Economic Evaluation of Single-Inhaler Triple Therapy (FF/UMEC/VI) for COPD

An explorative cost-effectiveness analysis in a Norwegian perspective

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Abstract

***Introduction**:* The cost-effectiveness of prescribing single-inhaler triple therapy containing the long-acting muscarinic antagonist (LAMA) umeclidinium bromide (UMEC), the long-acting beta$_2$-agonist (LABA) vilanterol (VI), and the inhaled corticosteroid (ICS) fluticasone furoate (FF) versus once-daily double therapy inhalers as a chronic obstructive pulmonary disease (COPD) maintenance treatment in Norway is unknown.

Methods: This analysis evaluated the cost-effectiveness of the following three treatments in COPD: FF/UMEC/VI, UMEC/VI, and FF/VI. A Markov model was developed to estimate the costs and health outcomes associated with FF/UMEC/VI, UMEC/VI, and FF/VI treatment in patients with COPD. The model's inputs were treatment efficacy, utility, mortality, and costs. Information regarding treatment efficacy, utility, and mortality was acquired from the published literature, clinical trial results, and established guidelines. Resource utilisation information was primarily obtained from established guidelines and the published literature. Costs were gathered from established guidelines and the Norway's national tariff payment system. Costs were presented in Norwegian *kroner* (NOK) based on 2019 prices. The model's outputs were total costs (i.e., medical direct-costs and productivity loss), quality-adjusted life-years (QALYs), and life-years (LYs). Costs and outcomes were discounted at a 3% annual rate. Incremental cost-effectiveness ratios (ICERs) were calculated and compared between treatments. Probabilistic sensitivity analyses (PSAs) were performed to assess the uncertainty of the results, and the expected value of perfect information (EPVI) calculations were performed to explore the cost of uncertainty.

Results: FF/UMEC/VI is dominant compared to UMEC/VI. FF/UMEC/VI costs 175,141 NOK less per quality-adjusted life-year (QALY). When compared to FF/VI, FF/UMEC/VI is associated with incremental costs of 24,381 NOK, per quality-adjusted life-year (QALY) and 441,087 NOK per LY gain. At the willingness-to-pay threshold of 500,000 NOK per QALY, FF/UMEC/VI is associated with greater cost-effectiveness than FF/VI and UMEC/VI.

Conclusions: The use of FF/UMEC/VI to UMEC/VI is associated with greater effectiveness and lower costs. When compared to FF/VI, FF/UMEC/VI is associated with higher costs than FF/VI but is cost-effective in most cases. This study shows that additional information is needed to reduce uncertainty in COPD treatment selection.

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List of Abbreviations

COPD	Chronic Obstructive Pulmonary Disease
CEAC	Cost-effectiveness Acceptability Curve
CEAF	Cost-effectiveness Acceptability Frontier
DRG	Diagnosis-Related Group
EVPI	Expected Value of Perfect Information
FEV_1	Forced Expiratory Volume in one second
FF	Fluticasone Furoate
FULFIL	Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-related Quality of Life
HUNT	Helseundersøkelsen i Nord-Trøndelag
ICER	Incremental Cost-Effectiveness Ratio
ICS	Inhaled Corticosteroid
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IMPACT	Informing the Pathway of COPD Treatment
LABA	Long-acting $Beta_2$-agonist
LAMA	Long-acting Muscarinic Antagonist
LY	Life-year
mMRC	Modified Medical Research Council Dyspnea Scale
NICE	National Institute for Health and Care Excellence
QALY	Quality-adjusted Life-year
SGRQ	St. George's Respiratory Questionnaire
SmPC	Summary of Product Characteristic
SMRs	Standardised Mortality Ratios
UMEC	Umeclidinium
VI	Vilanterol
WTP	Willingness to Pay

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a global public health problem; it is one of the major causes of death worldwide. In 2006, the World Health Organisation (WHO) predicted that COPD would become the third-leading cause of death in the world by 2030 (Mathers & Loncar, 2006). However, the COPD burden grew faster than predicted; according to the Global Burden of Disease Study, COPD was the third-leading cause of death in the world in 2010 (Lozano et al., 2012). The number of people affected by COPD is quite large. In 2016, 251 million people suffered from COPD globally. In 2015, COPD caused 3.71 million deaths globally, which was 5% of all deaths that year, and low- and middle-income countries experienced 90% of all COPD deaths (Lozano et al., 2012; Quaderi & Hurst, 2018). In Norway, 150,000 individuals over age 40 have COPD, which is 5% of this population (SKDE, 2017).

The economic burden of COPD is substantial. COPD is a progressive disease that is not fully curable because the associated airflow obstruction is irreversible. Thus, it has a long-term impact on patients' quality of life and healthcare costs. The prolonged direct cost of COPD and other indirect costs, such as productivity loss, can have a significant impact on healthcare systems and society as a whole. COPD is the fifth-leading cause of life-year loss in Western Europe (Lozano et al., 2012), and in the United States (US), 10.3 million physician visits, 1.5 million emergency department visits, and approximately 700,000 hospitalisations occur annually due to COPD (Ford et al., 2013). In Norway, approximately 10,000 COPD patients are admitted to the hospital within a year after diagnosis, and one-third of them are readmitted within 30 days. It is estimated that COPD treatment costs account for 0.7% of Norway's healthcare budget (Lozano et al., 2012; Nielsen et al., 2009). Thus, there is a need to explore the management of COPD and its impact on patients and healthcare systems.

The goals of COPD management are to postpone deterioration and reduce inflammation. Although COPD is incurable, the symptoms can be controlled and reduced via lifestyle changes and medication. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, COPD patients are encouraged to stop smoking. In addition to lifestyle management, inhalation therapy is the most common medical therapy prescribed for COPD patients to open their blocked airways and reduce inflammation. For occasional,

moderate exacerbation, short-term or once-daily single-inhaler therapy can control symptoms and improve patients' quality of life. However, if patients experience an acute episode several times or more per year, once-daily double- or triple-inhaler (i.e., combination) therapy may be required. Combination therapy implies that patients need to use more than one medication in the inhaler or use multiple inhalers. However, using an inhaler multiple times per day is not the best practice for COPD management. The National Institute for Health and Care Excellence (NICE) guidelines recommend minimising the frequency of inhaler use when considering treatment options (NICE, 2018) because it potentially reduces the chances of incorrect usage and enhances patients' quality of life by making treatment more convenient. Once-daily single-inhaler triple therapy simplifies the treatment process and reduce medication costs when compared to using two or three separate inhalers for targeted COPD patients in the current study.

Long-acting bronchodilators and inhaled steroid medications are commonly prescribed to treat COPD symptoms. Long-acting beta$_2$-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are bronchodilators with different mechanisms of action that reduce airway inflammation. Inhaled corticosteroids (ICSs) have a similar anti-inflammatory effect. LABAs, LAMAs, and ICSs can be applied in one or more doses depending on the route of administration. In this analysis, we select the most recently developed fixed-dose triple therapy, fluticasone furoate/umeclidinium bromide/vilanterol (FF/UMEC/VI), which combines fixed amounts of a LAMA, a LABA, and an ICS, and compare its composition with dual therapies. It was approved by the Norwegian Medicines Agency in 2018 for use in patients whose symptoms are inadequately controlled by ICS/LABA. Thus, the comparators in this study are LABA/LAMA and ICS/LABA, which are UMEC/VI and FF/VI medications.

Two phase-three clinical trials, Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy trial (FULFIL) and Informing the Pathway of COPD Treatment trial (IMPACT), have shown that the efficacy of fixed-dose triple therapy outweighs either dual treatments. Thus, there has been some discussion in the literature regarding whether COPD patients should be upgraded to the fixed-dose triple therapy if they meet the criteria (Dabscheck, 2018; Lopez-Campos et al., 2018; Suissa & Drazen, 2018), and the NICE guidelines state that a decision on whether fixed-dose triple therapy should be recommended as a standard treatment for COPD will be released in June

2019. As of May 2019, single-inhaler triple therapy is only recommended when patients' symptoms are inadequately controlled by LABA + ICS treatment and require open-dose triple therapy.(Vanfleteren et al., 2019)

A cost-effectiveness analysis is conducted in the current study to compare once daily single-inhaler triple therapy and dual therapies. The objective of this study is to explore the cost-effectiveness of FF/UMEC/VI triple therapy in comparison to two dual therapies, UMEC/VI and FF/VI, in Norway. Thus, we can determine whether the newest fixed-dose single-inhaler triple therapy is a better alternative for patients who are currently prescribed dual therapies. Alternatively, single-inhaler triple therapy should only be a replacement for open triple therapy and taken by patients occasionally.

2 Background

2.1 The Etiology of COPD

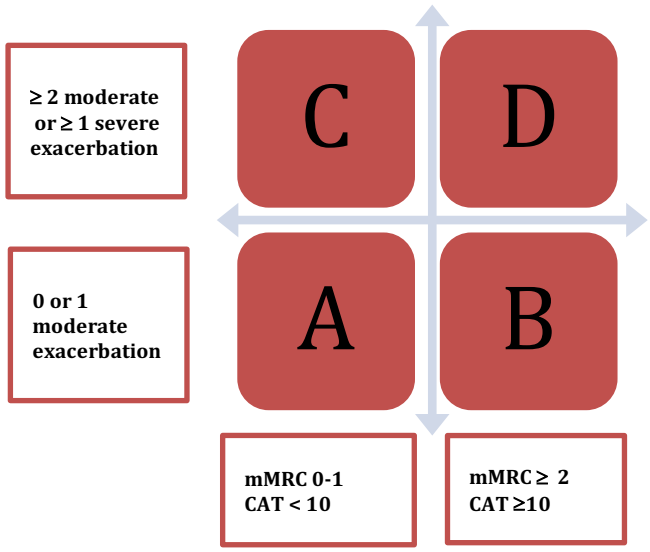
COPD is a chronic lung disease that leads to a persistent reduction in the patient's airflow. People who have COPD experience breathlessness, chronic coughing, and increased sputum production; these symptoms gradually worsen over time and limit the patients' ability to perform daily activities. The main risk factor for developing COPD is active or passive exposure to tobacco smoke, for example, smoking or being in close proximity to someone who is smoking. Another risk factor is air pollution, which includes outdoor air pollution from industry and vehicles and indoor air pollution from cooking (Laniado-Laborín, 2009; May & Li, 2015; Quaderi & Hurst, 2018; Sana et al., 2018).

The assessment of COPD is based on the severity of the airflow limitation and exacerbation of symptoms. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) publishes guidelines for COPD diagnosis, management, and prevention annually. The GOLD guidelines are considered the standard reference for assessing COPD. The GOLD classification system is widely used in selecting treatment pathways for different COPD patient groups. The diagnosis of COPD is confirmed through a breathing test, called 'spirometry', which is used to measure the maximum volume and airflow going through the lungs when the patient inhales and exhales. Patients' forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) values are obtained via spirometry. FVC measures the amount of air one can exhale after taking a deep breath, and FEV_1 is the air volume measured during the first second of the FVC measurement process. The ratio of FEV_1 to FVC is identified as the airflow obstruction level. When the ratio is below 70%, the patient is diagnosed as having COPD.

In the GOLD guidelines, the severity of COPD is classified into four stages: GOLD I, GOLD II, GOLD III, and GOLD IV based on a comparison of the measured FEV_1 to the predicted FEV_1 of the general population. The predicted FEV_1 percentage is calculated by entering a formula that includes age and height as the parameters. GOLD I is considered mild COPD (i.e., the measured FEV_1 is 80-99% of the predicted FEV_1), while GOLD II is considered moderate (i.e., the measured FEV_1 is 50–79% of the predicted FEV_1), and GOLD III is considered severe (i.e., the measured FEV_1 is 30–49% of the predicted FEV_1). GOLD IV is

considered advanced COPD (i.e., the measured FEV_1 is below 30% of the predicted FEV_1; (GOLD, 2018).

Figure 1 COPD ABCD classification



Within each GOLD stage, patients are divided into four groups (i.e., A, B, C, and D) based on the frequency of their exacerbation episodes. Symptomatic assessment was first introduced into the classification system in the 2011 GOLD guidelines. The assessment includes the frequency of moderate or severe exacerbations in the past 12 months and one symptom scale, the Modified Medical Research Council Dyspnea Scale (mMRC) or COPD Assessment Test (CAT). Exacerbation is defined as when symptoms are worsened for a few days or weeks. The symptoms refer to the frequency of dyspnoea, increased sputum volume or colour changes, and coughing or wheezing. In many studies, moderate and severe exacerbations are distinguished based on whether the exacerbation requires hospitalisation. Moderate exacerbations require self-administered medical treatment or a brief visit to a physician or emergency primary healthcare service if necessary. Severe exacerbations require hospitalisation and, therefore, utilise considerably more healthcare resources (Borg et al., 2004; Erdal et al., 2016; Hoogendoorn et al., 2010). The interaction of symptom scales and exacerbation history form a matrix that is used to assign a specific management process for different phenotypes of COPD (see Figure 1). Patients in groups C and D experience more discomfort and require more healthcare utilisation due to the frequency of moderate or severe exacerbations and more serious symptoms compared to patients in groups A and B. A British

study shows that COPD patients who have one exacerbation per year cost about 50% more than patients who did not experience an exacerbation (Punekar et al., 2014). Exacerbations also lead to negative impacts on the patient's quality of life and increase the mortality risk (Erdal et al., 2016; May & Li, 2015). For patients in group D, each additional exacerbation reduces more lung function (measured by FEV_1) than non-exacerbators; even when they are in stable condition, the loss of lung function is more rapid (Dransfield et al., 2016).

2.2 The Treatment of COPD

This study is based on GOLD and NICE guidelines. The latest Norwegian guideline for COPD diagnosis and management was published in 2012, which is considered outdated in comparison to the GOLD and NICE guidelines, which are published annually and provide more detailed and updated pharmacological treatment pathways for different levels of COPD severity and patient groups. Triple therapy has been included in the GOLD guidelines, and NICE will include it later this year. The GOLD guidelines are also the main reference for the NICE guidelines on pharmacological treatment. Other management options (e.g., lung treatment and rehabilitation), processes, and resource use are incorporated into the NICE guidelines.

In COPD, lung functioning worsens gradually and is irreversible. The management of COPD patients in group D, who experience frequent exacerbations, aims to delay the decline in airflow and reduce the frequency of acute exacerbations with the help of several management pathways. The treatment of COPD combines lifestyle management strategies, medications, and lung therapies.

Smoking is the most recognised risk factor for COPD. Therefore, smoking cessation is the first priority for minimising deterioration in COPD. However, lifestyle changes are not easy to implement. Many studies show that some COPD patients continue smoking after being diagnosed with COPD. Studies conducted in the US show that more than 20.6% of COPD patients continue to smoke (Laniado-Laborín, 2009; Pleis et al., 2009). Several other clinical studies also show that 54–77% and 38–51% of patients with mild and severe COPD, respectively, continue to smoke (Burge et al., 2000; Vestbo et al., 1999; Vestbo et al., 2004; Watson et al., 2006; Wedzicha et al., 2008). In Norway, 15–19% of COPD patients are

current smokers (Bhatta et al., 2018). Although smoking cessation is the most effective method to prevent impairment, implementing it requires considerable effort. Thus, medication therapy is combined with smoking cessation in most cases.

Medication use for COPD is stepwise and changes based on the severity of the patient's symptoms. For patients who have had two or more moderate or severe exacerbations (Group D), the medication combines two phases: maintenance therapy and therapy administered during exacerbations. Regular maintenance medication includes the combination of two bronchodilators or one bronchodilator and one inhaled steroid. Pharmacological treatment includes the following three main medications:

1. Two types of bronchodilators – the function of bronchodilators is to prevent COPD exacerbation by expending baseline expiratory flow. Thus, it reduces the risk of air trapping and critical air trapping during exacerbations. LAMA and LABA both improve airflow limitation and anti-inflammation; however, they function in different modes (Gulati & Wells, 2017; Horita et al., 2017):
    a. Long-acting muscarinic antagonist (LAMA) – LAMAs prevent airway constriction (bronchoconstriction) by blocking selected acetylcholine M_3 receptors (Alagha et al., 2014). Due to changes in airways environment and the effect of anti-inflammation, LAMAs have been considered the primary medication for COPD patients (Horita et al., 2017; Price et al., 2014).
    b. Long-acting beta$_2$-agonist (LABA) – LAMAs improve the airflow limitation by relaxing the airway muscles. They also reduce inflammation (Tashkin & Cooper, 2004) .
2. Inhaled steroids
    a. Inhaled corticosteroids (ICS) – ICSs help to reduce airway inflammation and exacerbation risk.

The combination of the two medications above is the initial treatment for group D patients: LABA/ LAMA and ICS/LABA. LAMA/LABA is preferred over ICS/LABA according to the most recent GOLD guidelines (GOLD, 2018). Concerns regarding the increased risk of pneumonia among ICS users have been discussed. However, some studies show that prescribed ICS/LABA accounts for a large percentage of COPD prescriptions. Statistics

provided by the Swedish National Board of Health and Welfare show that approximately 55% of COPD patients were treated with ICS/LABA in 2013, and another study shows that 40% of GOLD I and GOLD II (mild and moderate COPD) patients were treated with ICS/LABA (Price et al., 2014). Thus, it implies that there is a need to determine which treatment can be more beneficial for COPD patients.

Dual therapy can be provided separately in two inhalers or in one combined inhaler. NICE guidelines suggest that the number of inhaler applications should be as few as possible because it reduces the potential for misapplication, which reduces the treatment's effectiveness. When the exacerbation continues after administering a dual therapy treatment, adding LAMA for a current ICS/LABA user or adding ICS for a current LAMA/LABA user is recommended; this is called open triple therapy. However, the pathway of escalation to triple therapy is not consistent in the current guidelines. The 2018 GOLD guidelines recommend that dual therapy users be stepped up to triple therapy, especially LAMA/LABA users. For ICS/LABA users, GOLD recommends either stepping up to triple therapy or switching to LAMA/LABA before stepping up to triple therapy (GOLD, 2018). The NICE guidelines suggest that open triple therapy should only be prescribed for ICS/LABA users who continue experiencing exacerbations. Two clinical trials show that treatment effects are not significantly different between open- and fixed-triple therapy; the latter requires only one inhaler application daily and, thus, is preferred (Bremner et al., 2018; Vestbo et al., 2017; Zheng et al., 2018). The decision on whether daily single inhaler triple therapy should be extended to other patient groups and as a regular medication for COPD is still under discussion because the efficacy evidence is not yet sufficient (NICE, 2018).

There are two single inhaler triple medications with different compositions currently on the market: beclometasone dipropionate/formoterol/ glycopyrronium (Trimbow, Chiesi Limited) and fluticasone furoate/ umeclidinium/vilanterol (Trelegy, GSK). However, the former requires two inhalers daily, while fluticasone furoate/ umeclidinium/vilanterol/ (FF/UMEC/VI) requires only once-daily inhaler. Thus, it is the only once daily single inhaler triple therapy currently on the market.

Other medications, for example, theophylline and phosphodiesterase-4 inhibitors, are provided as additional medication options for patients. Other COPD maintenance therapies include long-term oxygen therapy (LTOT) and pulmonary rehabilitation. Long-term oxygen

therapy implies that patients have an either portable or standing oxygen device at home and use it when they feel they have difficulty breathing. Pulmonary rehabilitation programmes involve disease education, exercise, and dietary advice provided by specialists. These programmes improve patients' quality of life (Puhan et al., 2016; SKDE, 2017) and are delivered either individually or as a group and can last from a few days to a month. Influenza and pneumococcal vaccines are recommended for COPD patients, and these vaccinations can help to reduce the occurrence of exacerbations (Kopsaftis et al., 2018; Poole et al., 2000; Walters et al., 2017).

Treatments for acute exacerbation vary depending on the severity of the exacerbation. A moderate exacerbation can be controlled with medications, including antibiotics, oral steroids, or both these medications. When the exacerbation is more advanced, hospitalisation and oxygen therapy or ventilation treatment may be required. Ventilation support is provided for emergent COPD cases and is a resource-consuming treatment that requires healthcare personnel to assist when operating it (SKDE, 2017).

2.3 COPD in Norway

The estimated prevalence of COPD in Norway is about 6–8% of people age 40 or older, which is about 150,000–210,000 people (FHI, 2018; SKDE, 2017). However, whether the prevalence is increasing or decreasing in unclear. The Hordaland County Cohort Study shows that the prevalence of COPD increased from 7% to 14% between 1997 and 2005 (Waatevik et al., 2013). The link between smoking and COPD is strongly related. The decline in the percentage of the Norwegian population who smoke may imply a decline in the prevalence of COPD. Although the prevalence is unclear, the number of COPD patients using healthcare service has increased each year between 2008 and 2014, and in 2016, 55,000 people were treated for COPD (FHI, 2018). The opposite trend in the prevalence and number of COPD treatment services provided shows that underdiagnosis is an issue for COPD management. More than half of patients are unaware they have COPD until the symptoms are severe and require a visit to a physician (Helse- og omsorgsdepartementet, 2006; Hetlevik et al., 2016; Hvidsten et al., 2010).

The Norwegian government developed a national COPD strategic programme between 2006 and 2011 (Ministry of Health and Care Services, 2006). The main focuses of the programme are COPD (1) prevention and (2) detection/diagnosis, as well as (3) the follow-up/rehabilitation of COPD patients. Since the main risk factor for COPD is smoking, reducing the incidence of smoking in the population is considered a priority. The percentage of the Norwegian population who smoke has declined over the past decade. In 2008, 21% of females and males between the ages of 16 and 74 were smokers, and this percentage has declined gradually. In 2018, it was reported that 11% of females and 12% of males were smokers (SSB, 2018). Of the COPD patients who participate in a smoking cessation programme, 38% quit smoking within 3 years, and only 10% of COPD patients quit without participating in the programme (Sundblad et al., 2008).

COPD management is a collaboration between primary and secondary healthcare services according to the Norwegian national COPD management guidelines published in 2012 (Norwegian Directorate for Health and Social Affairs, 2012). General practitioners (GPs) are usually the first contact point when people experience respiratory symptoms. The recommended procedure for GPs to first ask patients symptom-related questions derived from GOLD guidelines and about the patients' smoking habits. Once the patient develops COPD symptoms, GPs should perform a spirometry test to confirm the diagnosis. Most GP clinics in Norway have spirometers. In most cases, GPs plan a management pathway for patients that includes prevention, treatment, and rehabilitation. When there is a need for secondary healthcare services, GPs should refer patients to the relevant healthcare sector for more in-depth diagnostic procedures and optimised treatment. GPs have also the responsibility of performing follow-up care for COPD patients, for example, performing an annual spirometry test for COPD patients with mild or moderate symptoms and twice spirometry test yearly for patients with severe symptoms. Also, follow-up is recommended for COPD patients within four weeks after a hospitalisation. In most exacerbation episodes, patients can be treated by GPs or emergency primary healthcare services. When the exacerbation is severe, hospitalisation may be required. During the hospitalisation, oxygen or non-invasive ventilation can be performed to reduce patients' breathing difficulties. In Norway, pulmonary rehabilitation is provided as a specialist healthcare service in hospitals. The programme requires at least a physician, a nurse, and a physiotherapist to formulate a rehabilitation plan for each patient (Norwegian Directorate for Health and Social Affairs, 2012; SKDE, 2017).

The pharmacological treatment guidelines for group D COPD patients in Norway suggests providing LAMA/LABA to patients as the first-line treatment. According to Norway's 2012 guidelines, patients who continue to experience exacerbations more than twice per year should be switched to ICS/LABA as triple therapy was not yet included. It is assumed that the Norwegian guidelines follow the NICE guidelines regarding the escalation of dual therapy to triple therapy due to the similarity between the British and Norwegian healthcare systems. Most Norwegian COPD patients begin treatment in primary healthcare clinics and are also followed up there, which also occurs in the United Kingdom (UK; Liaaen et al., 2010; NICE, 2018; Nielsen et al., 2009) Thus, for convenience, NICE guidelines are applied as the foundation of resource utilisation.

2.4 Cost-effectiveness of daily single inhaler triple therapy –FF/UMEC/VI

In 2017, the first daily single inhaler triple therapy FF/UMEC/VI was approved in the US and the European Union (EU). In Norway, the Norwegian Medicine Agency (NoMA), called the *Legemiddelverket* in Norwegian, approved triple therapy FF/UMEC/VI as a reimbursed medication for COPD treatment in May 2018. The reimbursement decision (*Refusjonsvedtak*) showed that it compared the price of FF/UMEC/VI treatment with the sum price of one dose of FF/VI (ICS/LABA) and one dose of UMEC, which is open triple therapy. This decision implies that single-inhaler triple therapy is more cost-saving in comparison to open triple therapy, and the need for two or more inhaler applications is another drawback of open triple therapy. The documents may also imply that the prescription of FF/UMEC/VI in Norway follows the NICE guideline that recommends stepping up people who currently receive ICS/LABA treatment to open triple therapy.

Because the FF/UMEC/VI medication is relatively new in the market, few published articles exist regarding the cost-effectiveness of this medication in comparison to the same type of dual therapies. One conference poster shows FF/UMEC/VI is more cost-effective in comparison to UMEC/VI in Canada (Risebrough et al., 2018), and another published study compares the cost-effectiveness of FF/UMEC/VI and a twice-daily LAMA/LABA medication in the UK. These two studies seem to indicate FF/UMEC/VI is more cost-effective (Ismaila et al., 2017). To gain a better understand of whether to include once-daily

triple therapy into the standard COPD maintenance medication and for which patient group, there is a need to explore the cost-effectiveness of once-daily triple therapy in comparison to once-daily dual therapies: LAMA/LABA (UMEC/VI) and ICS/LABA (FF/VI). UMEC/VI is considered a cost-effective LAMA/LABA treatment. From previous studies, UMEC/VI shows comparable efficacy with other LAMA/LABA (i.e., IND/GLY and TIO/OLO) medications (Buikema et al., 2018; Maqsood et al., 2019). Two studies show that IND/GLY and UMEC/VI have better treatment effects when compared to older medications (Celli et al., 2014; Horita & Kaneko, 2015). Previous studies show that the efficacy of different ICS/LABAs (i.e., FF/VI, BUD/FM, and FP/SAL) is comparable, especially in lung function improvement (Bernstein et al., 2018; Devillier et al., 2018; Hozawa et al., 2016; Svedsater et al., 2016). UMEC/VI and FF/VI both present a paralleled efficacy with other medications in the same category, and the benefit of once-daily dosing can be assumed that it is a preferred choice in each treatment, following a suggestion in the NICE guidelines (NICE, 2018). Data that is difficult to obtain for either UMEC/VI or FF/VI, we will adopt the treatment effect of LAMA/LABAs and ICS/LABAs respectively from previous studies.

Some studies show the efficacy of FF/UMEC/VI outweighs either LAMA/LABA or ICS/LABA. Lung function improvement and exacerbation reduction are the main goals of COPD management, especially decreasing the frequency of exacerbation. Exacerbations largely reduce patients' quality of life and accelerate the decline in lung functioning. Exacerbations are also a major economic burden on the healthcare system. A Swedish study shows that the direct medical cost of patients who experience frequent exacerbations (i.e., more than once per year) is about 2.4 times that of patients who do not. Severe exacerbations cost 10 times more than moderate exacerbations, which require only medication treatment (Lisspers et al., 2018). Research conducted by Lipson et al. (2018) shows the rate of moderate and severe exacerbations for daily single-inhaler triple therapy patients are 15% and 25% lower than FF/VI and UMEC/VI, respectively, and the time to first exacerbation is longer in once-daily triple therapy patients. Two additional studies show FF/UMEC/VI improves lung function more effectively when compared to twice-daily LAMA/LABA (Lipson et al., 2017; Wise et al., 2018). One study with different medication agents also shows twice-daily triple therapy reduces the risk of exacerbation (Papi et al., 2018). These three studies also find improvements on St. George's Respiratory Questionnaire (SGRQ) scores.

The issue of whether once-daily triple therapy should be preferred over LAMA/LABA or ICS/LABA is not yet resolved. According to the NICE guidelines, the decision on including daily single inhaler triple therapy as the preferred COPD maintenance pharmacological treatment will be published in June 2019 (NICE, 2018). Therefore, the current study can be considered an early exploration in the decision-making process.

3 Methods and Material

3.1 Research Question

The primary objective of this study was to determine whether utilising FF/UMEC/VI once-daily triple therapy as a standard treatment would be cost-effective compared to the other two common therapies for COPD patients. Cost-effectiveness was determined based on the Norwegian perspective.

3.2 Comparators

As mentioned in the 2.2, once-daily triple therapy was not yet the primary treatment option for COPD patients who experienced frequent exacerbations. In the NICE guidelines, the common practice for this patient group included two possible pharmacological treatments: dual therapy with LABA and LAMA or dual therapy with LABA and ICS. Thus, these two therapies were the comparators in this analysis, and three treatments were included:

1. Triple therapy (FF/UMEC/VI)
2. Dual therapy (LAMA/LABA, UMEC/VI)
3. Dual therapy (ICS/LABA, FF/VI)

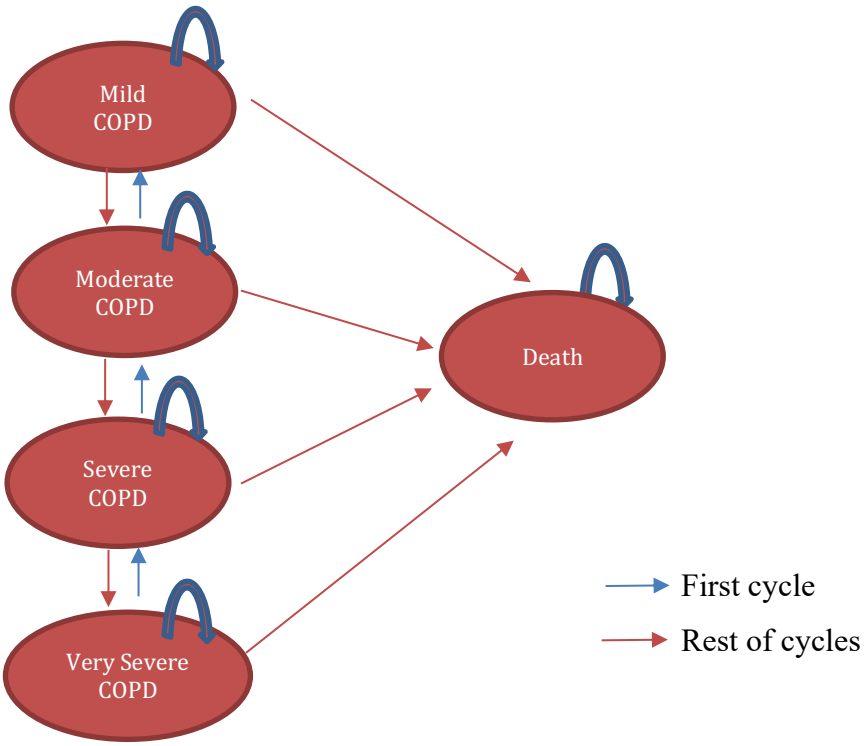
The focus of this study was on the clinical- and cost-effectiveness of once-daily triple therapy compared to different common practices. Thus, the study's scope included two separate economic evaluations: one with single inhaler triple therapy as the intervention arm and LAMA/LABA as the control arm and another one with triple therapy as the intervention arm and ICS/LABA as the control arm. The reason for dividing them into two models was that the therapy regimen involved making two decisions for different current medication users. Determining which current medication users would benefit more from stepping up to triple therapy required two paralleled models.

3.3 Model Structure

To follow the natural history of COPD progression, this study used a Markov model with four health states based on COPD severity stages, which were based on GOLD guidelines.

The GOLD classification was based on the patient's rate of decline in FEV_1: mild COPD (FEV_1 > 80% predicted), moderate COPD, (50% <= predicted FEV_1 < 80% predicted) severe COPD (30% predicted <= FEV_1. < 50% predicted), and very severe COPD (FEV_1 < 30% predicted) Due the irreversibility of lung damage, patients could either stay in the current health state longer, move to a more severe stage, or die in each cycle in the model, but not move to a less severe GOLD stage. However, the first cycle of the model allowed patients to move from a less severe GOLD stage due to the initial benefit of triple therapy on FEV_1 when patients moved from dual- to triple therapy (see Figure 2). This model structure was generated and modified based on the NICE economic model report for its COPD guidelines (NICE, 2018). The probability of death was defined as stage-specific mortality. Within each COPD stage, there were rates of exacerbation. It was assumed that the rate of exacerbation was related to COPD severity. The model used a three-month cycle length since it corresponded to the endpoints of the clinical trial data used in the analysis.

Figure 2 Markov Model



3.4 Population

Adults who had been diagnosed with COPD and were currently undergoing long-acting bronchodilator therapy (i.e., LAMA/LABA or ICS/LABA) but continued to experience

exacerbations or breathlessness were included in the analysis. The setting of this analysis was based on the Norwegian population and the Norwegian healthcare sector.

Baseline data regarding Norwegian COPD patients were extracted from the Norwegian Nord-Trøndelag Health Study (HUNT) population study (Leivseth et al., 2013), which was the largest and the most recent COPD population study conducted in Norway. It included 1,540 participants with post-bronchodilator FEV_1 / FVC < 0.70. The mean age of the COPD patient population was 63.6 years old, and the percentage of male COPD patients was 62.1%.

3.5 Perspective

This analysis was conducted from a societal perspective. COPD was a chronic disease, and due to the nature of COPD, its impacts on patients were long-lasting. The negative impacts affected patients' quality of life, mortality, and productivity. Some studies showed that COPD patients incurred more indirect costs due to productivity loss (Erdal et al., 2016; Tachkov et al., 2017; Wilson et al., 2017). This analysis included both healthcare costs and productivity loss to provide a more comprehensive understanding of the cost of COPD for society as a whole.

3.6 Time horizon

This analysis incorporated the costs and effects of the treatments on a lifetime horizon. A reasonable time horizon should be sufficient to include the health outcomes and all relevant costs. Two common methods were stated in the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)'s Good Research Practices: modelling to the age of 120 or until 99.9% of patients were dead (Siebert et al., 2012).

This analysis sets 30 years as the lifetime horizon. COPD was considered a chronic mid-age disease that was more likely to develop in people over 40 years old. The mean age of COPD patients in Norway was 63 (Nielsen et al., 2011). The expected lifespan of the Norwegian population was 82.7 years (81 for males and 84.5 for females). One Swedish study showed that COPD patients' lifespan was 8 years shorter on average (Lisspers et al., 2018). A report from ISPOR also suggested using 16-34 years as the lifelong horizon for lung disease (Tolley

et al., 2016). Thus, this analysis used 30 years for the cycle length to represent the lifetime horizon.

3.7 Discount rate

This analysis was conducted using a long-term horizon; thus, adjustments must be made when transforming future values to current values. The discount rate was set at 3%, which was the Norwegian Consumer Price Index obtained from *Statistisk Sentralbyra* [Statistics Norway] (SSB). This rate was commonly used in other economic evaluations from the Norwegian perspective (Erdal et al., 2016; Nielsen et al., 2009).

3.8 Health outcomes

Quality-adjusted life-year (QALY) was widely applied to evaluate the effect of medical treatment or healthcare services because it was a single measure that could be used to make comparisons between interventions (Drummond et al., 2015). It also captured both the quantitative and qualitative benefits or loss of a healthy state as it generated by a utility weight in a particular health state, which was health-related quality of life (HRQoL), and then multiplied the length of time a person remained in that particular health state (Starkie et al., 2011). Thus, QALY was the primary health outcome measure of this analysis. The model of this analysis contained different utility weights for each COPD stage, and the reduction of utility was applied to exacerbations based on their severity.

3.8.1 Stable utilities

EQ-5D was one of the HRQoL utility indices. It was applied to compare the utility differences between different patient groups with different diseases and in different areas. The design of EQ-5D was not disease-specific; thus, it provided a standardised index for utility comparisons. COPD was a complex disease that impacted a considerably large population over a long period of time. Therefore, the quality of a patient's life during the time period was also an important index when comparing the effect of different treatments. SGRQ was a disease-specific health-related quality of life instrument designed for COPD patients.

An SGRQ score was not a utility measurement; however, it could be transformed into an EQ-5D utility index (Starkie et al., 2011).

SGRQ was a questionnaire used to measure the health status of patients experiencing chronic airflow limitation. The questionnaire was comprised of three parts: symptoms, activity, and impact on daily life, and there was a total score. In total, there were 76 items in the questionnaire (Jones et al., 1992). The total score ranged from 0 to 100. Zero was the best health state, and 100 was the worst health state. To transform an SGRQ score into an EQ-5D index score, an algorithm developed by Starkie et al.(2011) was used:

$$EQ-5D\ utility\ =\ 0.9617\ -\ 0.0013\ SGRQ\ Total\ -\ 0.0001\ SGRQ\ Total^2\ +\ 0.0231\ Male$$

This formula was an alternative when clinical trial information was inadequate and had been used in NICE economic reports (NICE, 2018). To the researcher's knowledge, the COPD stage-specific SGRQ scores had not been updated for COPD patients in Norway. Hence, this analysis adopted the SGRQ points for each level of COPD severity from a European study conducted in 2011 that included seven countries: Germany, France, Spain, Belgium, the Netherlands, the UK, and Italy. These data were considered more up-to-date and detailed (Jones et al., 2011). Another US study also conducted in 2011. One problem with the SGRQ points from the US study was there was almost no change in SGRQ points at different levels of severity. For example, there was only a 0.1 point difference between severe and very severe COPD (Pickard et al., 2011). The difference between severe and very severe COPD is around 13 SGRQ points in Nordic and Swedish studies (Gudmundsson et al., 2006; Ståhl et al., 2005). Thus, this analysis adopted the SGRQ scores from the European study. The male COPD population percentage was based on the second Norwegian HUNT study (HUNT2), which showed 59 percent of mild COPD, 62 percent of moderate COPD, and 69% of severe and very severe COPD patients were male (Leivseth et al., 2013). Thus, the baseline utility weights for different COPD stages were 0.78 for mild, 0.76 for moderate, 0.66 for severe, and 0.56 for very severe COPD. Table 6 in the Appendix showed different SGRQ points from different studies and their corresponding EQ-5D score after calculations based on Norwegian demographics.

A comparison between the calculated EQ-5D scores and different EQ-5D scores from previous studies were listed for validation purposes (see Table 7 in the Appendix). According

to the NICE committee, the difference between moderate and severe COPD on quality of life should be larger (NICE, 2018). Some studies in Table 7 showed that there was no difference between severe and very severe COPD or between moderate and severe COPD. Thus, instead of using the existing EQ-5D scores, this analysis used SGRQ points collected from previous studies and used the formula presented in 3.8.1 to calculate the corresponding EQ-5D score. The utility improvement of 3.7 SQRQ were applied to dual therapies (Lipson et al., 2018). After performing calculations, the EQ-5D scores were 0.809, 0.794, 0.701, and 0.605, which corresponded to mild, moderate, severe, and very severe COPD, respectively. It was assumed there were no obvious differences in utility between the dual therapies. This was supported by the NICE guidelines, where the utility difference between the two dual therapies was less than 0.005 (NICE, 2018). The utility improvement of once-daily triple therapy was taken from a clinical trial. It showed a mean of 1.8 SGRQ higher than both dual therapies (Lipson et al., 2018). After performing calculations, the EQ-5D scores were 0.824, 0.809, 0.720, and 0.627, which corresponded to mild, moderate, severe, and very severe COPD, respectively.

3.8.2 Disutility of exacerbation

In addition to stable utility, disutility caused by exacerbations were also modelled in this analysis. The reduction in quality of life-years due to exacerbation was separated into non-hospitalised moderate exacerbation and severe exacerbation requiring hospitalisation. The disutility of exacerbation was generated using an approach described by Rutten-van Mölken et al. (2009), who used visual analogue scale (VAS) and time trade-off (TTO) values to calculate a utility decrement for an exacerbation: 0.01 and 0.04 for moderate and severe exacerbations, respectively, within a three-month time period.

3.9 Cost-effectiveness outcomes

Cost-effectiveness results were presented using an incremental cost-effectiveness ratio (ICER), which was a measure designed to compare the cost for every QALY gain from an intervention. The formula was written as follows:

$$ICER = \frac{Cost\ of\ triple\ therapy - Cost\ of\ dual\ therapy}{QALY\ of\ triple\ therapy - QALY of\ dual\ therapy}$$

Each healthcare system had a threshold for cost per QALY. It was standard for each system to decide whether an intervention was cost-effective for society. In Norway, a willingness-to-pay (WTP) of 500,000 NOK per incremental QALY was widely used. Ottersen et al. (2016) suggested using 500,000–750,000 NOK per QALY for lung diseases such as severe asthma and idiopathic pulmonary fibrosis. Thus, this analysis used 500,000 NOK and increased the threshold in probabilistic models when applicable.

3.10 Mortality

It was assumed that mortality was only based on COPD severity and age as there was no significant difference in dual therapy and triple therapy according to two clinical trials and a meta-analysis (Lipson et al., 2017, 2018; Zheng et al., 2018). Standardised mortality ratios (SMRs) by COPD severity were generated from the Norwegian HUNT study (Leivseth et al., 2013). An SMR was defined as follows:

SMR = (Observed number of deaths per year) / (Expected number of deaths per year)

The SMR of different levels of COPD severity was 0.84 for mild, 1.47 for moderate, 2.7 for severe, and 3.99 for very severe. The results were shown in Table 1. It was estimated that patients with mild COPD had lower mortality risk, which was consistent with a study based on the US population with a mean COPD patient age of 67. The US study showed the relative risk for mild and moderate COPD is 0.9 and 1.4, respectively, and the relative risk for severe and very severe COPD was 2.6 (Shavelle et al., 2009; Wilson et al., 2017).

Table 1 Standardised mortality ratio for each level of COPD severity

	Females (95% CI)	**Males (95%CI)**	**Norwegian COPD patients**
Mild COPD	0.75 (0.59 to 0.95)	0.91 (0.76 to 1.08)	0.84*
Moderate COPD	1.7 (1.46 to 1.99)	1.33 (1.20 to 1.47)	1.47*
Severe COPD	4.72 (3.62 to 6.08)	1.77 (1.47 to 2.12)	2.70*
Very Severe COPD	5.15 (2.45 to 9.92)	3.47 (2.70 to 4.39)	3.99*
NOTE	*Based on the HUNT sex ratio		

To adjust all-cause mortality to the probability of death among the Norwegian population, the 2017 Norwegian lifetable was extracted from SSB. The one-year age-group yearly probabilities of death between the ages of 40 and 69 were applied to the model. According to the lifetable, the one-year probability of death for the general population for this age range was 0.06–1.28%. Thus, we established a function based on the ratio of mortality between the UK lifetable and Norwegian lifetable at difference ages, followed by multiplying it with the SMRs to adjust for different COPD stages. The formula below was applied to calculate a 3-month-probability of death. Thus, when a person enters the first cycle at the age of 40, the 3-month probability of death for different levels of COPD severity was as follows: mild = 0.01%, moderate = 0.02%, severe = 0.04%, and very severe =0.06%. The equation used to transform a rate into a probability was as follows:

$$p = 1 - \exp(-rt)$$

where p was the probability, r was the rate, and t was the time period. The details were described in (Briggs et al, 2006). Since our model's cycle was 3 months, the age-and stage-adjusted mortality rates were updated every 4 cycles.

3.11 Transition probability

Transition probabilities between different levels of COPD severity were obtained from a NICE economic report for COPD (NICE, 2018). According to the NICE guidelines, due to the potential beneficial effect of a new treatment on lung function, there was a probability of reducing the severity of COPD symptoms. However, this only applied to the first cycle of triple-therapy as the standard treatment pathway implied that triple therapy was prescribed for patients who were already receiving dual therapy. Thus, this analysis involved constructing two transition probability matrices: one for the first cycle of triple therapy and another for all cycles of dual therapies and all cycles of triple therapy after the first cycle. The latter should be the same for all treatments. For the first cycle, the calculation baseline transition probability was based on unpublished trial data (SCO10047) for triple therapy. The rate of decline was estimated according to the treatment effect on FEV_1. The rest of cycles

was based on the natural decline in FEV_1 during the 3-month period, which was applied as different COPD severity levels. (NICE, 2018a)

It was assumed that the probability of death was the same regardless of which treatment the patients received, which meant the only improvement in mortality for triple therapy was due to reducing the speed of COPD progression applied only in the first cycle. The assumption was based on the results of two clinical trials (NCT02345161 and NCT02164513) for fixed-dose triple therapy and a meta-analysis consisting of 14 clinical trials for both separate- and fixed-dose triple therapy. The studies showed there was no significant difference in all-cause mortality between triple therapy and either of the two dual therapies (Lipson et al., 2017, 2018; Zheng et al., 2018).

The probability of transitioning to either a better or worse health stage was calculated using the same ratio of mortality rates at the age of 40 between the UK and Norwegian population. Therefore, the probability of staying in the current state was calculated by the subtracting age- and stage-specific mortality and transition probability from 1. The resulting transition probabilities were shown in Table 2 and Table 3.

Table 2 Transition probability matrix for triple therapy in the first cycle

COPD stage	Mild	Moderate	Severe	Very Severe	Death
Mild	1-7.94%-p(age)	7.94%			p(age)
Moderate	9.3%	1-4.2%-9.3%-p (age)	4.2%		p(age)
Severe		17.8%	1-3.5%-17.8%-p(age)	3.5%	p(age)
V. Severe			26.2%	1-26.2%-p(age)	p(age)

Table 3 Transition probabilities for other cycles.

COPD stage	Mild	Moderate	Severe	Very Severe	Death
Mild	1-1.8%-p(age)	1.8%			p(age)
Moderate		1-1.1%-p(age)	1.1%		p(age)
Severe			1-0.05%-p(age)	0.5%	p(age)
V. Severe				1-p(age)	p(age)

3.12 Rate of Exacerbation

The stage- and treatment-specific 3-month exacerbation rates were extracted from the NICE guidelines. The source of moderate and severe exacerbation rates was a large British study (Rothnie et al., 2018). The study included 48,075 COPD patients with GOLD classification and the information was collected through clinical practice data records. Although it was from the British perspective, its large sample size and quality of the data might be a good reference for the Norwegian setting. This dataset also provided a detailed overview of the exacerbation rate stratified by COPD stages, which was difficult to find in the Norwegian perspective. The moderate exacerbation rate was between 0.38 to 0.60, and the severe exacerbation rate was between 0.03 and 0.08 for ICS/LABA patients. The moderate exacerbation rate was between 0.34 to 0.53, and the severe exacerbation rate was between 0.02 and 0.6 for LAMA/LABA patients. For triple therapy, the exacerbation rates were calculated based on the relative risk obtained from a clinical trial (Lipson et al., 2018). The exacerbation rate relative risk for triple therapy versus ICS/LABA (FF/VI) was 0.85, and for severe exacerbation, the rate was 0.87. When compared with LABA/LAMA (UMEC/VI), the exacerbation rate ratio was 0.75, and for severe exacerbation, it was 0.66. Therefore, there were two sets of exacerbation rates with respect to different dual therapies. The full list of exacerbation rates was presented in Table 8.

3.13 The Cost of COPD

This analysis was conducted from a societal perspective. Thus, the cost of COPD included two large categories: direct costs and productivity loss. Direct costs included most of the relevant medical costs, and they were divided into three parts: medication costs, maintenance costs, and exacerbation costs. Productivity loss included sick leave and disability pension costs.

3.13.1 Direct Costs

Medication costs

To calculate the cost per cycle for each treatment regime, we used a unit cost from the NoMA medicine database, and the dosage data were obtained from the summary of product

characteristic (SmPC) for each product. The three treatments included in this study all contained long-acting agonists. Thus, the effects of the medication lasted 24hrs. The recommended dose for all three treatments was one puff per day. There was no specified dose adjustment among the study population. The total cost per 3-month cycle of FF 92mg/ VI 22mg, UMEC 55mg/ VI 22mg, and FF 92mg/UMEC 55mg/ VI 22mg were 1,020 NOK, 1,544 NOK, and 2,115 NOK, respectively.

Maintenance costs

Maintenance costs included the regular costs of COPD treatment, for example, physician visits, spirometry tests, vaccination, and rehabilitation services. Resource utilisation calculations were performed based on the framework of a NICE economic report (NICE, 2018) with numbers generated from different studies. If the data were based on annual figures, they were divided by 4 to fit the 3-month cycle. Details regarding maintenance resource utilisation and their sources were listed in Table 9. The costs of resources were generated from the Norwegian national tariff system, DRG weights, and NoMA medicine database. Norwegian national tariffs were applied as the base cost of primary healthcare services. However, the tariff represented only 40% of the total healthcare cost. To reflect the total cost, we multiplied the tariff by 2.5. For hospital services, the DRG weight was used for cost calculations. The Norwegian DRG baseline cost in 2019 was 44,654 NOK. The DRG cost only accounted for half of the total resource costs. Thus, doubling the DRG costs was needed. The material utilised for unit costs was listed in Table 10. The total maintenance costs during different COPD stages were similar: 21,270 NOK, 20,678 NOK, 21,329 NOK, and 23,770 NOK for mild, moderate, severe, and very severe, respectively.

Exacerbation costs

Exacerbation costs were divided into two categories: costs related to moderate exacerbation and severe exacerbation. The former required outpatient oral corticosteroid and antibiotic treatments, while the latter required hospitalisation, which was the main source of COPD's economic burden. On average, about 17,000 patients were admitted annually to the hospital as emergency cases between 2013 and 2015. Of these patients, 18% required ventilation, which was a high resource-consuming healthcare service (SKDE, 2017). Thus, approximately

3,060 COPD patients required ventilation annually. However, severe exacerbations happened much less frequently than moderate exacerbations as only about 10% of exacerbations were severe. For convenience, we used 2% as the percentage of severe exacerbations that required ventilation.

Ambulance transportation costs were extracted from SSB. In 2017, there were about 726,000 ambulance cases at a cost of about 6.2 billion NOK. Thus, it costed about 8,510 NOK per ambulance episode. The cost was high because it included emergency transport (i.e., ambulance) services provided cars, boats, and airplanes. The resource utilisation sources were listed in Table 11. Costs were based on the national tariffs and DRG data, and the detailed unit costs were shown in Table 10. The cost per moderate exacerbation was 3,790 NOK, and per severe exacerbation, which required hospitalisation, is 94,868 NOK.

3.13.2 Productivity loss

Several methods were used to calculate productivity loss. The human capital approach assumed the state of full employment. Thus, any absence or disability was counted as a cost. Another approach was to not include productivity loss in the indirect cost of a disease under the assumption that an employee on sick leave from work could be replaced by a temporary worker if needed. Or, if the work was not urgent, it could be postponed until the worker returned to from sick leave. In this case, the impact of job absenteeism was minimal on production. The third approach was the friction cost method, which calculates production loss within a period of time that was impacted by a disease (Koopmanschap et al., 1995; Koopmanschap & van Ineveld, 1992).

This analysis used the assumption of full employment; thus, any work absenteeism was counted as a loss. Previous studies showed that COPD patients had high rates of sick leave usage, and many of them received a disability pension. Compared to the general population (9.8%), a much higher proportion of COPD patients received a disability pension. The EconCOPD study showed that 30% of general population COPD cases and 65% of hospital-recruited COPD cases received a disability pension. In the Norwegian study, it was only 7% for the control group.(Erdal et al., 2014) A study conducted in 2009 found that about 10% of COPD patients had taken sick leave in the past 12 months, and 14% were receiving a

disability pension (Nielsen et al., 2009). Thus, it was believed that COPD conditions might be related to production loss.

Sick leave

Sick leave costs were calculated by multiplying the number of days of missed work and the worker's average daily income, which was calculated by the yearly average national income divided by the number of working days in a year. According to SSB, in 2018, the yearly GDP per capita in Norway was 665,662 NOK. By definition, according to the Norwegian Tax Administration (*Skatteestaten*), the number of working days per year was 230 in Norway. After deducting the 5 weeks of paid leave provided to all workers in Norway, the cost of productivity for every sick leave day was 3,247 NOK.

Disability pensions

The annual disability pension was 220,893 NOK in 2018 according to the Norwegian Labour and Welfare Administration (NAV). We used a disability pension weight of 2.28 for people who lived with a partner/spouse/cohabitant in the same household. In 2014, according to NAV, 2,624 people received a disability pension due to COPD.

The annual number of sick leave days and the percentage of disability pensions were generated from a German study conducted by Wacker et al.(2016), who stratified them by COPD stages. The average number of sick leave days utilised by COPD patients was about 31.3 days, 26.3 days, 34.1 days and 40.1 days annually for mild to very severe COPD patients, and approximately 20% receive a disability pension. Because productivity loss was calculated for a one-year period, this cost was included in every fourth cycle.

3.14 Uncertainty

Uncertainty in the parameters was addressed probabilistically. Probabilistic sensitivity analysis (PSA) was conducted to explore the probability that the given results were correct. This analysis involved conducting a Monte Carlo simulation with 5,000 iterations for each parameter. The randomised results of cost and QALYs for each therapy were summarised and compared. To handle the uncertainty, the net monetary benefit (NMB) framework was applied. The formula of NMB was written as follows: (Briggs et al., 2006)

NMB = (WTP threshold * incremental effectiveness) – incremental cost.

The incremental NMB compared the difference in NMB between treatments. A positive incremental NMB indicates that the new intervention was cost-effective compared with the comparator. Therefore, uncertainty was reflected in the number of iterations that had positive incremental NMB. When the proportion of positive incremental NMB was high, the uncertainty of the results was low and vice versa. If less than 95% of the iterations showed the same pattern, it was considered as uncertain results in current study. The results were shown in cost-effectiveness acceptability curves (CEACs). CEACs indicated the probability that a treatment would be cost-effective at different thresholds. The cost-effectiveness acceptability frontiers (CEAFs) demonstrated the probability of interventions having the highest NMB for a given WTP threshold. The probability of making decision error was 1 minus the value of CEAF(Briggs et al., 2006). In order to consider the opportunity loss due to the error made, expected value of perfect information (EVPI) was represented. EVPI is calculated as the average of the maximum NMBs across the 5,000 iterations minus the maximum of the average expected NMBs across the treatments. (Oostenbrink et al., 2008)

Different probability distributions were assigned for each parameter to reflect the parameter's uncertainty in PSA. A table of the probabilistic distribution of parameters was presented in Table 8 in the Appendix. Transition probabilities were assigned as Dirichlet distributions because the data were multinomial. The number of patients transferred between states were estimated from NICE economical report (NICE, 2018).

Utility weights were assigned beta distributions. Because the utility weights were transformed from an SGRQ score to EQ-5D based on a formula developed by Starkie et al. (2011), we did not have the standard errors. However, we applied the ratio of standard errors to point estimates from Starkie et al. (2011). The standard errors were assumed to be 4%, 3%, 5% and 11% of the point estimate for mild, moderate, severe, and very severe COPD, respectively. For the disutility of exacerbation, we applied the same standard errors from the data source by Rutten-van Mölken et al.(2009).

Costs were allocated as a gamma distribution as cost data were often very skewed. Due to the lack of real data, the standard error was assumed to be 10% of the mean cost. According to

research conducted by Tachkov et al. (2017) and Wacker et al.(2016), the cost of productivity loss was about 4–19% of the point estimates. Thus, we took the mean of the percentages and resulted in a 10%-point estimate for the standard errors. Thereafter, we could calculate α and β using an equation described by Briggs et al. (2006):

$$\alpha = \frac{\bar{\mu}^2}{s^2} \quad , \qquad \beta = \frac{s^2}{\bar{\mu}}$$

Where $\bar{\mu}$ was the mean, and s was the standard error.

The rate of exacerbation and rate of productivity loss were allocated to a gamma distribution since these parameters contained only positive values and were usually skewed. As COPD severity increased, the rate of exacerbations, the rate of disability pension and the number of sick leave days also increased. For the rate of exacerbation, the standard errors we applied referred to the NICE guidelines. Thus, we used the average ratios of standard error and point estimates, which resulted in a 3%-point estimate for the standard error of the rate of moderate exacerbation for patients with mild COPD, 2% for moderate COPD, 4% for severe COPD, and 4% for every severe COPD. For the severe exacerbation rate, the percentages used were 9%, 7%, 6%, and 10% for mild, moderate, severe, and very severe COPD, respectively. Log-normal distributions were allocated for relative risks of exacerbation.

It was assumed that the standard error was 10% of the point estimates for the rate of disability pensions since it was difficult to estimate the standard error without the preliminary data. Two previous studies showed that the standard error of the number of disability days was approximately 0.4–20% of the mean (Erdal et al., 2014; Tachkov et al., 2017). Thus, after taking the mean of the percentages, it was assumed to be 10% of the point estimate in this analysis for our convenience. The standard errors of sick leave days were based on Wacker et al. (2016). Since the point estimates were obtained from the same study, it might be reasonable to apply; however, the drawback was the research was based in the German setting.

4 Results

At the threshold of 500,000 NOK per QALY, fixed-dose FF/UMEC/VI triple therapy is expected to be more cost-effective than both UMEC/VI and FF/VI in most cases. With a probability of 85%, the FF/UMEC/VI is more cost-effective than UMEC/VI. When compared to FF/VI, FF/UMEC/VI therapy is more cost-effective in 77% of the cases.

4.1 Cost-effectiveness of treatment: FF/UMEC/VI versus UMEC/VI

The deterministic cost-effectiveness results show that FF/UMEC/VI is dominant to UMEC/VI treatment. That is, FF/UMEC/VI is less costly and more effective when compared to UMEC/VI dual therapy. The expected healthcare direct cost per person for FF/UMEC/VI is 1,988,174 NOK, and the expected productivity loss is 2,567,868 NOK. The expected QALY gain from FF/UMEC/VI therapy is 14.2 QALYs and a life-year gain of 18.79 years. UMEC/VI has an expected direct cost of 2,050,256 NOK and a productivity loss of 2,579,232 NOK. The expected QALY gain of UMEC/VI is 13.78 QALYs and a life-year gain of 18.76 years. Thus, the ICER is a negative value, which implies FF/UMEC/VI is an economically dominant treatment.

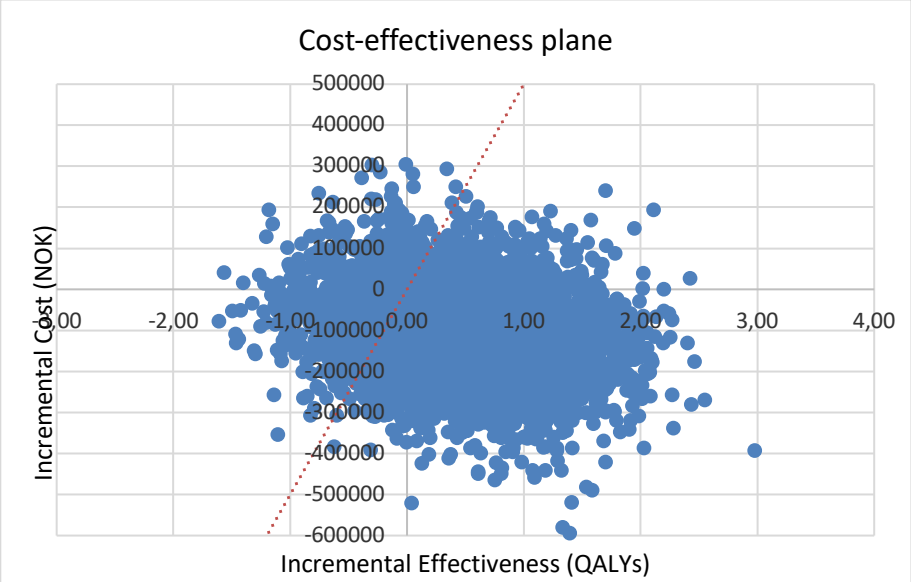
Table 4 Base-case analysis results over a lifetime horizon – FF/UMEC/VI vs. UMEC/VI

Parameter	FF/UMEC/VI	UMEC/VI
Cost		
Direct Cost	1,988,174 NOK	2,050,256 NOK
Productivity loss	2,567,868 NOK	2,579,232 NOK
Total Cost	4,556,042 NOK	4,629,758 NOK
Life-years	18.79	18.76
QALYs	14.20	13.78
ICER		
Cost per life-year gained	-	**FF/UMEC/VI dominates**
Cost per QALY gained	-	**FF/UMEC/VI dominates**
Notes: Costs are based on 2019 prices.		

After considering the uncertainty of the model, the probabilistic results present the percentage of the 5,000 iterations that shows the FF/UMEC/VI is cost-effective. As depicted in the cost-effectiveness (CE) plane (Figure 3), approximately 85% of the simulated results are located

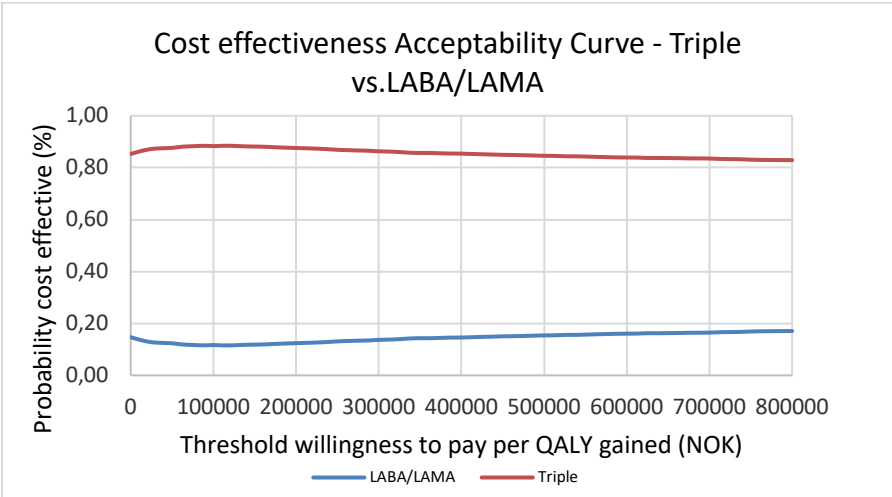
in the southeast quadrant, which indicates FF/UMEC/VI is more cost-effective and dominant to UMEC/VI at the willingness-to-pay threshold of 500,000 NOK per QALY.

Figure 3 Cost-Effectiveness plane - FF/UMEC/VI vs. UMEC/VI



As shown in Figure 4, the cost-effectiveness probability curve (CEAC) of FF/UMEC/VI lies above the curve of UMEC/VI at all thresholds. The proportion of simulated iterations that shows FF/UMEC/VI is cost-effective ranges between 83–88% according to different thresholds. The probability of FF/UMEC/VI being cost-effective peaks at 88% when the threshold is between 50,000 to 200,000 NOK and then drops steadily after that. However, the probability of UMEC/VI being cost-effective is between 12–17%. Thus, it is more likely that FF/UMEC/VI is cost-effective.

Figure 4 Cost-Effectiveness Acceptability Curve - FF/UMEC/VI vs. UMEC/VI



From the EVPI for population curve depicted in Figure 5, we can see that the EVPI fells slightly as the WTP threshold increases from 0 to 50,000 NOK because the decreased probability of having an opportunity loss offsets the increased cost of this opportunity loss. It reflects to the increased probability of FF/UMEC/VI having the highest net monetary benefit in the CEAF (see Figure 6). However, at higher thresholds, the expected cost of uncertainty is higher. It is because the effect of increased probability of making error (see Figure 6) and the increased value of opportunity costs. If additional research is expected to cost under 428 million NOK (or 28,345 NOK per person), then the research may be considered cost-effective when the willingness-to-pay threshold is 500,000 NOK per QALY.

Figure 5. Expected Value of Perfect Information- FF/UMEC/VI vs. UMEC/VI

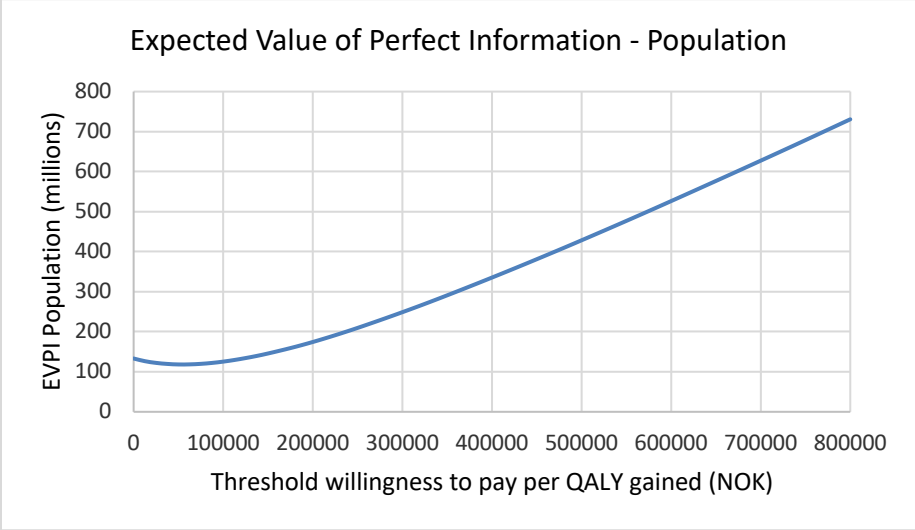
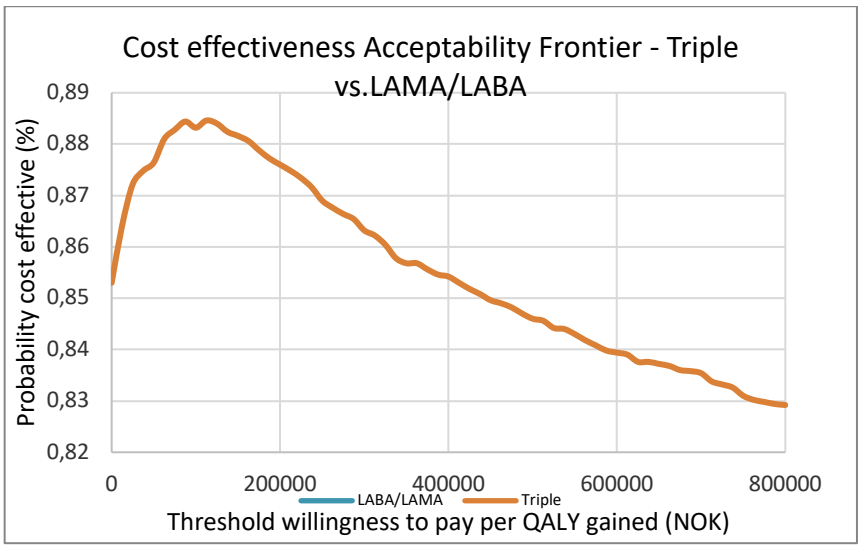


Figure 6 Cost-effectiveness acceptability frontier - FF/UMEC/VI vs. UMEC/VI



There is no clear difference when healthcare direct costs are focused on in the model. The results show a similar trend where FF/UMEC/VI is still more likely to be cost-effective than UMEC/VI.

4.2 Cost-effectiveness of treatment: FF/UMEC/VI vs. FF/VI

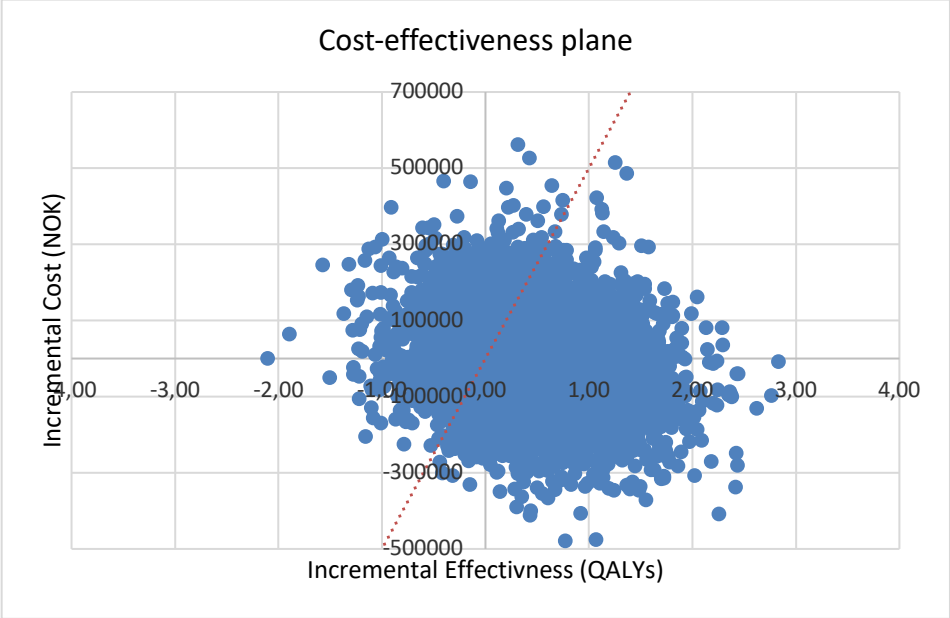
FF/UMEC/VI is considered cost-effective in comparison to FF/VI treatment in the deterministic model at the willingness-to-pay threshold of 500,000 NOK per QALY. FF/UMEC/VI is associated with gains of 0.02 LYs and 0.41 QALYs, and the incremental total cost is 10,024 NOK. The estimated direct cost per person of FF/UMEC/VI and FF/VI are 2,119,996 NOK and 2,098,609 NOK, respectively. The estimated productivity loss costs per person are 2,567,868 NOK and 2,579,232 NOK for FF/UMEC/VI and FF/VI, respectively. The ICER is 24,381 NOK per QALY and 441,087 NOK per LY. Thus, FF/UMEC/VI is considered cost-effective (Table 5).

Table 5 Base-case analysis results over a lifetime horizon – FF/UMEC/VI vs. FF/VI

Parameter	FF/UMEC/VI	FF/VI
Cost		
Direct Cost	2,119,996 NOK	2,098,609 NOK
Productivity loss	2,567,868 NOK	2,579,232 NOK
Total Cost	4,687,865 NOK	4,677,841 NOK
Life-years	18.78	18.76
QALYs	14.17	13.76
ICER		
Cost per life-year gained	441,087 NOK	-
Cost per QALY gained	24,381 NOK	-
Notes: Costs are based on 2019 prices.		

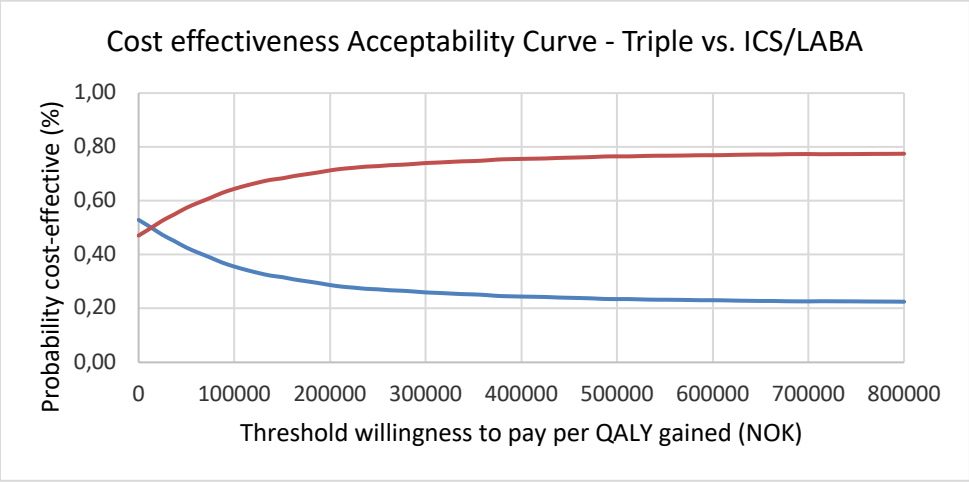
The CE plane results show that approximately 77% of the time, FF/UEMC/VI is located in the northeast quadrant of the ICER plane (see Figure 7). It implies that in these cases, FF/UMEC/VI therapy is considered cost-effective when compared with FF/VI at a willingness-to-pay threshold of 500,000 NOK.

Figure 7 Cost-Effectiveness plane - FF/UMEC/VI vs. FF/VI (total cost)



There are some differences in the results when looking at costs with or without productivity loss. Thus, in this section, we use two models. From the results based on healthcare direct costs, the CEAC (Figure 8) shows that about 77% of simulated values imply that FF/UMEC/VI may be considered cost-effective when the willingness-to-pay threshold is 500,000 NOK. About 50–53% of the time, FF/VI is considered more cost-effective when the threshold is reduced to under 12,500 NOK per QALY. It is the interception point between the two CEAC curves.

Figure 8 Cost-Effectiveness Acceptability Curve - FF/UMEC/VI vs. FF/VI (direct cost)



The CEAF depicted in Figure 9 shows that decision uncertainty falls when a WTP threshold is over 25,000NOK. However, the constantly increased valuation of opportunity loss outweighs the reduction of the probability of error, the EVPI increases steadily as threshold

increases (see Figure 10). The EVPI drop between WTP threshold of 37,500NOK and 150,000NOK corresponds to the substantial increased probability of FF/UMEC/VI to have the highest net monetary benefit in Figure 9. The population EVPI is 728 million NOK (or 48,161NOK per person) when the willingness-to-pay threshold is 500,000 NOK per QALY.

Figure 9 Cost Effectiveness Acceptability Frontier - FF/UMEC/VI vs. FF/VI (direct cost)

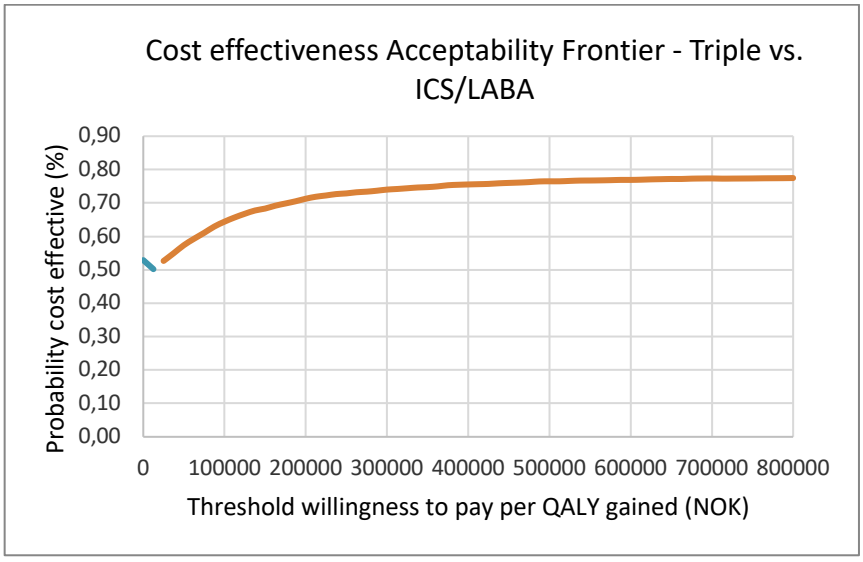
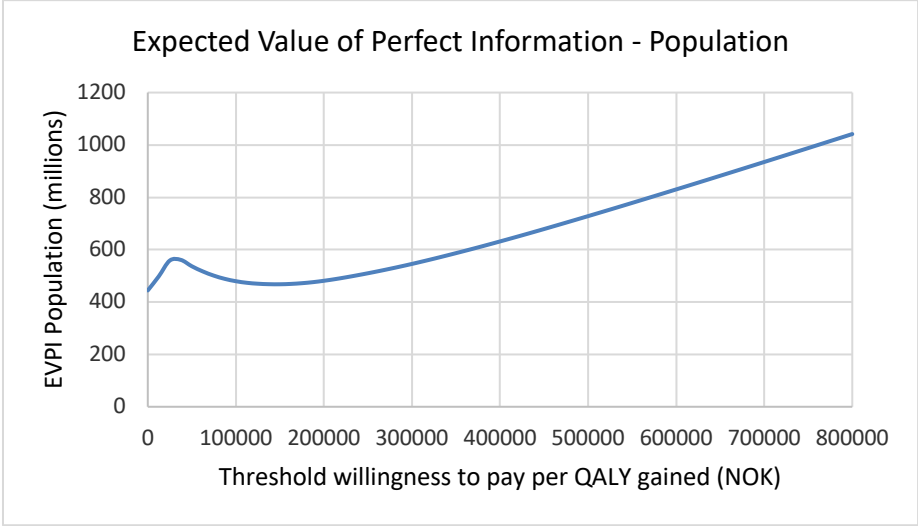


Figure 10 Expected Value of Perfect Information - FF/UMEC/VI vs FF/VI (direct cost)



FF/UMEC/FI is associated with being cost-effective relative to FF/VI when the model includes both direct and indirect costs. As shown in Figure 11, there is no intersection point between the two CEACs. FF/UMEC/VI's curves are always above the FF/VI's. The probability of FF/UMEC/FI being cost-effective is about 77% at the threshold of 500,000 NOK per QALY. As indicated in Figure 12, the cost of uncertainty is high. The EVPI shared

the similar pattern as in Figure 5, where the EVPI drops at the starting point and increases gradually after a point. This EVPI curve is consistent with CEAF in Figure 13. At the threshold of 500,000 NOK, it reflects 714 million NOK (or 47,207 NOK per individual). Thus, if additional patient information costs less than 47,207 NOK per person, it can be viewed as cost-effective information.

Figure 11 Cost-Effectiveness Acceptability Curve - FF/UMEC/VI vs. FF/VI (total cost)

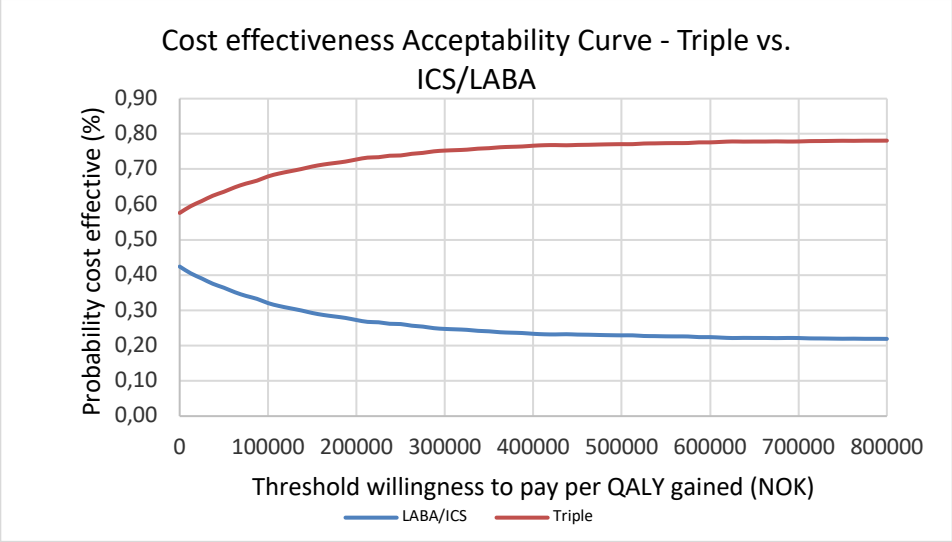


Figure 12 Expected Value of Perfect Information - FF/UMEC/VI vs FF/VI (total cost)

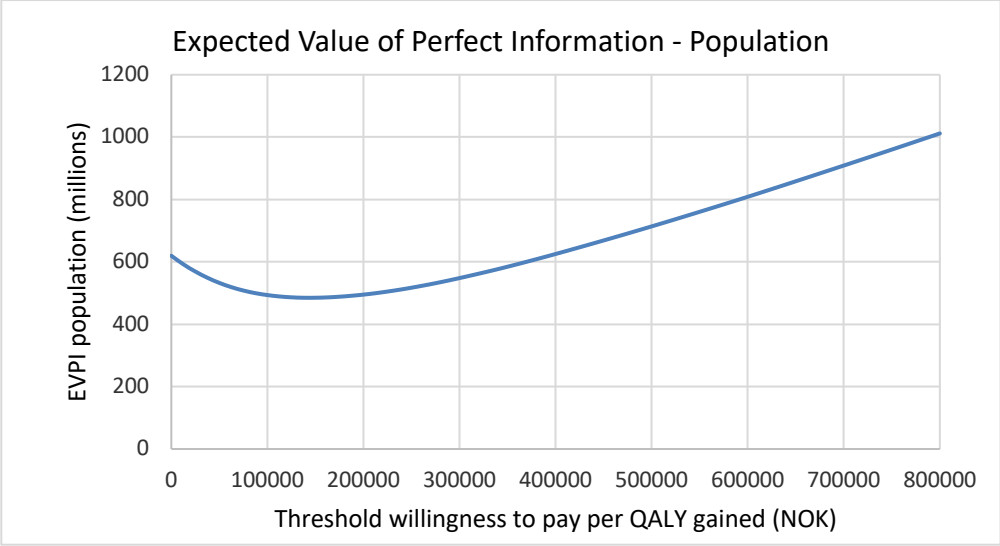
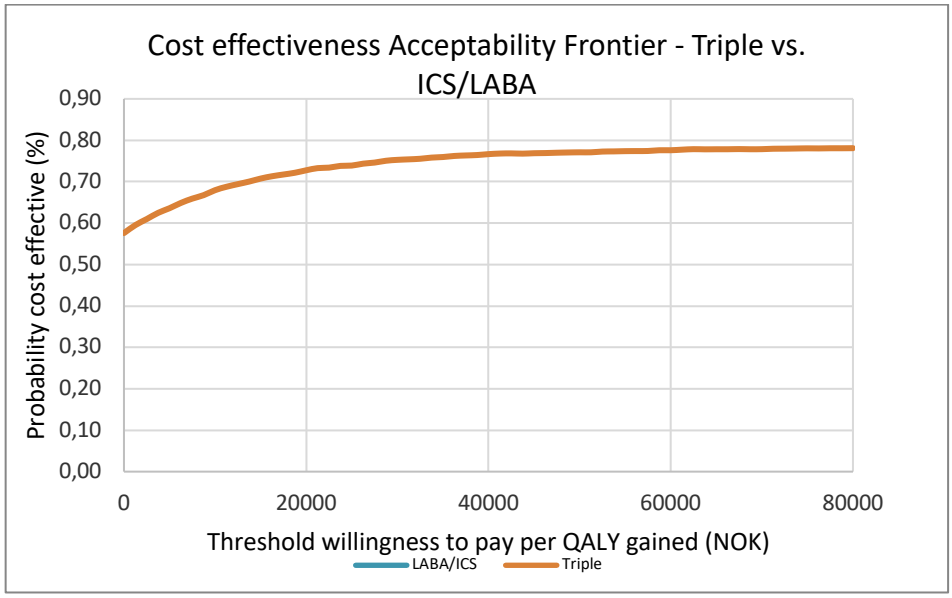


Figure 13 Cost Effectiveness Acceptability Frontier - FF/UMEC/VI vs. FF/VI



From the results above, it is concluded that FF/UMEC/VI is cost-effective compared to UMEC/VI and FF/VI. However, all models show a below 95% of certainty. Thus, additional information is needed to reduce the probability of making the wrong decision and to reduce the expected cost of uncertainty.

5 Discussion

This study is the first economic evaluation study of FF/UMEC/VI treatment for COPD patients who experience exacerbations after they receive dual therapies (i.e., UMEC/VI or FF/VI) in the Norwegian perspective. FF/UMEC/VI (2,115 NOK) treatment costs more than UMEC/VI (1,544 NOK) or FF/VI (1,020 NOK); however, it produces a life-year gain of 0.02 when compared to UMEC/VI or FF/VI and improves QALY by 0.42 and 0.41 when compared to UMEC/VI and FF/VI respectively. These treatment efficacy benefits are supported by previous studies (Bremner et al., 2018; Ismaila et al., 2017; Lipson et al., 2018; Risebrough et al., 2018; Zheng et al., 2018). After including the benefits of the treatment in monetary terms, it can be concluded that FF/UMEC/VI is cost-effective. However, the uncertainty and cost of uncertainty are high in this analysis. Triple therapy's effects on life-year and utility improvement are subtle, and the probability of error is high. Therefore, if any of triple therapy's treatment efficacy does not exist, applying triple therapy may lead to redundant costs or the increased risk of pneumonia, an adverse event of using ICS medications. (Lopez-Campos et al., 2018; Suissa & Drazen, 2018)

This analysis estimated the cost-effectiveness of FF/UMEC/VI compared with other combined bronchodilator treatments for patients with COPD at a threshold of 500,000 NOK willingness-to-pay per QALY. The comparators included a combined dual long-acting bronchodilator treatment and one combined treatment with a long-acting bronchodilator and an inhaled steroid. In the deterministic analysis, FF/UMEC/VI was found to be more cost-effective than the combined dual long-acting bronchodilators treatment, UMEC/VI. The efficacy of FF/UMEC/VI is higher and costs less on the lifetime horizon. Furthermore, in comparison to the combination of a long-acting bronchodilator and an inhaled steroid therapy, FF/VI, FF/UMEC/VI is expected to have better health outcomes, but the total cost of FF/UMEC/VI is higher. However, it is still considered cost-effective as the incremental cost per QALY is under our threshold. The sensitivity analysis shows that all the cost-effectiveness models contain a fairly high degree of uncertainty. It implies further investigation may be recommended. The uncertainty may be due to defects in the research design.

Although this analysis was restricted by the assumptions made due to the lack of data, the results were consistent with a similar study that measured the cost-effectiveness of open triple therapy which requires two inhalers. To the researcher's knowledge, no fixed FF/UMEC/VI cost-effectiveness analyses have been published to date, but two posters have been presented in conferences. (Risebrough et al., 2018; Zhang et al., 2017)Thus, we compared the results with an open triple therapy cost-effectiveness analysis. In the study, the UMEC add-on FF/VI was compared with FF/VI, and UMEC+FF/VI was shown to be cost-effective (Driessen et al., 2018). Fixed triple therapy is preferred over open triple therapy because it reduces the risk of misapplying the inhaler and, thus, producing the same treatment effect as open triple therapy. Therefore, it is expected that the cost-effectiveness results also correspond to this analysis.

The opportunity cost of this analysis is high. Due to the high uncertainty of the results, the EVPI is high. These results were comparable with other EVPI curves that compared the cost-effectiveness of two or more long-acting bronchodilators (Oostenbrink et al., 2008; Ramos et al., 2011).

5.1 Limitations

The study is mainly based on guidelines established in the UK. Some changes were made to fit them to the Norwegian perspective. Because some challenges and limitations exist due to the lack of real patient-level data, this analysis applied several assumptions.

Transition Probability: The transition probabilities applied in this analysis are obtained from the NICE guidelines. The baseline FEV_1 score is from a British patient dataset between 2014 and 2016. This dataset was the source for calculating the transition probabilities, so it may not be representative of Norwegian COPD patients. However, Norwegian patient information regarding lung function was unavailable. Another assumption of the transition probability is that the treatments' initial beneficial effect on FEV_1 is reflected only in the first 3-month cycle. Thus, there is a chance a patient can move to a less severe COPD stage. One limitation is that for a stage one patient, there is no possibility of moving to a less severe stage. Another potential issue was it can possibly underestimate the effect of the treatment in the long-term.

However, applying the treatment benefit to all the cycles may lead to overestimating the effect.

Mortality: Mortality was assumed to be affected by the COPD stage and the patient's age rather than by the treatment because a meta-data analysis has shown there is no statistically significant difference between dual and triple therapies on all-cause mortality (Zheng et al., 2018). The impact of treatment on mortality could still be subtle, and determining its strength will require additional patient-level data.

Utility: The SGRQ scores used in this study were acquired from a cross-sectional study conducted in Europe that did not contain Norwegian samples, which may cause some bias in the results. Another problem is the formula used to transform SGRQ values into utility weights. Although the formula has been widely used in many studies (Briggs et al., 2017; Driessen et al., 2018; NICE, 2018), according to the researchers who developed it, using an algorithm-predicted utility score is not the best solution for health technology assessment and decision-making in the field. However, it is a useful way to assess utility differences (Starkie et al., 2011). In Table 7, we can see the variation in stage-specific effects between studies. Ideally, using clinical trials for the targeted population may produce more precise output.

Healthcare Costs: Resource utilisation in healthcare systems is challenging to determine if access to patient-level records or hospital data is restricted. The cost items chosen in this study are mainly built on the NICE guidelines and modified to accommodate the Norwegian healthcare system. However, some information is outdated, such as the cost of pulmonary rehabilitation and home oxygen therapy. Some healthcare cost information was ambiguous in this analysis. The cost of ambulance transportation was estimated by the overall use of different modalities (i.e., air, boat, and car) of ambulance transportation. Thus, it did not specifically reflect the use of these services by COPD patients, and utilisation was derived from UK data. There are some geographical and population density differences in how patients use ambulance services, so more detailed information is required. For example, the cost of an exacerbation requiring hospitalisation is 2,111 GBP (27,140 NOK) in the UK, while in the Norwegian healthcare system, it is expected to cost 94,868 NOK, which is more than three times the UK cost. (NICE, 2018a)

It is assumed the differences may due to the calculation method. The UK setting's data are based on committees' opinions and NHS reference costs. However, in the Norwegian setting, this analysis applied a diagnosis-related group (DRG) payment weight system. Thus, outpatient visits and hospitalisation costs were calculated based on using the DRG codes for COPD and then using the corresponding weight to calculate the cost. This analysis assumed that all hospital visits were assigned COPD-related DRG codes, which implies a higher cost. Hence, the cost of severe exacerbations soared, which may potentially overestimate the cost since it is unclear how many of the hospitalisations are utilising resources for COPD treatment or other complications.

Productivity Loss: Including production loss in the model provides a more comprehensive overview of chronic disease costs because it impacts patients' daily lives over a longer period of time. However, the effect may be more complicated. The main source of productivity loss data was from a German study, which may not apply to Norwegian setting. The recorded number of sick leave days taken due to COPD and the proportion of patients who receive a disability pension are not easily accessed. The number of sick leave days may vary depending on the patient's age; however, we did not include this factor.

Treatment Effect: In addition to transition probability in the first cycle, this analysis focused on treatment efficacy's effects on exacerbation and SGRQ scores because exacerbation is the main source of the COPD economic burden, and the treatments in this study aim to reduce the exacerbation rate. For our convenience, we only selected the two most common measurements. From the NICE guidelines, symptomatic index scores and adverse event rates are two additional important factors included in the economic evaluation. These two components shall be embedded in further studies for a more comprehensive evaluation of the treatment.

5.2 Sensitivity analysis

The results of this analysis are based on the deterministic values of parameters that lack a standard error or confidence interval. Therefore, we made assumptions regarding the standard error of the cost and effect parameters. However, a probabilistic sensitivity analysis was applied to explore the uncertainty around the parameters, and the expected value of perfect

information was used to evaluate the cost of the uncertainty. Hence, parameter uncertainty is high in this study, and the value of additional research is high. It may imply that a larger patient dataset should be included in the future.

5.3 Transparency

The structure of the Markov Model is shown in the Model Structure section. The transition probability and parameters used in the model are also listed in the Appendix. Thus, by using the material attached to this study, the process can be duplicated.

5.4 Validation

To assess the face validity of the model, its structure, inputs, and results were inspected. The structure of the health state transitions was based on the GOLD framework of COPD progression. It is the main guideline used to define COPD stages. The current study reproduced this structure; thus, it is reasonable. As mentioned previously, the inputs were based on previous studies and then adjusted for the Norwegian perspective with some supporting evidence. The results of the model may not be comparable to other studies involving cost-effectiveness analysis. However, a similar study conducted by Driessen et al. (2018) found that UMEC+ FF/VI open triple therapy is more cost-effective than FF/VI.

There is a limited number of published studies on fixed-dose triple therapy. With regard to external validation, the information used in this study was adjusted for the Norwegian healthcare and welfare system, as well as the Norwegian cost index. Thus, some or all of the information may not be applicable to other countries.

6 Conclusions

The results of this study suggest that FF/UMEC/VI is cost-effective in comparison to either of the two dual therapies when the willingness-to-pay threshold is set at 500,000 NOK per QALY. FF/UMEC/VI has better treatment effects and is less costly than UMEC/VI treatment in patients with stable COPD. The benefit of FF/UMEC/VI in reducing the rate of exacerbation could be the main reason for this outcome. ICS has a positive effect on reducing airway inflammation; thus, it could reduce the occurrence of exacerbation. Compared with FF/VI treatment, FF/UMEC/VI also reduces the rate of exacerbation, but the improvement is relatively smaller compared with UMEC/VI.

However, making the decision to use single-inhaler triple therapy as a stable COPD medication and applying it to all patients who are eligible for dual therapy is questionable. Based on the simulation data, this study has notably high uncertainty, and more information will be required in further studies. For example, including more effect endpoints and subgroup analyses. From a clinical perspective, using triple therapy for stable COPD is still debatable because the benefit of triple therapy in reducing exacerbations is limited and may not apply to all stable COPD patients. Furthermore, triple therapy increases the risk of adverse events, such as pneumonia (Dabscheck, 2018; Lopez-Campos et al., 2018; Suissa & Drazen, 2018; Vanfleteren et al., 2019;Vanfleteren et al., 2018). Therefore, more studies are needed in the future.

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Appendix

Table 6 SGRQ transformation

	Mild	Moderate	Severe	Very Severe	Area	Source
SGRQ	**38.5**	**40.4**	**50.2**	**58.6**	**Europe**	**(Jones et al., 2011)**
Corresponding EQ-5D	**0.78**	**0.76**	**0.66**	**0.56**		
SGRQ	28.8	37.2	52.2	52.1	US	(Pickard et al., 2011)
Corresponding EQ-5D	0.85	0.79	0.64	0.64		
SGRQ	51.4	51.4	54.7	63.0	Nordic	(Gudmundsson et al., 2006)
Corresponding EQ-5D	0.64	0.65	0.61	0,50		
SGRQ	25	32	36	53	Sweden	(Ståhl et al., 2005)
Corresponding EQ-5D	0.88	0.83	0.80	0.63		

Table 7 List of EQ-5D scores with COPD

	Mild	Moderate	Severe	Very Severe	Area	Source
EQ-5D	-	-	0.75	0.66	Switzerland	(Samyshkin et al., 2013)
EQ-5D	-	-	0.70	0.59	US	(Solem et al., 2013) – poster session
EQ-5D	0.82	0.80	0.77	0.74	UK	(Asukai et al., 2012) -poster session
EQ-5D	0.73	0.59	0.63	0.63	US	(Pickard et al., 2011)
EQ-5D	-	0.75	0.71	0.67	General	(Starkie et al., 2011)
EQ-5D	-	-	0.73	0.68	Germany	(Menn et al., 2010)
EQ-5D	0.84	0.73	0.74	0.52	Sweden	(Ståhl et al., 2005)
EQ-5D	0.90	0.76	0.75	0.55	Sweden	(Borg et al., 2004)
EQ-5D	0.82(0.77-0.87)	0.78(0.74-0.82)	0.72(0.69-0.75)	0.62(0.57-0.68)	Meta-study	(Moayeri et al., 2016)
EQ-5D	0.81(0.76–1.02)	0.77(0.74–0.89)	0.70(0.71–0.79)	0.62(0.59–0.72)	Meta-study	(Moayeri et al., 2016)
EQ-5D	0.89(0.75-0.87)	0.81(0.74–0.80)	0.75(0.67–0.74)	0.65(0.56–0.68)	Modelling studies	(Moayeri et al., 2016)

Table 8 Full list of model input parameters

Parameter	Point estimate	Source	Distribution
Exacerbation Rate – ICS/LABA			
Mild, moderate exacerbation	0.380	(NICE, 2018)	Gamma
Moderate, moderate exacerbation	0.390	(NICE, 2018)	Gamma
Severe, moderate exacerbation	0.499	(NICE, 2018)	Gamma
V. Severe, moderate exacerbation	0.599	(NICE, 2018)	Gamma
Relative risk to LABA ICS moderate exacerbation	0.85	(Lipson et al., 2018)	Log normal
Mild, severe exacerbation	0.029	(NICE, 2018)	Gamma
Moderate, severe exacerbation	0.024	(NICE, 2018)	Gamma
Severe, severe exacerbation	0.052	(NICE, 2018)	Gamma
V. Severe, severe exacerbation	0.082	(NICE, 2018)	Gamma
Relative risk to LABA ICS, severe exacerbation	0.87	(Lipson et al., 2018)	Log normal
Exacerbations Rate– LAMA/LABA			
Mild, moderate exacerbation	0.337	(NICE, 2018)	Gamma
Moderate, moderate exacerbation	0.347	(NICE, 2018)	Gamma
Severe, moderate exacerbation	0.443	(NICE, 2018)	Gamma
V. Severe, moderate exacerbation	0.532	(NICE, 2018)	Gamma
Relative risk to LAMA/LABA, moderate exacerbation	0.75	(Lipson et al., 2018)	Log normal
Mild, severe exacerbation	0.022	(NICE, 2018)	Gamma
Moderate, severe exacerbation	0.018	(NICE, 2018)	Gamma
Severe, severe exacerbation	0.039	(NICE, 2018)	Gamma
V. Severe, severe exacerbation	0.062	(NICE, 2018)	Gamma
Relative risk to LAMA/LABA, severe exacerbation	0.66	(Lipson et al., 2018)	Log normal
Rate of disability pension, yearly			
Mild COPD	0.13	(Wacker et al., 2016)	Gamma
Moderate COPD	0.14	(Wacker et al., 2016)	Gamma
Severe COPD	0.2	(Wacker et al., 2016)	Gamma
V. Severe COPD	0.3	(Wacker et al., 2016)	Gamma
Number of sick leave day, yearly			
Mild COPD	31.3	(Wacker et al., 2016)	Gamma
Moderate COPD	26.3	(Wacker et al., 2016)	Gamma
Severe COPD	34.1	(Wacker et al., 2016)	Gamma
V. Severe COPD	40.1	(Wacker et al., 2016)	Gamma
Utility			
Mild COPD, dual therapy	0.809	(Jones et al., 2011; Starkie et al., 2011)	Beta
Moderate COPD, dual therapy	0.794	(Jones et al., 2011; Starkie et al., 2011)	Beta
Severe COPD, dual therapy	0.701	(Jones et al., 2011; Starkie et al., 2011)	Beta
V. Severe COPD, dual therapy	0.605	(Jones et al., 2011; Starkie et al., 2011)	Beta
Mild COPD, triple therapy	0.824	(Jones et al., 2011; Starkie et al., 2011)	Beta
Moderate COPD, triple therapy	0.809	(Jones et al., 2011; Starkie et al., 2011)	Beta

Severe COPD, triple therapy	0.720	(Lipson et al., 2018; Starkie et al., 2011)	Beta
V. Severe COPD, triple therapy	0.627	(Lipson et al., 2018; Starkie et al., 2011)	Beta
Disutility of moderate exacerbation	0.01	(Rutten-van Mölken et al., 2009)	Beta
Disutility of severe exacerbation	0.04	(Rutten-van Mölken et al., 2009)	Beta
Medical Cost			
FF 92mg/UMEC 55mg/ VI 22mg	2115		Gamma
UMEC 55mg/ VI 22mg	1544		Gamma
FF 92mg/ VI 22mg	1020		Gamma
Maintenance Cost			
Mild COPD	21270		Gamma
Moderate COPD	20678		Gamma
Severe COPD	21329		Gamma
V. Severe COPD	23770		Gamma
Exacerbation Cost			
Moderate exacerbation	3790		Gamma
Severe exacerbation	94868		Gamma
Productivity Loss			
Sick leave cost, daily	3247		Gamma
Disability pension, yearly	220893		Gamma
SGRQ to EQ-5D			
Intercept	0.9671	(Starkie et al., 2011)	
Coefficient - SGRQ	-0.0013	(Starkie et al., 2011)	
Coefficient – SGRQ^2	-0.0001	(Starkie et al., 2011)	
Coefficient -% male	0.0231	(Starkie et al., 2011)	

Table 9 Annual maintenance resource utilisation

Resource Category	Mild	Moderate	Severe	V. severe	Source
GP visit (3month)	1.9	2.3	2.4	2.2	(Wacker et al., 2016)
Outpatient visit (3month)	4.0	3.8	3.7	3.3	(Wacker et al., 2016)
Spirometry- number of tests	1	2	2	4	(Oostenbrink et al., 2005)
Pulmonary rehabilitation- portion of patient	0.02	0.03	0.06	0.09	(Price et al., 2013)
Home oxygen therapy – portion of patient	0	0	0.05	0.4	(Price et al., 2013)
Influenza vaccine – portion of patient	0.48	0.48	0.78	0.78	(Jouleh et al., 2018)
Pneumococcal vaccination	0.69	0.69	0.69	0.69	(Price et al., 2013)
SABA -(number of scripts)	3.74	4.65	6.87	9.78	(Price et al., 2013)
SAMA- (number of scripts)	0.59	0.65	0.91	1.19	(Price et al., 2013)
Oral corticosteroids (number of scripts)	0.88	0.96	1.7	2.7	(Price et al., 2013)

Theophylline (number of scripts)	0.26	0.32	0.73	1.63	(Price et al., 2013)
Mucolytics (number of scripts)	0.35	0.40	0.8	2.05	(Price et al., 2013)

Table 10 Detailed unit costs

Resource Category	Unit Cost	Source
GP visits	554	Normaltariff
A&E visits	554	Normaltariff
Outpatient visits	4921	DRG904b
Spirometry- number of tests	450	Normaltariff 507c / 507d
Pulmonary rehabilitation-	50016	DRG8620(16 days) (R. Nielsen et al., 2009)
Home oxygen therapy programme	44812	(R. Nielsen et al., 2009)
Influenza vaccine – per patient	109	Legemiddelsøk
Pneumococcal vaccination	345	Legemiddelsøk
SABA-Buventol Easyhaler,100mcg-200 dose	170.2	Legemiddelsøk
SAMA- Atrovent - 20 mikrog, 200dose	105.4	Legemiddelsøk
Oral corticosteroids prednisolone 5mg, 50 tablets	62.5	Legemiddelsøk
Theophylline - Theo-Dur - 200 mg, 100 tablets	229.6	Legemiddelsøk
Mucolytics - Acetylcystein Sandoz 200mg, 25 tablets	80.6	Legemiddelsøk
Antibiotics – amoxicillin 500mg, 20	92.3	Legemiddelsøk
Ambulance journey to ER	8510	SSB
Hospital stay	77252	DRG88

Table 11 Exacerbation resource utilisation

Resource Category	Resource use	Source
Non-hospitalised		
ER visit	0.3	NICE
GP visit	0.6	NICE
Outpatient visit	0.1	NICE
Oral corticosteroids	1	Legevakthåndboken
Antibiotics	2	Legevakthåndboken
Hospitalised		

Ambulance journey to ER	0.7	NICE
COPD Hospital stay	0.98	
Oral corticosteroids	1	Legevakthåndboken
Antibiotics	2	Legevakthåndboken
Em. admissions where the patient received ventilation support	0.02	Helseatlas