COST UTILITY ANALYSIS OF LONG ACTING MUSCARINIC ANTAGONISTS (LAMAs) AS AN ALTERNATIVE TO LONG ACTING BETA AGONISTS (LABAs) FOR TREATMENT OF SEVERE COPD IN THE SOUTH AFRICAN PUBLIC SECTOR

Peggy Thompson

Research Report for a Master degree by coursework and research report: 'A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree.
MASTER OF PUBLIC HEALTH: HEALTH ECONOMICS

Midrand, 03 June 2023.

Supervisor: Dr Evelyn Thsehla

DECLARATION

I, Peggy Thompson, declare that this research report is my original work submitted for the Degree Master of Public Health: Health Economics at the University of the Witwatersrand, Johannesburg. There has not been any prior submission of this report to any other University for any other degrees.

……

(Signature of candidate)

03rd June 2023 in Midrand

In memory of my late mother and grandmother

Elly Thompson and Flora Jacobs.

Thank you for believing and investing in me.

ABSTRACT

Objective

The study purposed to estimate the cost-effectiveness of Tiotropium, compared with Salmeterol and Indacaterol for chronic obstructive pulmonary disease (COPD) patients within the South African public sector.

Methods

A global Markov model was adapted for the local setting and developed in Microsoft Excel. Transition probabilities and data on costs, resource use and effectiveness were obtained from literature. Outcomes were calculated for 3-years in the base case, then extrapolated over a 10-year and lifetime time horizon. A 5% discounting rate was applied according to local guidelines. Cost-effectiveness was estimated as the incremental cost per quality adjusted life year (QALY). One-way and probabilistic sensitivity analyses were conducted to consider model uncertainty.

Results

When compared with Indacaterol (300µg), Tiotropium was dominant (less costly and more effective) across all time horizons. Conversely, Tiotropium was not cost-effective when compared with Indacaterol (150µg) and dominated by Salmeterol over the 3- and 10-year time horizons. The resulting ICURs exceeded the estimated willingness to pay thresholds for all scenarios. The deterministic sensitivity analysis revealed the new intervention cost and utility for mild COPD impacted most on intervention cost-effectiveness.

Conclusion

Tiotropium was deemed not cost-effective at the proposed price, when compared to usual care for COPD. A price reduction should be considered, to determine the feasibility of displacing existing maintenance therapies. Indacaterol 150µg appeared more cost-effective at the current price and effectiveness demonstrated.

ACKNOWLEDGEMENTS

I would like to thank my supervisor Dr Evelyn Thsehla for her guidance and feedback on the research project, Dr Ijeoma Edoka for her assistance with the research protocol and my peer Ibrah Sinande for sharing his insights and constructive criticism of the Markov model I developed.

TABLE OF CONTENTS

NOMENCLATURE

B/D	Twice-daily (dose)
BOLD study	Burden of Obstructive Lung disease study
CAT	COPD Assessment Test
CD	Communicable Diseases
CEA	Cost-effectiveness analysis
CEP	Cost-Effectiveness Plane
CEAC	Cost-Effectiveness Acceptability Curve
CMS	Council for Medical Schemes
CUA/s	Cost-utility analysis/es
COPD	Chronic obstructive pulmonary disease
DPI	Dry powdered inhaler
ED	Emergency Department
EML	Essential Medicines List
EQ-5D	European Quality of life 5 Dimension
FDC/s	Fixed-Dose Combination/s
FEV_1	Forced Expiratory Volume per second
GP	General Practitioner
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-Related Quality of Life
ICS/s	Inhaled corticosteroid/s
ICER/s	Incremental Cost-Effectiveness Ratio/s
ICUR/s	Incremental Cost-Utility Ratio/s
LAB/s	Long-acting bronchodilator/s
LABA/LABAs	Long-acting beta agonist/s
LAMA/LAMAs	Long-acting muscarinic antagonist/s
LMIC	Low-Middle-Income-Countries
LY	Life Year/s
LYG	Life Year/s Gained
MA	Meta-analysis/es
MCID	Minimal Clinical Important Difference
MHPL	Master Health Product List

mMRC	Modified Medical Research Council dyspnoea questionnaire
MPR	Medicine Price Registry
NCD	Non-Communicable Diseases
NDoH	National Department of Health
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
O/D	Once-daily (dose)
pppa	per patient per annum
PSA	Probabilistic Sensitivity Analysis
q.i.d	Four times daily (dose)
QALM/s	Quality Adjusted Life Year/s
QALY/s	Quality Adjusted Life Month/s
QoL	Quality of life
RCT/s	Randomized Control Trial/s
SA	South Africa/n
SABA/s	Short-acting Beta Agonists
SEP	Single Exit Price
SGRQ score	Saint George's Respiratory Questionnaire score
SHI	Statutory Health Insurance
SR	Systematic Review
StatsSA	Statistics South Africa
TDI score	Transition Dyspnoea Index score
μg	microgram
UPFS	Uniform patient fee schedule
WHO	World Health Organization
WTP threshold	Willingness to pay threshold
ZAR	Zuid-Afrikaanse Rand

LIST OF FIGURES

CHAPTER TWO

CHAPTER THREE

CHAPTER FOUR

LIST OF TABLES

CHAPTER TWO

CHAPTER THREE

CHAPTER FOUR

Chapter 1 - Introduction

1.1 Background

The ongoing increase in communicable- (CD) and non-communicable diseases (NCD), including chronic obstructive pulmonary disease (COPD) proves burdensome globally (Vestbo *et al.*, 2004; Buist *et al.*, 2007). This is especially true for low-middle income countries (LMICs) like South Africa (SA).

COPD is debilitating and amongst the leading causes of death and disability globally. (Vogelmeier *et al.*, 2011; NICE, 2019; GOLD committee, 2020). The prevalence of COPD and the cost of treatment increased exponentially in recent years, both globally and in South Africa (Buist *et al.*, 2007; Council for Medical Schemes, 2020; StatsSA, 2020). This increase necessitates more effective disease control- and prevention strategies (Horita *et al.*, 2017). LMICs are not only disproportionately affected by NCD prevalence, but also accounts for over 90% of global COPD deaths (Allwood *et al.*, 2018; StatsSA, 2020).

COPD is a preventable and incurable chronic inflammatory lung condition that generally presents in adults over 40 years. The condition manifest in structural changes to lung parenchyma, airflow limitation, decline in lung function and impaired exercise capacity (GOLD, 2023). Debilitating effects may worsen over time, if not managed appropriately (Horita *et al.*, 2017; Kim and Aaron, 2018) and may also result in avoidable costs and adverse consequences.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) COPD guidelines distinguished four disease severity categories that range from mild to very severe COPD [GOLD 1-4]. The classification is based on spirometric grading of lung function capacity or degree of airflow limitation (Buist *et al.*, 2007; GOLD committee, 2020), (Appendix A). More advanced disease stages place a considerable demand on limited healthcare resources, affects quality of life more adversely and attracts significantly higher costs.

The disease classification approach evolved over time to include patient symptoms (dyspnea) and exacerbation history [Group A-D] (GOLD committee, 2020). This manner of classification allowed for a more individualized approach, to inform best possible treatment algorithms (Diamant, Brusselle and Russell, 2018; GOLD committee, 2020), (Appendix A). Ongoing efforts to produce a more simplified and consistent assessment method led to the release of a revised classification approach (published in January 2023). The updated method combines Group C and D to Group E, representing patients with frequent symptoms and at risk of exacerbating (GOLD, 2023) (Appendix A).

The rate at which COPD and other disease burden increases threatens the sustainability of healthcare financing resources. Decision makers are faced with a daunting task to decide where and how to focus limited resources, to achieve best and maximum population health (Diamant, Brusselle and Russell, 2018). Another key challenge is to find sustainable solutions to increase healthcare financing, in addition to developing more efficient ways to allocate limited resources.

While the average private sector expenditure for out-of-hospital COPD patients (per person per month) saw an increase of 10.27% from 2019 to 2020 (CMS, 2020), the unprecedented burden of Covid-19 infections made a further demand on already stretched healthcare budgets. The South African private sector reported Covid-19 claims in excess of 10 billion ZAR in 2020 alone (Council for Medical Schemes, 2020). Healthcare priorities and budgets had to be redirected to fund care for Covid-19 infections that were not initially budgeted for (WHO, 2022). This translated into disruption of essential services provision and deprioritization of preventative healthcare, which could potentially result in adverse long-term public health consequences (WHO, 2022). In the aftermath of a catastrophic pandemic, the need for prudent use of scarce healthcare resources became even more imperative (Council for Medical Schemes, 2020; StatsSA, 2020).

COPD therapies aim to preserve lung function and keep symptoms to a minimum (Cope *et al.*, 2013). The main classes of COPD pharmacotherapies long-acting muscarinic antagonists (LAMAs), long-acting beta agonists (LABAs) and inhaled corticosteroids

(ICSs) differ in terms of their efficacy and safety. The newer LAMAs are generally more effective and preferred (Oba, Sarva and Dias, 2016; Horita *et al.*, 2017; Rodrigo *et al.*, 2017; Diamant, Brusselle and Russell, 2018).

Novel therapies are generally less affordable than older alternatives and for this reason excluded from the South African Public Sector Essential Medicines List (Appendix B). Inhaled corticosteroids (Fluticasone), older long-acting beta agonists (Formoterol) and combinations of these classes (Salmeterol/Formoterol: Seretide and Sereflo) currently serves as the standard of care. The South African public healthcare sector is overburdened and under resourced (de Villiers, 2021); hence the crucial need to ascertain if newer therapies may potentially be cost-effective alternatives to replace the older ones.

1.2 Problem Statement

Healthcare for approximately 84% of the total South African population is funded from approximately half of the country's total gross domestic product (GDP) healthcare spent (Council for Medical Schemes, 2020). The inequitable distribution of both resources and access to healthcare between the two sectors is a result of a highly fragmented organization of the healthcare system (public and private split).

Based on limited resources, a highly price sensitive approach is taken to procure medicines within the public sector. Different treatment options are carefully considered in terms of costs and benefits. There is significant price variation between and within the two long-acting bronchodilator treatment classes. The private sector single exit price (SEP) for Tiotropium is the highest priced amongst all classes, ranging from R374.48 to R942.64 for a month supply. Indacaterol is available at a SEP range of R350.14 to R484.55. Salmeterol, an older genericized LABA, is available at a SEP of R497.12 (CMS Price Committee, 2022).

Novel long-acting muscarinic antagonists, including Tiotropium, are more readily accessible to patients within the private sector. The Public Sector Standard Treatment

Guidelines are outdated (National Department of Health, 2019) and not necessarily reflective of the latest (2023) evidence-based GOLD treatment recommendations. Inclusion of this drug class in the public sector may potentially improve health outcomes and prevent undesirable health consequences and additional expenditures that relates to uncontrolled COPD (Martinez *et al.*, 2016; NDoH, 2022). Optimal COPD management and targeted care may ultimately translate into more efficient use of limited resources.

To my knowledge, no cost-utility analysis has been performed to date to establish if the addition of Tiotropium as usual care would result in more efficient use of scarce resources within the public sector. It is not yet known if the health benefits produced would justify the high drug acquisition cost.

1.3 Justification

COPD is a leading cause of mortality and morbidity and a key driver of escalating healthcare costs. Poorly controlled patients place an avoidable *additional* demand on limited healthcare resources, both from a healthcare system- and societal perspective (Tariq and Thomas, 2017; Diamant, Brusselle and Russell, 2018). Inadequately controlled patients progress more swiftly to more severe disease and experience more frequent symptoms and events. This results in more frequent hospitalizations, emergency department (ED)- and unscheduled doctor visits, rescue therapy and antibiotic use (Martinez *et al.*, 2016; Tariq and Thomas, 2017; Diamant, Brusselle and Russell, 2018).

The disease burden therefore warrants more effective prevention and management strategies to improve health outcomes in both healthcare sectors (Diamant, Brusselle and Russell, 2018). Over and above concerns relating to inappropriate and suboptimal treatment, Abdool-Gaffar recently highlighted issues with late diagnosis and underdiagnosis of COPD in South Africa. This suggests a need to improve disease management (Abdool-Gaffar *et al.*, 2019). Improved diagnostics and optimal therapy at initiation may improve prognosis and get more patients under control much sooner.

A blanket approach to treat COPD and prescribing restrictions imposed on physicians to follow highly restricted medicine formularies, are some of the key reasons why patients remain poorly controlled. There is therefore a need to expand access to the broader range of therapies available for the wider patient population, to cater for all patient phenotypes. This is especially important for patients in more severe disease stages where swift control can avoid costly health consequences.

Inclusion of long-acting muscarinic antagonists (LAMAs) in the public sector can fulfil an unmet need to effectively and optimally treat patients not responding to conventional therapies, to essentially address the high burden of uncontrolled COPD. Allowing access to more potent and safer treatment alternatives will however come at a higher cost (Tariq and Thomas, 2017; Diamant, Brusselle and Russell, 2018; CMS Price Committee, 2022). The higher drug cost of LAMAs can potentially be offset by healthcare resource savings that result from avoiding exacerbations and adverse events.

We do not know if long-acting muscarinic antagonists (LAMAs) are more cost-effective compared to the current standard of care in the South African public sector. A comparative analysis in the form of a cost-utility analysis will be employed to establish whether LAMAs offer more value for money, compared to what is currently available. The analysis will employ local costing data and scientific evidence from the literature, to estimate incremental costs and benefits associated with the use of LAMAs versus long-acting beta agonists (LABAs).

1.4 Research Question

Is Tiotropium (LAMA) more cost-effective than LABAs for use as initial maintenance therapy for mild to very severe COPD in the public sector.

1.5 Study Aims and Objectives

Study Aims

To evaluate, from a payor perspective, the cost-effectiveness of the LAMA Tiotropium 18ug once-daily (O/D) versus LABAs: Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug twice-daily (B/D) in the management of COPD.

Study Objectives

1. Estimate the cost of Tiotropium 18ug O/D (LAMA) and LABAs Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug B/D for management of mild to very severe COPD (category A-D).

2. Estimate the health benefits expressed in terms of total life years (LY) and total quality adjusted life years (QALYs) for the different interventions: Tiotropium 18ug O/D, Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug B/D.

3. Estimate an incremental cost-utility ratio (ICUR) for Tiotropium 18ug O/D compared to LABAs: Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug B/D.

4. Explore through application of sensitivity analyses, the impact of uncertainty on results.

Chapter 2 - Literature Review

2.1 Introduction and Conceptual framework

This section purposed to identify trends in health outcomes measures and costing inputs used to estimate incremental cost-utility ratios for cost-utility analyses (CUAs). This section also aimed to scope different treatment modalities endorsed by guidelines for use as COPD maintenance therapy. A review of published literature was conducted to determine key parameters commonly used to measure effectiveness of interventions in CUAs.

A cost-utility analysis is an economic evaluation that aims to quantify, value and compare costs (monetary) and health effects/ outcomes (QALYs as the measure of effectiveness) for different healthcare interventions. The resulting outcome of such an analysis is represented as a ratio:

$$\frac{C_{\text{ost of New Treatment}} - C_{\text{Standard of care}}}{E_{\text{ffects of New Treatment}} - E_{\text{ffects of Standard of care}}} = \text{Incremental Cost- Utility Ratio [ICUR]}$$

(Cost per QALY gained)

Results from cost-utility analyses can be employed to make recommendations, inform healthcare budget allocations and to determine the feasibility of displacing existing therapies with newer therapies in settings where resources are scarce.

Interventions that produces more health benefits (QALYs) and incur less costs results in more favourable (lower) ICURs and are considered more cost-effective and dominating over alternative therapies. Conversely, those with less health benefits and more costs are considered less cost-effective and dominated. When both QALYs and costs for new interventions are higher than alternative therapies, a willingness to pay threshold value is required to determine if higher costs incurred can be justified by additional health effects produced. The ICUR is a function of cost per QALY (unit of effectiveness) gained (Figure

2.1). The objective of the economic evaluation is therefore to ascertain whether the new treatment offers more value for money or not, when compared to existing therapies.

The number of QALYs gained are dependent on an intervention's effectiveness to improve lung function and to reduce the incidence of COPD exacerbations. Greater lung function improvements result in greater utilities, which produces more QALYs. A higher incidence of exacerbations results in more loss of utilities (disutilities) and reduces the number of QALYs produced and vice versa. Lung function improvement and exacerbation reductions essentially are key objectives to improve COPD prognosis.

2.2 Epidemiology and Burden of Disease

The World Health Organization's Global Burden of Disease study projected COPD as a third leading cause of death at a global scale by 2030 (Oba, Sarva and Dias, 2016). In 2017 the prevalence was reported at 11.7% globally and 13.4% in Africa. The numbers are even higher in South Africa (SA), estimated at 20% of the global burden.

The prevalence of chronic airflow obstruction in Cape Town was estimated at 23.1% in 2005 (Allwood *et al.*, 2018). In 2018, STATS SA ranked diseases of the respiratory system as the 6th highest main cause of death. This accounted for almost 10% of all deaths in SA (StatsSA, 2020). In 2019, the South African Thoracic Society (SATS) highlighted the fact that chronic airway diseases are underdiagnosed, suggesting the prevalence of COPD may be grossly underestimated (Abdool-Gaffar *et al.*, 2019).

The projected rise in COPD prevalence can be attributed to increased exposure to risk factors, with tobacco smoke implicated as a main cause globally (Salvi, 2015; Oba, Sarva and Dias, 2016; Yang *et al.*, 2021; Awokola *et al.*, 2022). Key risk factors pertinent in SA includes tuberculosis (TB), human immunodeficiency virus (HIV), an ageing population, low baseline lung function, occupational irritant exposure or environmental air pollutants (Oba, Sarva and Dias, 2016; Kim and Aaron, 2018).

Low and Middle Income Countries (LMICs) and rural communities are significantly more exposed and impacted by risk factors (Awokola *et al.*, 2022). The observation was highlighted in the BOLD study that found participants in Cape Town South Africa were disproportionately affected. A higher prevalence of mild to very severe COPD was subsequently reported. A history of TB, HIV, smoking history, occupational dust, age and illiteracy were notably greater in South Africa, compared to other Latin American countries (Buist *et al.*, 2007; Abdool-Gaffar *et al.*, 2019). Predisposing risk factors were more pronounced in rural SA, where literacy and living conditions are below desired levels.

2.3 Treatment of COPD

Inhaled corticosteroids and Long-acting beta agonists used to be the golden standard in treating COPD. The use of Inhaled corticosteroids, especially long-term, is however associated with serious adverse events such as pneumonia, pulmonary tuberculosis, osteoporosis, bone fracture and cataracts (Wu *et al.*, 2016). The adverse events risk highlights the need for a more prudent approach to therapy (Martinez *et al.*, 2016; Oba, Sarva and Dias, 2016; Horita *et al.*, 2017; Rodrigo *et al.*, 2017; Tariq and Thomas, 2017; Diamant, Brusselle and Russell, 2018).

Studies further indicated that inhaled corticosteroid monotherapy resulted in clinically insignificant lung function improvement and limited protection against its decline in COPD patients (Oba, Sarva and Dias, 2016; Horita *et al.*, 2017; Rodrigo *et al.*, 2017; Diamant, Brusselle and Russell, 2018). Based on evidence from ongoing research, the latest guidelines no longer recommend ICS for low exacerbation risk COPD patients (Guillermo Ariza *et al.*, 2012). Its use is now reserved for frequent exacerbators not controlled on long-acting bronchodilator combinations (Oostenbrink *et al.*, 2005).

Long-acting bronchodilator (LAB) therapies have now become the cornerstone approach to treat COPD patients successfully (Buist *et al.*, 2007; Horita *et al.*, 2017; Diamant, Brusselle and Russell, 2018; Kim and Aaron, 2018; NDoH, 2022). New innovative therapies are developed with the aim to treat diseases more effectively and to help

patients reach their highest attainable health status. The GOLD and NICE treatment guidelines endorses the use of long-acting bronchodilators: long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) as COPD maintenance therapy (Karabis *et al.*, 2013; GOLD committee, 2020).

These guidelines acknowledge the key role of LAB therapy in alleviating COPD symptoms and reducing exacerbations (Vogelmeier *et al.*, 2011). LAMAs are the most preferred single therapy for COPD (Abdool-Gaffar *et al.*, 2019). A revised treatment guideline released by the GOLD scientific committee in 2023 however recommends initiation of a combination of these two classes, for use much earlier on in the course of the disease (GOLD, 2023).

Proper management of COPD considers the heterogenous nature of patient responses to pharmacotherapy. Subgroup and individual patient factors are considered to inform most appropriate therapies (Horita *et al.*, 2017; Tariq and Thomas, 2017; Diamant, Brusselle and Russell, 2018). This approach recognizes not all patients responds favourably to conventional therapies (Diamant, Brusselle and Russell, 2018). Patient specific characteristics that influence treatment responses can include disease severity, tobacco smoke, pneumonia risk, comorbidities, sputum/blood eosinophil count, atopy and others (Horita *et al.*, 2017; Tariq and Thomas, 2017).

Newer therapies provide an opportunity for broader access to more individualised care, to accommodate patient heterogeneity and different phenotypes. Novel pharmaceutical therapies introduced to markets addresses the need for access to more effective, convenient and tolerable treatment options. The wide range of long-acting bronchodilators available differ in terms of their mode of action, dosage, route of administration, delivery device, effectiveness and adverse event profiles.

2.4 Efficacy

Treatment efficacy relates to the ability of interventions to improve lung function, delay deterioration as well as effectiveness in symptom control. A systematic literature search for prior systematic reviews and meta-analyses identified FEV_1 (lung function) improvement and exacerbation reduction as the two key outcomes measures. These parameters exert a strong influence on cost-utility analyses results (Cope *et al.*, 2013; Karabis *et al.*, 2013; Donohue *et al.*, 2017; Manoj J. Mammen *et al.*, 2020).

2.4.1 Lung function: FEV_1 Improvement

Forced expiratory volume in 1 second (FEV_1) is an objective reproducible measure of airflow limitation, calculated as the maximum volume of air that an individual can forcibly exhale in 1 second. FEV_1 is used to define, assess and classify COPD severity (mild to very severe disease) and to monitor progression of disease. The criteria for classification of disease severity is aligned with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. FEV_1 measures represents lung function of COPD patients as a percentage of predicted normal (healthy) lung function (Price *et al.*, 2013). A decline in lung function indicate progression of disease to more severe stages and deterioration of quality of life.

Transition matrices from the INHANCE and INLIGHT2 trials (Donohue et al., 2010; Kornmann et al., 2011) reflected the probabilities for patients to move between disease severity stages and to progress to worse stages. FEV_1 change over the first 3 months was the primary study endpoint. Patients on different therapies were assessed for initial lung function (FEV_1) improvement from baseline to week 12, which was adjusted to 1-year (Price et al., 2013). Patients whose lung function improved adequately transitioned to milder disease states and enjoyed greater health utility.

Conversely, a rapid decline in lung function predisposes patients to more frequent and severe exacerbations (Gani *et al.*, 2010). This increased incidence in turn expedite more

rapid lung function decline, loss in quality of life and increased mortality (Horita *et al.*, 2017; Kim and Aaron, 2018). A delay in lung function decline thus also deliver an indirect mortality benefit (Gani *et al.*, 2010).

2.4.2 Exacerbations

The GOLD guidelines define exacerbations as ”An acute worsening of respiratory symptoms that results in additional therapy” (Gani *et al.*, 2010). There is general consensus about its incapacitating nature, which typically involve increased shortness of breath, cough, sputum production and -purulence (Gani *et al.*, 2010). COPD exacerbations and related hospital admissions are furthermore recognized as key drivers of resource use and costs (Hogan, Geddes and Gonzalez, 2003).

Suboptimal therapy and inadequate disease control causes more swift deterioration to more severe disease. A higher incidence of exacerbations can be observed with suboptimal therapy and with poor disease control, which further expedites the loss of quantity and quality of life. Frequent episodes of exacerbations may therefore signal a need for treatment modification. Adequate control is achievable through appropriate treatment, patient adherence and application of correct inhaler techniques (Horita *et al.*, 2017; Kim and Aaron, 2018; GOLD, 2023). Effective therapy can therefore assist with slowing down disease progression, in mitigation of escalating healthcare costs.

Despite the adverse consequences associated with COPD exacerbations, not all studies from network meta-analyses sufficiently reported on exacerbation frequency and severity (Hogan, Geddes and Gonzalez, 2003; Donohue *et al.*, 2017). COPD exacerbations are key predictors of poor prognosis, frequent hospitalization and increased fatalities (Martinez *et al.*, 2016). Future research to differentiate exacerbations by type, treatment option and disease severity can benefit efforts to improve disease management. Prior researchers encouraged development of specific criteria and definitions to address inconsistent exacerbation reporting (Gani *et al.*, 2010; Donohue *et al.*, 2017). Some studies applied a ‘symptom based’ criteria (patient reporting of worsening symptoms),

while others used an 'event based' definition which focus on reporting episodes that necessitated a change in treatment.

2.4.3 Comparative Clinical Efficacy of COPD treatment

(Results summary and systematic search strategy: Appendix C - Table 2.1)

This section aimed to examine scientific evidence from the literature, to compare how COPD therapeutic interventions differ in their ability to improve lung function and prevent symptoms and exacerbations.

Long-acting muscarinic antagonist (LAMA) intra-class comparison

A within class effectiveness comparison conducted by Karabis et al., 2013 investigated lung function improvement, health-related quality of life and dyspnoea. As anticipated, the study revealed all active LAMAs performed better than placebo for all outcomes measures. Point estimates were above the defined minimal clinical important difference (MCID) of 100ml. Results for Aclidinium 400ug bromide were comparable to the other LAMAs (Tiotropium and Glycopyronium). The probability of being the most effective option improved over longer periods (Karabis *et al.*, 2013).

Long-acting beta agonist (LABA) intra-class comparison

Comparison of different LABAs for outcomes parameters similar to what Karabis et al., 2013 used indicated Indacaterol performed better. Indacaterol consistently demonstrated better trough FEV_1, health status and dyspnoea (St. George's Respiratory Questionnaire- and Transition dyspnoea scores) over different time points. The effectiveness of Indacaterol appeared to be dose-dependent (increased with higher doses). Results between active treatment arms were however not statistically different (Donohue *et al.*, 2017).

Long-acting bronchodilator (LAB) inter-class comparison: LAMA versus LABA

A network meta-analysis (NMA) conducted by Cope et al., 2013 focused on both objective lung function (FEV_1) improvement and subjective health status (quality of life) measures

as the main outcomes. Both measures are important for decision making. FEV_1 was used as the measure to stage disease severity. The newer pharmacological therapies Indacaterol, Tiotropium and Glycopyronium were most effective and superior in bronchodilatory capacity. Indacaterol 300μg had the highest probability of being most effective in both lung function and quality of life metrics. Results were however not meaningfully different (Cope *et al.*, 2013).

The study by Decramer, 2006 demonstrated promising results for LAMAs in various efficacy parameters, including reducing exacerbations and rescue therapy use. Results were inconsistent for LABAs, especially with regard to patient-centred outcomes such as dyspnoea and exacerbations (Decramer, 2006). Head to head studies demonstrated superior efficacy for LAMAs versus LABAs in reducing dyspnoea and exacerbations. The new GOLD treatment guideline positioning of LAMAs as initial therapy for patients with severe and very severe COPD was based on these observations (Costa-Scharplatz *et al.*, 2015; GOLD committee, 2020). Results from another investigation concur with the findings of superior efficacy with LAMAs over LABAs to reduce COPD exacerbations and related hospitalizations (Manoj J. Mammen *et al.*, 2020).

Combination- versus Monotherapy (LAMA or LABA) comparison

When single therapies were compared to LAMA/LABA fixed-dose combinations (FDCs), the latter proved superior in reducing the risk for hospitalisation and the frequency of acute COPD exacerbations with 11% and 17% respectively in patients with symptomatic COPD. Outcomes such as hospital admissions, dyspnoea, exacerbations, health-related quality of life (HRQoL) and treatment-related adverse events were rated and ranked as critical. While these patient-centred outcomes were prioritized, lung function (FEV_1) was considered only as an secondary endpoint (M J Mammen *et al.*, 2020; Manoj J. Mammen *et al.*, 2020).

Although fixed-dose combination (FDC) therapies showed statistically significant improvements over monotherapies in FEV_1, HRQoL, dyspnoea reduction and exercise

intolerance, these improvements did not cross the prespecified minimal clinical important difference (MCID) thresholds. Combination therapies furthermore proved to be well tolerated through demonstration of treatment-related adverse event risks that were comparable to that of monotherapies. This included the incidence of pneumonia and all-cause mortality. Health benefits accrued clearly outweighed adverse risks associated with the use of combination therapy (M J Mammen *et al.*, 2020; Manoj J. Mammen *et al.*, 2020).

A multitude of studies corroborated with the findings that LAMA/LABA combination therapies were most effective as maintenance therapy for various outcomes parameters. Treatment effectiveness consistently improved over longer periods (Oba, Sarva and Dias, 2016; Tariq and Thomas, 2017). The LAMA/LABA combinations were preferred over ICS/LABA, based on lower exacerbation risks demonstrated, fewer pneumonia episodes, greater lung function, quality of life, exercise capacity, less rescue medicine use and comparable safety profiles (Horita *et al.*, 2017; Rodrigo *et al.*, 2017; Tariq and Thomas, 2017).

The study by Tariq and Thomas, 2017 demonstrated that the efficacy of LAMA/LABA combinations in FEV_1 improvement, symptom control, patient-reported outcomes and health-related quality of life were clinically- and statistically significant. The combination furthermore offered sustained FEV_1 improvement greater than the set minimally clinically important difference of 60mL for the initial 3 months, whereafter the superior benefit stabilized (Calzetta *et al.*, 2017). The GOLD guidelines encourage use of combination therapy for patients who experience frequent symptoms and those with a high exacerbation risk (Rodrigo *et al.*, 2017; Tariq and Thomas, 2017; Hahn *et al.*, 2018).

The potent efficacy of the LAMA/LABA combination is a result of the complimentary effect of dual bronchodilation, each with its own different mechanisms of action (Horita *et al.*, 2017; Rodrigo *et al.*, 2017). The efficacy of the combination is believed to be similar to LAMA monotherapy, with the benefit of a reduced risk of withdrawal due to lack of efficacy for the former (Rodrigo *et al.*, 2017). Withdrawal rates due to adverse events were lower for LAMA/LABA combinations, compared to ICS/LABA (Rodrigo *et al.*, 2017).

Multiple studies from different network meta-analyses focused on within class comparisons and considered indirect relative effectiveness (treatment effect versus placebo). This was due to a lack of head to head studies with all long-acting bronchodilators. Study participants were furthermore not fully representative of real world COPD populations. Mild COPD, the elderly and patients with concomitant diseases such as asthma were generally excluded. Treatment effect estimates were highly sensitive to disease severity, a measure of lung function (Price *et al.*, 2013).

Lung function improvement and exacerbation reductions were considered as the primary effectiveness endpoints across multiple studies. These two parameters correlated positively through exerting a notable influence on each other. A high incidence of exacerbations expedited FEV_1 deterioration and consequently disease progression. Patients in more severe disease stages exacerbated more frequently and more severely. There was overall very limited focus on death, drug-induced adverse events, rescue medication use and COPD exacerbation rates (Cope *et al.*, 2013; Karabis *et al.*, 2013; Donohue *et al.*, 2017; Manoj J. Mammen *et al.*, 2020).

Tiotropium was the LAMA that demonstrated superior potency in sustained bronchodilation, reduction in the incidence of exacerbations and related hospital admissions, improved lung function and health-related quality of life metrics (Oostenbrink *et al.*, 2005; Rodrigo *et al.*, 2017; Oba *et al.*, 2018). In studies powered to detect COPD exacerbations, the use of Tiotropium resulted in superior reductions compared to alternative therapies (Decramer, 2006; Vogelmeier *et al.*, 2011; Decramer *et al.*, 2013). Exacerbations were identified as potentially life-threatening and the cause of substantial quality of life impairment.

Results from Indacaterol trials reported Indacaterol as a preferred long-acting bronchodilator for effective lung function improvement (Price *et al.*, 2013). This was of particular importance to deter progression to more severe disease. While Tiotropium demonstrated more favourable outcomes in terms of prevention of exacerbations and hospital admissions (Halpin *et al.*, 2016; Oba *et al.*, 2018), Indacaterol proved superior in

lung function improvement (Price *et al.*, 2013). Both these measures demonstrated a key role in disease prognosis, management and resource use.

2.5 Cost

Prior studies routinely distinguished between maintenance cost, intervention cost and exacerbation treatment costs to estimate the total costs incurred through managing COPD patients (Rutten-van Mölken, Maureen P. M. H. Oostenbrink, Miravitlles and Monz, 2007; Guillermo Ariza *et al.*, 2012). Hogan et al., 2003 conducted a cost-effectiveness analysis with and without exacerbation costs, which notably impacted total costs and cost-effectiveness results.

Intervention costs differed substantially across different countries, especially in terms of which treatment was most expensive. The cost of Tiotropium was generally higher than Salmeterol in many countries explored. In the United Kingdom, the price for Indacaterol 150µg and 300µg were the same. In the study by Price et al., 2013 and others, intervention cost and costs related to exacerbation care made the greatest contribution to total costs, compared to other resources used (García Ruiz, Leiva Fernández and Martos Crespo, 2005; Hoogendoorn *et al.*, 2013; Price *et al.*, 2013).

2.6 Cost-Utility Analysis

(Results summary and search strategy: Appendix D - Table 2.2)

Cost-effectiveness analyses (CEA) and cost-utility analyses (CUA) in healthcare are economic evaluations conducted with the objective to compare one health intervention to another, in terms of both estimated costs incurred and estimated health benefits (quality adjusted life years) produced.

This section aimed to review published literatures for prior CUAs conducted for different COPD maintenance therapies. The search focused on comparing individual bronchodilator constituents (monotherapy) as well as fixed-dose combination therapies from a payor perspective. The literature review further explored key interventions, common approaches and model input parameters routinely used to conduct cost-utility analyses. The search also attempted to identify parameters with the greatest impact on incremental cost-utility ratios. Interventions of particular interest for this analysis were Tiotropium 18ug O/D (LAMA) compared to LABAs: Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug B/D.

A 'within randomised trial' cost-effectiveness analysis conducted by Hoogendoorn et al.,2013 compared Tiotropium 18ug to Salmeterol 50ug in terms of costs, number- and days of exacerbations. A German statutory health insurance perspective was adopted. Tiotropium was associated with an increase in overall costs due to a higher drug acquisition cost (~60%). The higher drug cost was partially offset by cost savings that resulted from a reduced incidence and prolonged time to a 1st exacerbation that led to hospitalisation. Tiotropium was more cost-effective than Salmeterol, based on the reduced rate and days of exacerbations. Parameters with a notable impact on cost-effectiveness results (incremental cost-effectiveness ratios) were the reduction and probability of exacerbations, initial health state distribution of patients and the costs incurred through hospitalisation (Hoogendoorn *et al.*, 2013).

A cost-utility analysis in a Dutch healthcare setting compared Tiotropium 18ug to Salmeterol 100ug in terms of cost per quality adjusted life year (QALY) and cost per exacerbation avoided over a 1- and 5-year time horizon. The study utilized exacerbation data from a prior clinical trial and local costs to develop a Markov model. Results were in favour of Tiotropium for both outcomes measures. Tiotropium produced more QALYs and resulted in greater annual exacerbation reductions (including hospitalisations). Tiotropium was more cost-effective after 1-year and completely dominated after 5-years, despite its higher drug acquisition costs. The probability of being cost-effective at the maximum willingness to pay threshold value of €20k was 73% in the 1-year analysis. Benefits increased and the incremental cost-effectiveness ratio (ICER) improved over a longer time horizon, as a result of greater reductions in exacerbation costs. The exacerbation benefit and difference in effect with Tiotropium also improved with more severe disease. The ICER was most sensitive to disease severity distributions (Hoogendoorn *et al.*, 2012).

A cost-utility analysis performed by Oba, 2007 employed local costs in the United States and effectiveness data from a systematic literature review, to examine whether Tiotropium 18ug daily would make for a cost-effective maintenance therapy replacement of Salmeterol 50ug twice daily and Ipratropium 40µg q.i.d *(*four times daily*)*. A third-party payer perspective was explored. The main outcomes were cost per QALY gained, quality of life improvement and frequency of rescue medicine use. The Markov model demonstrated that Tiotropium had a superior effect in all outcomes measures, including hospitalisation, which resulted in cost savings. The cost per QALY gained was favourable for Tiotropium and health benefits produced were sufficient to offset and compensate for the higher drug cost. A scenario analysis found the cost of hospitalization had a substantial impact on total costs and incremental cost-utility ratios (ICURs). Although Tiotropium was more cost-effective, an overlap in results created some uncertainty which warranted further investigation (Oba, 2007).

A cost-effectiveness analysis for the Spanish National Health System employed a Markov model to compare Tiotropium 18ug with Salmeterol 100ug, in terms of both objective (FEV_1 improvement) and subjective outcomes (dyspnoea and health status scores). The

analysis combined resource use and outcomes data from prior clinical trials from a systematic review, with locally published costing data. Tiotropium demonstrated greater effectiveness in exacerbation reductions and related hospital stay duration. These were both strong drivers of COPD costs and key parameters that impacted on the resulting ICER. Tiotropium was more cost-effective than Salmeterol, based on the health benefits achieved (FEV_1 improvement, exacerbation reduction, St. George's Respiratory Questionnaire- and Transition Dyspnoea scores improvement) and the cost savings that correlated with the reduced hospital stay (107 days saving in 6 months) (García Ruiz, Leiva Fernández and Martos Crespo, 2005).

An existing Markov model was adapted to conduct a cost-utility analysis for the United Kingdom (England, Scotland, Wales and Northern Ireland), which explored incremental health outcomes and -costs for Tiotropium 18ug against Salmeterol 50ug and Ipratropium 40µg. Parameters with a notable influence on the ICUR were mortality benefits derived from intervention use, the model population composition (disease severity distribution) and model time horizons. Tiotropium produced more QALYs and resulted in lower costs. Tiotropium consequently dominated widely (72-87%) when compared to both Ipratropium and Salmeterol, except for the severe COPD group comparison with Ipratropium. The probability of Tiotropium being cost-effective ranged from 72-100%. The savings gained with Tiotropium was mainly a result of exacerbation reductions. Tiotropium improved disease severity distribution and reduced disease progression and exacerbations when compared to the other interventions. The exacerbation rates were however low overall, because exacerbations were not considered as an entry criteria for participant recruitment. Improvement in FEV_1 as a result of treatment choices were modelled, but deaths were excluded based on a low incidence (Gani *et al.*, 2010).

A cost-utility analysis for the Spanish National Health System examined 3 different transition- and exacerbation probability scenarios. The probabilistic Markov model compared Tiotropium 18ug with Salmeterol 50ug and Ipratropium 40µg. Outcomes (exacerbation-free months and incremental QALYs gained) were consistently better with Tiotropium. Despite the higher intervention and total costs, Tiotropium use resulted in

exacerbation reductions, longer exacerbation-free months and more QALYs gained. The higher drug costs were partially offset by exacerbation cost savings. Tiotropium was preferred at the threshold of €7,600, €8,800 and €12,500 respectively for moderate, severe and very severe COPD. Tiotropium resulted in the highest expected net benefit for cost per exacerbation-free month at the threshold of €560, €700 and €1,200 for moderate, severe and very severe COPD respectively. Below these thresholds, Ipratropium proved more favourable. The threshold increased for more severe disease. The distribution of patients across disease severity stages was found to impact the ICUR substantially (Rutten-van Mölken, Maureen P. M. H. Oostenbrink, Miravitlles and Monz, 2007).

A cost-effectiveness analysis conducted by Oostenbrink et al., 2005 quantified health benefits as quality adjusted life months (QALMs) and exacerbation reductions. The analysis compared results for the Canadian setting to that of the Netherlands. The probabilistic Markov model used a 1-year time horizon. The comparison was between Tiotropium 18ug, Salmeterol 50ug and Ipratropium 40µg for COPD patients in the Netherlands and Canada. The results corroborated with previous analyses in showing Tiotropium demonstrated superior effectiveness in exacerbation reductions, with approximately 95% of iterations appearing in the right quadrant of the cost-effectiveness plane. When compared to Salmeterol, Tiotropium reduced exacerbations by 17%. Salmeterol in turn demonstrated better outcomes than Ipratropium. QALMs between treatment arms differed only modestly. Tiotropium was more cost-effective in the Netherlands analysis versus Canada. This was based on additional cost-savings that resulted from higher hospitalisation costs for exacerbations in the Netherlands. Patients on average stayed longer in hospital, compared to Canada. Exacerbation probabilities was shown to have the greatest influence on ICERs (Oostenbrink *et al.*, 2005).

Guillermo Ariza et al., 2012 employed a Markov model to conduct a cost-utility analysis for the Columbian Health System, exploring intervention effectiveness in lung function (FEV_1) improvement as the main outcomes parameter. The analysis compared Indacaterol to Tiotropium and fixed-dose combination therapies. Indacaterol proved superior in FEV_1 improvement and dominated in over half of the iterations against

Tiotropium. Indacaterol furthermore demonstrated a 78% probability that the incremental cost-utility ratio (ICUR) would fall below the United States willingness to pay threshold, making it a cost-effective alternative. The results (ICURs) were most impacted by patient COPD severity distribution and lung function improvement (Guillermo Ariza *et al.*, 2012).

The cost-utility study by Price et al., 2011 was conducted from a German health service perspective, to compare Indacaterol 150ug and 300ug to Tiotropium 18ug and Salmeterol 50ug. The Markov analysed outcomes over a 3-year time horizon. Indacaterol 150ug dominated and produced more favourable incremental cost-utility ratios (ICURs), attributed to greater effectiveness in FEV_1 improvement. The lung function changes occurred during the initial 12-weeks and was assumed to be sustained over a lifetime. FEV_1 improvement resulted in more patients moving back to milder disease stages and a cohort that ultimately progressed more slowly to worse stages and death. Mortality rates were higher in more severe disease stages. The superior lung function benefit of Indacaterol was assumed to produce an indirect mortality benefit. Although ICURs were highly sensitive to exacerbation rates, the study was not powered to differentiate the impact of treatment. The sensitivity analysis highlighted the model time horizon, mortality rates by disease severity (especially severe COPD) and intervention costs as other key parameters that impacted on ICUR results (Price *et al.*, 2011).

In a follow-up cost-utility analysis by Price et al., 2013, Indacaterol was compared to Tiotropium and Salmeterol in a Markov model with extrapolation over longer time frames (5- and 20-year time horizons). A United Kingdom National Health Service perspective was employed. Both the high and low doses of Indacaterol consistently dominated other active treatments over the different time horizons. More than 72% and 89% of the iterations in the probabilistic sensitivity analysis (PSA) showed dominance over Salmeterol and Tiotropium respectively. The incremental cost-utility ratio (ICUR) improved over longer time horizons. Results (ICURs) were again markedly impacted by the disease stage distribution of patients and the mortality rates in very severe COPD. Quality of life improvement and cost saving benefits were reflective of Indacaterol's greater FEV_1

improvement. Moving patients to milder disease stages were key in producing more favourable ICURs (Price et al., 2013).

An economic assessment (cost-effectiveness analysis) that was conducted in the United States of America utilized local costing data and effectiveness data from a local clinical trial. The comparators were Ipratropium 40µg and Formoterol (high and low dose). The analysis examined FEV_1 and quality of life. The low dose of Formoterol (12µg) was superior and demonstrated the greatest quality of life improvement, although only clinically relevant. When compared to Ipratropium, improvement in quality of life was achieved at an incremental cost of $554.28 per annum. For cost per FEV_1 outcomes, the high dose of Formoterol (24µg) was less effective and more expensive than the low dose and therefore dominated. The analysis examined intervention- and rescue medication costs and tested the impact of a 50% cost variance in a sensitivity analysis. Based on the reduced hospital rates observed with Formoterol 12µg, the incremental cost-effectiveness ratio (ICER) became more favourable (lower) when hospital costs were included in the analysis. The cost of hospitalization due to exacerbations had a notable impact on the ICER. Ipratropium was least effective in both lung function and quality of life outcomes (Hogan, Geddes and Gonzalez, 2003).

Lung function improvement and decline correlated with disease improvement and deterioration and determined how patients were distributed across disease stages. Having a higher proportion of patients in more severe disease stages impacted negatively on cost-effectiveness results (ICER and ICUR). Exacerbations and related hospitalisation significantly inflated COPD management costs and impacted negatively on ICERs/ICURs. Both parameters were key effectiveness outputs for estimation of health benefits (QALYs) in most analyses explored (Vestbo *et al.*, 2004; Cope *et al.*, 2013; Hoogendoorn *et al.*, 2013). More severe COPD stages resulted in more loss of life (both quantitative and qualitative), more frequent and more severe exacerbations and hospitalisations.

Exacerbation reduction benefits and the associated cost savings increased with disease severity. This was based on the higher incidences observed in more severe disease. Willingness to pay threshold values and ceiling ratios in the above analyses also appeared increased with disease severity.

In some of the analyses explored, the cost of exacerbation-related hospitalisation was so high that very high intervention acquisition costs could be overturned if the intervention demonstrated sufficient ability to reduce exacerbations. Overall net cost savings observed in prior analyses predominantly resulted from the effectiveness of interventions to reduce exacerbations and to lengthen the time to a first exacerbation. More effective therapies have demonstrated mitigation of risk factors to curb higher healthcare costs that resulted from disease deterioration.

Multiple parameters have demonstrated considerable influence on cost-effectiveness results (ICER and ICUR). The extent to which each influenced the results appeared to be dependent on contextual factors (differences in intervention costs, length of hospital stay permitted and other factors). Uncertainty pertaining to key parameters were investigated in most of the literature through application of one way- and probabilistic sensitivity analyses, to explore the magnitude and direction of their impact on results.

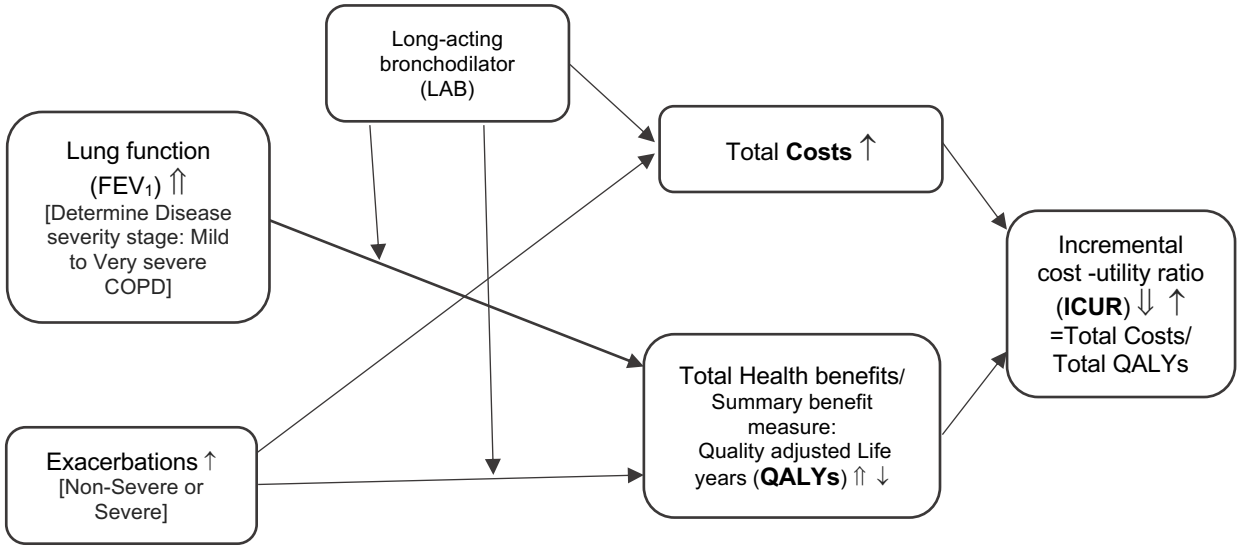


Figure 2.1 Conceptual Framework

Chapter 3 - Methods

3.1 Introduction

This section aims to explain the methods used in this analysis to construct and analyse the Markov model and to reveal the sources of evidence used to estimate model outputs. The Markov model aimed to depict the very nature of COPD (disease and events), modelling how patients progress from mild to severe disease.

3.2 Study Design

A cost-utility analysis was conducted through application of decision analysis modelling (Markov model in excel- Microsoft 365 version). Cycle lengths in the model were set at 1-year. The model differentiated utility values according to disease severity stages. Distinct probabilities of transitioning to different disease stages (Price *et al.*, 2013) and probabilities of patients experiencing severe or non-severe exacerbations were accounted for in the model (Donohue *et al.*, 2010; Vogelmeier *et al.*, 2011; Decramer *et al.*, 2013). The expected total costs and benefits were estimated for each intervention arm, to calculate incremental cost-utility ratios (ICURs).

The long-acting muscarinic antagonist Tiotropium 18ug was compared to long-acting beta agonists: Indacaterol 150ug O/D, Indacaterol 300ug O/D and Salmeterol 50ug B/D. Health benefits were expressed as quality adjusted life years (QALYs). In the absence of local data, the model adopted disease transition probabilities and health state utilities from the literature to estimate total QALYs (Price *et al.*, 2013). Utilities and disutilities (resulting from exacerbations) were derived from generic EQ-5D index scores, which reflect on both the impact of the disease and intervention used. Local costing data and healthcare resource use, as determined by treatment guidelines, enabled estimation of total treatment cost for each intervention.

3.3 Study Site and Perspective

The analysis explored cost-effectiveness of therapeutic interventions for patients within the South African public healthcare sector. A government payor perspective was used, with consideration of direct costs only.

3.4 Study Population

The population of interest included patients aged 40-years and older with a diagnosis of COPD, who receive treatment and care in public health sector facilities across all provinces in South Africa.

3.5 Model Structure

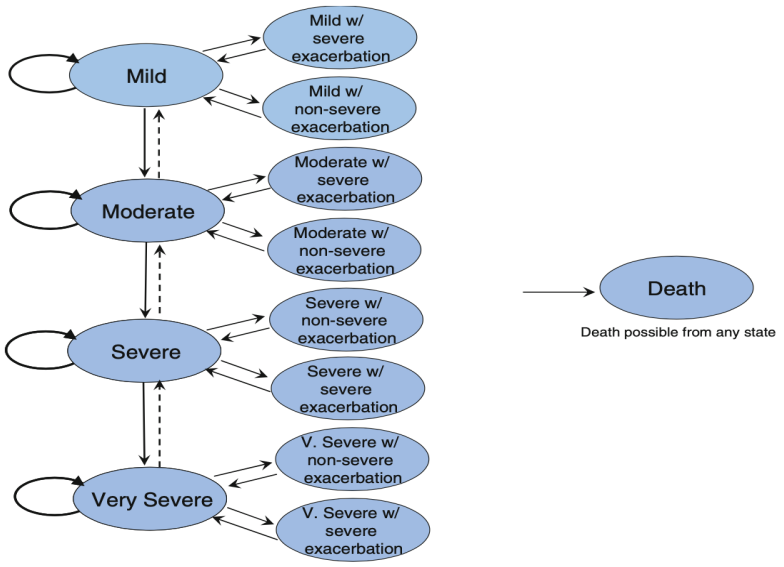


Fig. 1 Model schematic. Reprinted from Respiratory Medicine, Vol 105, David Price, Alastair Gray, Rupert Gale, Yumi Asukai, Laura Mungapen, Adam Lloyd, Lars Peters, Katja Neidhardt, Tobias Gantner, Cost-utility analysis of indacaterol in Germany: a once-daily maintenance bronchodilator for patients with COPD, pp 1635–1647, Copyright (2011), with permission from Elsevier

Figure 3.1 (Source Price et al., 2013)

The model (Figure 3.1) consisted of four transitory COPD health states and an absorbing state (death). All patients were assumed to have a confirmed diagnosis of COPD, which is progressive and chronic in nature. The initial distribution of patients across four distinct health states was informed by disease transition probabilities observed in randomised clinical trials conducted to compare efficacy of the three therapeutic interventions (Price *et al.*, 2013). A patient may either remain in a current health state, transition to a milder or worse state or die during a 1-year cycle (adopted from Price et al., 2013).

The probability of death was determined by the health state only and not the treatment effect, due to a lack of studies that demonstrate intervention mortality benefits (GOLD, 2023). Each of the four health states furthermore presented with two additional transitional states: the probability to experience a severe or non-severe exacerbation, whereafter they 'return' to the stable health state without exacerbating.

3.6 Model Parameters

3.6.1 Transition Probabilities

Transition probabilities indirectly represents the effectiveness of pharmacotherapies. Table 3.1 presents the transition probabilities by intervention and disease stage. The data was obtained from a published randomized controlled trial, through a systematic literature search (Price *et al.*, 2013). The clinical effectiveness of interventions are demonstrated in their ability to improve lung function and delay disease deterioration, which translates into milder and 'healthier' disease states. Table 3.2 shows the probability of dying during each of the disease stages. Effectiveness furthermore involves reduction of COPD symptoms (especially exacerbations), which impairs quality of life (Allwood *et al.*, 2018; GOLD committee, 2020).

Table 3.1 Disease State Transition Probabilities

Disease state	Description	TIO18 Value	IND150 Value	IND300 Value	SALM50 Value
Mild COPD	Transition probability to stay in Mild	0,6000	0,6000	0,6250	0,7500
	Transition probability to move from Mild to Moderate	0,4000	0,4000	0,2500	0,2500
	Transition probability to move from Mild to Severe	0,0000	0,0000	0,1250	0,0000
	Transition probability to move from Mild to Very Severe	0,0000	0,0000	0,0000	0,0000
Moderate COPD	Transition probability to move from Moderate to Mild	0,1111	0,0822	0,1507	0,0957
	Transition probability to stay in Moderate	0,8426	0,8425	0,7877	0,8087
	Transition probability to move from Moderate to Severe	0,0463	0,0753	0,0548	0,0957
	Transition probability to move from Moderate to Very Severe	0,0000	0,0000	0,0068	0,0000
Severe COPD	Transition probability to move from Severe to Mild	0,0052	0,0064	0,0060	0,0000
	Transition probability to move from Severe to Moderate	0,3089	0,3885	0,3832	0,2308
	Transition probability to stay in Severe	0,6440	0,5860	0,5868	0,7063
	Transition probability to move from Severe to Very Severe	0,0419	0,0191	0,0240	0,0629
Very Severe COPD	Transition probability to move from Very Severe to Mild	0,0000	0,0000	0,0000	0,0000
	Transition probability to move from Very Severe to Moderate	0,0233	0,0263	0,0909	0,0000
	Transition probability to move from Very Severe to Severe	0,5581	0,6316	0,6364	0,5385
	Transition probability to stay in Very Severe	0,4186	0,3421	0,2727	0,4615

TIO18: Tiotropium 18 **IND150:** Indacaterol 150 **IND300:** Indacaterol 300 **SALM50:** Salmeterol 50

Source: Price et al., 2013

Table 3.2 Death Probabilities

Other Model Parameters	Value	Range used in SA	Distribution	Source
Probability of death due to Mild COPD	0*	0-0	Beta	Price et al., 2013
Probability of death due to Moderate COPD	0.003*	0-009	Beta	Price et al., 2013
Probability of death due to Severe COPD	0.006*	0-0.018	Beta	Price et al., 2013
Probability of death due to Very Severe COPD	0.024*	0-0.053	Beta	Price et al., 2013

* Values from Rutten-van Molken - adjusted for 3-month model cycle length ((Price *et al.*, 2013)
SA: Sensitivity Analysis

3.6.2 Exacerbation Probabilities

Data from three different studies were combined to calculate relative exacerbation probabilities for each LABA, compared with Tiotropium. Exacerbation data was obtain from the INHANCE trial. The data was however limiting in comparing active interventions with placebo (Donohue *et al.*, 2010). The placebo data was reflective of baseline untreated rates. The low number of exacerbations and lack of 'incidence by disease severity' reporting was another limitation. For this reason, two more studies (specifically powered to detect exacerbations) were employed to calculate probabilities (Vogelmeier *et al.*, 2011; Decramer *et al.*, 2013). A formula used by Oostenbrink et. al informed the method for calculation of *relative* probabilities for each comparator, through use of multiple trials data (Oostenbrink *et al.*, 2005). Table 3.3 shows the exacerbation probabilities for each intervention, by disease severity and exacerbation type.

Table 3.3 Exacerbation Probabilities (Relative)

	Non-severe Exacerbation				Severe Exacerbation			
	Mild	**Moderate**	**Severe**	**Very Severe**	**Mild**	**Moderate**	**Severe**	**Very Severe**
TIO18	0,0018	0,0756	0,1312	0,0290	0,0010	0,0253	0,0633	0,0146
IND150	0,0019	0,0797	0,1383	0,0306	0,0014	0,0346	0,0865	0,0200
IND300	0,0017	0,0725	0,1259	0,0279	0,0010	0,0243	0,0608	0,0140
SALM50	0,0020	0,0849	0,1475	0,0326	0,0012	0,0281	0,0704	0,0163

TIO18: Tiotropium 18 **IND150:** Indacaterol 150 **IND300:** Indacaterol 300 **SALM50:** Salmeterol 50

3.6.3 Valuation of Cost and Resource Utilisation

A micro-costing approach was used to estimate the total annual costs (ZAR) for COPD treatment in the South African public sector. Total annual cost for each intervention comprised of maintenance-, intervention drug- and exacerbation/ hospitalisation costs (Table 3.4).

International and local data sources involved private and public sector entities' websites and repositories, including the South African (SA) National Department of Health (NDoH), Council for Medical Schemes (CMS), South Africa Thoracic Society, NICE and WHO. Secondary data obtained for the analysis included local resource utilization and cost data from the NDoH Master Health Product List, Uniform patient fee schedule, Standard treatment Guidelines and Essential Medicines List and single exit prices (SEPs) from the private sector Medicine Price Registry (MPR).

Local and international guidelines were consulted for treatment algorithms and recommendations, to inform the type, frequency and quantity of healthcare resources used for the management of COPD. These guidelines included the Adult Hospital and Primary Health Care Standard Treatment Guidelines and Essential Medicines List for South Africa, the South African Thoracic Society updated guidelines (Abdool-Gaffar *et al.*, 2019), the GOLD 2020 and 2023 Reports (GOLD committee, 2020; GOLD, 2023), guidelines from the National Institute for Health and Care Excellence (NICE, 2019) and the World Health Organization (WHO, 2022).

Patients with stable disease require maintenance treatment and chronic use of pharmacotherapy. Unstable COPD patients require additional resources to treat severe exacerbation episodes in hospital.

Maintenance treatment cost

Maintenance treatment involved routine general practitioner (GP) visits, spirometry tests to assess and manage disease, primary healthcare clinic facility fee, annual prophylactic vaccinations for influenza and pneumococcal disease and vaccine administration fees. Patients with less severe disease consulted with general practitioners annually, while severe disease required one additional visit annually to manage exacerbation episodes.

The NDoH Master Health Product List (NDoH, 2022) provided cost information for the relevant resources and treatment required. Unit and daily costs were calculated by dividing the price per pack by the number of units per pack. Administration of influenza and pneumococcal vaccines are recommended once annually; hence the unit cost equalled the annual cost per patient. A conservative approach was taken to estimate resource use in the public sector. In instances where more than one vaccine brand or treatment option was listed on EML, the unit price for the less costly alternative was used.

Intervention cost

Therapeutic intervention costs in the private and public sectors were compared to determine the difference in cost between sectors. The difference in ZAR (Zuid-Afrikaanse Rand) was used to calculate the percentage reduction applied to single exit prices (CMS Price Committee, 2022; NDoH, 2022) to arrive at a proposed price for the public sector. The average percentage reduction was calculated for each treatment class already included on the Essential Medicines List (EML). The average reduction was used as a benchmark to estimate the proposed price for interventions not yet included on the EML.

Dosing was assumed as per the manufacturer package inserts and guideline recommendations. The high dose of Indacaterol (300μg) was not yet available in South Africa (SA) but included, to enable comparison with the high dose of Tiotropium. The price assumed was double that of the 150μg registered in SA. Estimation of intervention costs proved challenging, since multiple contextual factors (competitor landscape and other factors) are usually considered to inform price setting for newly launched therapies. The

intervention cost was included in the sensitivity analysis for this reason, to assess how it may impact on cost-effectiveness results.

Exacerbation and hospitalisation costs

Appropriate treatment duration and dosing recommendations from the guidelines were considered for calculation of costs incurred to treat exacerbations. Resources used during exacerbation episodes include antibiotics, rescue therapy (short-acting bronchodilators) and oral or systemic corticosteroids. The NDoH Essential Medicines List and Master Health Product List (National Department of Health, 2020; NDoH, 2022) provided details of treatments approved and procured for use in the public sector.

Resource unit costs were calculated and multiplied by the quantity of units required per day and the number of days prescribed, to estimate the cost per episode in a bottom-up approach. The NDoH Uniform patient fee schedule (UPFS) dated 01 April 2021 (NDoH, 2021a) , provided unit costs as the total cost per day in hospital and distinguishes fees according to the type of ward (general ward or intensive care unit). A conservative approach of 1-day stay in a general ward was assumed for non-severe exacerbations and 2-days general ward stay plus 1-day in intensive care unit (ICU) for severe exacerbations.

Table 3.4 Resource use and Cost

Maintenance cost (annual)

Disease stage	Mean	Distribution	Description	Source
Mild	R639,18	Gamma	General practitioner consultation cost	National Department Of Health (NDoH) Master Health Product List (MHPL) (2022)
Moderate	R690,18	Gamma	Influenza and Pneumococcal vaccine costs Vaccine administration costs	
Severe	R1 014,18	Gamma	Diagnostic test costs (spirometry) Outpatient clinic facility costs	National Department Of Health (NDoH) Uniform patient fee schedule (UPFS) (2021)
Very Severe	R1 047,18	Gamma	(All of the above applicable for all disease stages, in varying quantities)	

Total Exacerbation cost (per episode)

Exacerbation type	Mean	Distribution	Description	Source
Non-severe Exacerbation	R1 350,86	Gamma	Diagnostic tests, Antibiotics, Steroids, Short-acting bronchodilators, Hospital Costs	NDoH MHPL (2022)
Severe Exacerbation	R7 283,56	Gamma	Diagnostic tests, Antibiotics, Steroids, Short-acting bronchodilators, Hospital Costs	NDoH MHPL (2022)

Intervention cost (annual)

Intervention	Mean	Distribution	Description	Source
TIO18	R3 356,48	Gamma	Annual Intervention drug cost: Tiotropium	Council for Medical Schemes-Medicine Price Registry (2022)
IND150	R2 058,82	Gamma	Annual Intervention drug cost: Indacaterol 150	
IND300	R4 117,65	Gamma	Annual Intervention drug cost: Indacaterol 300	NDoH MHPL (2022)
SALM50	R2 505,48	Gamma	Annual Intervention drug cost: Salmeterol 50	

TIO18: Tiotropium 18 **IND150:** Indacaterol 150 **IND300:** Indacaterol 300 **SALM50:** Salmeterol 50

3.6.4 Valuation of Health Outcomes

Quality adjusted life years (QALYs) were used as the measure of health benefit. QALYs were calculated as the sum of the total health utilities derived from each of the four health states through which a patient transitions, minus the disutilities that resulted from exacerbation episodes (either severe or non-severe). Utilities and disutilities (Table 3.5 and 3.6) were obtained from published literature (Price *et al.*, 2013).

Table 3.5 Utility values

Disease state	Utility Value	SE	Distribution	Description	Source
Mild	0,8200	0,0820	Beta	Utility Value for Mild COPD	Price et al., 2013
Moderate	0,8000	0,0800	Beta	Utility Value for Moderate COPD	
Severe	0,7700	0,0770	Beta	Utility Value for Severe COPD	
Very Severe	0,7400	0,0740	Beta	Utility Value for Very Severe COPD	

Table 3.6 Disutility by Exacerbation type

Exacerbation Type	Disutility Value	SE	Distribution	Description	Source
Non-severe Exacerbation	0,0100	0,0010	Beta	Utility decrement for Non-severe exacerbation	Price et al., 2013
Severe Exacerbation	0,0420	0,0042	Beta	Utility decrement for Severe exacerbation	

3.7 Model assumptions

The model assumed a patient remains in one specific health state during an annual cycle, whereafter they either continue to stay or move to a different health state at the end of the cycle. Based on the clinical trials' outcomes, the initial improvement in lung function that occur within the first year precedes a uniform decline that continues throughout the remaining life time (Price *et al.*, 2013).

Due to a lack of data, the probability of death was assumed to be the same for all intervention arms. Patients were furthermore assumed to experience only one exacerbation during any given cycle. The model assumed a conservative hospital length of stay of 1-day in a general ward for non-severe exacerbations and 3-days (2-days in a general ward and 1-day in intensive care) for severe episodes.

3.8 Time Horizon

Similar to the study by Price et al., 2013, a 3-year time horizon was used for the base case analysis. This time frame considered the public sector tender renewal period for selection of essential medicines, which occurs every 2-3 years. Based on the life expectancy for COPD patients, a 10-year (intermediary term) and lifetime time horizons were also explored to capture costs and effects beyond the initial limited time frame. This was of particular importance because prior studies demonstrated longer time horizons improved cost-effectiveness. Extrapolation over longer periods allowed for more adequate capture of health consequences and costs that resulted from different interventions used (Price *et al.*, 2013).

3.9 Discounting

A discounting rate of 5% was used for future costs and health benefits, as per recommendation by the SA National Department of Health (NDoH, 2021b). The discounting rate was applied from the second year of the analysis.

3.10 Data Analysis and Statistical Methods

A Markov model was constructed to estimate total health benefits (QALYs) and total costs for each intervention under investigation, to determine the incremental cost-utility ratios (ICURs). Transition probabilities for the different disease severity states and exacerbation probabilities were used to calculate total QALYs and LYs gained for each treatment arm. Health utilities were summed for all four disease states and disutilities that resulted from exacerbations were subtracted to estimate total number of QALYs.

The total cost per annum was estimated as the sum of costs incurred for maintenance treatment, interventions used and exacerbation management. The ICUR (cost per QALY gained) was calculated by dividing incremental costs by QALYs. The resulting ICURs were used to consider whether Tiotropium was cost-effective relative to LABAs.

A probabilistic sensitivity analysis (PSA) was performed with 1000 simulation. The PSA explored multiple probability distributions for key model parameters, to assess uncertainty pertaining to ICUR estimates. A beta distribution was used for health state utilities and exacerbation disutilities and a gamma distributions for cost estimates. A cost-effectiveness scatterplot was used to plot ICURs for each of the simulations. A cost-effectiveness plane informed whether the new intervention was cost-effective, based on where on the 4 quadrants most of the observations appeared (right side: cost-effective and bottom right: dominant). Results were also depicted on a cost-effectiveness acceptability curve (CEAC), to investigate the probability of the new intervention being cost-effective *relative to* different willingness to pay (WTP) thresholds explored.

A one-way sensitivity analysis furthermore assessed how changes in key parameter values impacted on cost-effectiveness results (ICURs). Parameters of interest were the model time horizon, cost of new intervention, disease state utilities and severe exacerbation costs and disutilities. Results of the assessment were displayed in a Tornado diagram to illustrate which of the parameters model results were most sensitive to, to ascertain which had the highest impact on cost-effectiveness. A 40% variation in the cost of the new intervention was also explored in a scenario analysis, to investigate the impact of a change in price on cost-effectiveness.

3.11 Ethics waiver approval

No direct or indirect contact was made with human participants to conduct the analysis. The analysis also did not involve collection or processing of personal identifiable patient information, which mandates written patient consent. Ethics waiver was obtained in 2020 from the Wits ethics committee before collection of data commenced (Ref. no: W-CBP-200622-01) (Appendix F).

Chapter 4 - Results

4.1 Introduction

In this section, results are presented for a cost-utility analysis that compared Tiotropium 18ug O/D (once-daily) with LAMAs Indacaterol 150ug, -300ug O/D and Salmeterol 50ug B/D (twice-daily) in the management of COPD. The average total costs and quality adjusted life years (QALYs) per annum are reported in Table 4.1. Incremental cost-utility ratios (ICURs) for a 1000 simulations performed in a probabilistic sensitivity analysis are presented on a cost -effectiveness plane (Figure 4.1), to examine intervention cost-effectiveness in the South African public sector.

ICURs are also presented in a cost-effectiveness acceptability curve (Figure 4.2), to determine what proportion of iterations are cost-effective (below the curve) at different willingness to pay threshold values. Uncertainty with regard to the influence of key parameters in the model was assessed in a deterministic sensitivity analysis, as reported in the Tornado diagram (Figure 4.3).

4.2 Cost and Incremental Cost-Utility Ratio (ICUR)

Tiotropium 18μg O/D versus Indacaterol 150μg O/D (once-daily)

In the 3-year analysis with Indacaterol 150μg once-daily as the comparator, the use of Tiotropium resulted in +0.002 (positive) incremental QALYs, at an additional average cost of R3059 per patient per annum (pppa). This yielded an ICUR of R1 352 255 per QALY gained. The total estimated annual cost for the Tiotropium arm was R10 375 per patient.

Incremental QALYs slightly increased to +0.013 when extrapolated over a 10-year time horizon, while the incremental cost more than doubled to R7230 pppa. The ICUR improved notably to less than half the initial value when the longer time range was assessed. The resulting ICUR was R564 787 per QALY over a 10-year and R418 498 per QALY over a lifetime time horizon. The latter resulted in +0.024 incremental QALYs and R10 216 incremental cost pppa.

Tiotropium 18μg O/D versus Indacaterol 300μg O/D (once-daily)

The 3-year analysis for Tiotropium versus Indacaterol 300μg resulted in a positive net benefit of +0.011 incremental QALYs and a cost saving of R2062 per patient in favour of Tiotropium.

Over the 10-year and lifetime time horizons, Tiotropium again produced positive net QALYs (+0.026 and +0.038 respectively) and a cost reduction of R4827 and R6726 pppa respectively. Analyses for all time horizons yielded negative ICURs, consistently indicative of cost-effectiveness and dominance in favour of Tiotropium.

Tiotropium 18μg O/D versus Salmeterol 50μg B/D (twice-daily)

In the 3- and 10-year comparison with Salmeterol 50μg, Tiotropium 18μg once-daily resulted in -0.009 and -0.012 (negative) incremental QALYs and R2184 and R4996 incremental average cost pppa. Tiotropium was dominated by Salmeterol 50μg in both analyses.

By contrast, Tiotropium resulted in +0.006 (positive) incremental QALYs over a lifetime time horizon. The incremental cost increased to R6890 and yielded an ICUR of R1 237 233 per QALY gained. Results are summarized in Table 4.1.

Table 4.1 Results

Scenario 1 3y Time Horizon

Tiotropium 18			Indacaterol 150			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	1,99	R10 375	8,74	1,99	R7 316	0,01	0,002	R3 059	R1 352 254

Tiotropium 18			Indacaterol 300			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	1,99	R10 375	8,73	1,98	R12 436	0,02	0,011	-R2 062	Dominant

Tiotropium 18			Salmeterol 50			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	1,99	R10 375	8,75	2,00	R8 190	0,00	-0,009	R2 184	Dominated

LY: Life Years **QALYs:** Quality adjusted Life Years **ICER:** Incremental cost-effectiveness ratio in ZAR/QALY

Scenario 2 10y Time Horizon

Tiotropium 18			Indacaterol 150			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	4,79	R25 498	8,74	4,78	R18 268	0,01	0,013	R7 230	R564 787

Tiotropium 18			Indacaterol 300			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	4,79	R25 498	8,73	4,77	R30 324	0,02	0,026	-R4 827	Dominant

Tiotropium 18			Salmeterol 50			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	4,79	R25 498	8,75	4,80	R20 502	0,00	-0,012	R4 996	Dominated

LY: Life Years **QALYs:** Quality adjusted Life Years **ICER:** Incremental cost-effectiveness ratio in ZAR/QALY

Scenario 3 Lifetime Time Horizon

Tiotropium 18			Indacaterol 150			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	6,79	R36 353	8,74	6,77	R26 137	0,01	0,024	R10 216	R418 498

Tiotropium 18			Indacaterol 300			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	6,79	R36 353	8,73	6,76	R43 079	0,02	0,038	-R6 726	Dominant

Tiotropium 18			Salmeterol 50			Incremental			Estimated
LYs	*QALYs*	*Cost*	*LYs*	*QALYs*	*Cost*	*LYs*	***QALYs***	***Cost (ZAR)***	***ICUR***
8,75	6,79	R36 353	8,75	6,79	R29 462	0,00	0,006	R6 890	R1 237 233

LY: Life Years **QALYs:** Quality adjusted Life Years **ICER:** Incremental cost-effectiveness ratio in ZAR/QALY

4.3 Sensitivity Analysis

4.3.1 Probabilistic Sensitivity Analysis (PSA)

Different willingness to pay (WTP) thresholds were explored to determine the probability of Tiotropium being cost-effective when compared with the long-acting beta agonists (LABAs). The threshold that local decisionmakers in South Africa (SA) would consider is currently estimated at R38 500. This value was obtained from a local study conducted by Edoka et al., 2021. The mean ICUR for 1000 iterations was used to explore the probability of it appearing below the defined WTP thresholds, which would imply cost-effectiveness for Tiotropium. These probabilities are graphically represented in a cost-effectiveness acceptability curve (Figure 4.2).

Tiotropium 18μg versus Indacaterol 150μg

All iterations appeared in the right quadrant of the cost-effectiveness plane, indicating Tiotropium produced greater health effects (QALYs on the x-axis). Majority of iterations were in the North-East quadrant, implying higher costs (y-axis) for Tiotropium. The smaller proportion in the South-East quadrant indicated Tiotropium dominated Indacaterol 150μg (Figure 4.1).

At the willingness to pay (WTP) threshold value of R10 000, R20 000 and R30 000 per QALY gained, Tiotropium demonstrated approximately 40%, 42% and 43% respective probabilities of being cost-effective compared to Indacaterol 150μg. Tiotropium appeared to be more cost-effective than Indacaterol 150μg when the WTP threshold exceeded R80 000 per QALY gained. Below this value, Indacaterol had a higher probability of being cost-effective. The resulting ICUR of R1 352 255 per QALY gained in the 3-year analysis was substantially above the locally estimated WTP threshold of R38 500 and therefore likely to be rejected.

Tiotropium 18μg versus Indacaterol 300μg

Most iterations were concentrated on the right side (North-East and South-East quadrants) of the plane (Figure 4.1). The spread suggested Tiotropium was predominantly cost-effective and dominating. Only a few iterations appeared North-West, where Indacaterol dominated. For the threshold values explored (R10 000, R20 000 and R30 000), Tiotropium demonstrated 58%, 59% and 60% probability of being cost-effective at the respective values.

Tiotropium 18μg versus Salmeterol 50μg

A greater proportion of iterations appeared in the North-West quadrant. Based on this distribution, Tiotropium was more costly but resulted in less health effects (QALYs) and therefore predominantly dominated by Salmeterol (Figure 4.1).

Tiotropium demonstrated in 48%, 46% and 44% of the iterations the probability of being cost-effective at the R10 000, R20 000 and R30 000 respective WTP thresholds. Salmeterol was preferred and mostly dominating (flat CEAC). Salmeterol showed 48%, 49% and 51% probability of being cost-effective at the WTP threshold of R10 000, R20 000 and R30 000 respectively.

For a threshold value of R40 000 (slightly above the SA WTP estimation), Tiotropium demonstrated a 44%, 61% and 44% probability of being cost-effective in the comparison with Indacaterol (150μg and 300μg) and Salmeterol respectively. In all three comparisons, only a small proportion of iterations appeared below the set WTP threshold of R38 500 per QALY gained. Tiotropium was therefore unlikely to be cost-effective at the proposed price.

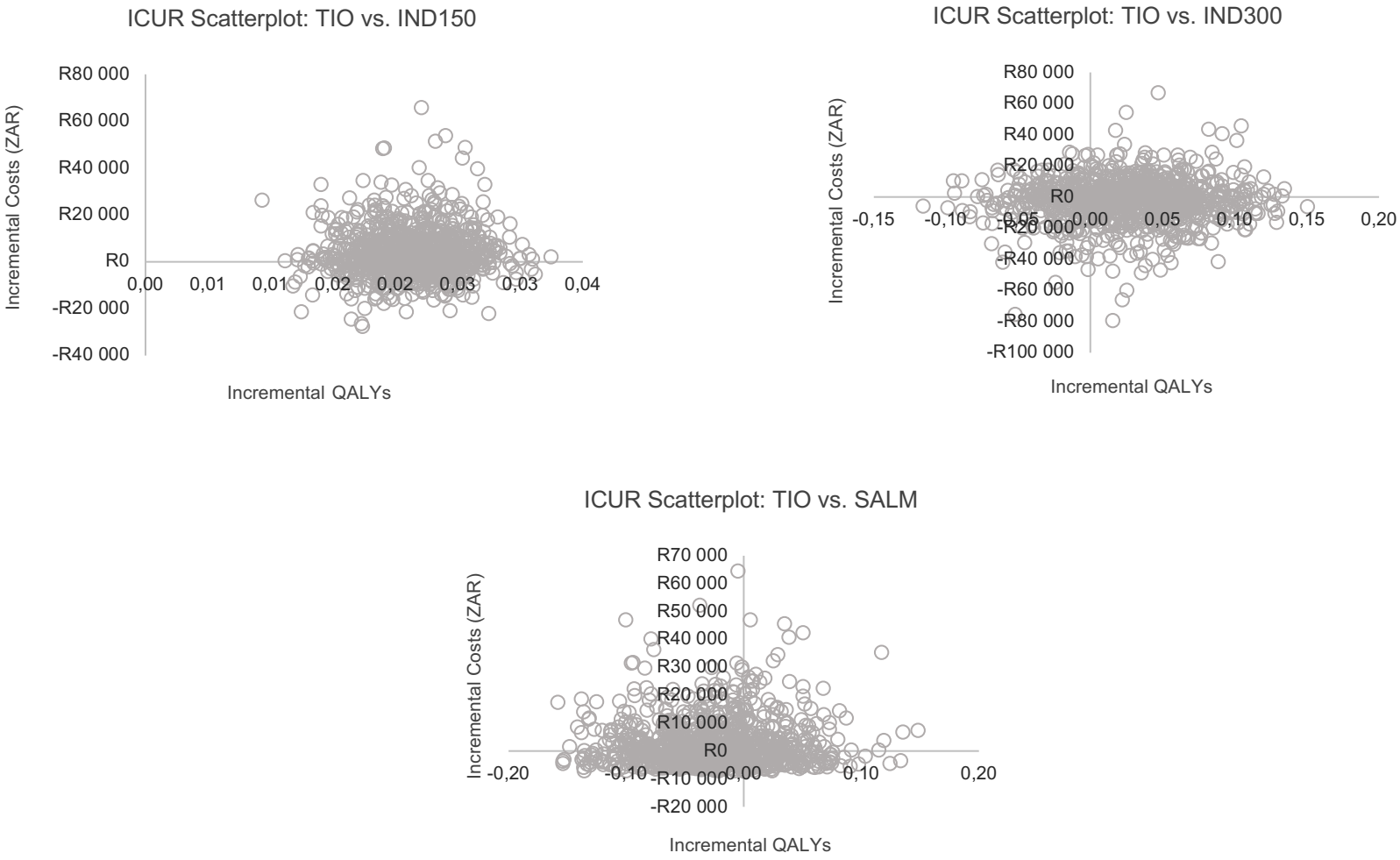
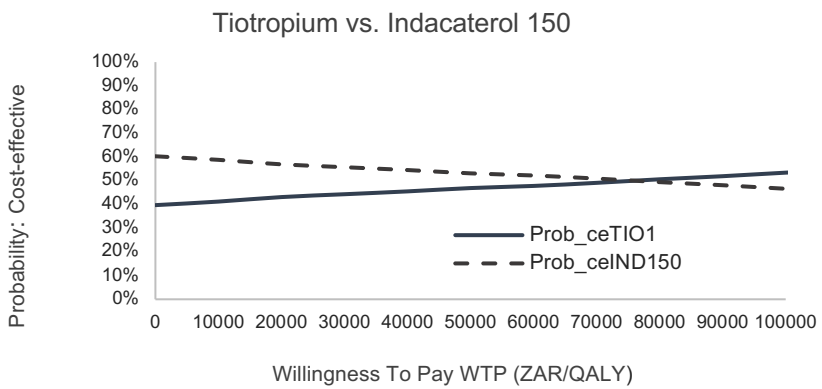
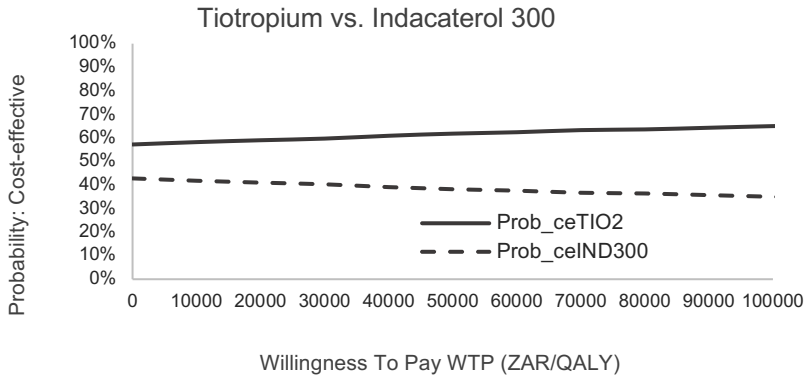


Figure 4.1 ICUR Scatterplots – Cost-Effectiveness Planes





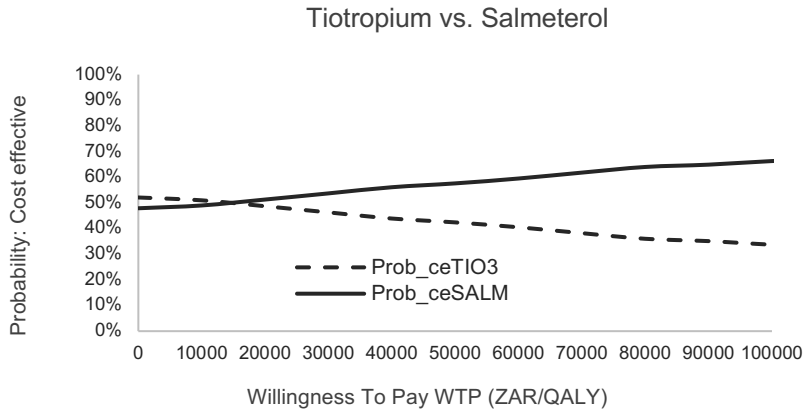


Figure 4.2 Cost-Effectiveness Acceptability Curves (CEACs)

4.3.2 Deterministic Sensitivity Analysis

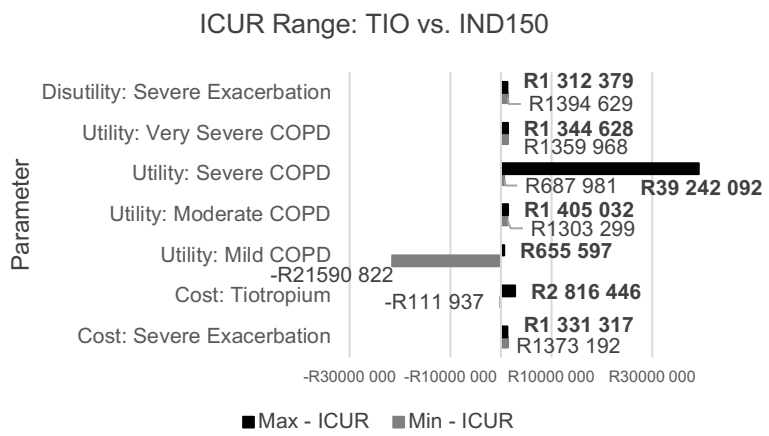
The deterministic sensitivity analysis explored lower and upper bound variance scenarios for key parameters, to determine how they impact on cost-effectiveness results. These parameters were varied one at a time, to calculate the corresponding incremental cost-utility ratio (ICUR) for each scenario. The range represented absolute values of the difference between the upper (maximum) and lower (minimum) bound. Parameters with the greatest difference in values indicated which were most impactful. The greatest variance between upper and lower bound values thus indicated which parameters results were most sensitive to.

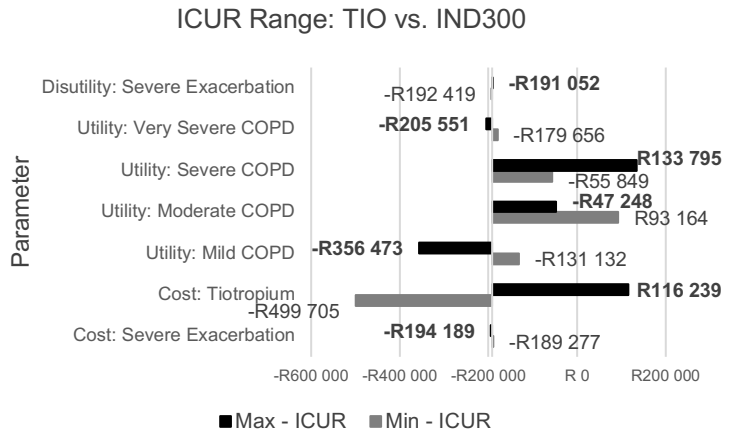
A Tornado diagram (Figure 4.3) graphically depicts the analyses results, with a central vertical line representing the base case (initial) ICUR values. Parameters that were varied included health utilities for all four disease severity states, disutilities and costs associated with severe exacerbations and new intervention acquisition costs. In the comparison with Indacaterol 150μg, the disease state utility values for severe and mild COPD had the greatest impact on results. Changes in these variables notably changed the ICURs.

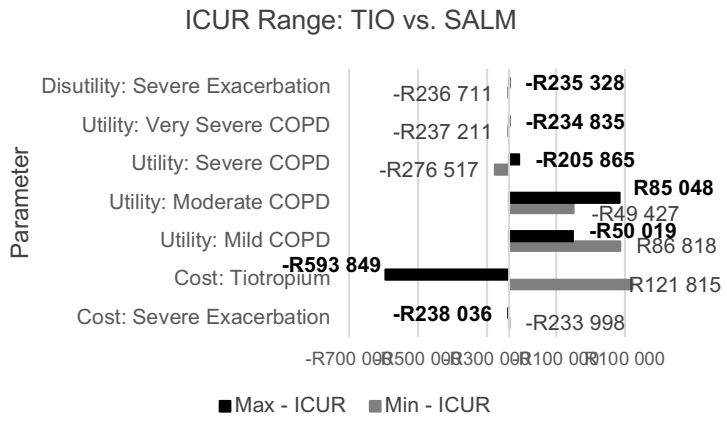
The new intervention cost was the most influential parameter in both comparisons with Indacaterol 300μg and Salmeterol. The utility value for mild COPD had the second largest impact on results in all comparisons. In the exploration between Tiotropium and Indacaterol 150μg, the ICUR increased substantially for the upper bound (maximum) utility value scenario for severe COPD (↑10%), lower bound (minimum) utility for mild COPD (↓10%) and upper bound value for Tiotropium intervention cost (↑40%).

In addition to investigating how results would be impacted by a Tiotropium price reduction, the analysis aimed to ascertain the maximum cost at which it will be cost-effective and more likely to be considered by the payor. This was based on the impact of the intervention price shown on both total cost and cost-effectiveness. A 40% reduction in the price of Tiotropium reduced the mean annual intervention cost per patient (pppa) from R3356.48 to R2013.89, while a 40% increase translated to R4699.07 pppa.

In the comparison with Indacaterol 150μg, the ICUR increased significantly from R1 352 254 to R2 816 446 with a 40% intervention price increase. When a 40% price decrease was effected, Tiotropium resulted in positive net health effects (QALYs) and cost savings of R253 and R5 374 respectively and dominated both Indacaterol 150μg and 300μg. When compared with Indacaterol 150μg, a 29% reduction in total costs for the Tiotropium arm produced an ICUR on par with the estimated willingness to pay threshold of R38 500/QALY. A 24% total cost reduction would produce the same outcome for the Salmeterol comparison.







Utility Variances

Min values (Base case value **-**10%):

- Utility values for Mild to Very Severe COPD
- Disutility-Severe Exacerbations

Min values (Base case value **+** 40%):

- Intervention cost: TIO
- Severe exacerbation cost

Max values (Base case value **+**10%):

- Utility values for Mild to Very Severe COPD
- Disutility-Severe Exacerbations

Max values (Base case value **+**40%):

- Intervention cost: TIO
- Severe exacerbation cost

Figure 4.3 Tornado Diagrams

4.4 Model Validation

The analysis adopted an approach similar to prior published evaluations through use of current resource use guidelines and local country-specific costing data, which is representative of the local public sector setting. The model employed the approach by Price et al., 2013 in adopting effectiveness data (health state-, mortality transition probabilities and utility estimates) from previously validated published randomized trials (Price *et al.*, 2013). The model structure, input parameters, assumptions and natural history of the disease are also aligned with the approaches followed in prior evaluations (García Ruiz, Leiva Fernández and Martos Crespo, 2005; Oba, 2007; Price *et al.*, 2011, 2013; Guillermo Ariza *et al.*, 2012).

Disease severity stage distribution- and disease progression/ transitioning patterns that were produced in the model were very similar to that observed in real world COPD populations. The model cohort was mostly concentrated in the moderate COPD disease stage. The proportion of patients and the probability of being in the very severe COPD stage during any given cycle was overall low and consistently lower than the severe disease stage. Results from prior clinical trials and analysis reflected a comparable distribution and trend (Hoogendoorn *et al.*, 2005, 2006; Bednarek *et al.*, 2008; Price *et al.*, 2011; Montes de Oca *et al.*, 2017).

The BOLD study results furthermore corroborated in demonstrating that moderate COPD was also the most prevalent stage for the local population in Cape Town (Abdool-Gaffar *et al.*, 2019). The study by Price et al., 2011 similarly reported the baseline clinical trials population distribution as 1.4%, 36.7%, 50.2% and 11.7% for mild, moderate, severe and very severe COPD stages, but showed both moderate and severe COPD had a higher prevalence (Price *et al.*, 2011).

Our model also showed an increase in mortality rates with an ageing population. The increasing probability of death with age is similar to incidences reported in prior studies (Rutten-van Mölken, Maureen P. M. H. Oostenbrink, Miravitlles and Monz, 2007).

The exacerbation probability distribution across different disease stages for the model population corroborated with the distribution and incidence of events in the trial reported by Price et al., 2011. The highest probabilities and the highest number of events occurred during the severe COPD disease stage. The low probabilities and low number of events during the very severe disease stage for both may potentially be attributed to the low probability of being in that state at any given time and the higher mortality rates observed.

Chapter 5 - Discussion

The analysis purposed to assess the cost-effectiveness of Tiotropium as COPD maintenance therapy in the local setting, compared with old and new LABA therapies Salmeterol (usual care) and Indacaterol. While the effectiveness of long-acting bronchodilators in the treatment of COPD is widely acknowledged, the need for more cost-effective and rationale use of scarce healthcare resources is equally important. In view of multiple competing healthcare needs and priorities, more efficiency resource allocation/spent and consideration for most appropriate, effective and affordable therapies are imperative. Disease progression can be retarded and events avoided with optimal therapy. Prompt diagnosis and targeted therapies are important to improve health outcomes.

The approach and methods used in the analysis were overall comparable with prior published evaluations (Price *et al.*, 2011, 2013; Hoogendoorn *et al.*, 2013). To my knowledge, this analysis is one of the first in attempting to investigate cost-effectiveness of Tiotropium relative to a recently published local willingness to pay threshold that was determined for South Africa (Edoka and Stacey, 2020). This study also allowed comparison of two novel, once-daily potent long-acting bronchodilators from different drug classes. The analysis furthermore aspired to value resource consumption for COPD management through use of local unit costs within the South African public sector, in a bottom-up approach.

In the 3-year analysis comparing Indacaterol 150μg and 300μg, Tiotropium was more effective in producing slightly more QALYs (+0.002 and +0.011) but less effective with negative incremental QALYs in the comparison with Salmeterol (-0.009). In the comparison with Indacaterol 150μg, the modest incremental health effects (QALYs) and much higher costs incurred (R3059 pppa) yielded an inflated incremental cost-utility ratio (ICUR) of R1 352 254. If decision makers accept the current estimated willingness to pay threshold of R38 500 as the set maximum, the ICUR would be significantly above the threshold and Tiotropium would not be considered cost-effective.

In the Indacaterol 300μg comparison, Tiotropium resulted in annual cost savings of R2062 and consequently dominated. On the contrary, Tiotropium was dominated when compared to Salmeterol as a result of much higher costs incurred and less health effects (QALYs) produced.

Results for this analysis corroborated with findings from Price et. al., in demonstrating Indacaterol 150μg was more cost-effective than Tiotropium. Their analysis however found that both high and low dose strengths of Indacaterol (150μg and 300μg) dominated Tiotropium, while Tiotropium dominated the Indacaterol high dose in our analysis (Price *et al.*, 2013). This could in part be explained by the price parity (same price) observed between the low and high doses of Indacaterol in the United Kingdom, a scenario extremely unlike for our context.

For the 10-year analysis, Tiotropium resulted in positive health gains in the comparison with both strengths of Indacaterol but not with Salmeterol where it was dominated. Tiotropium dominated Indacaterol 300μg and yielded cost savings of R4827 per annum. This was attributed to a much higher acquisition cost for Indacaterol 300μg. In the South African setting the treatment costs for Indacaterol 300μg and Tiotropium were very high, compared to other alternatives.

The incremental QALYs and -costs accrued through intervention use are more adequately captured in the application of longer time horizons. The ICURs were found to improve over longer time horizons. This finding corroborated with the results from prior analyses (Price *et al.*, 2013). When compared with the 3-year analysis, the ICUR for the Indacaterol 150μg comparison was reduced to less than a third when extrapolated to a lifetime time horizon. The ICUR produced when Tiotropium was compared to Indacaterol 300μg remained negative and dominating in favour of Tiotropium, regardless of the time frame applied. In the Salmeterol comparison, Tiotropium resulted in positive incremental QALYs only for the lifetime analysis, while Salmeterol dominated over the shorter time horizons.

Both Indacaterol 150μg and Salmeterol had a higher probability of being cost-effective (relative to Tiotropium), for all willingness to pay thresholds explored (Figure 4.2). The price of Tiotropium was higher than LABAs, assisting dominance of Salmeterol over the 3- and 10-year time horizons. The incremental cost-utility ratio (ICUR) for the 3-year analysis between Tiotropium and Indacaterol 150μg was substantially higher compared to the analysis that was done in the United Kingdom (UK) (Price *et al.*, 2013). This can in part be attributed to the higher price for Tiotropium in South Africa, which resulted in a greater difference in treatment cost between interventions.

The UK price difference between Tiotropium and Indacaterol 150μg was approximately 8%, whereas for this setting the difference is 63%. Inference can be drawn about the notable impact of the price of the intervention on cost-effectiveness outcomes. This finding was substantiated by the impact that the price variation scenarios for Tiotropium demonstrated in the deterministic sensitivity analysis. Effecting a 40% Tiotropium price increase markedly increased the ICUR to double the initial base case value observed, whereas a 40% price decrease favourably reduced the ICUR almost 12-fold (Figure 4.3).

In view of the estimated willingness to pay threshold for South Africa (which is substantially lower than values accepted in developed countries), the ICURs remained relatively high and did not suggest cost-effectiveness for Tiotropium despite the 40% price reduction scenario. In the Price et al., 2013 study, Tiotropium also remained dominated by Indacaterol 150μg regardless of the different scenarios explored (Price *et al.*, 2013).

Tiotropium is not yet available on the public sector Essential Medicines List (National Department of Health, 2019). The price assumed for Tiotropium was an estimation based on the average percentage ‘discount’ applied for other interventions already included on the list. Results suggested the estimated price for Tiotropium may require a considerable reduction to increase the likelihood of being a cost-effective alternative for consideration in the public sector. Indacaterol 150μg, at the current price, may be a more feasible option to consider since it offers both a less costly alternative with novelty and potency combined.

The price of Tiotropium, relative to comparators, varied greatly across countries. In the cost-effectiveness analysis conducted by Gani et al., 2010, the intervention cost for Tiotropium was lower than Salmeterol. This resulted in cost savings and dominance in favour of Tiotropium (Gani *et al.*, 2010). In the study by Hoogendoorn et al., 2012, the price for Tiotropium was almost 50% higher than Salmeterol, which resulted in higher total costs. Based on the reduction in exacerbation costs observed in the Tiotropium arm, the higher total cost was completely offset and the results suggested Tiotropium was the cost-effective alternative over a 5-year time horizon (Hoogendoorn *et al.*, 2012).

Our analysis reinforced the notable impact of intervention cost on cost-effectiveness observed in prior published models. Although our analysis demonstrated exacerbation benefits for Tiotropium, it was not sufficient to overturn its higher intervention cost to achieve the certainty of cost-effectiveness as was seen with prior analyses (Oostenbrink *et al.*, 2005; Oba, 2007; Gani *et al.*, 2010; Hoogendoorn *et al.*, 2012).

A greater price difference between interventions in the South African setting may explain why the exacerbation benefits of Tiotropium did not overturn the higher intervention costs in this analysis, to sway results in favour of Tiotropium. The analysis by Oostenbrink et al., 2005 also found Tiotropium was more expensive than Salmeterol. Tiotropium produced modest incremental health benefits (quality adjusted life months), but yielded ICERs that were predominantly cost-effective and dominant in the analysis that explored the costs per exacerbation avoided (Oostenbrink *et al.*, 2005).

Oba, 2007 found Tiotropium produced net positive health effects (QALYs) and less exacerbation days in hospital, compared to Salmeterol. The result was a favorable low ICER suggesting cost-effectiveness for Tiotropium. Their study employed a different approach to factored St. George's Respiratory Questionnaire scores to estimate total QALYs gained for each comparator (Oba, 2007).

The deterministic sensitivity analysis examined model assumptions and parameter uncertainty. The analysis explored a 10% decrease and increase in base case health utilities. A change in utilities for mild COPD had the greatest impact on the ICUR (shown in Figure 4.3). Mild COPD represents the healthiest attainable disease state, where the highest level of utility and quality of life can be derived. It would therefore justify the substantial influence of mild COPD on cost-effectiveness results and outcomes that was observed in the analysis. Cope et al., 2013 also reported that '' Treatment effect estimates were most sensitive to adjustment for disease severity'' (Cope *et al.*, 2013).

The model structure, inputs, approach and results were overall comparable and consistent with prior published papers in showing lung function improvement and exacerbation reductions were the key parameters that resulted in more health effects (QALYs) and improved cost-effectiveness (Oostenbrink *et al.*, 2005; Hoogendoorn *et al.*, 2013; Price *et al.*, 2013). Intervention costs are vastly different across different countries. The variation in incremental intervention costs (between-comparator price *differences)* is subject to influences from various contextual factors. The magnitude of the price/cost differences impacted on cost-effectiveness results (ICURs), which explains the differences in outcomes for different countries.

Limitations

In conducting the analysis, some limitations were encountered that may impact on model estimates and conclusions drawn.

Due to a lack of real world effectiveness evidence that reflect the local population and setting, effect estimates for the model was sourced from published trials. Despite a thorough systematic literature search, effectiveness inputs were not available for South Africa. Health state utilities and exacerbation disutilities from developed countries do not necessarily reflect how patients in low-middle income countries value health. Further differences may also exist between the public and private sectors, based on different

levels of access to health services and resources. Socio-economic and cultural context may also influence patient experiences and valuation of their health status.

The generic EQ-5D scores used to generate health state utilities are not disease specific: hence low transferability but widely used in economic evaluations (Oba, 2007; Price et al., 2011, 2013). Real-world locally representative treatment effectiveness data may prove useful to accurately capture local experiences. This may be of great value to support rational decision making and selection of optimal COPD therapies in the public sector in future.

Not all available long-acting bronchodilator (LAB) therapies were considered for the analysis. Newer inhaler device types (slow mist inhalers) were excluded, based on higher costs. The use and cost of inhaled corticosteroids were also not considered but equally excluded for all treatment arms.

At the time of conducting the analysis, Indacaterol 300μg was not yet registered in South Africa. The proposed intervention cost was calculated based on the price available for the low dose. A lack of head-to-head trials limited the analysis to be selective with comparators and to use aggregated trials data from network meta-analyses. The trials, through indirect comparison, used similar criteria to determine relative effectiveness for active therapies versus placebo. Future local studies for inter- and intra-class comparisons may be of benefit.

The full range of treatment benefits, adverse events and impact of device type on treatment adherence were not explored and may underestimate cost-effectiveness. The focus was rather on parameters known to exert a key influence on cost-effectiveness results. In our analysis and the one conducted by Price et al., 2013, probabilities of death were differentiated according to disease severity only and not by treatment option. This presents an opportunity for more comprehensive future research to consider the impact of treatment-specific mortality and adverse events in the local setting.

As with other published models, the impact of comorbidities was not considered in the analysis. Elderly patients and those with comorbid respiratory conditions were predominantly excluded from prior studies. Patients were therefore not a true representation of what is observed in clinical practice with real-world populations. The risk for misclassification is furthermore eminent since other respiratory conditions such as asthma presents with symptoms very similar to COPD (i.e., exacerbations). A more pronounced concern for South Africa is the significant overlap of post-tuberculosis structural lung disease and emphysema (Allwood *et al.*, 2021).

The payor perspective employed in the model underestimate total expenditures associated with COPD management. Untreated patients and indirect costs such as productivity losses, travel and mortality costs were not considered. The perspective also excludes over-the-counter medicine use, home oxygen and private general practitioner visit costs incurred by patients through self-management. These potential additional expenses were equally excluded for all treatment arms. In a societal perspective, they may impact on total costs and cost-effectiveness if one intervention arm result in more resource use than the other.

A concern that may limit the accuracy of total costs estimation involves the approach to base hospital length of stay on the type of exacerbation only, not considering individual patient factors. Hospitalization due to severe exacerbations make out a substantial proportion of total COPD costs. The underlying causes of exacerbations influence its severity, which in turn impact on the length of hospital. While healthcare resource use estimations are based on treatment guidelines, utilization may vary by patient, facility, province, healthcare system and country. Future engagement with local clinical experts may better enable validation of true local resource utilization for reporting of more accurate estimates.

An inherent limitation with the design of Markov models is that they do not consider individual patient history, in this instance a history of events (exacerbations). The patient

history of exacerbations happens to be a critical predictor and risk factor for future exacerbations (Kim and Aaron, 2018).

Future studies

Costing studies within public sector hospitals are recommended to differentiate resource use and potential cost-savings associated with the different interventions, based on their exacerbation reduction effects. Funding for locally conducted head-to-head trials and surveys would also be useful to accurately record differential lung function improvement and exacerbation rates for each treatment, to enable generation of disease-specific utilities and disutilities for the local public sector population.

Chapter 6 - Conclusion

In the backdrop of a steady rise in COPD prevalence globally, the high burden of uncontrolled disease is also on the increase. Patient management through therapies endorsed by the latest treatment guidelines (as a replacement for usual care) can aid in the quest to have more patients adequately controlled. Treatment optimization and broader equitable access to effective therapies will improve quality of life for patients and ultimately enable attainment of the best possible health outcomes.

More severe stages of COPD make a greater demand on limited healthcare resources. It is therefore imperative to prioritize the delay of disease progression, avoid costly exacerbations and employ more efforts to mitigate the risks associated with uncontrolled disease.

Another key objective of equal importance is the need to procure more cost-effective therapies, to stretch limited healthcare budgets and maximize population health. Prudent selection of cost-effective interventions to improve care will translate into more efficient spent, that will ultimately allow more deserving patients better access to life-transforming therapies. The ideal maintenance therapy constitute one that offers maximum incremental health gains with the greatest cost savings benefit.

Tiotropium 18μg was assessed as a potential cost-effective maintenance therapy replacement for LABAs, to support sound rational decision making for COPD maintenance therapy selection in the public sector. Results from this analysis suggested Tiotropium was cost-effectiveness and dominating only in the comparison with the high dose of Indacaterol.

The intervention cost for Tiotropium was a key determinant of cost-effectiveness and produced ICURs substantially above the estimated willingness to pay threshold for South Africa. A substantial reduction in the higher intervention cost (at least 40% reduction of

the proposed price) should be considered in a future analysis to improve the likelihood of Tiotropium being cost-effective and to demonstrate potentially greater cost savings. Low dose Indacaterol at its current price appears to be a more suitable alternative for consideration versus usual care, based on its effectiveness and lower treatment cost compared to Tiotropium.

References

1. Abdool-Gaffar, M. S. *et al.* (2019) 'Management of chronic obstructive pulmonary disease—A position statement of the South African Thoracic Society: 2019 update', *Journal of Thoracic Disease*, 11(11), pp. 4408–4427. doi: 10.21037/jtd.2019.10.65.
2. Allwood, B. W. *et al.* (2018) 'Five-year follow-up of participants diagnosed with chronic airflow obstruction in a south african burden of obstructive lung disease (BOLD) survey', *South African Medical Journal*, 108(2), pp. 138–143. doi: 10.7196/SAMJ.2018.v108i2.12688.
3. Allwood, B. W. *et al.* (2021) 'Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge', *Respiration*, 100(8), pp. 751–763. doi: 10.1159/000512531.
4. Awokola, B. I. *et al.* (2022) 'Chronic obstructive pulmonary disease in sub-Saharan Africa', *International Journal of Tuberculosis and Lung Disease*, 26(3), pp. 232–242. doi: 10.5588/ijtld.21.0394.
5. Bednarek, M. *et al.* (2008) 'Prevalence, severity and underdiagnosis of COPD in the primary care setting', *Thorax*, 63(5), pp. 402–407. doi: 10.1136/thx.2007.085456.
6. Buist, A. S. *et al.* (2007) 'International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study', *Lancet*, 370(9589), pp. 741–750. doi: 10.1016/S0140-6736(07)61377-4.
7. Calzetta, L. *et al.* (2017) 'LABA/LAMA combination in copd: A meta-analysis on the duration of treatment', *European Respiratory Review*, 26(143), pp. 1–11. doi: 10.1183/16000617.0043-2016.
8. CMS (2020) *Industry Report 2020/202 1*. Pretoria. Available at: https://www.medicalschemes.co.za/industryreport2020/.
9. CMS Price Committee (2022) *Medicine Price Registry SEP*. Pretoria.
10. Cope, S. *et al.* (2013) 'Comparative efficacy of long-acting bronchodilators for C', *Respir Res.*, 14(1), p. 100.
11. Costa-Scharplatz, M. *et al.* (2015) 'Cost-Effectiveness of Glycopyrronium Bromide Compared with Tiotropium in Patients with Chronic Obstructive Pulmonary Disease in Sweden', *Applied Health Economics and Health Policy*, 13(6), pp. 637–645. doi: 10.1007/s40258-015-0193-2.
12. Council for Medical Schemes (2020) *MEDICAL SCHEMES INDUSTRY REPORT 2020*. Pretoria. Available at: https://www.medicalschemes.co.za/download/3611/industry-

report-2020-21/24593/cms_industry-report-2020_web.pdf.

13. Decramer, M. (2006) 'Tiotropium as essential maintenance therapy in COPD', *European Respiratory Review*, 15(99), pp. 51–57. doi: 10.1183/09059180.00009906.
14. Decramer, M. L. *et al.* (2013) 'Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): A randomised, blinded, parallel-group study', *The Lancet Respiratory Medicine*, 1(7), pp. 524–533. doi: 10.1016/S2213-2600(13)70158-9.
15. Diamant, Z., Brusselle, G. and Russell, R. E. (2018) 'Toward effective prescription of inhaled corticosteroids in chronic airway disease', *International Journal of COPD*, 13, pp. 3419–3424. doi: 10.2147/COPD.S174216.
16. Donohue, J. F. *et al.* (2010) 'Once-daily bronchodilators for chronic obstructive pulmonary disease: Indacaterol versus tiotropium', *American Journal of Respiratory and Critical Care Medicine*, 182(2), pp. 155–162. doi: 10.1164/rccm.200910-1500OC.
17. Donohue, J. F. *et al.* (2017) 'Comparative efficacy of long-acting β2-agonists as monotherapy for chronic obstructive pulmonary disease: A network meta-analysis', *International Journal of COPD*, 12, pp. 367–381. doi: 10.2147/COPD.S119908.
18. Edoka, I. P. and Stacey, N. K. (2020) 'Estimating a cost-effectiveness threshold for health care decision-making in South Africa', *Health Policy and Planning*, 35(5), pp. 546–555. doi: 10.1093/heapol/czz152.
19. Gani, R. *et al.* (2010) 'Economic analyses comparing tiotropium with ipratropium or salmeterol in UK patients with COPD', *Primary Care Respiratory Journal*. Primary Care Respiratory Society UK, 19(1), pp. 68–74. doi: 10.4104/pcrj.2010.00001.
20. García Ruiz, A. J., Leiva Fernández, F. and Martos Crespo, F. (2005) 'Cost-Effectiveness Analysis of Tiotropium Compared to Ipratropium and Salmeterol', *Archivos de Bronconeumología ((English Edition))*, 41(5), pp. 242–248. doi: 10.1016/s1579-2129(06)60217-6.
21. GOLD (2023) *GOLD-2023-ver-1.1-2Dec2022_WMV.pdf*. GOLD Science Committee. Available at: www.goldcopd.org.
22. GOLD committee (2020) *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2020 Report-GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE (GOLD)*, *Global Initiative for Chronic Obstructive Lung Disease*. Spain, Germany. Available at: https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf.

23. Guillermo Ariza, J. *et al.* (2012) 'The Cost-Effectiveness and Budget Impact of Introducing Indacaterol into the Colombian Health System', *Value in Health Regional Issues*. Elsevier, 1(2), pp. 165–171. doi: 10.1016/j.vhri.2012.09.003.
24. Hahn, B. *et al.* (2018) 'Rates of escalation to triple COPD therapy among incident users of LAMA and LAMA/LABA', *Respiratory Medicine*. Elsevier, 139(November 2017), pp. 65–71. doi: 10.1016/j.rmed.2018.04.014.
25. Halpin, D. M. G. *et al.* (2016) 'Effect of tiotropium on COPD exacerbations: A systematic review', *Respiratory Medicine*. Elsevier Ltd, 114, pp. 1–8. doi: 10.1016/j.rmed.2016.02.012.
26. Hogan, T. J., Geddes, R. and Gonzalez, E. R. (2003) 'An economic assessment of inhaled formoterol dry powder versus ipratropium bromide pressurized metered dose inhaler in the treatment of chronic obstructive pulmonary disease', *Clinical Therapeutics*, 25(1), pp. 285–297. doi: 10.1016/S0149-2918(03)90039-7.
27. Hoogendoorn, M. *et al.* (2005) 'A dynamic population model of disease progression in COPD', *European Respiratory Journal*, 26(2), pp. 223–233. doi: 10.1183/09031936.05.00122004.
28. Hoogendoorn, M. *et al.* (2006) 'Severity distribution of chronic obstructive pulmonary disease (COPD) in Dutch general practice', *Respiratory Medicine*, 100(1), pp. 83–86. doi: 10.1016/j.rmed.2005.04.004.
29. Hoogendoorn, M. *et al.* (2012) 'Which long-acting bronchodilator is most cost-effective for the treatment of COPD?', *Netherlands Journal of Medicine*, 70(8), pp. 357–364.
30. Hoogendoorn, M. *et al.* (2013) 'Cost-effectiveness of tiotropium versus salmeterol: The POET-COPD trial', *European Respiratory Journal*, 41(3), pp. 556–564. doi: 10.1183/09031936.00027212.
31. Horita, N. *et al.* (2017) 'Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD)', *Cochrane Database of Systematic Reviews*, 2017(2). doi: 10.1002/14651858.CD012066.pub2.
32. Karabis, A. *et al.* (2013) 'Comparative efficacy of aclidinium versus glycopyrronium and tiotropium, as maintenance treatment of moderate to severe COPD patients: A systematic review and network meta-analysis', *International Journal of COPD*, 8, pp. 405–423. doi: 10.2147/COPD.S48967.
33. Kim, V. and Aaron, S. D. (2018) 'What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement', *European Respiratory Journal*,

52(5). doi: 10.1183/13993003.01261-2018.

34. Kornmann, O. *et al.* (2011) 'Once-daily indacaterol versus twice-daily salmeterol for COPD: A placebo-controlled comparison', *European Respiratory Journal*, 37(2), pp. 273–279. doi: 10.1183/09031936.00045810.
35. Mammen, Manoj J. *et al.* (2020) 'Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease A Systematic Review and Meta-analysis in Support of the American Thoracic Society Clinical Practice Guideline', *Annals of the American Thoracic Society*, 17(9), pp. 1133–1143. doi: 10.1513/AnnalsATS.201912-915OC.
36. Mammen, M J *et al.* (2020) 'Dual LABA/LAMA therapy versus LABA or LAMA monotherapy for COPD: a systematic review and meta-analysis in support of the American Thoracic Society Clinical Practice Guideline', *Ann Am Thorac Soc*, 17(9), pp. 1133–1143.
37. Martinez, F. J. *et al.* (2016) 'Effect of roflumilast and inhaledcorticosteroid/long-acting b2-agonist on chronic obstructive pulmonary disease exacerbations (RE2SPOND): A randomized clinical trial', *American Journal of Respiratory and Critical Care Medicine*, 194(5), pp. 559–567. doi: 10.1164/rccm.201607-1349OC.
38. Montes de Oca, M. *et al.* (2017) 'Classification of COPD Patients According to ALAT and GOLD Staging Systems Using PUMA Study Data', *Archivos de Bronconeumologia*, 53(3), pp. 98–106. doi: 10.1016/j.arbr.2016.11.004.
39. National Department of Health (2019) *Standard Treatment Guidelines And Essential Medicines List for South Africa: Hospital Level 2012 Edition*.
40. National Department of Health (2020) 'Standard Treatment Guidelines And Essential Medicines List for South Africa: PHC'. South Africa.
41. NDoH (2021a) 'ANNEXURE_A1_UPFS_TARIFFS_01APRIL2021_FULL_PAYING'. Pretoria: NDoH.
42. NDoH (2021b) *ndohDRAFT_HTA-Methods-Guide_v1*. Pretoria. Available at: https://www.health.gov.za/wp-content/uploads/2021/09/DRAFT_HTA-Methods-Guide_v1.2_14Jun21_WORD-VERSION.docx.
43. NDoH (2022) *Current Master Health Product List, 1 August 2022*. Available at: https://www.health.gov.za/wp-content/uploads/2022/08/Current-Master-Health-Product-List-1-August-2022.xlsx.
44. NICE (2019) *Chronic obstructive pulmonary disease in over 16s: Diagnosis and management*, *Practice Nurse*. UK. Available at:

https://www.nice.org.uk/guidance/ng115/resources/chronic-obstructive-pulmonary-disease-in-over-16s-diagnosis-and-management-pdf-66141600098245.

45. Oba, Y. (2007) 'Cost-effectiveness of long-acting bronchodilators for chronic obstructive pulmonary disease', *Mayo Clinic Proceedings*, 82(5), pp. 575–582. doi: 10.4065/82.5.575.
46. Oba, Y. *et al.* (2018) 'Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis', *Cochrane Database of Systematic Reviews*, (12), pp. 1–439. Available at: https://doi.org/10.1002/14651858.CD012620.pub2.
47. Oba, Y., Sarva, S. T. and Dias, S. (2016) 'Efficacy and safety of long-acting β-agonist/long-acting muscarinic antagonist combinations in COPD: A network meta-analysis', *Thorax*, 71(1), pp. 15–25. doi: 10.1136/thoraxjnl-2014-206732.
48. Oostenbrink, J. B. *et al.* (2005) 'Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries', *Value in Health*, 8(1), pp. 32–46. doi: 10.1111/j.1524-4733.2005.03086.x.
49. Price, D. *et al.* (2011) 'Cost-utility analysis of indacaterol in Germany: A once-daily maintenance bronchodilator for patients with COPD', *Respiratory Medicine*, 105(11), pp. 1635–1647. doi: https://doi.org/10.1016/j.rmed.2011.06.005.
50. Price, D. *et al.* (2013) 'A UK-based cost-utility analysis of indacaterol, a once-daily maintenance bronchodilator for patients with COPD, using real world evidence on resource use', *Applied Health Economics and Health Policy*, 11(3), pp. 259–274. doi: 10.1007/s40258-013-0021-5.
51. Rodrigo, G. J. *et al.* (2017) 'LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis', *International journal of chronic obstructive pulmonary disease*. Dove Press, 12, p. 907.
52. Rutten-van Mölken, Maureen P. M. H. Oostenbrink, J. B., Miravitlles, M. and Monz, B. U. (2007) 'Modelling the 5-year cost effectiveness of tiotropium, salmeterol and ipratropium for the treatment of chronic obstructive pulmonary disease in Spain', *Eur J Health Econ*, 8, pp. 123–135. doi: 10.1007/s10198-007-0039-4.
53. Salvi, S. (2015) 'The silent epidemic of COPD in Africa', *The Lancet Global Health*. Salvi. Open Access article distributed under the terms of CC BY, 3(1), pp. e6–e7. doi: 10.1016/S2214-109X(14)70359-6.
54. StatsSA (2020) *Mortality and causes of death in South Africa: Findings from death notification 2017*, *Statistical release*. Pretoria. Available at:

www.statssa.gov.za,info@statssa.gov.za,Tel+27123108911.

55. Tariq, S. M. and Thomas, E. C. (2017) 'Maintenance therapy in COPD: Time to phase out ICS and switch to the new LAMA/LABA inhalers?', *International Journal of COPD*, 12, pp. 1877–1882. doi: 10.2147/COPD.S138006.
56. Vestbo, J. *et al.* (2004) 'The TORCH (TOwards a Revolution in COPD Health) survival study protocol', *European Respiratory Journal*, 24(2), pp. 206–210. doi: 10.1183/09031936.04.00120603.
57. de Villiers, K. (2021) 'Bridging the health inequality gap: an examination of South Africa's social innovation in health landscape', *Infectious Diseases of Poverty*. BioMed Central, 10(1), pp. 1–7. doi: 10.1186/s40249-021-00804-9.
58. Vogelmeier, C. *et al.* (2011) 'Tiotropium versus Salmeterol for the Prevention of Exacerbations of COPD', *New England Journal of Medicine*, 364(12), pp. 1093–1103. doi: 10.1056/NEJMoa1008378.
59. WHO (2022) *World Health Statistics, 2022*. Geneva. Available at: https://www.who.int/news/item/20-05-2022-world-health-statistics-2022.
60. Wu, M. F. *et al.* (2016) 'Post-inhaled corticosteroid pulmonary tuberculosis and pneumonia increases lung cancer in patients with COPD', *BMC Cancer*. BMC Cancer, 16(1), pp. 1–8. doi: 10.1186/s12885-016-2838-4.
61. Yang, X. *et al.* (2021) 'Global burden of COPD attributable to ambient PM2.5 in 204 countries and territories, 1990 to 2019: A systematic analysis for the Global Burden of Disease Study 2019', *Science of the Total Environment*. The Authors, 796, pp. 1–12. doi: 10.1016/j.scitotenv.2021.148819.

APPENDIX A:

COPD GRADING, CLASSIFICATION AND TREATMENT RECOMMENDATIONS

GOLD 2020 ABCD assessment tool

Assessment of lung function (airflow limitation)

FEV_1 (% predicted):	
GOLD 1: Mild COPD	$FEV_1 \geq 80\%$ predicted
GOLD 2: Moderate COPD	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3: Severe COPD	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4: Very Severe COPD	$FEV_1 < 30\%$ predicted

(GOLD committee, 2020)

Assessment of symptoms/ risk of exacerbations

GOLD grade	mMRC breathlessness score	Exacerbations in past year
A	0–1	<2
B	≥2	<2
C	0–1	≥2
D	≥2	≥2

The mMRC scale:

Grade	Exacerbations in past year
0	Dyspnea with strenuous exercise
1	Dyspnea when hurrying on level ground or walking up a slight hill
2	Walks slower than people of same age group, due to dyspnea
3	Stops for breath after walking 91m, or after a few minutes on level ground
4	Too breathless to leave the house, or dyspnea when dressing/undressing

COPD grading on severity of symptoms and frequency of exacerbations (National Department of Health, 2019)

GOLD 2020 Treatment recommendations

Exacerbations and symptoms	Recommended initial pharmacotherapy
GOLD Group A	Bronchodilator
GOLD Group B	LABA or LAMA
GOLD Group C	LAMA
GOLD Group D	LAMA or LAMA + LABA or ICS + LABA

(GOLD committee, 2020)

GOLD 2023 COPD grading, classification and treatment recommendations

Exacerbations and symptoms	**Recommended initial pharmacotherapy**
GOLD Group A	Bronchodilator (long-acting preferred)
GOLD Group B	LABA + LAMA
GOLD Group E: (previous C + D combined)	LABA + LAMA or LABA + LAMA + ICS (if blood eosinophile count > 300 cells/μL)

(GOLD, 2023)

APPENDIX B:

SOUTH AFRICAN PUBLIC SECTOR ESSENTIAL MEDICINES LIST (EML)

COPD INHALER THERAPIES - 2019 version (National Department of Health, 2019)

Recommendation for Grade A:

Short-acting Beta agonist (SABA): Salbutamol

Recommendation for Grade B:

Long-acting beta agonist (LABA): Formoterol - for patients uncontrolled on SABA

Long-acting muscarinic antagonist (LAMA): Tiotropium Bromide - procured on buy-out but not included on EML)

Recommendation for Grade C and D:

SABA + ICS/LABA [Salmeterol/Fluticasone (Seretide & Sereflo)] - for frequent exacerbators (2 or more per annum)

Patients on Protease Inhibitors:

Inhaled Corticosteroids (ICS) instead of ICS/LABA FDC: Beclomethasone (Beceze & Beclate)

Short-acting Muscarinic antagonist (SAMA) : Ipratropium Bromide - procured on buy-out but not included on EML)

APPENDIX C:

Comparative Clinical Effectiveness of long-acting bronchodilators

Search Strategy

Systematic literature search for clinical effectiveness of LAMA versus LABA in COPD. No restrictions in terms of year of studies applied. Search for literature with all relevant comparators in the same study with direct comparison of key outcomes (lung function exacerbation rates) yielded no results. Search for specific interventions limiting: hence the approach for the treatment class instead. Searches performed on Pubmed, Google scholar and key studies' reference lists for any publications that may be relevant or include relevant study drugs.

Excluded:

- Dual and triple fixed-dose combination therapy comparisons
- Inhaled corticosteroid/Theophylline/Systemic/Non-LAB comparators
- Treatment for Asthma
- Studies not comparative Efficacy or Effectiveness/Safety comparison studies/Other outcomes measure studies
- Comparators that are not of interest

	Search terms	**No of Results**	**Relevant papers**
Pubmed	(**COPD**[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic])) AND (Systematic review[Title])) AND (Meta-analysis[Title])) NOT (Combination[Title])) AND (Effectiveness).	26	*Manoj J. Mammen et al., 2020*
Pubmed	(**COPD**[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic]))))) AND (Efficacy[Title/Abstract])) AND (Effectiveness[Title/Abstract])) AND (Systematic review)) AND (Meta-analysis)))	31	Donohue *et al*., 2017
Pubmed	**COPD**[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic])) AND (Systematic review[Title])) AND (Meta-analysis[Title])) NOT (Combination[Title]).	27	Karabis *et al*., 2013 *Manoj J. Mammen et al., 2020*
Google Scholar	'Comparative efficacy of long-acting bronchodilators'	1	*Cope et al., 2013*

Search yielded: Total 4 relevant studies

Failed Search terms:
(COPD[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic]))))) AND (Efficacy[Title/Abstract])) AND (Effectiveness[Title/Abstract])) AND (Systematic review)) AND (Meta-analysis))) - 2 studies USE THIS, include Laba & lama
(((((COPD[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic]))))) AND (Efficacy[Title/Abstract])) AND (Effectiveness[Title/Abstract])) AND (Systematic review)) AND (Meta-analysis)
(((COPD[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic]))))) AND (Efficacy[Title/Abstract])) AND (Effectiveness[Title/Abstract])
Search: ((((COPD[MeSH Major Topic]) AND (Bronchodilator[MeSH Major Topic])) AND (Systematic review[Title])) AND (Meta-analysis[Title])) NOT (Combination[Title]) Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review

((((((((((COPD[MeSH Major Topic]) OR (Chronic obstructive pulmonary disease[MeSH Major Topic])) AND (Chronic obstructive lung disease[MeSH Major Topic])) AND (Clinical effectiveness[MeSH Major Topic])) AND (Tiotropium)) AND (Ipratropium)) AND (Glycopyrronium)) AND (Salmeterol)) AND (Formoterol)) AND (Indacaterol)) AND (FEV_1)) AND (Exacerbations)
(((((COPD[MeSH Major Topic]) OR (Chronic obstructive pulmonary disease[MeSH Major Topic])) AND (Effectiveness[MeSH Major Topic])) AND (long acting bronchodilators)) AND (lung function)) AND (exacerbations)

Table 2.1: Summary of Comparative Clinical Effectiveness study results

1. **Comparative efficacy of long-acting bronchodilators for COPD - a network meta-analysis.** (Cope *et al.*, 2013)
Systematic research: Medline & Embase databases (period 1989 – 2011), Cochrane library
NMA: Studies from SR + Novartis clinical trial Perspective: Payor
Country: Europe, North & South America, Africa, Asia

Evaluation type	Population & COPD Stage	Interventions & Comparators	Outcome measure	Sensitivity Analysis
Comprehensive Systematic Review (SR) & Bayesian Network Meta-analysis (NMA) enabled simultaneous synthesis of multiple trials(40 RCTs) **Evaluation period** 2w,6mo	*7250 patients* *Adults 40 years & older with COPD* *Current/ ex-smoker (10-20 years)* ***Moderate II*** ***Severe III***	***LAMAs:*** *-Tiotropium 5 & 18 µg OD* *-Glycopyrronium 50 µg OD* ***LABAs:*** *-Indacaterol 75, 150, 300 µg O/D* *-Salmeterol 50 µg B/D* *-Formoterol 12 µg B/D* *-Placebo =Overall Reference Treatment* ***Comparators:*** *-Placebo* -Or Any monotherapy	Lung function • Trough FEV_1(continuous) Primary endpoint • *Post-dose FEV_1 (2h post)* QoL Health Status • *SGRQ Total score* (continuous) • *SGRQ Responders = min 4 unit score improvement* *QoL Dyspnoea* • *TDI total score* (continuous) • *TDI Responders = min 1 unit score improvement*	**Sensitivity analysis** PSA (Second-Order Monte Carlo simulations, 5000) **Scenario analysis** (meta regression models) to investigate impact of alternative treatment, disease severity and exacerbation history. **Treatment effect modifiers investigated** • Disease severity • Concomitant COPD medication (+ or -) • Exacerbation history Results most sensitive to disease severity adjustment Least sensitive to concomitant drug use (ICS use) Exacerbation history adjustment had minimal impact
***2.* Comparative efficacy of long-acting β2-agonists as monotherapy for COPD: a network meta-analysis** (Donohue *et al.*, 2017) Systematic research: Medline, Medline In process, Embase, Cochrane databases 2013-2015 Country: *Multiple countries including USA & Netherlands*				
SR & Bayesian NMA synthesized evidence from 33 RCTs to estimate Relative effectiveness **Evaluation period** 12w, 24w	*Adults 40 years & older with Smoking history ≥10 pack-years* *FEV_1 of ≤80%* ***Moderate II*** ***Severe. III***	***LABAs:*** ***-Indacaterol 75, 150, 300 OD*** *-Salmeterol 50 µg B/D* *-Formoterol 12 µg B/D* *-Olodaterol 5, 10 µg OD* *-Vilanterol 25 µg OD)* *-Placebo* ***Comparators:*** *-Placebo or* ***-****Any Monotherapy*	Lung function • Trough FEV_1 (Primary endpoint) QoL Health Status • SGRQ total score *QoL Dyspnoea* • TDI focal score • Exacerbation rate	**Sensitivity analysis (meta regression):** **Treatment effect modifiers considered** • **FEV_1as primary efficacy outcome** • Disease severity • Concomitant COPD medication (+ or -). ICs/LABA • Female % Minimal changes, NMA results were therefore robust

RCT *Randomised controlled* **trials** **12w** 12 weeks **24w** 24 weeks ***FEV_1*** *forced expiratory volume in 1 second*
SGRQ *St. George's Respiratory Questionnaire* ***TDI*** *Transition Dyspnoea Index* ***QoL*** *Quality of Life*
PSA *Probabilistic Sensitivity Analysis*

3. **Comparative efficacy of Aclidinium versus Glycopyrronium and Tiotropium, as maintenance treatment of moderate to severe COPD patients:**
(Karabis *et al.*, 2013) *Search: Medline, Medline In-Process, Embase, and Cochrane Controlled Trials Registry databases*
Country: South Africa, Europe, Canada, USA

Evaluation type	**Population// COPD Stage**	**Interventions & Comparators**	**Outcome measure**	**Sensitivity analysis Method**
SR & (Bayesian NMA 21 RCTs ≥10 weeks (high proportions (30%) of Mild and/or Very Severe COPD) 22542 patients	*Adults* *Smoking history min 10 pack-years* *FEV_1/FVC of #70%,* *FEV_1% predicted from 50% - ,80%.* *diseases ~ 8.7y*	***LAMAs*** ***-Aclidinium 400 µg B/D*** *-Glycopyrronium 50 µg O/D* *-Tiotropium 18 µg O/D* *-Tiotropium 5 µg O/D* *-Placebo =reference treatment*	Changes from Baseline (CFB) Lung function • Trough FEV_1(continuous) Primary endpoint • *Post-dose FEV_1 (2h post)* QoL Health Status • *SGRQ Total score* (continuous) • *SGRQ Responders* *QoL Dyspnoea* • *TDI focal score* (continuous) • *TDI Responders*	**Treatment effect modifiers considered** **Scenario Analyses** covariate meta regression analysis **adjustment**: for potential treatment effect modifiers • % current smokers • COPD severity distribution • FEV_1 % predicted at baseline • % patients with concomitant ICS use • concomitant use of LABA -- (**Sensitivity Analysis** all except LABAs users to address risk) *Mean & Standard error* for Continuous outcomes % of responders for dichotomous outcomes
Evaluation period 12w, 24w	***Moderate II*** ***Severe III***	***Comparator:*** ***-****All active interventions* *-Placebo*		

4. Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease A Systematic Review and Meta-analysis in Support of the American Thoracic Society Clinical Practice Guideline (Manoj J. Mammen *et al.*, 2020)
Data sources: Medline, EMBASE, Cochrane library database, Pubmed, Reference lists and other relevant publications.

SR & MA: 24 RCTs 45441 patients Evidence summarised & outcomes data pooled	*Symptomatic COPD pts who complained of dyspnoea and or exercise intolerance* ***Moderate II*** ***Severe III***	***Dual FDC LABA/LAMA vs.*** ***-LABA*** ***-LAMA*** ***(****investigating monotherapy. Class effect, not individual bronchodilator therapies)*	**Critical Outcomes** • Dyspnoea score • Acute Exacerbation risk (no of episodes) • Hospital admissions • HRQoL score • Adverse events (treatment related) • Exacerbation risk (no of episodes) ***Important outcomes*** • *FEV_1* • *ICU admissions* • *Frequency of pneumonia* • *Out of pocket costs for patients* • *Exercise capacity*	**Sensitivity Analysis** (Post hoc) **Acute COPD Exacerbations** (to investigate increased heterogeneity) *Continuous outcomes:* reported as Mean Differences (MD) and *Standardized Mean Differences* (SMD)to accommodate variability *Dichotomous outcomes* reported as relative risks or odds ratios Absolute Risk difference/effect

FEV_1 forced expiratory volume in 1 second **SGRQ** St. George's Respiratory Questionnaire **TDI** Transition Dyspnoea Index
MA Meta-Analysis **FDC** Fixed-dose combination **QoL** Quality of Life **HRQoL** Health-Related Quality of Life
ICU Intensive Care Unit

APPENDIX D:

Cost-Effectiveness Analysis

Systematic literature search for cost-effectiveness/utility analysis comparing the use of Long-acting muscarinic antagonists (LAMAs) to Long-acting beta agonists (LABAs) in COPD patients.

Search Strategy

	Search terms	No of Results	No of Relevant papers
Pubmed	(COPD[MeSH Major Topic]) OR (Chronic obstructive pulmonary disease[MeSH Major Topic])) OR (Chronic obstructive pulmonary disease[Title]))) OR (COPD[Title]))) AND (Cost-effectiveness[MeSH Major Topic])) OR (Cost-effectiveness analysis[MeSH Major Topic])) OR (Cost-effectiveness)) OR (Cost-effectiveness analysis)) OR (Cost-utility analysis[Title])) AND (Tiotropium)) OR (Glycopyrronium)) OR (Ipratropium)) AND (Formoterol)) OR (Salmeterol)) OR (Indacaterol)) NOT (Asthma)) NOT (dual therapy)) NOT (fixed dose combination)) NOT (FDC)) NOT (combination therapy)	998	*11*

Exclusion and elimination criteria

- Dual and triple combination therapies excluded, focused on monotherapy
- Excluded interventions not approved for use in South Africa
- Excluded within class comparisons
- Excluded Inhaled corticosteroids and Roflumast (other available treatment classes)
- Excluded studies with no economic evaluation in the form of CEA/CUA- that is excluded budget impact analysis, costing studies, efficacy studies, cost savings and all other types
- Excluded studies that did not include the specific interventions of interest for this analysis.
- Excluded lower dose intervention drugs.

Failed Search terms:
(COPD) AND (cost-effectiveness analysis)) OR (cost utility analysis)) AND (long-acting beta-agonists)) OR (LABAs)) AND (long-acting muscarinic -antagonists)) OR (LAMAs)) NOT (triple)) NOT (dual)) NOT (fixed dose combination)) NOT (Asthma)) NOT (Efficacy)) NOT (Effectiveness)) NOT (safety)) 1098 results not relevant

Table 2.2: Summary of Cost-Effectiveness study results

Author	Costs	QALYs Benefit	ICER	Efficacy Outcomes/ Sensitivity analysis
1.Hoogendoorn et al., 2013 **Tiotropium (TIO)** **vs.** Salmeterol (SALM) German C & B discounting: 3% **7250pts** **Mod - Very Severe COPD**	**SHI** Mean **Total costs** pp p/a **TIO:** €1089 **SALM:** €963 **Cost Difference 1y:** €126 Exacerbation Cost ↓: €87 **Cost Difference 5y:** €287	TIO **1y Incr. QALYs**: 0.012 **5y Incr. QALYs**: 0.082 TIO Annual ↓ Exacerbation: 0.064 (TIO 0.644 & SALM 0.708) Days (TIO 9 & SALM 10.1)	**1y TH trial** €9,926 per QALY gained €1961 per exacerbation avoided €118 per exacerbation day avoided **5y TH model** €3,488 per QALY gained **Favour LAMA TIO18**	**Exacerbations Numbers & Days (Mean)** **Exacerbation-related costs** **ICER/QALY & ICER/exacerbation avoided** **One way & PSA** **CEP, CEAC** **1-way sensitivity analysis**: cost/QALY gained <€10,000 for all SAs CER below WTP At max WTP of €20000: 62% probability of Tiotropium CE <€10000 generally very CE internationally
2.Ariza et al., 2012 **Indacaterol 150** Tiotropium 18 Columbia Cost and Benefit discounting: 5% 3,5y TH	**Payor perspective** Price per day **Indacaterol:** $2.17(=3850 COP) **TIO:** $1.94(=3443 COP)	**Indacaterol vs. FDCs** **LYs gained** vs S/F 0.003 & F/B 0.007 **QALYs** vs S/F 0.004 & F/B 0.010 (QALYs only for 1st analysis)	ICUR vs TIO (2nd Analysis): US $2584. 5y Cost per LY gained US $2899 **Favour LABA Indacaterol**	**FEV_1improvement (trial endpoint)** ICUR of US $2584 was below WTP of US $5274 (COP 9,340,940 equal to per - capita GDP) 47.2 % of simulations: INDACA more effective, more costly after 5y 51.4%: INDACA as dominant **PSA:** 78% probability that ICUR is ≤ to US WTP threshold of R5274 (per capita GDP) & 94.5% probability at 3 times GDP per capita. **Scenario analysis:** Disease severity distribution key influence
3. Hoogendoorn et al., 2013 **Tiotropium** (TIO) vs. Salmeterol (SALM) **Which LAB** **5000 iterations** **Mod-Very Severe COPD**	**HC Payor perspective:** **Total cost:** 1y **TIO**: € 1370 (UI 1268-1482) **SALM**: € 1359 (1191-1544) 5y **TIO:** € 6618 (5957-7296) **SALM**: € 6895 (5757-8073)	**QALYs** **1y TH: +0.11 QALYs** TIO: 0.747 (0.726-0.763) SALM:0.736 (0.700-0.756) **5y TH: +0.79 QALYs** TIO: 3.355 (3.108-3.522) SALM: 3.276(2.869-3.517) **Exacerbation reduction:** 1y: TIO Annual ↓ Exacerbation: 0.068 5y: TIO ↓ Exacerbation: 0.435	**ICUR** (TIO -SALM) €1015: **cost per QALY** gained €162: **cost per exacerbation** avoided **maximum WTP** of €20000 per QALY, probability TIO cost-effective 73% and 67% for 1- and 5-year analysis **Favour LAMA TIO18**	**Total no of QALY** **Total no of Exacerbations: Severe & Non-severe** **Sensitivity Analysis: 1 way & PSA** Disease severity state distributions - results most sensitive Exacerbation probabilities, risk differences Discount rates, In hospital costs, Exacerbation disutility values **Uncertainty:** Transition & Exacerbation Probabilities, Utility, Costs **CE Plane QALYs:** 41% of simulations: TIO more effective, more costly 36% TIO more effective and cost saving/dominant **Outcome: Exacerbations(Counts)** 51% simulations TIO more effective, more costly 45% TIO more effective and cost saving
4. Price et al., 2011 **Indacaterol 150** Tiotropium Salmeterol	**Total cost:** **Indacaterol: € 2067** **Tiotropium: € 2415** **Difference: - € 348**	**Total QALYs** **Indacaterol:** 2.13 **TIO**: 2.12 **Difference: 0.009**	**Indacaterol: dominant** UK NICE threshold (£20000-£30000)	**FEV_1 improvement at 12w (trial endpoint)** **Univariate USA (Tornado diagram) &** **Probabilistic Sensitivity analysis PSA** **Indacaterol 150µg**: cost-effective and Dominant vs. Tiotropium

German C & B discounting: 3% **Mild - Very Severe COPD**		Trials: 6mo Model: 3y TH	*No defined WTP threshold for Germany **Favour LABA: Indacaterol**	**Indacaterol 300µg:** vs Tiotropium - ICER €28000: below upper level
5.* Oba,** 2007 Tiotropium (TIO) Salmeterol (SALM) vs. Placebo USA ***Moderate - Severe COPD	***3rd party Payer perspective*** ***Total additional costs:*** ***TIO:*** *US $ 835* ***SALM:*** *$ 1066*	***Mean incremental QALYs per patient-year*** ***Net QALY gain vs Placebo:*** ***TIO****: 0.032/11.7 quality-adjusted days (QAD)* ***SALM****: 0.026/9.5 quality-adjusted days (QAD)*	***ICER*** *(cost per QALY gained):* ***TIO*** *vs placebo:* ***$26,094*** ***SALM*** *vs. placebo:****$ 41,000*** ***Favour LAMA: TIO18***	***TIO Net gains vs Placebo****: (Head to head trial data)* *QALYs 0.045,16 QAD, Cost $900 CER: $20,000/ QALY gained* ***SALM Net gains vs Placebo:*** *QALYs 0.030,11 QAD, Cost $1119 CER: $37300/ QALY gained* ***Sensitivity analysis:*** *Cost of hospitalisation, unscheduled visits, incremental QALYs* ***Cost-effectiveness acceptability curve****.* *Probability of Cost-effectiveness @ WTP threshold of $50,000:* ***TIO****: 93% probable &****SALM****: 67% probable*
6. Ruiz et al., 2005 Tiotropium (TIO) Vs. Salmeterol (SALM) Spain ***Moderate - Severe COPD***	***Payor*** ***Cost of medication pp:*** ***TIO****: € 344.64* ***SALM****: € 231.42* ***Exacerbation-related hospital costs per 100 patients*** ***TIO:*** *€ 25 548* ***SALM:*** *€ 32 199*	**Outcomes** SGRQ score **SALM TIO** –3.54 –5.14 Hospital stay saving with TIO (6mo): 107 days	**ICER (6 mo) TIO vs SALM** **ICER SGRQ**: € 75.48 **ICER TDI:** € 191.90 **ICER trough FEV$_1$, mL**: € 2.76 **(1y) TIO vs SALM** **ICER SGRQ**: *€ 182.67* **ICER TDI:** € 615 **ICER trough FEV$_1$, mL**: *€ 3.69* ***Favour LAMA: TIO18***	***CE 12% final trough FEV$_1$:*** ***SALM TIO*** ***€ 2.72*** *€2.51* ***CE: 4 points SGRQ:*** ***CE: 1-point TDI:*** ***SALM TIO*** ***SALM TIO*** ***€261.49*** *€268.20* *€ 964.25.* *€ 337.88*

SHI **C & B Discounting** Cost and Benefits Discounting **TH** Time Horizon **Incr.** Incremental **LY** Life Year **pp** per patient **p/a** per annum. **FEV$_1$** forced expiratory volume in 1 second **QAD** Quality Adjusted Days **QALY** Quality adjusted Life Year **PSA** Probabilistic Sensitivity Analysis **SGRQ** St. George's Respiratory Questionnaire **mo** months **TDI** Transition Dyspnoea Index **WTP** Willingness To Pay **ICER** Incremental Cost-Effectiveness Ratio **ICUR** Incremental Cost-Utility Ratio **CE** Cost-Effective **CER** Cost-Effectiveness Ratio **COP** Canadian **SAs** Sensitivity Analyses **CEP** Cost-Effectiveness Plane **CEAC** Cost-Effectiveness Acceptability Curve **GDP** Gross Domestic Product

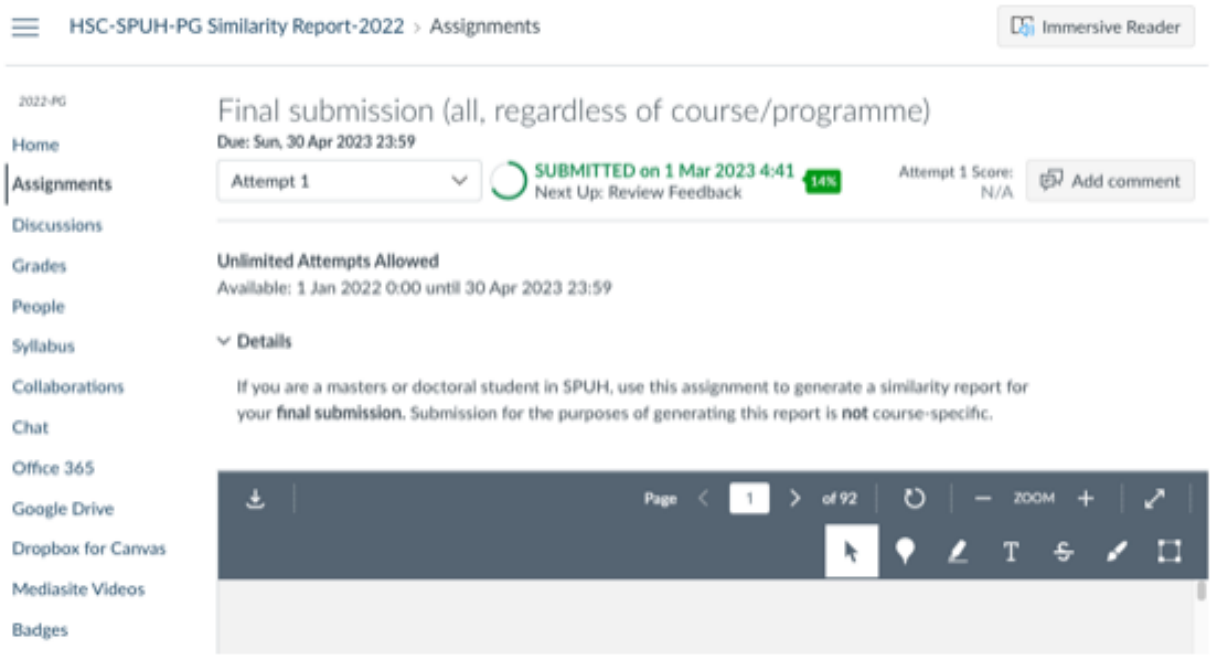
Author	Costs	QALYs	ICER	Sensitivity analysis
7. Gani et al., 2010 **Tiotropium** (TIO) O/D vs. Salmeterol (SALM) B/D Ipratropium (IPRA) q/d i) England and ii) Scotland/Wales/ Northern Ireland: **Mild - Severe COPD** Trials: 6mo & 1y	**NHS Payor** **Cost pppa (i)** **TIO**: £ 1439 **SALM**: £ 1565 (+126) **IPRA**: £ 1631 (+192) **Cost pp p/a (ii)** **TIO**: £ 1305 **SALM**: £ 1404 (+99) **IPRA**: £ 1427 (+122)	**TIO18 vs. SALM incremental QALYs** Mild: 0.012 Moderate: 0.018 & Severe COPD: 0.012 **TIO vs. IPRA incremental QALYs** Mild: 0.022 Moderate: 0.022 & Severe COPD: 0.020	NICE threshold: **WTP** £ 20000 - £ 30000/ QALY **Mean incremental Costs & QALYs:** **TIO vs. SALM** **i)-** £ 169 & 0.014 **ii)** - £ 136 & 0.014 **TIO vs. IPRA** **i)-** £ 348 & 0.021 **ii)** - £ 272 & 0.021 **Severe COPD TIO vs. IPRA ICER**: i) £1600/ QALY ii) £ R3450/ QALY **Favour LAMA: TIO 18**	**Univariate subgroup analysis**: varying disease state distribution for each treatment **Multivariate** PSA: Mean incremental costs & QALYs **Probability of being cost-effective or (I & ii)** @WTP threshold of £.0 £20k £30k: TIO vs SALM: 86/84% 97% 98% TIO vs IPRA: 87/72% 99/98% 100/99% TIO Dominance Range: 72%-87%
8. Price et al., 2013 **Indacaterol O/D 150 & 300 (INDACA)** **Tiotropium**18 (TIO)O/D **Salmeterol** (SALM) B/D Netherlands **Mod - Severe COPD** Cycle: 3mo TH: 3y ,5y, 20y Trials: 6 mo	**Total costs-3y:** **INDACA**150: £ 4534 **TIO**18: £ 4781 Difference: - £248 - **INDACA**150: £ 4583 **TIO**18: £ 4692 Difference: - £110 - **INDACA**300: £ 4501 **Tio**18: £ 4760 Difference: - £259-	**Total QALYs-3y**: **INDACA** 150µg: 2.158 **TIO**18µg: 2.150 Difference: 0.008- **INDACA** 150µg: 2.158 **SALM50**µg: 2.149 Difference: 0.008- **INDACA 300**µg:2.162 **TIO** 18µg: 2.151 Difference: 0.011 -	ICUR vs tiotropium (2nd Analysis): US $2584 **Indacaterol Dominant for All scenarios** **Favour LABA INDACA**	**USA:** Disease stage distribution & Mortality rate (especially very severe COPD) **PSA:** 72% iteration INDACA dominant vs. SALM 89% iteration INDACA dominant vs. TIO @WTP £ 20k per QALY gained: 82% & 84% probability that INDACA is CE compared to SALM & TIO Threshold analysis: TIO price reduction variations
9. Rutten-van Molken et al., 2007 **Spain** **Tiotropium**18 (TIO) **Salmeterol** (SALM) **Ipratropium** (IPRA)	**Mean SE 5-year costs:** **TIO**: € 6424 (€ 305) **SALM** € 5869 (€ 505) **IPRA** € 5181 (€ 682)	**Mean SE 5y no of QALYs** **TIO**: 3.15 (0.08) **SALM** 3.02 (0.15) **IPRA** 3.00 (0.20) **Mean SE 5y no of EXACs** **TIO**: 3.50 (0.14) **SALM** 4.16 (0.40) **IPRA** 4.71 (0.54)	**Incremental CE-ratios** **TIO vs SALM** **Base case** Cost per **exa-free month**: €360 Cost per **QALY**: €4118 **Scenario 2** Cost per exa-free month: €217 Cost per QALY: €2239 **Scenario 3** Cost per exa-free month: €777 Cost per QALY: €6446 **Favour LAMA: TIO 18**	Tiotropium preferred when WTP exceeded € 639 per exacerbation-free month & € 8,157 per QALY **Disease severity:** Tiotropium preferred when threshold is above: €7,600 for moderate COPD, €8,800 for severe COPD & €12,500 for very severe COPD **Tiotropium had the highest expected net benefit** when ceiling ration for **cost per exacerbation-free month** were €560 for moderate , €700 for severe & €1,200 for very severe COPD

Author	Costs	QALYs	ICER	Sensitivity analysis
10. Oostenbrink et al., 2005 Netherlands & Canada **Tiotropium**18 (TIO) **Salmeterol** (SALM) **Ipratropium** (IPRA)	**Total Costs** **Netherlands** **TIO** 1760€ (116) **SALM** 1802€ (175) **IPRA** 1930€ (267) **Canada** **TIO** €1309 (47 **SALM** €1306€ (96) **IPRA** 1307€ (150)	**Total No of Exacerbations** **TIO** 0.85(0.80; 0.91) **SALM** 1.02(0.84; 1.22) **IPRA** 1.14(0.92;1.40) **QALMs:** **TIO** 8.42(7.59; 9.20) **SALM** 8.17(7.24;9.06) **IPRA** 8.11(7.08;9.04)	**Netherlands** TIO vs. SALM Difference in: Costs -42€ (-484; 353) Exacerbations: 0.17 (-0.02; 0.37) QALMs: 0.25 (-0.90; 1.47) **Canada** Costs 3€ (-227; 203) **Favour LAMA: TIO**	**Cost-effectiveness Acceptability frontier of Exacerbations** showed TIO had max expected net benefit for all values of ceiling ratio above 0€ (Netherlands) and 10€ Canada in base case Length of stay in hospital was significantly different for the 2 countries: longer stay for exacerbations in Netherlands
11. Hogan et al., 2003 **Formoterol** (FORM) **Ipratropium** (IPRA) Placebo **12w TH**	**Cost per treatment:** **IPRA: $ 76.34** **FORM** 12µg**: $ 214.91** **FORM** 24µg**: $418.92** **Placebo: $ 38.93** **Incremental cost** vs. Placebo **IPRA: $ 37.41** **FORM** 12µg**: $ 138.57** **FORM** 24µg**: $204.01**	**Effectiveness: FEV$_1$** **IPRA:**: 1.427 **FORM** 12µg: 1.513 **FORM** 24µg: 1.484 **Placebo**: 1.290 **Effectiveness: QoL SGRQ scores** **IPRA:**: 1.1 **FORM** 12µg: 6.6 **FORM** 24µg: 4.8 **Placebo**: 1.5	**Incremental Effectiveness (FEV$_1$)** vs. **Placebo** **IPRA**: 0.137 **FORM12**µg: 0.086 **FORM24**µg: 0.029 **Incr. Effectiveness (QoL)** vs. **Placebo** **IPRA**: (0.40) **FORM12**µg: 5.50 **FORM24**µg: (1.80) **FORM** vs. **IPRA**: $554.28 p/a additional cost for + 0.086 FEV$_1$ or +5.5 SGRQ **Favour LABA: FORM12µg**	**CER,$/FEV$_1$:** **Placebo**: $30.18 **IPRA**: $53.50 **FORM12**:: $142.04 **FORM24**: $282.29 **ICER,$/FEV$_1$: vs placebo** **IPRA**: $273.03 **FORM12**:: $1611.32 **FORM24**: DOMINATED **CER,$/QoL**: **Placebo**: $ 25.96 **FORM12**: $32.56 **IPRA**: ($69.40) **FORM24**:: $87.28 **ICER,$/QoL$_1$: vs placebo** **IPRA**: DOMINATED **FORM12**:: $25.20 **FORM24**: DOMINATED **Economic efficiency Frontier** **FORM12**:: $34.51. **IPRA** & FORM24 not on the frontier

QALY Quality adjusted Life Year **ICER** Incremental Cost-Effectiveness Ratio **FEV$_1$** Forced expiratory volume in 1 second QoL Quality of Life **SGRQ** St. George's Respiratory Questionnaire **CER** Cost-Effectiveness Ratio **Incr. OALM** Incremental Quality Adjusted Life Months

APPENDIX E:

PLAGIARISM FORM



APPENDIX F:

ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Human Research Ethics Committee (Medical)

Research Office Secretariat:
Faculty of Health Sciences, Phillip Tobias Health Sciences Building, 3rd Floor, Office 301/2/4, 29 Princess of Wales Terrace, Parktown, 2193
Private Bag 3, Wits 2050
Office email: HREC-Medical.ResearchOffice@wits.ac.za
Website: www.wits.ac.za/research/about-our-research/ethics-and-research-integrity/

Ref: W-CBP-200721-01 21/07/2020

TO WHOM IT MAY CONCERN:

Waiver:	This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical)
Investigator:	Miss Peggy Thompson (Student No: 1946476)
Supervisor:	Dr Ijeoma Edoka
School:	Public Health
Project title:	Cost utility analysis of Long Acting Muscarinic Antagonists (LAMAs) as an alternative to Long Acting Beta Agonists (LABAs) for treatment of severe Chronic Obstructive Pulmonary Disease (COPD) in the South African Public Sector
Reason:	Study will be Literature-based. No human participants, human data or human tissues will be involved.

CB Penny

Dr CB Penny

Chairperson: Human Research Ethics Committee (Medical)

Copy – HREC (Medical) Secretariat: Ms Zanele Ndlovu, Ms Mapula Ramaila and Mr Rhulani Mkansi