: DE identified individual participant data will not be made available.

If you will be sharing your data, refer to the table in the data sharing section of the ICMJE clinical trials page for examples of how to incorporate the required information into your statement, and refer to the example below.

Data Sharing Statement: DE identified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to _____ [INSERT EMAIL ADDRESS OR OTHER CONTACT INFORMATION].

Formatting Requirements

All submissions must adhere to the following format:

- Times New Roman font, size 12, black
- Title Page, Contributors' Statement Page, Abstract, Acknowledgments, and References should be single-spaced
- Only the Main Body Text should be double-spaced
- Main Submission Document as Microsoft Word or RTF file (no PDFs)
- Do not include page headers, footers, or line numbers in new submissions.
- Do not include footnotes within the manuscript body. Footnotes are allowed only in tables/figures.

Refer to the “Article Types” section for specific guidelines on preparing a manuscript in each category. Note in particular the requirements regarding abstracts for different categories of article.

Title Page

The “title page” should appear first in your manuscript document, and depending on the individual needs of a paper may encompass more than one page.

Title pages for all submissions must include the following items (as shown in the sample Title Page):

1. Title (97 characters [including spaces] or fewer)
2. Author listing. Full names for all authors, including degrees, and institutional/professional affiliations. These affiliations should list the institution where the research presented in the article took place; if the affiliation has changed, add a note indicating the additional affiliation. Paediatrics permits a statement of equal contribution for two first authors only; on the title page, includes asterisks by each name and a statement that reads: * Contributed equally as co-first authors.
3. Corresponding Author. Contact information for the Corresponding Author (including: name, address, telephone, and e-mail). Again, note that the affiliation should list the institution where the research presented in the article took place; if the affiliation has changed, add a note indicating the additional affiliation.
4. Short title (55 characters [including spaces] or fewer). Please note: the short title may be used on the cover of the print edition.

5. Financial Disclosure Statement for all authors. Disclose any financial relationships that could be broadly relevant to the work. If none say “Financial Disclosure: The authors have no financial relationships relevant to this article to disclose.”
6. Funding source. Research or project support, including internal funding, should be listed here; if the project was done with no specific support, please note that here. Technical and other assistance should be identified in Acknowledgments. If your funding body has open access requirements, please contact the Editorial Office prior to submission. Paediatrics has a 12 month embargo on articles (followed by a 4 year open access period) and does not allow articles to be opened for Creative Commons or similar licenses.
7. Conflict of Interest Statement for all authors. If none say “Potential Conflicts of Interest: The authors have no conflicts of interest relevant to this article to disclose.”
8. If applicable, Clinical Trial registry name, registration number, and data sharing statement. We adhere to ICMJE guidelines, which require that all trials must be registered with ClinicalTrials.gov or any other WHO Primary registry. All articles reporting results of clinical trials must also include the Data Sharing Statement.
9. Abbreviations. List and define abbreviations used in the text. If none say "Abbreviations: none".
0. Table of Contents Summary. All articles with abstracts require this summary. This brief summary is limited

   To 25 words. For accepted manuscripts, this will appear under the author names in the table of contents to give the reader a brief insight into what the article is about. It should entice the reader to read the full article. For example: "Through linkage of state Medicaid and Child Protective Services databases, this study captures similarities and differences in health care expenditures based on a history of child maltreatment."
1. For Regular Article submissions, include both the “What’s Known on This Subject" and the "What This Study Adds” summaries (see below under Regular Article type for description). These are not needed for any other article type.

If a title page does not include all of the above items, the submission may be returned to the authors for completion.

Contributors' Statement Page

All submissions (excluding Commentaries) must contain a Contributors' Statement Page, directly following the Title Page(s) and in the specific format described below. Manuscripts lacking a properly formatted Contributors' Statement Page will be returned to the authors for correction.

All persons designated as authors must qualify for authorship (see "Publication Ethics" above), and all those who qualify should be listed. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. The Contributors' Statement Page lists the authors and specifies the contribution(s) made by each individual. If multiple individuals have identical contributions they may be listed together; do not list an author more than once.

You must follow the required format when creating your Contributors' Statement Page or your manuscript will be returned for correction.

- Each author should only appear once.
- Use names, not initials.
- If multiple authors have identical contributions, you can list them in the same sentence; otherwise, list each author separately.
- Conclude your statement by confirming that: All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Sample Contributors' Statement:

Dr Smith and Prof Jones conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.
Drs Brown, Grey, and Black and Ms Johnson designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.
Dr Green conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Note: Contributors who do not meet the criteria for authorship (such as persons who helped recruit patients for the study, or professional editors) should be listed in an Acknowledgments section placed after the manuscript's conclusion and before the References section. Because readers may infer their endorsement of the data and conclusions, these persons must give written permission to be acknowledged. These

permissions do not need to be submitted with the manuscript unless requested by the editors.

Word Count

To determine article length, count the body of the manuscript (from the start of the Introduction to the end of the Conclusion). The title page, contributors' statement page, abstract, acknowledgments, references, figures, tables, and multimedia are not included.

Figures, Tables, and Supplementary Material

For any figure, table, or supplementary material reproduced or adapted from another source, authors are required to obtain permission from the copyright holder, and proof of permission must be uploaded at the time of submission. The legend must include a statement that the material was used or adapted with permission.

Figures

Authors should number figures in the order in which they appear in the text. Figures include graphs, charts, photographs, and illustrations. Each figure must include a legend (placed as a list appearing after the References) that does not exceed 50 words. Abbreviations previously expanded in the text are acceptable.

Figure arrays should be clearly labelled, preassembled, and submitted to scale. Figure parts of an array (A, B, C, etc.) should be clearly marked in capital letters in the upper left-hand corner of each figure part.

Technical requirements for figures: Upload figures as separate files; do not paste them in the manuscript text file. The following file types are acceptable: TIFF, PDF, EPS, and PNG. Colour files must be in CMYK (cyan, magenta, yellow, black) mode. Paediatrics cannot accept Excel or PowerPoint files for any part of your submission. There is no maximum number for figures.

Style for figures: Readers should be able to understand figures without referring to the text. Avoid pie charts, 3-dimensional graphs, and excess ink in general. Make sure that the axes on graphs are labelled, including units of measurement, and that the font is large enough to read. Generally delete legends or other material from the graph if it makes the picture smaller. Colour graphs should be interpretable if photocopied in black and white.

There is no maximum number for figures or tables.

Tables

Tables should be numbered in the order in which they are cited in the text and include appropriate headers. Tables should not reiterate information presented in the Results section, but rather should provide clear and concise data that further illustrate the main point. Tabular data should directly relate to the hypothesis. Table formatting should follow the current edition of the AMA Manual of Style. There is no maximum number of tables.

Technical requirements for tables: Tables should be constructed using a Microsoft Word program and inserted in numerical order at the end of the manuscript, either within the main Word document (following the references) or as separate files. Do not provide tables in scan/image format. Paediatrics cannot accept Excel or PowerPoint files for any part of your submission. There is no maximum number for tables.

Style for tables: Tables should be self-explanatory. Avoid abbreviations; define any abbreviations in footnotes to the table. Avoid excess digits and excess ink in general. Where possible, rows should be in a meaningful order (e.g., descending order of frequency). Provide units of measurement for all numbers. In general, only one type of data should be in each column of the table.

Presentation of Numbers and Statistics

- Results in the abstract and the paper generally should include estimates of effect size and 95% confidence intervals, not just P- values or statements that a difference was statistically significant.
- Statistical methods for obtaining all P-values should be provided
- Units of independent variables must be provided in tables and results sections if regression coefficients are provided
- Authors should avoid expressing effect sizes in the form of highly derived statistics.

Equations should be typed exactly as they are to appear in the final manuscript. The following table, adapted from the guidelines for authors for the Annals of Internal Medicine by editors of Medical Decision Making, shows how to present certain percentages and some statistical measures:

Reporting:	Details:
Percentages	Report percentages to one decimal place (i.e., xx.x%) when sample size is greater than or equal to 200. To avoid the appearance of a level of precision that is not present with small samples, do not use decimal places (i.e., xx%, not xx.x%) when sample size is less than 200.
Error Measures	Report confidence intervals, rather than standard errors, when possible. Use "mean (error measures)" rather than "mean ± error measure" notation.
P values	Except when one-sided tests are required by study design, such as in noninferiority trials, all reported P values Should be two-sided. In general, P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P [is less than sign] 0.001. Notable exceptions to this policy include P values arising in the application of stopping rules to the analysis Of clinical trials and genetic-screening studies.
"Trend	Use the word trend when describing a test for trend or dose-response Avoid the term "trend" when referring to p-values near but not below 0.05. In such instances, simply report a difference and the confidence interval of the difference (if appropriate) with or without the p-value.

Supplemental Information

Authors may wish to include additional information as part of their article for inclusion in

the online edition of Paediatrics. References to any online supplemental information must appear in the main article. Such supplemental information can include but are not limited to additional tables, figures, videos, audio files, slide shows, data sets (including qualitative data), and online appendices. If your study is based on a survey, consider submitting your survey instrument or the key questions as a data supplement. Authors are responsible for clearly labelling supplemental information and are accountable for its accuracy. Supplemental information will be peer reviewed, but not professionally copyedited.

Videos

Paediatrics encourages the submission of videos to accompany articles where relevant. Links can be placed in the article for use when it is accessed electronically. All videos must adhere to the same general permission rules that apply to figures (i.e.: parental consent when a patient is identifiable).

All videos should be submitted at the desired reproduction size and length. To avoid excessive delays in downloading the files, videos should be no more than 6MB in size, and run between 30 and 60 seconds in length. In addition, cropping frames and image sizes can significantly reduce file sizes. Files submitted can be looped to play more than once, provided file size does not become excessive. Video format must be either .mov or .mp4.

Authors will be notified if problems exist with videos as submitted, and will be asked to modify them if needed. No editing will be done to the videos at the editorial office—all changes are the responsibility of the author.

Video files should be named clearly to correspond with the figure they represent (i.e., figure1.mov, figure2.mp4, etc.). Be sure all video files have filenames that are no more than 8 characters long and include the suffix “.mov” or ".mp4." A caption for each video should be provided (preferably in a similarly named Word file submitted with the

videos), stating clearly the content of the video presentation and its relevance to the materials submitted.

IMPORTANT: One to four traditional still images from the video must be provided. These still images may be published with the article and will act as thumbnail images in the electronic edition that will link to the full video file. Please indicate clearly in your text whether a figure has a video associated with it, and be sure to indicate the name of the corresponding video file. A brief figure legend should also be provided.

Regular Article

Abstract length: 250 words or fewer (structured, as noted below)
Article length: 3,000 words or fewer

Regular Articles are original research contributions that aim to inform clinical practice or the understanding of a disease process. Regular Articles include but are not limited to clinical trials, interventional studies, cohort studies, case-control studies, epidemiologic assessments, and surveys. Components of a Regular Article include:

- What's Known on This Subject
- What This Study Adds

These two brief summaries are each limited to 40 words. Please use precise and accurate language in paragraph form (i.e., not bullet points). For manuscripts accepted as Regular Articles, these summaries will become a highly visible part of your published paper, with prominence on the first page. Moreover, these summaries may be highlighted and presented in other areas of the journal. It is therefore paramount that you use language of the same calibre as the rest of your paper.

- Structured Abstract (four paragraphs with headings in boldface type; single-spaced)

The abstract should consist of: Background (or Objectives, or Background and Objectives), Methods, Results, and Conclusions. The Objective should clearly state the hypothesis; Methods, inclusion criteria and study design; Results, the outcome of the study; and Conclusions, the outcome in relation to the hypothesis and possible

directions of future study.

• Body of Article

For the body of your article, follow this general outline:

• Introduction

A 1- to 2-paragraph introduction outlining the wider context that generated the study and the hypothesis.

• Patients and Methods

This section should detail inclusion criteria and study design to ensure reproducibility of the research. All studies that involve human subjects must be approved or deemed exempt by an official institutional review board; this should be noted here.

• Results

This section should give specific answers to the aims or questions stated in the introduction. The order of presentation of results should parallel the order of the methods section.

• Discussion

The section should highlight antecedent literature on the topic and how the current study changes the understanding of a disease process or clinical situation, and should include a section on the limitations of the present study.

• Conclusion

A brief concluding paragraph presenting the implications of the study results and possible new research directions on the subject.

General submission instructions (including cover letter, title page requirements, contributors' statement page, journal style guidance, and conflict of interest statements) apply to Regular Articles