

# **COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF TIOTROPIUM TREATMENT FOR BRONCHIECTASIS: EVIDENCE FROM A CROSSOVER RANDOMISED TRIAL**

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## ABSTRACT

**Aim:** The aim of this study is to determine the relative cost-effectiveness of administering tiotropium compared to a placebo in adult patients with non-cystic fibrosis (CF) bronchiectasis with airflow obstruction, from a funder perspective.

**Methods:** Clinical efficacy data was obtained from a randomised placebo-controlled crossover study of tiotropium treatment in adult patients with stable, non-CF bronchiectasis in combination with aggregated hospital costs and cost of health services (NZ, 2016) obtained via self-reported health utilisation data. A decision tree/Markov model consisting of patient transition and outcomes was developed. A cost-effectiveness and cost-utility analysis was performed to produce incremental cost-effectiveness ratios (ICERs) and reported in costs per exacerbation avoided and costs per quality-adjusted life-years (QALYs) gained. Sensitivity and scenario analyses were also conducted to test the robustness of outcomes illustrated by using cost-effectiveness acceptability curves against a willingness-to-pay threshold (WTP) and identifying the conditions in which tiotropium could be cost-effective for bronchiectasis patients. The WTP threshold was based on the Gross Domestic Product (GDP) per capita as recommended by the World Health Organization (WHO).

**Results:** There were no significant differences between costs and outcomes for treatment and control arms. The mean (Standard error) number of exacerbations was 1.2 (0.12) for tiotropium and 1.23 (0.11) for the placebo; the mean QALYs was 0.88 and 0.87 respectively. First year costs per patient were NZD 641 (95% CI \$583, \$702) for tiotropium (TI) and NZD 503 (95% CI \$430, \$585) for placebo (PL) treatment in the year 2016. Patients treated with tiotropium gained 0.62 (95% CI 0.58, 0.65) quality adjusted life years compared to 0.59 (95% CI 0.56, 0.62) QALYs for the placebo. In incremental terms, TI gained additional QALYs of 0.03 units and 0.01 of exacerbation events at an incremental cost of NZD 137 resulting in the cost per exacerbation avoided of NZD 12,896 (95% CI \$5,850, \$15,300) and the cost per QALY gained of NZD 4,655 (95% CI \$3,900, \$7,650). The reported incremental cost effectiveness ratios are well-below the willingness-to-pay threshold for New Zealand (~ NZD 40,000).

**Conclusion:** The results from this study show that tiotropium may be cost-effective compared to a placebo, particularly in terms of improving QALYs, but less likely in respect of reducing exacerbations. Sensitivity analysis suggests that favourable outcomes may be

linked to patients with moderate to severe bronchiectasis. Further studies are required before a more definitive answer can be reached.

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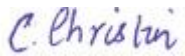


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# CHAPTER 1. INTRODUCTION

Bronchiectasis is a chronic, debilitating disease characterised by productive cough, narrowing of the airways that leads to breathlessness and repeated respiratory infections. Previous studies demonstrate the efficacy of *macrolides in preventing exacerbations* (Wong et al., 2012; Altenburg et al., 2013; Serisier et al., 2013; Gao et al., 2014). Tiotropium is a once daily inhaled medication that provides greater than 24-hour improvements in airflow and is highly effective in the treatment of chronic obstructive pulmonary disease (COPD). Bronchiectasis has similar clinical and inflammatory features to COPD. The aim of this study is to assess whether tiotropium is cost-effective in patients with bronchiectasis who have airflow obstruction. The benefits to patients were expected to include improved respiratory and general health, fewer exacerbations, improved quality of life, and reduced acute healthcare utilisation and costs.

This research study will utilise clinical data from a randomised, placebo-controlled, crossover trial of tiotropium treatment for adult New Zealand (NZ) patients with non-cystic fibrosis (CF) bronchiectasis study in combination with the aggregated average cost figures from hospital data and self-reported health utilisation data. The aim of this study is to determine the relative cost-effectiveness of administering tiotropium compared to a placebo in adult patients with non-CF bronchiectasis with airflow obstruction. A decision tree/Markov model was developed to estimate patient transition and their response to treatment.

## 1.1 BRONCHIECTASIS AS A PUBLIC HEALTH PROBLEM

Bronchiectasis is an obstructive respiratory disease where there is a persistent dilatation of bronchial wall and airway inflammation (Reid, 1950; McShane, Naureckas, Tino and Streck, 2013). Rather than being characterised as a single disease, bronchiectasis is termed as an anatomical abnormality usually due to bronchial damage from infections resulting in distorted airways (Reid, 1950). Patients presented with this condition suffer from chronic cough and sputum production, recurrent breathlessness and progressive lung damage which can lead to increased morbidity and lessen quality of life (Seitz et al., 2010; Boyton and Altmann, 2016; Polverino et al., 2017).

Although there have been a reduction in the incidence of bronchiectasis with the aid of antibiotics and vaccinations in the medical field, it is still seen as a health problem in developing countries (Bulcun, Arslan, Ekici & Ekici, 2015). Patients living with bronchiectasis experience recurrent lower tract respiratory infections due to their increased susceptibility to infection and microbial colonisation (Cole, 1986; Keistinen, Säynäjäkangas, Tuuponen, & Kivelä, 1997). These exacerbations often require frequent hospitalisation due to the progressive loss of lung function (Ellerman & Bisgaard, 1997). Bronchiectasis patients suffer from a high level of morbidity and have a high risk of premature mortality Keistinen, Säynäjäkangas, Tuuponen, & Kivelä, 1997; Loebinger et al., 2009; Twiss, Metcalfe, Edwards & Byrnes, 2005; Roberts, Lowndes, Milne & Wong, 2012).

The study done by Bulcun, Arslan, Ekici and Ekici (2015) used the Seattle Obstructive Lung Disease Questionnaire (SOLQ) in order to measure the quality of life of patients suffering with bronchiectasis and compare them with subjects who do not have this disease. This study was done in order to find any effective factors (Bulcun, Arslan, Ekici & Ekici, 2015). It shows that patients with bronchiectasis “had a poorer quality of life, lower baseline spirometric values and more frequent exacerbations” (Bulcun, Arslan, Ekici & Ekici, 2015). In addition to this, there have been other studies which show that depression and anxiety are common for subjects suffering with bronchiectasis which further degrades the quality of life for an affected person (Cruz, Marciel, Quittner & Schechter, 2009; Katon, Lin & Kroenke, 2007).

## 1.2 SYMPTOMS OF BRONCHIECTASIS

Common symptoms and signs of bronchiectasis are found usually during examination. The key symptoms are: persistent cough, sputum volume and/or consistency, sputum purulence, dyspnea (breathlessness) and/or exercise tolerance, malaise and haemoptysis (coughing up of blood) (Hill et al., 2017). Signs include; wheezing, crackles, chest pain, weight loss, rhinosinusitis, finger-clubbing and general fatigue (Reid, 1950; McDonnell, Ward, Lordan & Rutherford, 2013).

Hill and colleagues defined bronchiectasis exacerbation as a person having bronchiectasis with deterioration in three or more of the following key symptoms for at least 48 hours.

Bronchiectasis exacerbations are commonly compared to chronic obstructive pulmonary disorder (COPD), usually using increased breathlessness and purulent sputum production as indicators (Anthonisen et al., 1987). Typically, an exacerbation is any period of deterioration seen in the respiratory condition (Tsang & Tipoe, 2004). Exacerbations often present as a worsening of the broad symptoms, for example, increased sputum production, deteriorated cough or change in cough character (Kapur & Karadag, 2011). The definition of exacerbations for adults is different from that required for children (Murray, Turnbull, Macquarrie & Hill, 2009). Severe exacerbations will require hospitalisation and the eventual use of either intravenous or oral antibiotics (Kapur, Masters & Chang, 2009). Currently, the rate of hospitalisation due to exacerbations is increasing worldwide.

### 1.3 CAUSES OF BRONCHIECTASIS

There is substantial evidence that indicates a wide range of disorders linked to the onset of bronchiectasis (Gao et al., 2016). Therefore, knowing the specific aetiology may have a clinically significant impact on the patient's management (Gao et al., 2016). Several studies have prospectively investigated the aetiology of bronchiectasis in adults (Lonni et al., 2015; Guan et al., 2015). The most common known aetiologies include post-infection, a build-up of foreign objects in the airways, immunodeficiency, COPD, connective tissue disease and inherited disorders such as CF and primary ciliary dyskinesia (Seitz et al., 2010; Gao et al., 2016).

Finding a causative factor is vital in the long-term management of the condition, as it has the potential to influence therapeutic options. There are several papers investigating the pathogenesis of bronchiectasis (Twiss, Metcalfe, Edwards & Byrnes, 2005; Anwar et al., 2013; Pasteur et al., 2000; Chang, Grimwood, Mulholland & Torzillo, 2002). Consequently, these bronchiectasis cases are likely to be more complex than other studies, composed mainly of individuals struggling to control symptoms. The study by Gao et al., 2016 showed that the underlying cause could not be found in nearly 45% of the patients with bronchiectasis, i.e., deemed to be idiopathic (Pasteur et al., 2000). Most idiopathic instances are probably due to unknown immunological mechanisms.

Post-infection is the next most frequent contributing factor in providing the initial insult for bronchiectasis, of which post-tuberculosis was the predominant category (Gao et al., 2016).

This also includes various childhood respiratory conditions, for example, pneumonia, whooping cough (pertussis), adenovirus and complicated measles (Barker, 2002; McDonnell, Ward, Lordan & Rutherford, 2013).

The second most dominant cause of bronchiectasis might be linked to COPD as recent studies have reported that 29-69% of patients with COPD have some evidence of concomitant bronchiectasis based on tomography scans and tend to suffer from poorer lung function and higher mortality than without (Gao et al., 2016). Congenital causes only make up a small proportion but often therapy can be given in these instances. CF is a well-known autosomal recessive disorder; it is most predominant in white populations with a rate of one in every 2,500 births (Tsang & Tipoe, 2004). Bronchiectasis is a significant factor in CF mortality (Patel et al., 2004). This research is only focused on non-CF bronchiectasis.

#### 1.4 DIAGNOSIS OF BRONCHIECTASIS

Bronchiectasis is often difficult to diagnose and therefore commonly misdiagnosed (McDonnell, Ward, Lordan & Rutherford, 2013; Nicotra, Rivera, Dale, Shepherd & Carter, 1995). Bronchiectasis most often gets mistaken for other common respiratory conditions, for example, asthma or COPD. A delay usually exists between the onset of bronchiectasis and a confirmed diagnosis. One bronchiectasis phenotyping study has shown a delay in diagnosis of 17 years. The mean age of diagnosis was 54 years, yet the mean age of onset of symptoms was 37 years (Anwar et al., 2013). Symptoms often first present themselves in childhood; however, a diagnosis is often not obtained until adulthood. The current 'gold standard' for diagnosis is the use of high resolution computed tomography (HRCT) scans (Barker, 2002; O'Donnell, 2008). HRCT confirms bronchiectasis if the bronchi are internally dilated by more than 1.5 times the pulmonary artery size (Pasteur et al., 2000; Desai, Wells, Cheah, Cole & Hansell, 1994).

There is very limited data available worldwide that has measured the prevalence and incidence of bronchiectasis. Understandably, this makes comparing data from different prevalence studies difficult. The underestimation of bronchiectasis is a major issue, as most individuals are outpatients and often are misdiagnosed with COPD or asthma (McDonnell, Ward, Lordan & Rutherford, 2013; Tsang & Tipoe, 2004). The impression stands that

bronchiectasis is a neglected and poorly understood condition, placing limitations on its management (Kapur & Karadag, 2011).

Bronchiectasis is often the end path of various systemic and respiratory diseases (Tsang & Tipoe, 2004). Bronchiectasis is often diagnosed in patients with inflammatory bowel disease (IBD) including Crohn's disease, and ulcerative colitis; all of which are manifestations of the bowel (Barker, 2002). The occurrence of bronchiectasis is also commonly associated with rheumatoid arthritis (a collagen vascular disease) (Barker, 2002; Pasteur, Bilton & Hill, 2010; Anwar et al., 2013; Chang, Grimwood, Mulholland & Torzillo, 2002). Panbronchiolitis is an obstructive airway disease found predominantly in Japanese individuals that is determined by the presence of parenchymal nodules. Panbronchiolitis is also known to contribute to the onset of bronchiectasis, particularly in Japanese populations (Tsang & Tipoe, 2004).

Comorbidities are a common feature in bronchiectasis patients, especially those with asthma and COPD (McDonnell et al., 2016). In individuals with COPD it has been shown that up to 50% may also have bronchiectasis on Computed Tomography (CT) scans (Patel et al., 2004). In fact, a combination of bronchiectasis and COPD represents a more severe phenotype (Novosad & Barker, 2013). Comorbidities are regarded as risk factors as they increase the chance of mortality (Keistinen, Säynäjäkangas, Tuuponen, & Kivelä, 1997).

## 1.5 NATIONAL AND GLOBAL BURDEN OF BRONCHIECTASIS

A recent two-year study of bronchiectasis in New Zealand children provides the most recent national prevalence rates. The investigation revealed an estimated national incidence rate of 3.7/100,000 per year, in children less than 15 years of age. The only other comparable data available is the national incidence rate from a contemporary study of under-15 year olds in Finland. Their estimated incidence rate is 0.5/100,000 per year (Säynäjäkangas, Keistinen, Tuuponen & Kivelä, 1998). New Zealand's national incidence rate of below-15 year olds is seven times the national incidence rate in Finland. These two studies similarly highlight the concept that bronchiectasis most often develops during early childhood; but recognises the significant delay in diagnosis.

Interestingly, the New Zealand study identified ethnic and regional variances in the incidence of bronchiectasis. An incidence of 17.8/100,000 in Pacific Island children and 4.8/100,000 in Maori children was reported. This incidence is twelve times and three times higher,

respectively, than for NZ European children (Twiss, Metcalfe, Edwards & Byrnes, 2005). These ethnic findings were also supported by older New Zealand data which reported a prevalence of 1/6,000 children (Edwards, Asher & Byrnes, 2003). Similar findings have been reported in other indigenous populations. A rate of 16/1,000 is reported in Southwest Alaskan Native Children from the Yukon Kuskokwim Delta region (Singleton et al., 2000). Another study shows an incidence of 15/1,000 in central Australian Aboriginal children (Chang, Grimwood, Mulholland & Torzillo, 2002). In both populations respiratory disease is the largest preventable cause of death in infants (Singleton et al., 2000; Chang, Grimwood, Mulholland & Torzillo, 2002).

Another study in New Zealand reported a mortality rate in bronchiectasis patients of 21% (32/152) over twelve months, however there is limited data available for the prevalence of bronchiectasis in New Zealand adults (Roberts, Lowndes, Milne & Wong, 2012). When compared to a Finnish study of 842 individuals (diagnosed in 1982-1986), there is a mortality rate of 28% (longest follow up period was 12.9 years) (Keistinen, Säynäjäkangas, Tuuponen, & Kivelä, 1997).

The average US hospitalisation rate for bronchiectasis from the years 1993-2006 is 16.5/100,000 and has increased approximately 3% every year (Seitz et al., 2010). Research indicates an exacerbation rate of 1.5-6.5 per year for bronchiectasis patients (O'Donnell, Barker, Ilowite & Fick, 1998; Pasteur, Bilton & Hill, 2010). A contemporary study of 152 patients showed that there was a total of 307 exacerbations, of which at least 46% were readmitted with another exacerbation within the year (Roberts, Lowndes, Milne & Wong, 2012). Another 2009 study identified 115 exacerbations in 30 children during the study period. This gave a rate of 1.6 exacerbations per year, of which 35% of exacerbations required hospitalisation and treatment with intravenous antibiotics (Kapur, Masters & Chang, 2009).

Regarding the extremes of age, a US study has shown an increase from 4.2/100,000 in 18-34 year olds to 271.8/100,000 in over 75 year olds (Shoemark, Ozerovitch & Wilson, 2007). The higher frequency of bronchiectasis in females is supported by the recent New Zealand incidence study, where 37 out of 65 participants were female (Twiss, Metcalfe, Edwards & Byrnes, 2005). Other global prevalence rates include the Hong Kong government estimate of 16.4/100,000 in 1990 (Tsang & Tipoe, 2004). In the US, 110,000 adults were determined to have developed bronchiectasis in a 2005 study (Shoemark, Ozerovitch & Wilson, 2007).



Newer US data indicates a rate of 52/100,000 at an additional cost of 1.1 billion dollars per annum (Seitz et al., 2010). This study also showed that the prevalence of bronchiectasis increased by 8.7% per year between 2007 and 2008 in the US (Seitz et al., 2010). Clearly, bronchiectasis prevalence is on the rise and should now be regarded as a ‘common’ disease worldwide.

## 1.6 ECONOMIC BURDEN OF BRONCHIECTASIS

Bibby, Milne and Beasley (2015) show that in New Zealand, during the five-year period from 2008-2012, there were 5,494 admissions in total with an estimated cost of NZD 25.6 million. Thus, indicating a benchmark of potential reduction in costs to the health system if there was an effective treatment or prevention of bronchiectasis. During the year 2012/13 alone, the average cost per admission that was diagnosed with bronchiectasis was NZD 4,555 and the total cost for that year was NZD 5.34 million (Bibby, Milne & Beasley, 2015). According to this study there were no statistical differences in the mean cost across the years (Bibby, Milne & Beasley, 2015). About 82% of the total annual cost was constituted of elderly patients’ admissions, and within children and youth less than 20 years of age, there is a disproportionately high cost for Maori children (Bibby, Milne & Beasley, 2015).

Based on the US study conducted from 1993-2006, the median cost of inpatient care was USD 7,827 (Seitz et al., 2010). However, this can range from USD 13 to USD 543,914 (Seitz et al., 2010). As indicated by the study done by Weycker, Edelsberg, Oster and Tino (2005), the average total medical care expenditures were about USD 5681 higher for bronchiectasis patients in 2001. Overall, the additional medical cost for patients having bronchiectasis was about USD 630 million annually in the US during 2001 (Weycker, Edelsberg, Oster & Tino, 2005).

## 1.7 TREATMENT OPTIONS FOR BRONCHIECTASIS

The aim of treatment therapy for bronchiectasis is to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve both health quality and exercise

tolerance. Even though bronchiectasis is incurable, a patient's symptoms may be managed to maximise quality of life, subject to resource limitations.

Treatment of patients with bronchiectasis often requires ongoing long-term management depending on the severity of the disease (Ten Hacken, Wijkstra, & Kerstjens, 2007). Since there is no standardised treatment for bronchiectasis due to limited evidence-based data, current management of bronchiectasis are often based on the treatment plans used in other respiratory disease, i.e. Cystic Fibrosis (CF) and Chronic Obstructive Pulmonary Disease (COPD) (Gao et al., 2014). Due to the heterogeneric nature of bronchiectasis, planning treatment is often difficult (O'Donnell, 2008).

Bronchiectasis can also either be focal or diffuse, depending on the number of lobes and lung segments that are affected (Barker, 2002). Long-term management of the condition aims at reducing frequent exacerbations and further damage to lung function, hence increasing the overall quality of life for those sufferers (Tsang & Tipoe, 2004). Lung function decline is monitored by measuring the forced expiratory volume of patients in one second (%FEV1) (Barker, 2002). Studies have shown an estimated mean decline in %FEV1 of 33-55mL per year in patients with non-CF bronchiectasis (Nicotra, Rivera, Dale, Shepherd & Carter, 1995; Chang, Grimwood, Mulholland & Torzillo, 2002). There has been so far no long-term treatment having any impact the declining FEV1 in bronchiectasis. The evidence for long-term treatments except for chest clearance techniques are lacking and therefore needed to reduce the growing clinical burden of this disease (Gao et al., 2014).

Current treatment of bronchiectasis includes antibiotics, anti-inflammatories, chest physical therapy, and surgery (Murray & Hill, 2009). Antibiotics are usually administered upon admittance for an exacerbation and considered the mainstay of treatment. Antibiotics with a high penetrance (macrolides, azalides, and quinolones) are recommended in severe cases because high concentrations of bacteria are located intraluminally in association with mucus, and because thickening and scarring of the bronchial wall may reduce local bioavailability (O'Donnell, 2008). There has been a move towards the use of inhaled antibiotics (e.g. nebulised aminoglycoside) as they are more specific, rather than intravenous antibiotics (Decramer et al., 2004). Recommendations exist for a more individualised approach for patients, by culturing the sputum and selecting antibiotics based on results (O'Donnell, 2008). However, more evidence was needed for the use of antibiotics in bronchiectasis as very few randomised controlled trials exist (Murray & Hill, 2009).

There is a possibility for the use of prophylactic non-macrolide antibiotics, particularly for stable bronchiectasis patients. This aims to reduce their bacterial burden, thereby breaking the 'vicious cycle' (Murray & Hill, 2009) but very limited evidence is available to support this approach (Pasteur, Bilton & Hill, 2010). On the other hand, there is accumulating evidence that macrolides have anti-inflammatory and immune-regulatory properties in addition to their anti-microbial effects (Fan et al., 2015). Macrolides have been effectively used in treating CF, COPD, asthma and diffusing panbronchiolitis but there remains ambiguity in how well it can serve in managing non-CF bronchiectasis (Gao et al., 2014; Fan et al., 2015). Until more recently, the effects of macrolide antibiotics have been reported to be mainly optimistic in treating non-CF bronchiectasis (Fan et al., 2015).

The systematic review and meta-analysis of two studies (Gao et al., 2014; Fan et al., 2015) assessed the efficacy and safety of macrolides in patients with bronchiectasis in adults and children. Studies showed that macrolide therapy significantly reduced acute pulmonary exacerbations, increased quality of life, improved lung function and increased the eradication of pathogens. There were also three randomised studies that showed beneficial effect of macrolides antibiotics (azithromycin or erythromycin) on exacerbation events in adults with bronchiectasis (Polverino et al., 2017). EMBRACE, a randomised double-blind trial of 141 patients was undertaken (EMBRACE) in New Zealand using the macrolide antibiotic azithromycin (Wong et al., 2012). Findings showed an exacerbation rate of 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group which is a 62% relative reduction in exacerbations. The BAT study (Altenburg et al., 2013) showed higher median number of exacerbations in the placebo group compared to the azithromycin group (2 versus (vs.) 0) and BLESS study (Serisier et al., 2013) showed erythromycin significantly reduced exacerbation events compared to placebo (mean 1.29, 95% CI 0.93-1.65 vs. 1.97, 95% CI 1.45-2.48). This data therefore indicates the usefulness of macrolides in reducing frequency of exacerbations. However, care needs to be taken though as macrolide maintenance treatment might be associated with an increase in the risk of getting side effects such as diarrhoea and abdominal discomfort and to prevent the development of antimicrobial resistance (Wong et al., 2012 ; Gao et al., 2014).

Another commonly used therapy is physical chest exam for clearance of sputum from the airways. Surgery or lung transplants are reserved for very end-stage bronchiectasis; therefore, only considered if bronchiectasis is focal, resistant or no longer responding to aggressive medical therapy (McDonnell, Ward, Lordan & Rutherford, 2013; Wong et al., 2012). The

role of pulmonary rehabilitation and inspiratory muscle training has been investigated in one randomised controlled trial so far. It compared an eight-week training programme of pulmonary rehabilitation alone, pulmonary rehabilitation plus inspiratory muscle training, and a control group. The authors concluded that pulmonary rehabilitation does improve exercise tolerance (O'Donnell, 2008).

Significantly more research is needed in the development of suitable long-term treatments for individuals with bronchiectasis. The heterogeneric nature of bronchiectasis suggests that treatment should become more individualised. Additionally, it would be beneficial if specific biomarkers were identified to guide therapy during exacerbations (McDonnell et al., 2013). Prevention and early diagnosis should be the focus of future treatment options (Twiss, Metcalfe, Edwards & Byrnes, 2005).

## 1.8 RATIONALE FOR ESTIMATING COST-EFFECTIVENESS ANALYSIS OF TIOTROPIUM TREATMENT FOR BRONCHIECTASIS

There was one study which looked at the therapeutic effect of tiotropium bromide on bronchiectasis which was administered in the form of powder by inhalation. The sample size included 22 patients and this study looked at the percentage of the Forced Expiratory Volume (FEV1%), symptom score and body-mass index, the degree of airflow obstruction and dyspnea and exercise capacity (BODE index). The BODE index is composite marker of disease taking into consideration the systemic nature of COPD (Celli et al., 2004). The results showed that after one month of inhalation of this powder there was a significant decrease in the symptom score and BODE index but not a significant increase in FEV1% (Li et al., 2010).

To my knowledge, no studies have examined the economic evaluation of tiotropium in bronchiectasis patients. The effectiveness of tiotropium for bronchiectasis patients is unknown in the literature as it was performed on COPD patients to provide a baseline. Since the year 2000 there has been an emergence of new treatments for COPD including long-acting bronchodilator drugs, respiratory rehabilitation services, and non-invasive ventilation in respiratory failure. Two combination products entered the market; the first in 2000 was combination of fluticasone and salmeterol (Seretide), and the second, in 2001 was combination of budesonide and formoterol (Symbicort). A third product, tiotropium

(Spiriva), a long acting anticholinergic, entered the market in 2002. Clinical trials providing evidence on tiotropium are briefly described below, to provide information on the trials supporting this treatment, the size of the patient population and the outcome measures used within the trial.

UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) was a four-year study of 6,000 COPD patients published in 2008, comparing tiotropium to placebo. Outcome measures included lung function: Forced Expiratory Volume (FEV1), Forced Vital Capacity (FVC), and Slow Vital Capacity (SVC), health status as measured by the St. George's Respiratory Questionnaire (SGRQ) and the rate of exacerbations (Celli et al., 2009; Decramer et al., 2004).

The INSPIRE trial followed 1,270 patients from 20 countries who were randomised to either salmeterol/fluticasone or to tiotropium over 104 weeks. The primary outcome was the rate of exacerbations and secondary outcomes including post-dose FEV1, SGRQ, and all-cause mortality (Wedzicha et al., 2008).

The OPTIMAL trial was a 52-week Canadian trial developed and implemented by the Canadian Thoracic Society Clinical Trials group (an academic group) in a sample population of 432 COPD patients, randomised to one of three treatments: tiotropium plus placebo, tiotropium plus salmeterol or tiotropium plus Seretide. The trial was designed to answer a question about which combination of products is the best for treating COPD patients. The primary outcome measure was the proportion of patients in each arm experiencing an exacerbation, secondary endpoints included the SGRQ, changes in dyspnea as measured by the BDI (Baseline Dyspnea Index), the TDI (Transition Dyspnea Index) and the dyspnea domain of the chronic respiratory disease questionnaire, number of exacerbations and hospitalisations, time to first exacerbation, FEV1 and FVC (Aaron et al., 2007).

Bronchiectasis and COPD have similar symptoms as both conditions involve airway diseases characterised by airflow obstruction, chronic airway inflammation and infections (Milne, Hockey, & Rea, 2014; Weycker, Edelsberg, Oster & Tino, 2005). So, the therapies used for bronchiectasis patients may be similar to those used for COPD, which includes inhaled short and long-acting bronchodilators and the use of macrolides (O'Donnell, 2008; Pasteur, Bilton & Hill, 2010; Tsang & Tipoe, 2004; Barr, Bourbeau, Camargo & Ram, 2006; Tashkin et al., 2008; Polverino et al., 2017).

Tiotropium, an inhaled long-acting anticholinergic bronchodilator, has the potential to cause substantial change in bronchiectasis patients as it has shown to improve airflow and lung function within 24 hours in patients with COPD (Barr, Bourbeau, Camargo & Ram, 2006; Tashkin et al., 2008; Celli et al., 2009). Previous studies have suggested the following improvements associated with the use of tiotropium in COPD patients: reducing severe exacerbations and improving health-related quality of life, exercise tolerance, dyspnea and lung function (Barr, Bourbeau, Camargo & Ram, 2006; Tashkin et al., 2008; Joos, 2010). So, evaluation of the efficacy of such anticholinergic therapy on the incidence of acute pulmonary exacerbations of bronchiectasis may provide evidence to determine best practice guidelines in the NZ population (Lee et al., 2010; Weycker, Edelsberg, Oster & Tino, 2005). Data from 13 randomised controlled trials have shown to decrease exacerbations by 24% and hospital admission by 41% (Rodrigo & Nannini, 2007). In a 4-year UPLIFT trial, the use of tiotropium reduced mortality rates by 16% (Celli et al., 2009). There was a non-randomised study in China that looked at the effect of tiotropium in patients with bronchiectasis which showed improvement in the clinical symptoms and BODE index (Li et al., 2010).

A Cochrane review published in 2001 stated that there was a limited randomised clinical trial of a reasonable timeline that looked at the role of anticholinergic therapy in bronchiectasis (Lasserson, Holt, Evans & Greenstone, 2001). Since this review, there have not been any randomised trials conducted worldwide which looked at the efficacy of tiotropium in the bronchiectasis population. But now we have an opportunity to look at the study worldwide to see if tiotropium improves quality of life and reduces exacerbations because of the high prevalence of bronchiectasis relative to other developed countries.

## 1.9 THE PARENT STUDY (ROBUST)

The parent study (ROBUST) was a Health Research Council funded randomised placebo-controlled crossover study of tiotropium treatment in adult patients with stable, non-CF bronchiectasis. The ROBUST study stands for ‘Reduction Of exacerbations in Bronchiectasis Using Tiotropium.’ (Australian New Zealand Clinical Trials Registry, n.d.)

The study involved patients recruited from three centres: Waikato Hospital, Middlemore Hospital and Auckland Hospital. The clinical trial ran over a period of 54 weeks and was divided up into two study periods. Eligible patients were randomised per centre to either receive tiotropium capsules (18 µg) or 1 capsule of placebo daily for the first period, followed by a washout period of four weeks and then subjects were crossed over to receive the alternative treatment for the second period.

The study population looked at patients aged between 18-80 diagnosed with bronchiectasis and with FEV1/FVC ratio  $\leq 70\%$ . The inclusion criteria considered patients with a history of at least one pulmonary exacerbation in the past 12 months requiring antibiotic treatment. Patients with asthma and COPD were also included if they were initially diagnosed with bronchiectasis. Patients excluded from the study were those who had either a smoking history of more than 20 years, were allergic to tiotropium, CF hypogammaglobulinaemia, history of non-tuberculosis mycobacterial infection, primary diagnosis of asthma or bronchiectasis exacerbation or respiratory infection requiring oral or intravenous treatment.

#### 1.9.1 THE CURRENT MPHIL STUDY

The current research is a sub-study of the parent study (ROBUST), which means data collected by the ROBUST study was used to determine the cost-effectiveness and cost-utility of tiotropium treatment. In addition to the parent dataset, other data will be sourced to complement the study. However, the methodology underlying this proposal is independent of the ROBUST study and will focus on carrying out the economic evaluation.

#### 1.10 RESEARCH QUESTION

The primary question that this study seeks to answer is: Is tiotropium a cost-effective treatment for adult non-CF bronchiectasis patients in NZ?

##### 1.10.1 STUDY OBJECTIVES

The primary objective of the study was to determine the cost-effectiveness and cost-utility of tiotropium in stable bronchiectasis patients relative to a placebo treatment. Data for this study comes from the parent study as mentioned in section 1.9.1. The secondary objective was to identify the conditions where tiotropium can be cost-effective.

### 1.10.2 STRUCTURE OF THESIS

The thesis is presented in six chapters: Chapter 1 provides background details on bronchiectasis and begins by introducing the disease and describing the associated health and financial burdens that arise and possible treatment options. Chapter 2 describes in detail the key theoretical concepts and methods commonly used in economic evaluation, followed by Chapter 3 in which a literature review of published economic evaluations for tiotropium is provided. Chapter 4 details the development of an economic model, description of the sources of data inputs and methods used for the current study. Chapter 5 presents the key findings that emerged from this research. Lastly, Chapter 6 offers a discussion of the results, limitations and future recommendations.



## **CHAPTER 2. THEORETICAL FRAMEWORK FOR ECONOMIC EVALUATION**

### **2.1 IMPORTANCE OF CARRYING OUT AN ECONOMIC EVALUATION**

Economic evaluation is considered an important aspect and key component in decision-making in regards to the health care sector, especially when it comes to funding interventions from available resources (Briggs, Sculpher & Claxton, 2006). Due to the limitation of available resources, the provision of beneficial health services to a population can be quite challenging. According to Drummond, Sculpher, Torrance, O'Brien, & Stoddart (2005), economic evaluation is defined as a comparison of alternative options in terms of their costs and consequences. Costs to the value of resources relating to an intervention can include healthcare and social care provided by other agencies (Gray, Clarke, Wolstenholme & Wordsworth, 2010). Subsequently, consequences can be described as the effect produced from the treatment (Gray, Clarke, Wolstenholme & Wordsworth, 2010). The basic tasks involved in an economic evaluation are, therefore, "to identify, measure, value, and compare the costs and consequences of the alternatives being considered" (Drummond et al., 2005, p. 9).

The concept of an opportunity cost, which is the cost of foregoing an option for the next best choice, is of fundamental importance within economic evaluation. The true cost of any option is what is given up to achieve it. This not only includes the money spent in buying the option (treatment/procedure), but also the economic benefits (utility) foregone because of buying that option and hence cannot be used to buy something else. Everything has an opportunity cost – where one drug is accepted for use within the New Zealand Healthcare System, other drugs or treatments within the system are displaced. When a treatment is economically evaluated, the opportunity cost is often considered to be the value of the current treatment.

Economists seek to make one explicit set of criteria which can be used to decide between different effective uses of scarce resources. In this way, decisions about which treatments to adopt or not adopt are made based on the criteria of value rather than on a value judgment.

Many countries around the world include a role for the incorporation of economic evidence into the decision-making process for health; mainly in the European countries, Australia and Canada. In England and Wales, the relevant decision-making agency is the National Institute for Health and Care Excellence (NICE) which is an organisation independent of their Government, which is responsible for providing guidance on the use of health technologies and deciding on any implementation processes of public health programmes. Thus, economic evaluation is an important decision-making tool to decide which healthcare interventions or programme options provide the greatest benefits in the defined population to improve health.

## 2.2 KEY CONCEPTS WITHIN ECONOMIC EVALUATION

### 2.2.1 TYPES OF ECONOMIC EVALUATION

There are three main types of economic evaluation consisting of Cost-Effectiveness Analysis (CEA), Cost-Utility Analysis (CUA), and Cost-Benefit Analysis (CBA) (Drummond et al., 2005). These types of economic evaluations express similar costs in terms of monetary value but differing consequences are presented as different terms or units (Drummond et al., 2005). These are further elaborated in this chapter.

#### **Cost-effectiveness analysis (CEA)**

The health outcomes used in the CEA are measured in terms of natural units, such as life years saved or gained, duration in terms of length of stay or episode-free days or number of adverse events averted. The CEA is suitable when comparing alternative programmes in which costs are related to a single, common effect which may differ in magnitude (Drummond et al., 2005). The results produced from the CEA are presented as an incremental cost-effectiveness ratio (ICER), i.e. ratio of incremental costs to incremental effects for an alternative treatment or programme compared with another option. It can be stated either in terms of incremental cost per unit or effects per unit of cost (e.g. life-years gained per dollar spent) (Drummond et al., 2005).

Cost-effectiveness analysis is most appropriate where a decision-maker, with a fixed budget, is encountering a limited range of options within a given field (Drummond et al., 2005). To maximise the health gains for a given budget, the alternative programmes are ranked from the

lowest to the highest value ICERs and the programmes beginning with the lowest ICER are implemented until the budget becomes depleted (Drummond et al., 2005).

The ICER produced from the CEA does not indicate to us whether an intervention is valuable due to the underlying social opportunity costs (i.e. benefits forgone) that come with its implementation (Drummond et al., 2005). Therefore, to decide on using a CEA, we would need an external criterion of value to compare the ICER to which would be a societal willingness-to-pay (WTP) threshold (Drummond et al., 2005). The WTP threshold is the highest amount of money that the society is willing to pay for a unit of health gain – this is often arbitrary and it can vary across different countries (Drummond et al., 2005).

### **Cost-Utility Analysis (CUA)**

CUA measures the effects of health care programmes in terms of utility – “the preferences individuals or society may have for any particular set of health outcomes” (Drummond et al., 2005, p. 14). CUA is considered a useful method because “it allows for health-related quality of life (HRQoL) adjustments to a given set of treatment outcomes, while simultaneously providing a generic outcome measure for comparison of costs and outcomes in different programmes” (Drummond et al., 2005, p. 14). This outcome is usually expressed as quality-adjusted life-years (QALYs) which are produced by adjusting the length of time affected through the health outcome, by the utility value. The utility value has a scale of 0 to 1 where 0 indicates death (death refers to the transition to being dead) and 1 as perfect health (Drummond et al., 2005). Healthcare interventions are meant to improve life and the advantage of having QALY as an output measure is that it simultaneously incorporates both quality and quantity of health changes, and combines these into a single measure (Drummond et al., 2005).

Disability-adjusted life-years (DALYs) is another health outcome used in CUA which measures the overall disease burden. The major difference between the two is that QALY calculations use health-related quality of life weights relating to the level of health status of how an individual functions. The DALY calculation uses disability weights that represent levels of loss of functioning due to disease. Hence, the scale in DALYs: 1 represents death and 0 represents no disability, which is the inverse of QALY. This implies that QALYs

should be maximised to gain, while DALYs should be minimised to avoid loss (Robberstad, 2005).

The results of CUA are presented as an incremental cost-effectiveness ratio (ICER) which is in the same format as the CEA but it is produced as a cost per QALY gained by implementing one intervention instead of another (Drummond et al., 2005). A CUA shares a lot of similarities with a CEA in the sense that the results of both the CEA and CUA are presented as the ratio of incremental costs to incremental effects, although each method measures effects differently. Also, both techniques are well suited when considering how best to allocate an existing budget, but they do not tell us whether it is worthwhile to expand the budget given the social opportunity costs of all the resources consumed. Like the CEA, a CUA cannot tell us whether an intervention is worthwhile as it also requires a WTP threshold to decide whether (or not) the intervention in question should be implemented (Drummond et al., 2005).

For this current study, both the CEA and CUA are carried out, which is quite important in terms of decision-making on the allocation of resources to the treatment of bronchiectasis compared to the alternative options (PHARMAC, 2015; Drummond et al., 2005). Due to the similarities between the CEA and CUA, some authors do not differentiate between the two (Drummond et al., 2005).

### **Cost-Benefit Analysis (CBA)**

The cost and effects of health interventions in the CBA are measured in monetary terms. In addition to the effects of interventions in the CBA, monetary values are also added which allow for comparisons across programmes not only in the health sector, but also other sectors of the economy (Drummond et al., 2005).

A CEA does not have any monetary value placed on the health outcomes, hence it does not measure the underlying worth or value to society of additional QALYs, but only just shows which options have more QALYs gained with the same resources (Drummond et al., 2005). According to Drummond et al., 2005, it does not indicate whether expenditure spent on health care is too high or too low, but rather confines itself to the question of how any given level of spending can be arranged to maximise the health outcomes yielded.

In a CBA, decision criterion as to whether or not to adopt the programme or intervention is based upon whether the benefits are greater than the costs subject to budget limitations (Drummond et al., 2005). Hence, a CBA weighs the benefits of each alternative intervention against its costs. A positive net social benefit (NSB) indicates that the program is worthwhile. If the programme is found to maximise the NSB within the given budget, it is then selected for implementation. But a CBA is generally not easy to put into practice as the estimation of benefit is difficult due to the presence of uncertainty and it is lacking in human flexibility. Also, the use of a CBA in health economic evaluation has been highly criticised, mainly because it places monetary value on human life (Drummond et al., 2005).

## **2.2.2 A MODELLING APPROACH**

Economic evaluation can involve a number of economic models that take place alongside a clinical trial and within a theoretical framework such as a decision tree, a Markov model, a simulation model or a regression model (Drummond et al., 2005; Briggs & Sculpher, 1998). Economic evaluation is conducted alongside a clinical trial that is used to evaluate the cost-effectiveness of various treatment options used in the trial itself based on a modelling framework that looks at the disease transitions under the study and the effects of treatment on the disease (Sonnenberg & Beck, 1993; Briggs & Sculpher, 1998). These methods can also be combined – for example, regression equations can be used to predict values for an economic evaluation alongside a clinical trial or could be used within a Markov model to produce a specific parameter of the model. The model design that will be used in conducting an economic evaluation in this study will include a decision tree/Markov model which is discussed further in Chapter 3.

### **2.2.2.1 Decision tree**

A decision tree represents an individual's possible events following an intervention through a series of pathways (Drummond et al., 2005). The tree consists of decision nodes depending on the alternative treatment options and chance nodes representing uncertainty (Drummond et al., 2005; Briggs, Sculpher & Claxton, 2006). Connecting the various nodes to outcomes are branches, where the branches have probabilities which show the likelihood of an event occurring, depending on the various states of health. Each mode through the tree represents a

pathway which has a probability attached to it, a cost and an effect value and from these, expected values for each decision can be determined for both cost and effects.

Even though a decision tree is widely used, it does have some limitations. Since events that occur happen over an instantaneous discrete period, time is not explicitly defined in a decision tree unless the analyst does so in characterising the different branches (Drummond et al., 2005). Therefore, parameters related to the costs and effects in the economic evaluation that are time dependent can be difficult to implement. Also, discounting cannot occur with this framework model. Another limitation of the decision tree is that they can become complicated to model, for example, in long-term prognoses related to chronic diseases. This is because in this condition, the tree could become very ‘bushy’, with many mutually exclusive pathways due to the patient being at risk of getting events for a longer duration (Drummond et al., 2005). As a result, this type of model would be very time consuming to programme and analyse.

#### **2.2.2.2 Markov model**

Markov models are based on a series of health states constructed from a disease within a patient that can happen at a given point in time. “Time elapses explicitly with a Markov model, with the probability of a patient occupying a given state assessed over a series of discrete time periods, called cycles” (Drummond et al., 2005). How long these cycles extend for will vary depending on the disease and interventions being evaluated, but they can be months or years. Each health state in the model generally has a cost as well as an outcome measure linked with it. Each state in the model is weighted depending upon the probability of the patient being in each state and this is used to calculate the expected cost and outcomes (Drummond et al., 2005). Patients can also move between states that are determined by a set of transition probabilities (Drummond et al., 2005).

Based on the evidence in the literature review, Markov models have been used frequently in the economic evaluation of COPD patients. As mentioned previously, Markov modelling is established in the classification of a disease into several discrete health states through which the disease will progress (PHARMAC, 2015). The classification into a particular state is dependent on the natural history of the disease. In COPD, patients are classified into a state depending upon the predicted FEV1 %. Movement between the states is dependent on decline

in lung function and can be estimated in a number of ways, such as with data from clinical trials or using a regression equation to predict the transition (PHARMAC, 2015; Sonnenberg & Beck, 1993; Briggs, Sculpher & Claxton, 2006).

In a Markov model it is assumed that the person is always in one of a finite number of health states (Sonnenberg & Beck, 1993). The model usually starts with a cohort assigned to an initial health state referred to as Markov state. The subjects being modelled can move between states at defined recurring intervals; typically they either stay in the same state, move to a worse state (or a state in which a specific event occurs), or they die (PHARMAC, 2015; Briggs, Sculpher & Claxton, 2006). The models extrapolate these cycles for a certain timeframe after which time the cohort is expected to have all but died and the marginal costs and effects are then negligible. Events occurring within disease states, such as exacerbations, can be modelled by attaching utilities and costs, weighted by event rates (Sonnenberg & Beck, 1993).

### 2.2.3 ESTIMATING AND VALUING COSTS AND OUTCOMES

#### **Costs**

There are two broad types of costs; *direct* health care costs generally include those related to treatment from the hospital, outpatient visits, and out-of-pocket costs such as transport to hospital, physician fees, drugs and laboratory tests (PHARMAC, 2015). *Indirect* costs refer to loss of resources, loss of work productivity and opportunities resulting from the disease. Studies tend to focus on tangible costs such as reduced productivity, which are usually calculated from average gross earnings and the amount of work time lost because of being diagnosed with bronchiectasis (PHARMAC, 2015; Drummond et al., 2005). In some settings, incorporating the reduced productivity of a caregiver may be appropriate. Indirect costs also include intangible costs such as reduced quality of life. Quality of life includes many components, such as job opportunities, access to schools and public services and participation in community life (PHARMAC, 2015).

The opportunity cost approach is used to value direct costs and this is estimated from the ‘market cost’ of the resources involved (Blakely et al., 2012). Therefore, if ‘purchase costs’ deviate from the ‘market value’ (e.g. because of subsidies on GP consultations or

pharmaceuticals), the cost should be adjusted to associate more closely to the ‘market value’ (e.g. by adding the subsidy amount to the ‘purchase cost’) (Blakely et al., 2012). Intervention costs are normally estimated by standard activity costing methods using event pathways and patient flowcharts (Blakely et al., 2012).

In carrying out an economic evaluation, it is very important to state the study perspective as it is the basis of determining which relevant costs are to be included for analysis (Drummond et al., 2005). There are three main perspectives: these consist of the health care institution provider’s perspective, the patient’s perspective, and the societal perspective (also referred to as a third-party payer) (PHARMAC, 2015). Choosing the right perspective on cost depends upon the audience that is targeted for the study (Philips, Bojke, Sculpher, Claxton, & Golder, 2006).

From the perspective of the healthcare provider, the relevant costs to be included in an economic evaluation includes pharmaceutical or medication costs, equipment involved in treatment, hospital admissions, visit to the doctor or physician, and other costs involved in health service delivery (Drummond et al., 2005). From the patient’s perspective, this involves costs related to the patient obtained from using the health service, such as travelling expenses to and from hospital, co-payments and home expenses due to installation of healthcare intervention (Drummond et al., 2005). The societal perspective accounts for all costs acquired by society in providing health services to the patient. This includes costs incurred by the patient, as well as the healthcare provider (i.e. in hospitals or privately). It also incorporates other components as mentioned earlier, cost of resources consumed in other sectors due to adoption of the healthcare intervention and productivity loss due to an absence from/inability to work (Drummond et al., 2005). The societal perspective represents the most widespread approach as it has the advantage of measuring costs and effects associated with all the relevant stakeholders in society (Drummond et al., 2005).

## **Outcomes**

The outcome of interest in an economic evaluation for healthcare is the effectiveness parameter which is usually described in terms of a utility measurement. NICE suggests that all health effects should be accounted for within an economic evaluation. If there are other non-utility based measures that can capture health effects, but are however, not captured



within the utility measure, the effectiveness of treatment on these measures can also be presented (Drummond et al., 2005). There are several non-utilities based HRQoL measures which can be routinely measured in COPD patients.

In valuing outcomes, the aim is to capture the benefit of treatment to the patient population. This is achieved through the administration of a tool directly accessible to the patients that can then capture these HRQoL benefits (Drummond et al., 2005). There have been many generic questionnaire tools that have been developed to measure HRQoL but the most commonly used have been the European quality of life five-dimension (EQ-5D) (Hurst et al., 1997), Health utilities index (HUI) (Drummond et al., 2005) and short form 36 questionnaires (SF-36) (Tarn & Smith, 2004), used to derive a utility score. The three generic tools do differ in the dimension of health they cover, the number of levels and severity, but mainly in the estimation of a scoring formula. Based on the literature review in COPD patients, the most commonly used questionnaire was EQ-5D and this was found to be the most generic tool preferred by NICE in the United Kingdom (Drummond et al., 2005). The SF-36 questionnaire was found to be problematic for older Maori and Pacific Island people (Tarn & Smith, 2004). Utility values derived using EQ-5D was validated in this group for different health states and estimated from a general population survey of New Zealand. It was found that there was no significant difference in the values of health states reported by Maori and non-Maori.

To make effective and efficient resource allocation decisions across disease areas, a generic form of outcome measure that can be assessed over time is useful to this cause. The QALY is grounded in utility theory. This is where a new treatment that leads to improved quality of life over a time period is compared to an existing treatment that will in turn generate greater utility than if the patient continued to take the existing treatment. QALY is a health outcome measure that captures gains from two components which include reduced mortality (quantity) and mobility (quality) and combines it into a single measure (Drummond et al., 2005). For making the right resource allocation decision, depending on the health condition, QALYs is an important health measure that is useful since it can be measured over time – for example, a new treatment that can lead to an improvement in the quality of life measured over a time period, compared to the alternative option. This can result in greater utility than if the patient continues to take the existing treatment. The QALY quantifies changes in utility over the life of the patient. NICE recommends the use of QALYs within a cost-effectiveness analysis (PHARMAC, 2015; Drummond et al., 2005).

In a chronic disease such as COPD/bronchiectasis, exacerbations may result in a reduced quality of life for a period of time with incomplete recovery. The QALY is by far the most accepted health-related utility measure and is the preferred outcome measure in many countries including Canada, New Zealand, Sweden, England, UK and the US (ISPOR, 2016). There are also several non-utility measures of COPD health effects including: hard endpoint data, clinical measures, and health outcome measures from health outcome questionnaires. Hard endpoint data consists of: mortality (survival), hospitalisations, and the number of exacerbations. Clinical measures such as FEV1 and FEV1% predicted, and exercise tolerance are limited in their scope to address questions of health benefits to the patients and may only be weakly correlated to actual health benefits as experienced by the patient. Health outcome questionnaires on the other hand, specifically lend themselves to monitor health benefits as perceived by the patient.

Economic evaluations attached to clinical trials are naturally constrained by the timeframe of the trial to which they are connected. Economic models have an advantage in that through applying adequate and transparent assumptions, the results can be extrapolated into the future, up to a lifetime timeframe. The timeframe of a study is crucial because the full effect of treatment may not occur within the period of the trial: the timeframe of the model should extend far enough into the future so that the key differences between the interventions in the analysis can be established (Drummond et al., 2005, Philips, Bojke, Sculpher, Claxton, & Golder, 2006). Half-cycle correction is a method used in health economic evaluations to improve these accuracies in the lifetime horizon. Rather than the basic assumption that patients move between health states at the beginning or the end of a cycle, a half-cycle correction operates on the assumption that patients, on average, move between the health states halfway through the cycle (Briggs & Sculpher, 1998).

#### 2.2.4 DISCOUNT RATE

A discount rate is often applied to cost-effectiveness analyses to represent the fact that immediate health gains are more highly valued in the present than in the future. As the discount rates increase, future benefits and costs become less important when compared to the present. Based on the lifetime horizon, a discount rate of 3.5% per annum is normally applied, as per PHARMAC (Pharmaceutical Management Agency) recommendation

(PHARMAC, 2015), as this rate is based on the five-year average risk-free long-term government bond rate.

## 2.3 PRESENTING RESULTS

### 2.3.1 CALCULATING THE INCREMENTAL COST-EFFECTIVENESS RATIO

The estimate from the cost-effectiveness derived within economic evaluations is often summarised as the incremental cost-effectiveness ratio (ICER) (Drummond et al., 2005). The ICER represents relationships between the difference in costs and the difference in health outcomes (i.e. exacerbation rates, QALYs) between alternative treatments. The cost-effectiveness ratio is defined as:

$$\frac{CostT - CostC}{EffectT - EffectC} = \frac{\Delta C}{\Delta Q} \quad (\text{PHARMAC, 2015})$$

Where, *CostT* is the arithmetical mean cost for intervention;

*CostC* is the arithmetical mean cost for the comparator;

*EffectT* is the arithmetical mean effect for intervention;

*EffectC* is the arithmetical mean effect for the comparator;

$\Delta C$  is the difference in cost; and  $\Delta Q$  is the difference in effect.

If  $\Delta C$  is negative and  $\Delta Q$  is a positive result in a negative ICER which indicates a cost saving for every additional gain per QALY, the new intervention is therefore cost-effective in comparison to the comparator. If both  $\Delta C$  and  $\Delta Q$  are positive results in additional cost per QALY gained and even though the ICER information is useful, it is hard to gauge whether the ICER is deemed as being acceptable and cost-effective since we cannot tell whether (or not) the QALY gained justifies the additional cost (Drummond et al., 2005). In order to make an informed decision on whether or not the intervention was cost-effective would require a cost-effective threshold/WTP threshold; this is the opportunity cost defined as “the health expected to be given up as a consequence of the incremental cost” (Drummond et al., 2005). So, if the ICER is less than the WTP threshold, then the decision would be use the intervention as it’s deemed to be cost-effective and that it yields a positive net expected benefit (Briggs, Sculpher & Claxton, 2006).

The outcome measures considered in this study look at the cost per exacerbation avoided per

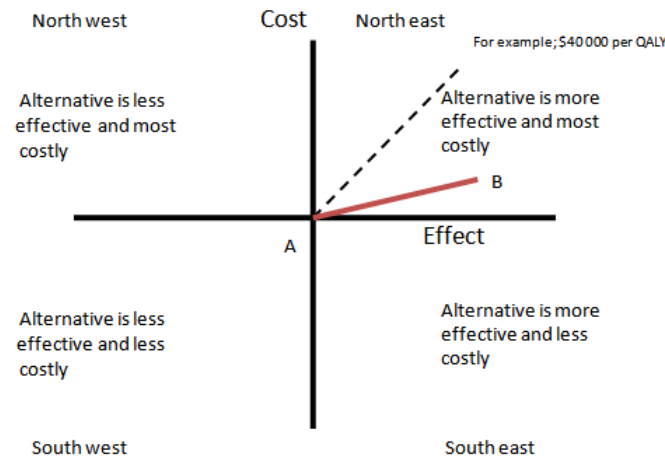
patient per year as well as cost per QALY gained per patient per year. ICERs were calculated as an additional cost per patient to prevent one exacerbation and additional cost per patient to gain one QALY. Because of the number of calculations required, especially when multiple event pathways are involved, cost-effectiveness and cost-utility analysis are carried out using TreeAgePro software 2016.

### 2.3.2 INCREMENTAL COST-EFFECTIVENESS PLANE

The cost-effectiveness plane (CE plane) is an important visualisation tool used in cost-effectiveness analysis. It is mainly used to show the incremental differences in costs and effects between different interventions. By visually representing the relative value of interventions, the CE plane helps to evaluate multiple interventions and make a more informed decision. In Figure 1, the horizontal axis divides the plane according to incremental effect, and the vertical axis divides the plane according to incremental cost. The slope of the line running from the origin of the figure to these points is the incremental cost-effectiveness ratio. This divides the incremental cost-effectiveness plane into four quadrants through the origin (Drummond et al., 2005). Each quadrant has a different implication for the decision. If the incremental cost-effectiveness ratio for a new intervention compared with the existing intervention is in the south-eastern quadrant, with negative costs and positive effects, intervention A would be more effective and less costly than intervention B. Interventions in this quadrant are always considered to be cost-effective.

If the incremental cost-effectiveness ratio is in the north-western quadrant, with positive costs and negative effects, intervention A would be costlier and less effective than intervention B (intervention A is more cost-effective than intervention B). If the incremental cost-effectiveness ratio is in the northeast quadrant, with positive costs and positive effects, or the south-western quadrant, with negative costs and negative effects, there is a trade-off between effect and cost (Gray, Clarke, Wolstenholme & Wordsworth, 2010). Additional health benefits can be obtained but at a higher cost (northeast), or savings can be made but only by sacrificing some health benefits (southwest) (Gray, Clarke, Wolstenholme & Wordsworth, 2010). The problem that arises with this is whether this trade-off is acceptable or not; that is, if the health gain is worth the additional cost or if cost saving is worth the additional health loss (Gray, Clarke, Wolstenholme & Wordsworth, 2010). Based on a maximum acceptable ICER (represented by the broken line in the figure), decision-makers

must decide if it is worth paying the additional cost for the additional benefit. So, there is always uncertainty in the cost-effectiveness analysis regarding where the intervention is placed in the CE plane and uncertainty of how much the decision-maker is willing to pay for health gain (Gray, Clarke, Wolstenholme & Wordsworth, 2010).



**Figure 1: The incremental cost-effectiveness plane (Drummond et al., 2005)**

### 2.3.3 INCREMENTAL COST-EFFECTIVENESS THRESHOLD

To evaluate and examine whether a given intervention is cost-effective relies on reference to a “predefined standard, or ‘threshold’ of the maximum acceptable level of cost-effectiveness, or WTP” (Gray, Clarke, Wolstenholme & Wordsworth, 2010). This is to “reflect the opportunity cost of the resources, in terms of the health gains produced by the treatments or programmes that would be displaced if the new treatment was adopted” (Gray, Clarke, Wolstenholme & Wordsworth, 2010). In areas where there is no standard threshold, analysts decide if a given treatment is cost-effective by comparing its ICER with those of other already funded treatment options (Gray, Clarke, Wolstenholme & Wordsworth, 2010). This, of course, assumes that the decisions to fund these existing interventions were made appropriately.

In some research fields, there may be general agreement on the value of this maximum acceptable cost-effectiveness analysis ratio; but in the NZ population there is currently no announced threshold. Once the incremental cost-effectiveness ratio for the new intervention

is calculated, the next question is whether this intervention presents good value for money. And this depends on the cost-effectiveness threshold used (Drummond et al., 2005).

Different countries use different thresholds. In the United Kingdom, for instance, the NICE uses a threshold value of £20,000 to £30,000 (equates to ~ NZD 36,000 to 55,000 for the financial year 2016) per QALY (NICE, 2008). Below £20,000 per QALY there is a high probability of the intervention being accepted and above £30,000 per QALY there is less chance of the intervention being accepted (NICE, 2008). But in NZ, there is currently no available WTP threshold, hence the threshold was based on the Gross Domestic Product (GDP) per capita as recommended by the World Health Organization (WHO) (Blakely et al., 2012). In NZ, GDP per capital was approximately NZD 40,000 as in 2016. The WHO suggested a threshold range of between 1-3 times GDP per capita. If the ICER is less than the NZ GDP then it is deemed very cost-effective, if the ICER is more than 3 times the GDP then it is deemed to not be cost-effective (Gray, Clarke, Wolstenholme & Wordsworth, 2010; Blakely et al., 2012).

## 2.4 UNCERTAINTY ANALYSIS

All estimates of costs and effects are subject to uncertainty, and the sources can be categorised in several ways (Edejer, 2003). This section describes three types of uncertainty: parameter uncertainty, structural uncertainty and generalisability uncertainty (Edejer, 2003). Parameter uncertainty occurs around inputs into the model such as utilities, resource use, cost and event rates used to calculate a cost-effectiveness ratio. The second is because there is no agreement about the value judgments required for the cost-effectiveness and cost-utility analysis. Models have in the past used data deterministically, that is, one value (usually the mean) is employed within the analysis and uncertainty exists around the mean values which were not accounted for. The use of Probabilistic Sensitivity Analysis (PSA) addresses the issue of parameter uncertainty by placing distributions around the parameter. Usually beta distributions are applied to transition probabilities and to utilities, and gamma distributions are applied to cost parameters.

Model uncertainty relates to uncertainty around the appropriate design of model used to estimate a parameter and the explanatory variables that should be included. Often the chosen

modelling structure is informed by historical models, carried out in the same disease area. This is an important starting point to building a new economic model, however, this may lead to inflexibility in structure. It is often therefore useful to look to models carried out in other (similar) disease areas to investigate alternative approaches to the model structure. The third type, generalisability uncertainty, relates to the need to extrapolate the results of the studies. For example, clinical trials of a pharmaceutical product might have been undertaken in a low-risk patient group, but policy-makers need to know the cost-effectiveness of the product as the general population would use it. Further, costs may have been determined sometime in the past and need to be extrapolated to the present for the cost-effectiveness and cost-utility analysis (Briggs, Sculpher & Claxton, 2006).

## **CHAPTER 3. LITERATURE REVIEW OF ECONOMIC EVALUATION FOR TIOTROPIUM IN COPD**

As mentioned earlier, this is the first economic evaluation conducted along clinical trials on the use of tiotropium treatment in bronchiectasis patients. Hence, this section will review published literature articles on the cost-effective analysis of tiotropium treatment in COPD patients to establish baseline trends. The focus is to review the methodological strengths and weaknesses which inform the current study and to examine known trends in differences in cost and outcomes associated with tiotropium.

### **3.1 SEARCH STRATEGY**

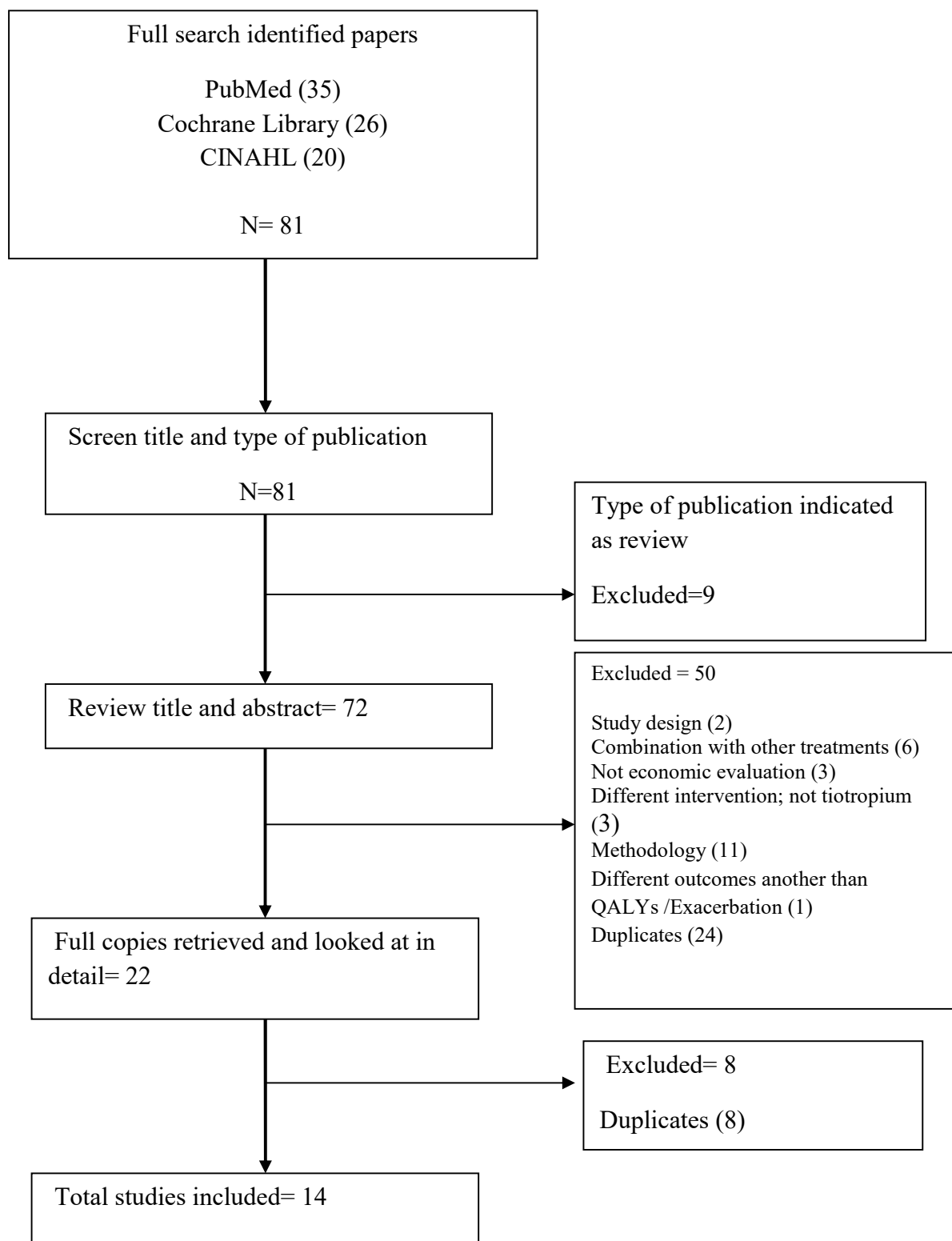
An electronic literature search was conducted using three databases found in the library resource website provided by Auckland University of Technology (AUT): PubMed, a free resource provided by the United States (US) National Library of Medicine; Cochrane Library, a subscription-based service provided by the British non-profit independent organisation; and CINAHL (Cumulative Index of Nursing and Allied Health), an index of journal articles provided on the web by EBSCO Publishing in the United States. These databases were chosen as they mostly contain research publication articles related to medical health and clinical trials. PubMed was recognised as having excellent coverage of English language papers and is well indexed, making it the first choice database for searching by most reviewers.

The search strategy involved looking at papers with randomised clinical trials that were presented with the economic analyses of tiotropium for COPD and was restricted from the years 2000 to June 2017. The PubMed database had a different design search strategy compared to the other two databases. The search strategy for PubMed is presented in the appendix (Table A1) and the search terms included “chronic obstructive pulmonary disease” or “COPD”, and “cost effectiveness” or “cost benefit/analysis” and “Tiotropium.” For the Cochrane Library and the CINAHL databases where this type of strategy was not available, search terms such as “tiotropium” and “cost effectiveness” and “COPD or chronic obstructive pulmonary disease” were used instead.



The relevant papers were selected by initially reviewing the abstracts and by applying the inclusion and exclusion criteria. If the paper was found to be appropriate; the full review was obtained. The studies that were considered for inclusion in the review were economic evaluations conducted along clinical trials which involved modelling based studies such as the Markov or decision tree methodology. The model inputs were populated by individual data from a trial, as this is the methodology that will be used. The types of economic evaluation that will be assessed include cost-effectiveness and cost-utility analyses. Studies that did not involve a tiotropium treatment arm were excluded or studies that used tiotropium in combination with other treatments were excluded, as we are interested in the cost-effectiveness only of tiotropium. Studies that looked at outcomes other than QALYs or exacerbation events or involving systematic reviews were excluded. Also studies that did not compare both costs and effectiveness of alternatives were excluded (i.e. no economic evaluation), as were studies in which the authors did not access individual patient data from a trial.

The literature search identified 81 studies from the three databases; PubMed listed 35 articles, Cochrane Library presented with 26 hits and CINAHL with 20 hits. Details of the paper selection process are illustrated in the flow diagram (Figure 2). Screening of the titles and types of publications led to 9 papers being excluded because the studies were review articles. On further screening of the titles and abstracts of the remaining papers, an additional 50 papers were excluded because the study focus was on using a different study design. The studies were excluded based on a different methodology involving empirical analysis and observational studies, which included a combination with other treatments. The studies also used different interventions and were not related to tiotropium and had no economic evaluation component. Twenty four of these were duplicate articles, hence excluded. The full text of the remaining 22 relevant studies was obtained. Of these, 14 randomised clinical trial based studies met the inclusion criteria for review due to 10 being duplicate papers. A list of excluded studies from the review can be found in Appendix (Table A-3).



**Figure 2: Flow chart of selecting studies in review**

## 3.2 REVIEW OF ECONOMIC LITERATURE

In this section, the 14 included studies were reviewed. Information was extracted in terms of study population, country, interventions, comparators, results of clinical outcome, costs, and setting of economic evaluations. The studies were further reviewed in detail in terms of the different Markov modelling approaches used and the assumptions relating to the model. The review also looked at how input data was populated and estimated in terms of outcome costs and outcomes. The different cost-effective results were also reviewed. Tables 1 and 2 summarise the model input as well as the results summaries from the previous literature. Each methodological component of the economic evaluations will be discussed below.

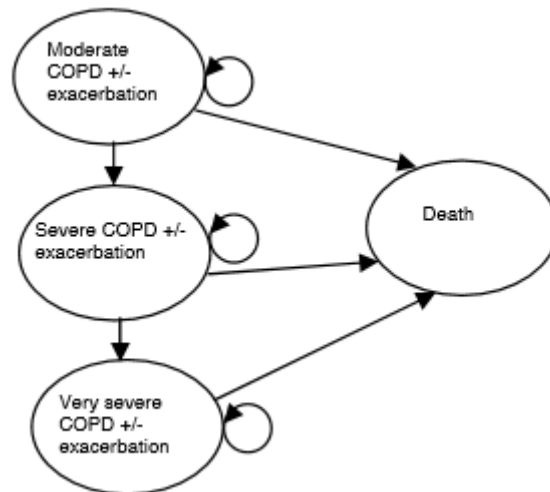
### 3.2.1 MODELLING APPROACHES USED

Based on the 14 included economic studies, there were seven studies that had both a cost-utility analysis and cost-effectiveness analysis of tiotropium compared to other treatments (studies number 2, 3, 4, 9 and 10 listed in Table 1), whereas six studies had cost-utility analysis and only one study presented cost-effectiveness analysis results. All the 13 studies used a modified version of the initial model developed by Oostenbrink and colleagues. The model was a one year Markov model based on three health states describing severity and exacerbation status (no exacerbation, mild exacerbation and severe exacerbation). The three-health states consisted of moderate ( $50\% < FEV1 < 80\%$  predicted), severe ( $30\% < FEV1 < 50\%$  predicted) and very severe ( $FEV1 < 30\%$  predicted), not including a mild state or a death state. This study looked at the one-year cost-effectiveness of tiotropium compared to ipratropium and to salmeterol in the Netherlands and in Canada. The perspective of the model was the local health care reimbursement authorities in the Netherlands and in Canada. The model had cycle lengths of one month to capture exacerbations and the transitions to more severe disease stages over time. Within each state, non-severe and severe exacerbations could occur and movement between states could be either: forwards, backwards or remaining in the same state. During a cycle in which an exacerbation occurred, utility was assumed to decrease (for the whole cycle) by 15% for a non-severe exacerbation and 50% for a severe exacerbation.

The Markov model by Rutten-van Molken et al. 2007 expanded upon the Oostenbrink et al. model which had another health state added of 'death' giving four health states based on FEV1% predicted as illustrated in Figure 3 in the 5-year model but not in the 1-year model. Movement between states was based on the annual decline in FEV1 derived from the trial data. Cycles were one month in duration. Backwards and forwards transitions were allowed during the first year, and for subsequent years only forward transitions were permitted. Exacerbation probabilities were based on first year rates. The second scenario applied transition and exacerbation probabilities from the first year throughout the five-year model. The third scenario assumed that neither disease progression or exacerbation frequency/intensity was affected by treatment after the first year. At the start of the model simulation in the Maniadakis et al., 20% of the patients were assumed to have moderate COPD, 50% severe and 30% very severe COPD according to the international Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.

In addition, there were four studies that included a death health state as well (Hettle 2012; Zaniolo 2012; Hoogendoorn 2013; Eklund 2015). Eklund et al. 2015 modelled patients from the age of treatment initiation (65 years old) until they were deceased or reached the age of 100. Three cohorts were analysed, one receiving the usual non-LAMA care like the placebo arm in the UPLIFT trial and two receiving additional treatment with either tiotropium 18 µg (Spiriva HandiHaler) or glycopyrronium 44 µg (Seebri Breezhaler). Upon entering the model, all patients were distributed across the separate states according to the observed distributions found in the UPLIFT trial (GOLD II: 48%, GOLD III: 44%, GOLD IV: 8%).

For the Markov model with four states in the Hoogendoorn paper, each COPD severity state has patients with a risk of either experiencing a non-severe or severe exacerbation. The risk of experiencing an exacerbation varies by the severity state of the COPD and treatment and was assumed to be constant over time. Zaniolo and colleagues developed a Markov model based on chain-based simulation where the model generates a cohort of virtual patients by individually assigning gender, age, height, smoking status (current or ex-smoker), and a baseline post-bronchodilator (PB)-FEV1 (% predicted). The transition between Markov states depends on PB-FEV1, and for the transition toward the death state, on treatment-specific mortality probabilities. Hettle and colleagues also used a similar health state Markov model in the Rutten-van Molken paper, except that the time-horizon was extended from one to four years instead of five to estimate the cost-effectiveness of tiotropium compared to ipratropium and salmeterol.



**Figure 3: The Rutten-van Molken et al. Markov model**

Naik (2010) also used a Markov model with a one-year time horizon based on Randomised Controlled Trial (RCT) data, but the model comprised of pairs of health states; ‘on treatment’ and ‘maintenance therapy’, ‘response’ and ‘inadequate response,’ and exacerbations of different severities. For all five model-based economic evaluations, probabilities for transition between states were based on pooled data from RCTs. The analytical perspective differed across the studies between societal and third-party payer, depending on the country the study took place. The countries of study were the UK and Belgium (Hettle, 2012), Greece (Maniadakis, 2006), USA (Naik, 2010; Campbell, 2014), Netherlands and Canada (Oostenbrink, 2005), Spain (Rutten-van Molken, 2007; Eklund, 2015), Sweden (Eklund, 2015), Germany (Hoogendoorn, 2013) and Italy (Zaniolo, 2012). The reported price year and currency differed between the studies (see Table 1) as well as the difference in comparators such as salmeterol, ipatropium, and glycopyrronium, aclidinium, usual care and placebo. Most of the economic evaluations were sponsored by Boehringer Ingelheim, the manufacturer of tiotropium. There were two studies (Campbell, 2014; Naik, 2010) which did not carry out any PSA analysis to changes in the baseline values of the model to account for the robustness of the result. Both studies looked at one-way sensitivity analysis which looked at the probability of exacerbation, probability of severe exacerbation, probability of hospitalisation, and compliance with medications.

### 3.2.2 ESTIMATING AND VALUING COSTS AND OUTCOMES

All the economic evaluations looked at maintenance costs and the costs for exacerbations. This generally included respiratory medications, hospitalisations, physician visits (inpatient or outpatient), visits to general practitioners, visits to emergency departments and laboratory tests. The effectiveness data on exacerbations were based on data from RCTs using the UPLIFT study or the SPARK study comparing tiotropium to salmeterol, ipratropium, glycopyrronium, usual care or placebo respectively. Utility data was based either on RCTs (Naik, 2010; Rutten-van Molken, 2007) or observational study data (Maniadakis, 2006; Oostenbrink, 2005).

The transition probabilities for the model were derived by pooling data from six tiotropium clinical trials; two compared with placebo (1-year studies), two compared to ipratropium (1-year studies), and two compared to the salmeterol model when adapted to run for a 5-year time horizon for the Netherlands and Spain. Hettle et al. 2012, derived sets of transition probabilities for tiotropium and usual care arms using data from the UPLIFT study. Although all studies were based on the same Markov model and used data from the same clinical trials, different studies presented different health outcome measures, including total number of exacerbations, number of severe exacerbations, number of non-severe exacerbations, exacerbation-free months, quality-adjusted months or years, percentage of patients in different disease stages at one year, time in different disease stages over the model time period, and life-years. The costs included in the models generally were shown as subdivided into study drug costs, costs for disease monitoring, and costs for treating exacerbations.

### 3.2.3 DISCOUNT RATES

Different discount rates were used in different studies as per the country setting and their standard guidelines, since studies with a time horizon of more than one year needs to be discounted to account for future costs and benefits. Three studies carried a lifetime horizon (Eklund, 2015; Eklund, 2015 (Sweden); Zaniolo, 2012) using a discount rate of 3% and 3.5%. The other three studies implemented a Markov model at a much shorter timeframe of one year and hence no discount rate was applied (Oostenbrink, 2005; Maniadakis, 2006; Hettle, 2012). But there was one study by Campbell et al. with a shorter time horizon of one year with 35 cycles and a 3% rate. This was applied to account for a lower value for future events in the model. Rutten-van Molken et al. adopted an annual discount rate of 6%. This study also used discount rates of 0% for both costs and effects, and 6% for costs combined

with 3% for effects in the sensitivity analysis. Hettle et al. had both costs and benefits discounted at a rate of 3.5% per annum in the UK and 3% and 1.5% per annum in Belgium.

### 3.2.4 PRESENTING RESULTS

One study from Sweden (Eklund, 2015) showed that tiotropium demonstrated the highest expected net benefit for ratios of the willingness-to-pay per QALY. Compared to glycopyrronium the QALY gained was estimated to 0.23 QALYs in favour of tiotropium at an incremental cost of SEK 2423, yielding a cost per QALY gained of SEK 10,456. Two studies from USA, one (Naik, 2010) comparing tiotropium to no treatment, leads to an ICER of \$1817.36 per exacerbation avoided, which confirms that in patients with moderate COPD, tiotropium is more cost-effective than salmeterol and no treatment, whereas the other study provides an ICER of \$63,718/QALY for aclidinium vs. tiotropium in the base case analysis. The two-way sensitivity analyses suggest that as the aclidinium cost falls below \$2,400 it is preferred to tiotropium at any cost. Costs above \$3,400 favour tiotropium therapy.

The study in the Netherlands and Canada favoured tiotropium in terms of the lower number of exacerbations and reduced cost when compared to salmeterol. The cost-effectiveness acceptability frontier of exacerbations showed that tiotropium was associated with the maximum expected net benefit for all values of the ceiling ratio above zero (the Netherlands) and 10€ (Canada) in the base case analysis. The study in Greece resulted in a mean number of exacerbations per patient of 0.92 in the tiotropium arm, and 1.1 in the salmeterol arm in one year, resulting in 0.18 exacerbations avoided per patient. The total cost per patient in one year was €1.3 in the tiotropium arm, and €1.2 in the salmeterol arm, resulting in a cost difference of €85. The incremental cost per exacerbation avoided was €472. Tiotropium was concluded to be cost-effective, however, there was no statistically significant difference found between the treatments.

The study in the UK and Belgium resulted in a probability of tiotropium being cost-effective at £30,000 (€50,000) per QALY gained, which was greater than 60% in the study. Another study in Italy had an ICER of €7,916 per QALY gained and in the cost-effectiveness acceptability curve (CEAC) tiotropium had a 90% probability of being cost-effective for a WTP threshold of €10,000/QALY. Some studies show that the annual total costs with tiotropium were lower than with the comparators, while other studies found that the

reductions in hospital and other costs were not sufficient to completely offset the increased drug costs with tiotropium. When incremental cost per QALY was estimated, the ICERs were generally below commonly accepted benchmark values for willingness-to-pay, depending on their country's threshold.



**Table 1: Summary of all included studies**

<b>Studies</b>	<b>Country</b>	<b>Currency</b>	<b>Cost year (unit)</b>	<b>Duration</b>	<b>Study population</b>	<b>COPD population</b>	<b>Comparators</b>	<b>Outcome measure</b>
Oostenbrink, Rutten-van Mölken , Monz and FitzGerald (2005)	NL,CA	Euro (€)	2001	Time horizon of the model set to 1 year	Patient-level data from six randomised controlled trials. Model was based on 1296 pateints treated with TI, 405 SL, 175 IP	II, III, IV	TI, SL, IP	Number of exacerbations, Quality-adjusted life months
Maniadakis, Tzanakis, Fragoulakis, Hatzikou and Siafakas (2006)	Greece	Euro (€)	2005	1 year		II, III, IV	TI, SL	Number of exacerbations', QALY months QALY years
Rutten-van Molken, Oostenbrink, Marc	Spain	Euro (€)	2005	1 year	Baseline distribution of patient among	II, III, IV	TI, SL, IP	Number of exacerbations',

and Brigitta (2007)					disease was based on a Spanish study by Miravittles et al. So, by severity of 436 COPD patients, 55% were moderate, 35% and 10% were severe and very severe respectively.			QALY months
Naik, Kamal, Keys and Mattei (2010)	US	Dollars(\$)	2006	1 year	Patient population of the model was a cohort of 10,000 male patients with a mean age of 65 years and disease duration of 9.5 years.	II	TI , SL, No Treatment	Number of exacerbations
Neyt, Devriese, Thiry and Van den	Belgium	Euro (€)	2004-2006	1 year		COPD	TI, No Treatment	QALY

Bruel (2010)								
Price et al. (2011)	Germany	Euro (€)	2010	3 years	Patient population was based on moderate to severe COPD classified by post FEV1 with a mean age of 63.6 years	I, II, III, IV, Death	TI, SL, ID	QALYs
Hettle et al. (2012)	UK	Pounds Stirling (£)	2011	4 years	The patients from the UPLIFT study had an average age of 64.5 years and 2986 (46%, 44%, 8% under GOLD stages II/III/IV) were treated with TI and 3,006 (45%, 44%, 9%) with placebo.	II, III, IV, Death	TI , UC	Number of exacerbations, QALY

	Belgium	Euro (€)	2011					
Zaniolo, Iannazzo and Padelli (2012)	Italy	Euro (€)	2010	Lifetime with 1 year cycles		II, III, IV	TI, RC	Number of exacerbations (EX), Life years (Lys), QALY
Hoogendoorn (2013)	Sweden	Swedish Krona (SEK)	2010	12 months		II, III, IV	TI, SL	QALY
Campbell (2014)	US	Dollars (\$)	2013	12 months		II, III, IV	TI, AC	QALY
Costa-Scharplatz et al. (2015)	Sweden	Swedish Krona (SEK)	2013	3 year, lifetime	Patient population based on data from GLOW 2 (GLY-bromide in COPD airways clinical Study 2). This study was a randomised, multicentre, double-blind,	I, II, III, IV, Death	TI, GLY, PL	LYs, QALY

					parallel-group phase III trial done in 1,066 moderate to severe COPD patients over 52 weeks compared to placebo or TI. Patients had a mean age of 64 years. Cohort consists of 0.78% mild, 42.8% moderate, 47.7% severe and 8.75% very severe.			
Eklund, Afzal and Borgstrom (2015)	Sweden	Swedish Krona (SEK)	2012	Lifetime		II, III, IV	TI, GLY, UC	QALY
Eklund, Afzal, Borgstrom, Ojanguren, Crespo	Spain	Euro (€)	2014	Lifetime horizon		II, III, IV	TI, GLY	Exacerbation rates, QALYs. Lung function

and Baldwin (2015)								
Eklund et al. (2016)	Canada, Spain, Sweden and UK	Euro (€)	2014	Lifetime horizon		GOLD II, GOLD III, and GOLD IV	TI , GLY	QALYs, life years

Tiotropium (TI) , Salmeterol (SL), Ipratropium (IP), Indacaterol (ID) Glycopyrronium (GLY), usual care (UC),

Routine COPD care (RC), Aclidinium (AC),placebo (PL)

Netherlands (NL), Canada (CA)

Transitional probabilities (TP), Probabilities (Prob), Exacerbations (EXA), QALYs (Quality adjusted life years),LYs (life-years)

Disease severity states based on pulmonary function measured by prebronchodilator FEV1 as % of predicted normal , using same severity classification as updated by GOLD criteria; mild (I; FEV1 >80% ) moderate (II; 50% < FEV1% < 80%), severe (III; 30% < FEV1 < 50% ) and very severe COPD (IV; FEV1< 30%) and death.

**Table 2: Summary of methods used**

<b>Studies</b>	<b>Source input Cost</b>	<b>Source input effect</b>	<b>Models/assumptions</b>	<b>Sensitivity analysis</b>	<b>Perspective</b>
Oostenbrink, Rutten-van Mölken , Monz and FitzGerald (2005)	Outpatient visit GP, visit to other HCP, ICU and non-ICU days, antibiotics, spirometry, influenza vaccination, Theophylline, beta-adrenergics, inhaled steroids, other medications expressed in per day	Efficacy based on combination of six trials	Markov model based on severity states deduced from prebronchodilation FEV1 and exacerbations	Sensitivity analysis, PSA (Second-Order Monte Carlo simulations, 5000)	Healthcare

Maniadakis, Tzanakis, Fragoulakis, Hatzikou and Siafakas (2006)	Cost of patient per year ranged from €360(~\$600)	Input derived from clinical trial presented in Oostenbrink and colleagues in 2005. Utility values derived from observational study of COPD patients		One way, PSA (Monte Carlo, 5000 simulations)	Greek National Health system (NHS)
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Rutten-van Molken, Oostenbrink, Marc and Brigitta (2007)		Probability of death was based on all-causes for patients with III or IV health state. Utilities were obtained from the EQ-5D score at baseline in a subset of patients in the UPLIFT trial. Each year, during months in which patients experience an EXA, utility value was reduced by 15% for non-severe EXA and by 50% for severe EXA		PSA	Spanish National Health system and society
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Naik, Kamal, Keys and Mattei (2010)	Healthcare utilisation derived from two studies and healthcare utilisation associated with maintenance therapy varied by disease severity and varied by severity of EXA	Efficacy data taken from published results of clinical trials. For TI, 3 studies were used	Markov model using a decision analytical model with a 6 month cycle and a shorter timeframe of 1 year. The decision model consisted of two states; on treatment and maintenance therapy which represents those patients who do not continue treatment and the alternative state	One way (used 20% range for base-case estimate), PSA ( Monte Carlo simulations)	Third party payer
Neyt, Devriese, Thiry and Van den Bruel (2010)				PSA, scenario analysis	Health care payer

Price et al. (2011)	Cost included maintenance (GP visit, spirometry), EXA (hospitalisation, physiotherapist per hour, ER visit, drug prices). Drug prices calculated as cost of physiotherapy taken from Bremen association of SHI physicians total annual maintenance Regional Sickness Funds	Clinical input derived from two clinical trials; INHANCE (comparing treatments ID, TI) and INLIGHT-2 (comparing ID and SL). Both trials had the same length (26 weeks), sample of size 1683 vs. 998	Markov model based on severity states of COPD plus a state for death. For each health state, patients were assigned with either the probability of getting severe or non-severe EXA to give 12 states plus death in total. Cycle length set to three to capture TP of patients who improve lung function to change severity state	One way, PSA (1000 interactions)	Health care provider (Statutory health insurance; doesn't consider societal or productivity loss)
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Hettle et al., (2012)	National Health Service (NHS) is responsible for healthcare provision and community care provided through Personal Social Service (PSS). Total cost includes direct medical costs, usual care treatment and cost of hospitalisation. Out of pocket expenses and indirect costs such as productivity were excluded	The exacerbation rates were derived from observed exacerbations in the UPLIFT trial defined by the disease state and exacerbation severity. Utility weights were derived from the subset of patients in the UPLIFT study	Cohort Markov model developed based on outcome of patients enrolled in UPLIFT study	One way (25% used for base-case results), PSA (Second-Order Monte Carlo simulations, 10,000), subgroup analysis by severity (moderate, severe and very severe)	Healthcare payer of UK and Belgium
	National Health Insurance. Federal Public Service, Public Health. Indirect cost excluded				

Zaniolo, Iannazzo and Padelli (2012)				PSA	National Health System
Hoogendoorn (2013)				1-yr and 5-yr time horizons	German statutory health insurance (SHI) perspective and the societal perspective
Campbell (2014)				Two way	Patient

Costa-Scharplatz et al. (2015)	Cost included direct (included drug costs, maintenance therapy costs and costs per exacerbation episode) and indirect costs (maintenance therapy and exacerbations were included if the patient was less than 65 years of age due to early retirement). Drug costs obtained from the Dental and Pharmaceutical Benefits Agency, TLV	TP taken from the GLOW 2 study was applied to the 1st cycle of the model. As the FEV1 improved due to the treatment effect, it was assumed to be applicable at therapy initiation. After the 1st cycle, patient experienced a uniform lung function decline and the annual rate of lung function decline was obtained from the OLIN study	Markov model based on four COPD health states including death, and each health state divided into three states: no EXA, non-severe EXA and severe EXA. Cycle lengths set to 3 months. 3-year time horizon selected based on FEV1 benefit. This assumes that it occurred at the beginning of treatment and the effect will not be lost over the course of the lifetime	One way, PSA (second order 2000 simulations), scenario analysis (assuming no difference in treatment effect between GLY and TI and all inputs were assumed to be equal except for costs related to the treatments)	Societal
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Eklund, Afzal and Borgstrom (2015)				PSA, one way	Societal (Swedish )
Eklund, Afzal, Borgstrom, Ojanguren, Crespo and Baldwin (2015)				PSA	Societal
Eklund et al., (2016)				One way	Societal

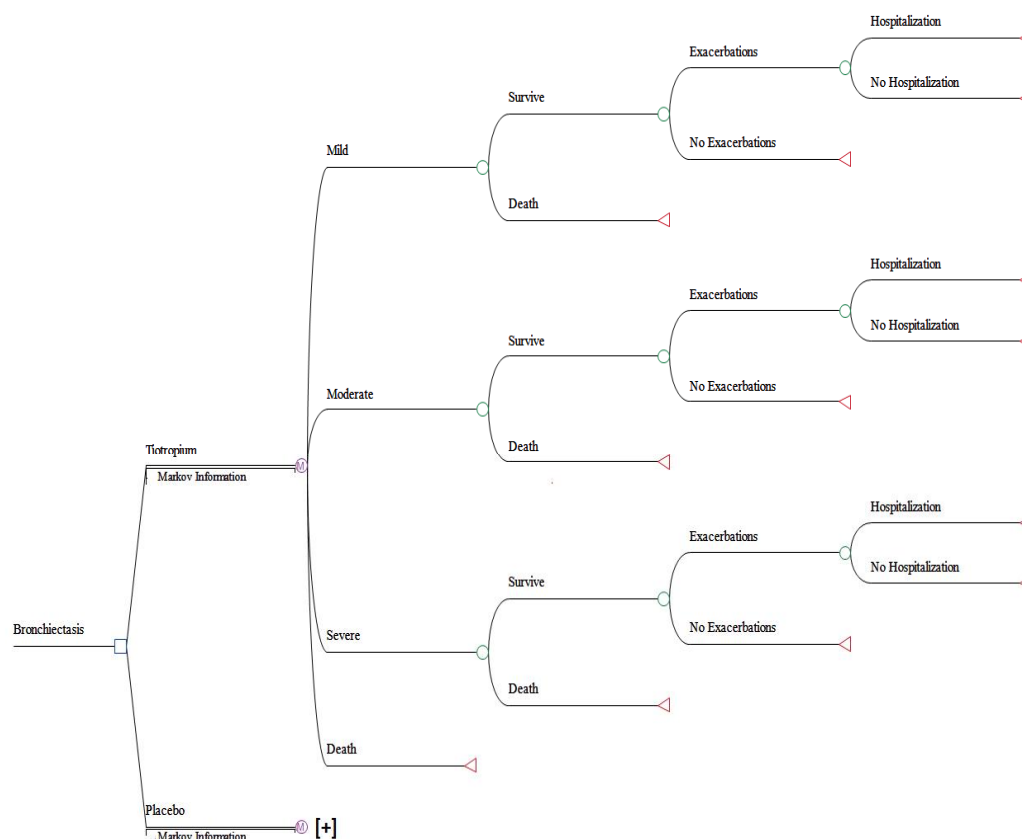
## CHAPTER 4. METHODS

### 4.1 MODEL DEVELOPMENT

#### 4.1.1 PHASE 1: BASED ON ECONOMIC LITERATURE

A decision tree/Markov model was constructed using a decision analytical model method using TreeAge Pro 2016 software (TreeAge Pro, 2016) to model patient flow transition and according to the response to treatment. This model was adapted and developed based on the literature review search from three studies, as mentioned in Figure 4. This model evaluated the cost-effectiveness of two treatments: tiotropium and a placebo in patients with non-CF bronchiectasis. The placebo mentioned here reflects no treatment and uses one data source from the ROBUST study. The decision tree starts with two intervention arms in the bronchiectasis population as depicted in the Figure. For each arm, a Markov model cycles patients through 1-year. For each cycle, the patient experience is observed in terms of mild, moderate or severe exacerbation depending on the severity or move towards the absorbing death state (Oostenbrink, Rutten-van Mölken, Monz, & FitzGerald, 2005). The patients who continue to suffer mildly or moderately and respond to treatment may experience an exacerbation or no exacerbation (Naik, Kamal, Keys & Mattei, 2010; Oostenbrink, Rutten-van Mölken, Monz, & FitzGerald, 2005). For patients that suffer an exacerbation, a percentage of them will be hospitalised and the remainder treated under the usual care setting. Both exacerbation arms are recycled back into either a ‘mild/moderate/severe’ arm (Campbell et al., 2014; Naik, Kamal, Keys & Mattei, 2010; Oostenbrink, Rutten-van Mölken, Monz, & FitzGerald, 2005).





**Figure 4: Decision tree/Markov model demonstrating the various Markov states**

Notes: (+) indicates the same tree is repeated for each of the arms

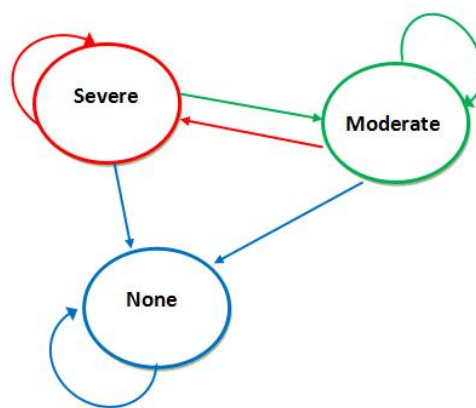
\*(adapted from Campbell et al., 2014; Naik, Kamal, Keys & Mattei, 2010; Oostenbrink, Rutten-van Mölken, Monz, & FitzGerald, 2005)

#### 4.1.2 PHASE 2: MODEL ADJUSTMENT BASED ON CLINICAL EXPERT OPINION

Phase two involves modifying the decision tree/Markov model based on the health states and severity of exacerbations, informed by the literature with observations from the ROBUST study. Expert clinical opinion was obtained from Dr Conroy Wong, who advised on some alterations made to the constructed decision tree/Markov model using the TreeAge Pro Software version 2016. Firstly, patient level data obtained from the ROBUST study revealed

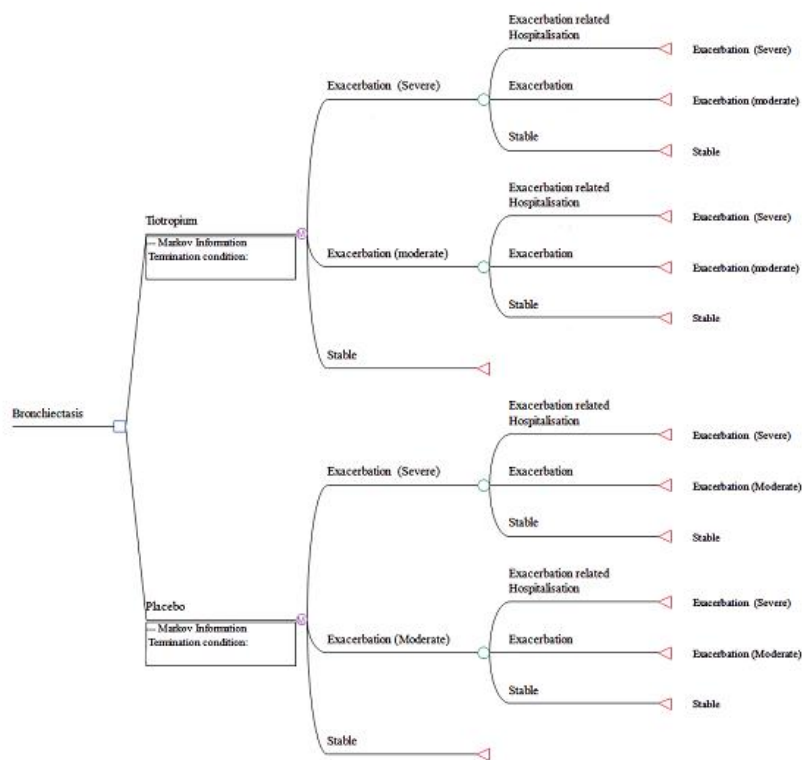
that there were no mild exacerbation events and deaths observed, therefore these states were modified in the revised model. Based on clinical expert opinion, the Markov model was amended to include three health events which included exacerbation-related hospitalisation (mostly those who experienced severe exacerbations), exacerbation (those who experienced moderate exacerbations) and no event (stable) under each intervention arm (Oostenbrink, Rutten-van Mölken, Monz & FitzGerald, 2005; Hettle et al., 2012).

In the Markov cycle, patients in each treatment group were assigned a probability of transitioning from one disease state to another. During the cycle, a patient who experienced severe exacerbations either remained in the same phase or progressed to the moderate stage, or ended up with no events. Similarly, a patient at the moderate stage may stay in this phase, or progress to a severe stage, or may remain stable. Those patients with no exacerbations continued being in this state which is referred to as the absorbing state mentioned earlier. These observations were consistent with patient outcome patterns observed from the ROBUST study (Australian New Zealand Clinical Trials Registry, n.d.). The disease states and structure of the decision tree/Markov model are presented in Figures 5 and 6 respectively. The period over which these transitions happen between these health states are observed over a shorter duration (i.e. cycle time) of one year.



**Figure 5: Modified Markov state diagram**

\*(adapted from R. Hettle et al., 2012)



**Figure 6: Graphical presentation of the redesigned decision tree/Markov model**

\*modified from Oostenbrink, Rutten-van Mölken, Monz & FitzGerald, 2005

## 4.2 MODEL ASSUMPTIONS

The decision tree/Markov model developed in this research assumes that the patient will be in one of the states at any one time and transitions between these states will take place at the end of a six month cycle. Since the time horizon chosen was one year, it is assumed that during this 1-year period, the patient who experienced no exacerbations remained the same and did not transition into a higher level of severity. For those with a severe exacerbation, we assumed that each patient would incur the cost of hospitalisation associated with the exacerbation. The risk of experiencing an exacerbation varied by a severity state however, was assumed to be constant over time. The mean exacerbation rates and QALYs per treatment were assumed to be the same across the severity.

## 4.3 DATA SOURCES AND INPUTS USED IN THE MODEL

### 4.3.1 TRANSITION PROBABILITIES

There are two cycles in total and the study was limited to a 1-year period. The cycle length of six months was selected as the duration of the ROBUST study of each treatment in bronchiectasis was six months.

To obtain transition probability for the shorter cycle, the following formula is used;

$$p = 1 - e^{-rt}, \quad (\text{PHARMAC, 2015})$$

Where  $p$  = probability of the event,

$r$  = constant rate

$t$  = time (using 1/2)

The rate is defined as the likelihood of being in that state, whereas a probability is the proportion of the population at risk that makes a transition from one state to another over a specified period. As a Markov model uses transitions measured at discrete time points, rates are converted to transition probabilities (Briggs, Sculpher & Claxton, 2006).

The value of real interest is the probability of the event, given (conditional on) which treatment the group patients are in. The proportion of patients who started the trial at the baseline in the moderate health state and then remained in the same state after treatment were estimated. In order to compute what the transition matrix will look like after six months, the starting probabilities (or the probabilities at baseline) are calculated.

Using the data from the parent study (ROBUST) which consisted of 90 participants, the starting probabilities with their 95% confidence intervals (CI) were calculated for those presented with severe and moderate exacerbations during the trial period of six months. The starting probabilities for those with moderate exacerbations were quite similar for both treatment groups, whereas for those with severe exacerbations, the probabilities were twice as much in the tiotropium group compared to the placebo group, but they were relatively much lower, as seen in Table 3. The transitional probability of progression was also calculated based on the starting probabilities for moderate and severe exacerbations, which is shown in

Table 4 (for instance, those with an starting probability of moderate exacerbation, what proportions of those either remained as moderate or had further severe exacerbations within the six month period. This was based on the length of the duration of the trial period under each treatment arm).

**Table 3: Starting probabilities during six months**

<b>Description</b>	<b>Estimate</b>	<b>Standard error</b>	<b>95% CI</b>
<i>Probability of developing a severe exacerbation (Tiotropium)</i>	0.022	0.0081	(0.0061, 0.077)
<i>Probability of developing a severe exacerbation (Placebo)</i>	0.011	0.0046	(0.0019, 0.060)
<i>Probability of developing a moderate exacerbation(Tiotropium)</i>	0.58	0.051	(0.48, 0.68)
<i>Probability of developing a moderate exacerbation (Placebo)</i>	0.61	0.051	(0.51, 0.72)

**Table 4: Transitional probabilities within a six month period**

<b>Treatment group</b>	<b>(From)</b>	<b>Severe exacerbation</b>	<b>Moderate exacerbation</b>	<b>Stable</b>
<b>Tiotropium</b>	<b>Severe exacerbation</b>	0	1	0
	<b>Moderate exacerbation</b>	0	0.135	0.865
	<b>Stable</b>	0	0	0
<b>Placebo</b>	<b>Severe exacerbation</b>	0	1	0
	<b>Moderate exacerbation</b>	0.018	0.055	0.927
	<b>Stable</b>	0	0	0

\*NA (Non-applicable as this is the absorbing state)

#### 4.3.2 VALUATION OF COSTS

For the purpose of this study, the cost of bronchiectasis included direct costs since this study assumes a funder payer perspective. This is because the intended audience for this study are healthcare funders and planners such as the Ministry of Health in New Zealand, District Health Boards and PHARMAC.

All cost data are valued in New Zealand dollars for the financial year 2016/17. The source of cost data used for this analysis included: inhaled study drug, antibiotics and other medication use, patient healthcare utilisation (i.e. outpatient hospital clinic visits, respiratory visits, GP visits, practise nurse visits and lab tests) as well as inpatient hospitalisation costs related to exacerbations. A resource use approach was undertaken to value health care consumption (Drummond et al., 2005).

All the sub-costs are combined to produce the overall cost for each patient. For each treatment option, the expected cost per the cohort in each cycle was calculated as follows:

$$\text{Expected cost} = \sum (C_i \times P_i)$$

Where:

$C_i$  = cost of state  $i$

$P_i$  = proportion of patients in the state  $i$

$i$  = moderate, severe

##### 4.3.2.1 Medication cost

The medication cost is based on the list of medications used by the patients then matched by national health index numbers sourced from decisions supported by Counties Manukau District Health Board and Auckland District Health Board. Details of the type of medication frequency and the dosage were also obtained. The unit price for each medication was derived using the unit price as per unit/dosage (measure in ml, tablets or mg etc.) taken from the PHARMAC schedule for 2016 (Pharmaceutical Schedule, 2016). The cost of medication was estimated by multiplying the dosage and frequency of use with the market price for each resource. The average costs of pharmaceutical use for each group are produced in Table 6.

### 4.3.2.2 Healthcare resource cost

Resource use was collected for each ROBUST study participant using weekly dairies. Healthcare utilisation (i.e. outpatient hospital clinic visits, respiratory visits, GP visits, practise nurse visits and lab tests) were recorded by frequency of outpatient health service each week. Frequency of service use was combined with a market price for each resource (i.e. cost of GP visit) to estimate the cost of the service. Sources of market prices were taken from the Accident Compensation Corporation (ACC), pharmaceutical schedule (PHARMAC) and Ministry of Health (MOH) as listed in Table 5. Unit cost per visit to the respiratory clinic, physiotherapist and the emergency department was obtained from the decision support team based at Middlemore and Auckland Hospital. The average estimated healthcare costs are indicated in Table 5. For the lower and upper ranges of this base-case estimate of inhaled study drug cost of tiotropium, a  $\pm 10\%$  range of the base-case estimate was used in the sensitivity analyses as there was no data available with regards to the variability of this cost. The inhaled drug tiotropium was purchased from manufacturer Boehringer Ingelhem (Boehringer Ingelhem, n.d.) in the form of capsules; Optimus Healthcare was the compounding pharmacy that prepared active and placebo study drug capsules and packed them in blister packs for the patients.

**Table 5: Cost of each item under the healthcare resource**

Items	Unit of pricing	Price/cost (NZD in	
		\$ for 2016)-	CMDHB Source
Inhaled study drug: Placebo	cost per study patient	\$210.0	Manufacturer Boehringer Ingelheim and Optimus Healthcare the compounding pharmacy
Inhaled study drug: Tiotropium	cost per study patient	\$424.66	Manufacturer Boehringer Ingelheim and Optimus Healthcare the compounding pharmacy
Prednisone	per 500 (tab 1mg)	\$10.68	PHARMAC Schedule

	per 500 (tab 2.5 mg)	\$12.09	PHARMAC Schedule
	per 500 (tab 5 mg)	\$11.09	PHARMAC Schedule
	per 500 (tab 20 mg)	\$29.03	PHARMAC Schedule
GP (real cost; not cost after subsidy)	Per consultation	\$60-80	MoH
GP's Practice Nurse	Per consultation	\$16.99	ACC (cost of treatment schedule)– Flat rate incl.GST
Respiratory Specialist Clinic (by a consultant)	Initially first visit	\$447.72	Decision support (Eric, Mary. personal communication, January 30, 2017)
	Follow-up visit	\$275.92	Decision support (Eric, Mary) personal communication, January 30, 2017)
Physiotherapist Visit	Initially first visit (up to 60 minutes)	\$117.65	Decision support (Eric, Mary) personal communication, January 30, 2017)
	Follow-up visit (up to 30 minutes)	\$78.59	Decision support (Eric, Mary) personal communication, January 30, 2017)
Hospital Emergency Department (ED)	Per ED event/up to 6 hours	\$383.03	Decision support (Eric, Mary)- ADHB personal communication, January 30, 2017)
	Based on triage		Decision support (Eric, Mary) personal communication, January 30, 2017)
	1	\$821.19	
	2	\$556.23	
	3	\$378.39	
	4	\$147.59	
	5	\$121.62	



\*CMDHB (Counties Manukau District Health Board), ADHB (Auckland District Health Board)

### 4.3.2.3 Hospitalisation cost

Cost of admission was taken from the Bibby, Milne and Beasley article (2015) which reported hospital admissions for non-CF bronchiectasis in New Zealand for the financial years (FY) 2008 to 2013. The mean cost of hospitalisation with 95% CI was \$4,555 (4,442, 4,668) based on the FY 2012/13. This cost value was inflated to the year 2016 since all the costs included in the study were for the same year. An inflation rate of 1.51 was used to calculate the hospitalisation cost value presented in Table 6.

**Table 6: Average unit costs of resources used in the model**

Description	Mean Cost (\$2016)	Standard error	95% CI	Source
Cost of hospitalisation for bronchiectasis patients	4764		(4646, 4883)	Bibby, Milne, Beasley ,2015
Cost of inhaled drug (Tiotropium)	424.66	10%		ROBUST study
Cost of inhaled drug (Placebo)	210	10%		ROBUST study
Cost of resource use during trial (Tiotropium)	300		(273, 333)	ROBUST study
Cost of resource use during trial (Placebo)	250		(227, 278)	ROBUST study
Cost of medication use during trial (Tiotropium)	38.11	3.00	(32.23, 43.98)	ROBUST study
Cost of medication use during trial (Placebo)	46.41	3.72	(39.12, 53.69)	ROBUST study

### 4.3.3 VALUATION OF HEALTH OUTCOMES

Two main outcomes of interest in the current economic evaluation for health care are the

clinical effectiveness and health related quality of life measure. The clinical effectiveness is defined as the number of exacerbation events observed by treatment obtained from the parent study (ROBUST). The exacerbations were produced for each patient as frequency over time at risk. Health related quality of life associated with treatment was measured as Quality Adjusted Life Years (QALYs) using EQ-5D instrument (Hurst et al., 1997).

#### 4.3.3.1 Exacerbation events

Frequency of exacerbations during the duration of the study was derived for each ROBUST participant to produce the mean number of exacerbations under each treatment arm. Exacerbation events were recorded at each of the eight visits measured at baseline, 4, 20, 23, 26, 34, 43 and 56 weeks. Estimates of the average number of exacerbations were very similar in both groups as indicated in Table 7 and based on the confidence intervals; this confirms that there is no significant difference in the exacerbation events between tiotropium vs. the placebo.

**Table 7: Average number of exacerbation per group with 95% CI**

<b>Treatment group</b>	<b>Mean</b>	<b>Standard error</b>	<b>95% CI</b>
Tiotropium	1.20	0.115	(0.97, 1.43)
Placebo	1.23	0.111	(1.01, 1.45)

#### 4.3.3.2 Quality Adjusted Life Years (QALYs)

The EQ-5D instrument (Hurst et al., 1997) was used to estimate QALYs (Briggs, Sculpher & Claxton, 2006). The EQ-5D standardised questionnaire was administered at the baseline and weeks 26, 30 and 56 and was transformed into utility scores for estimating quality-adjusted life year (QALYs) for the cost-utility analysis (PHARMAC, 2015). The EQ-5D instrument comprised of five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression sorted into three levels (no problem, some problems and extreme)

(Drummond et al., 2005). From the EQ-5D score responses from each of the participants, utility weight is calculated from a scoring mechanism that uses values that have been derived from NZ population preferences. For all EQ-5D scores, the NZ tariff 2 is employed to translate the responses into the utility values (PHARMAC, 2015; Devlin, Hansen, Kind & Williams, 2003). The utilities value ranges from a scale of 0 to 1 where 0 represent death and 1 indicates perfect health (Drummond et al., 2005). Utility scores were combined with time spent in that state to estimate QALYs.

The average estimated QALYs with 95% CI of the 90 patients for tiotropium vs. a placebo were 0.88 (0.80, 0.98) vs. 0.87 (0.79, 0.97) respectively. For the lower and upper ranges for this base-case estimate, the limits for the 95% CI were used in the sensitivity analyses.

#### 4.3.4 TIMEFRAME

A 1-year timeframe was chosen since the trial period of the randomised cross-over was within one year. This was deemed to be a conservative approach as less is known about the long-term effects ( $\geq 1$ -year) associated with tiotropium for bronchiectasis patients.

#### 4.3.5 DISCOUNT DATE

In this study, as mentioned previously, since we will only be analysing data within a 1-year time frame, no discount rate was applied.

### 4.4 COST-EFFECTIVENESS ANALYSES

Analyses were conducted on completed cases only (n=88). Firstly, a cohort analysis was carried out using a Markov simulation approach that assumed a hypothetical and homogenous cohort of 10,000 patients entering into the model at the start under each treatment group. At each cycle in the model, the transition probability was applied to reallocate the cohort into new proportions in different health states. Secondly, the results from the model are presented as an incremental cost-effectiveness ratio (ICER) that is, the ratio of the difference in cost

( $\Delta C$ ) to difference in effects ( $\Delta Q$ ) associated with tiotropium treatment compared to a placebo.

The results of the base-case analysis were expressed as cost per exacerbation avoided as well as cost per QALY gained. To determine whether, or not, tiotropium is cost-effective, the resulting ICER is compared to society's WTP threshold (i.e..society's willingness-to-pay for an extra unit of health gain in QALY or to avoid one exacerbation event. Tiotropium is deemed to be cost-effective only if the ICER is less than the willingness-to-pay threshold. Since New Zealand currently has no explicit standard WTP threshold, the threshold was estimated from the country's gross domestic product (GDP) per capita as recommended by the World Health Organization (Blakely et al., 2012). The GDP in NZ was approximated to \$40,000 based on the average GDP from 1977 to 2016 (Trading Economics, n.d.).

## 4.5 SENSITIVITY ANALYSIS

### 4.5.1 ONE-WAY ANALYSES

Uncertainty was explored by using a one-way sensitivity analysis, which tests whether plausible changes in the input variables affect the results of the cost-effective analysis (Briggs, Sculpher & Claxton, 2006). With one-way analysis, the parameter estimate (number of exacerbation events, QALY, probability of getting severe or moderate exacerbations, cost of medication use, resource use cost and cost of inhaled study drug, as well as hospitalisation cost) in the model was varied individually based on plausible ranges (see input Tables 3,4 6 and 7), while keeping the other parameters constant. The range of likely values for these parameters were derived from the confidence intervals which included the lower and upper limits and for those with no information on the variability, such as for the cost of inhaled study drug, a +/-10% input range was used.

### 4.5.2 SCENARIO-BASED ANALYSES

The scenario-based sensitivity analyses were undertaken to explore the various parameters (identified from the one-way sensitivity analysis) which influenced the ICER results. The

best and worst case scenarios were based on changing the parameters presented in two models A and B that had the greatest and least impact on the ICER results.

In addition, the transitional probabilities were also modified in both the scenarios taken from the literature since the starting transitional probabilities produced from the ROBUST data had fewer severe exacerbations and all of them changed to having moderate exacerbation in both groups. The transitional probabilities for those who had a severe exacerbation, given that they had a moderate or severe event for tiotropium and a placebo, were taken from Hettle et al., 2012, where the derived probabilities used data taken from the UPLIFT study (Tashkin et al., 2008).

The values listed in Table 8 were used since these have been frequently utilised in other studies. Also, the probability of exacerbations reported for usual care were similar to the moderate probabilities from the ROBUST data.

**Table 8: Transitional probabilities from Hettle et al., 2012 based on the first cycle**

<b>Treatment group</b>	<b>(From)</b>	<b>Severe exacerbation</b>	<b>Moderate exacerbation</b>	<b>Stable</b>
<b>Tiotropium</b>	<b>Severe exacerbation</b>	0.80	0.17	0.03
	<b>Moderate exacerbation</b>	0.08	0.92	0
	<b>Stable</b>	0	0	0
<b>Placebo</b>	<b>Severe exacerbation</b>	0.81	0.13	0.06
	<b>Moderate exacerbation</b>	0.13	0.86	0.01
	<b>Stable</b>	0	0	0

#### 4.5.2.1 BEST CASE

The best scenario includes two models, A and B. Model A includes parameters based on the 95% confidence interval that highly influenced the ICER and Model B consists of the transitional probabilities taken from the literature. A combination of various types of input were presented in Table 9. The parameters that were altered included exacerbation events, QALYs, the probability of getting severe exacerbations, the probability of getting moderate

exacerbation, cost of the inhaled drug, cost of resource use, medication and hospitalisation costs.

**Table 9: Parameters and plausible values used in the best-case scenarios**

Best scenarios	Parameters	Values used		Sources
		Tiotropium	Placebo	
Model A	Exacerbation events	1.43	1.01	Parent study (ROBUST)
	Probability of severe exacerbation	0.0061	0.0019	Parent study (ROBUST)
	Probability of moderate exacerbation	0.68	0.72	Parent study (ROBUST)
	Inhaled cost	-10%	10%	Parent study (ROBUST)
	Resources used cost	273	278	Parent study (ROBUST)
	Medication cost	32.23	53.89	Parent study (ROBUST)
	Hospitalisation cost	4646	4883	Parent study (ROBUST)
	QALYs	0.98	0.79	Parent study (ROBUST)
Model B	Transitional probabilities	Table 7 and all inputs in		Hettle et al., 2012,
	with inputs used in model A	Model A		Parent study (ROBUST)

#### 4.5.2.2 WORST CASE

The worst case scenario also includes the translational probabilities taken from the literature (model B) and model A inputs were the parameters that affected the ICER results. The parameters that were modified are illustrated in Table 10. The values in-corporated in the analyses were based on a combination of lower and higher limits of the confidence

intervals for the probability of getting severe exacerbations, the probability of getting moderate exacerbation and costs of both the inhaled drug, resource use and medication use and QALY.

**Table 10: Parameters and plausible values used in the worst-case scenarios**

Worst scenarios	Parameters	Values used		Sources
		Tiotropium	Placebo	
<b>Model A</b>	Exacerbation events	0.97	1.45	Parent study (ROBUST)
	Probability of severe exacerbation	0.022	0.0019	Parent study (ROBUST)
	Probability of moderate exacerbation	0.48	0.51	Parent study (ROBUST)
	Inhaled cost	-10%	10%	Parent study (ROBUST)
	Resources used cost	333	227	Parent study (ROBUST)
	Medication cost	43.98	39.12	Parent study (ROBUST)
	Hospitalisation cost	4883	4646	Parent study (ROBUST)
	QALYs	0.8	0.97	Parent study (ROBUST)
	Transitional probabilities with			Hettle et al., 2012, Parent study
<b>Model B</b>	inputs used in model A	Table 7 and all inputs in Model A		(ROBUST)

#### 4.5.3 PROBABILISTIC SENSITIVITY ANALYSIS

A probabilistic sensitivity analysis (PSA) was also conducted. This was undertaken using second-order Monte Carlo simulations based on the appropriate probability distribution (Drummond et al., 2005). The choice of distribution for the parameter depended on the type of data. For instance, binomial data such as transition probabilities and utilities, a beta

distribution and gamma distribution were applied to cost estimates. Poisson distribution was applied to the number of exacerbation events parameter.

Monte Carlo simulations were iterated for 10,000 times and provided 95% confidence intervals to illustrate uncertainty for cost per exacerbation event and cost per QALY gained. These were presented as a scatterplot on the cost-effectiveness planes and as cost-effectiveness acceptability curves (CEAC) (Drummond et al., 2005; Briggs & Sculpher, 1998). The cost-effectiveness acceptability curves show the probability of tiotropium being the optimal intervention compared to a placebo against an acceptable cost-effectiveness threshold which is the level of WTP.

Finally, to ensure ethical conduct of research, out-of-scope ethics approval was obtained from the Health and Disability Ethics Committee (HDEC) and Auckland University of Technology Ethics Committee (AUTEC) (Reference number; 16/293) .



## CHAPTER 5. RESULTS

### 5.1 COHORT ANALYSIS

A Markov cohort analysis of 10,000 hypothetical patients was estimated for tiotropium and a placebo using Monte Carlo simulation. Overall, over the 1-year period, it was estimated that in relation to disease severity, the expected number of patients in the tiotropium group with severe and moderate exacerbations were 0 and 135 respectively and the rest were stable with no exacerbations. In the placebo group, 8 patients were expected to have severe exacerbations and 134 were presented with moderate exacerbation.

### 5.2 BASE-CASE COST-EFFECTIVENESS ANALYSIS

Estimated mean costs and effectiveness are reported in Table 11. The base-case results of the decision tree/Markov model showed that the expected mean first year cost for treating bronchiectasis patients with tiotropium was higher (\$641) compared to a placebo (\$503) resulting in an incremental cost of \$137 (95% CI; \$117, \$153). The driver of the higher cost in tiotropium was contributed to by the cost of the inhaled drug as well as resource use cost.

The mean exacerbations avoided per patient per year for tiotropium and placebo were 0.84 and 0.83 respectively leading to a small incremental effect of 0.01 (95% CI; 0.01, 0.018). Furthermore, QALYs in the tiotropium arm was 0.62 and in the placebo was (0.59), a difference of 0.03 (95% CI; 0.02, 0.03).

**Table 11: Summary of base-case ICER results**

Group	Cost	Effectiveness	QALY	ICER (per Exacerbation avoided per patient per year)					ICER (QALY gained per year)
				Incremental Cost	Incremental Exacerbation	Incremental QALY			
Placebo	\$503	0.83	0.59						
	(430-585)	(0.79-0.87)	(0.56-0.62)						
Tiotropium	\$641	0.84 (	0.62	\$137	0.01	0.03	\$12,896		\$4,655
	(583-702)	0.8-0.89)	(0.58-0.65)	(117-153)	(0.010-0.018)	(0.02-0.03)	(5850-15300)		(3900-7650)

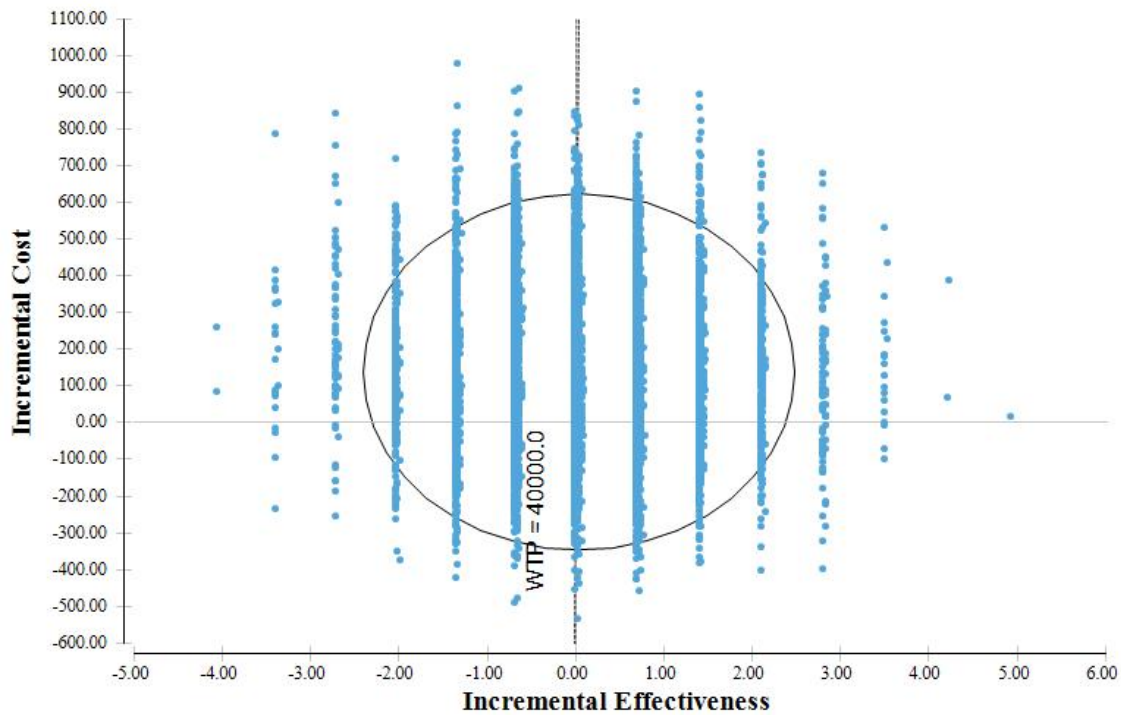
Taken together, tiotropium treatment for bronchiectasis patients in NZ yields an incremental cost effectiveness ratio of \$4,655 (95% CI; \$5,850, \$15,300) per each QALY gained and \$12,896 (95% CI; \$3,900, \$7,650) per exacerbation avoided. The 95% confidence intervals for ICERs were produced based on the base-case parameters input rather than for a predicting uncertainty based on the distribution.

### 5.3 SENSITIVITY ANALYSIS

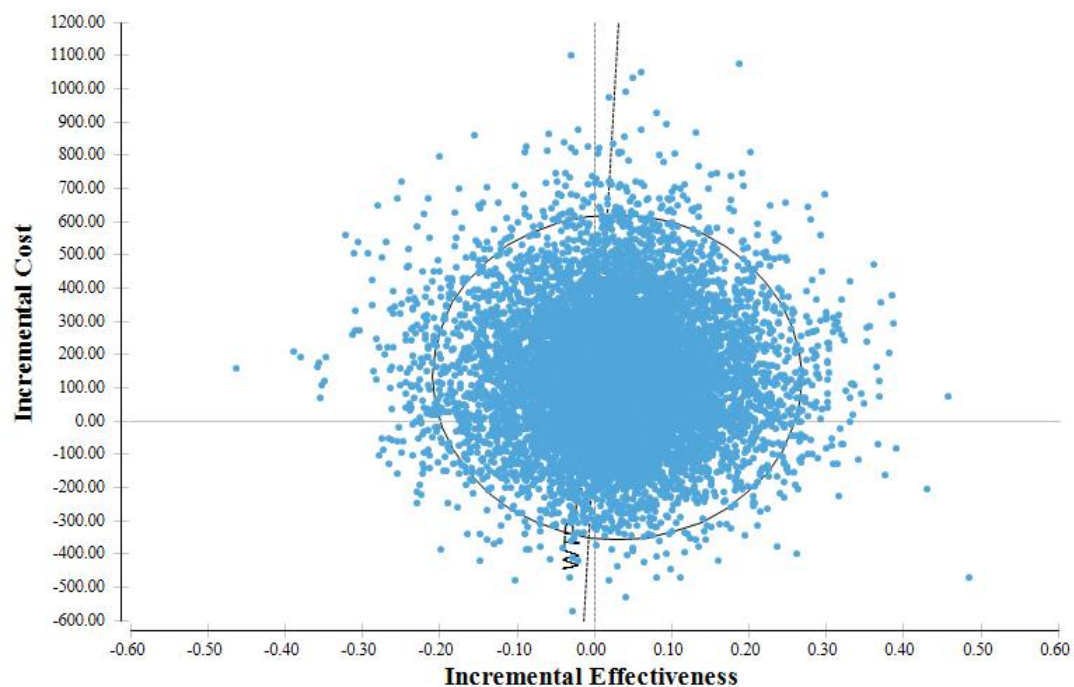
Figures 7 and 8 present the uncertainty around the incremental cost and effects. A one-way sensitivity analysis and the best and worst case scenarios were conducted to evaluate the robustness of parameters used in the decision tree/Markov model, and to identify the conditions where tiotropium might be cost-effective.

#### 5.3.1 PROBABILISTIC SENSITIVITY RESULTS

As illustrated in Figures 7 and 8 the incremental costs and incremental effectiveness values (ICERs) comparing tiotropium to a placebo are produced from 10,000 Monte Carlo iterations. Each dot represents one of the 10,000 model simulations. The solid line represents the willingness-to-pay threshold and all the points that are below the line indicate the points that are cost effective. The ellipses show the 95% confidence interval for the simulations.



**Figure 7: Cost-effectiveness plane of the difference in costs and the effect in terms of the number of exacerbations of tiotropium versus a placebo**



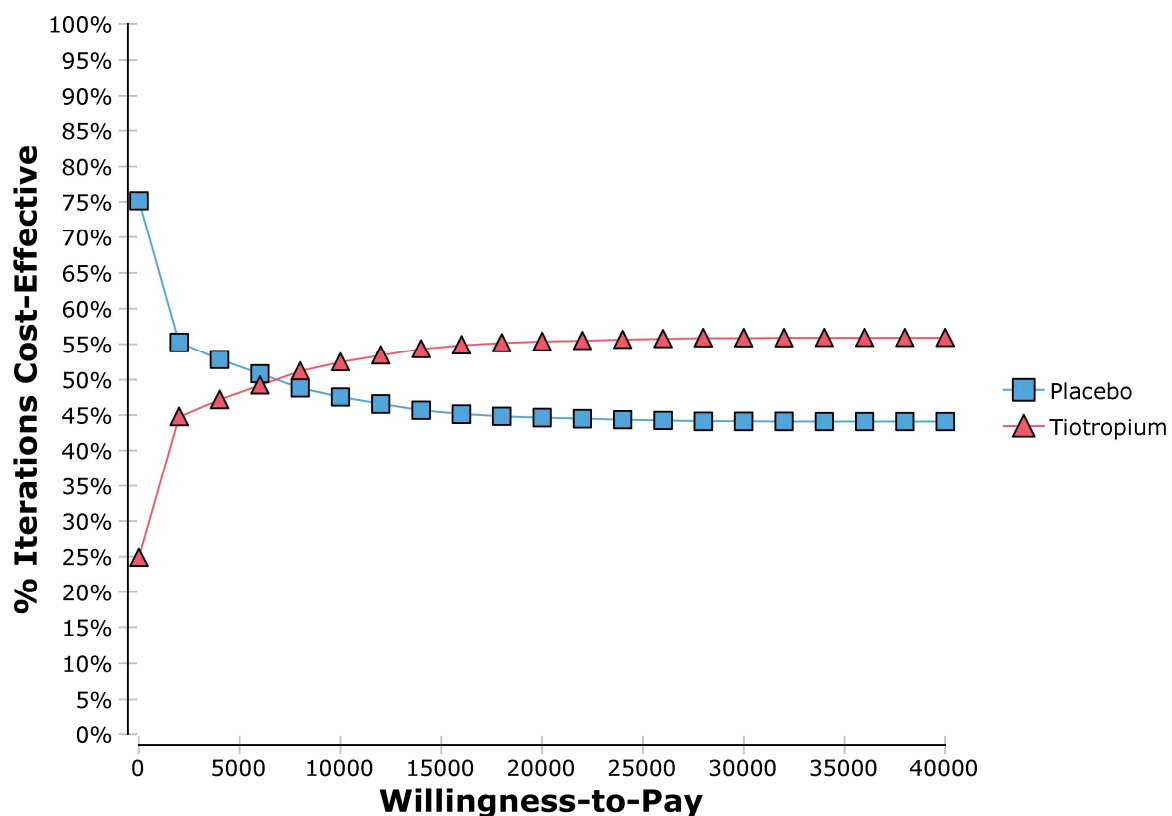
**Figure 8: Cost-effectiveness plane of the difference in costs and the effect in terms of the quality-adjusted life of tiotropium versus a placebo**

Almost 75% of the cost-effectiveness pairs were concentrated on the northeast and northwest quadrants in Figure 7. This suggests that tiotropium is more costly than a placebo. However the joint distributions were evenly spread over the upper and lower quadrants (56% fell in the northwest and southwest quadrants, while 44% fell in the northeast and southeast quadrants), showing the near effect-neutrality between tiotropium and a placebo with regard to exacerbation events. The CE-planes show that there was high uncertainty around the joint distributions of incremental costs and effects between treatment groups concerning a reduced number of exacerbations. The locations of the ICER points on the cost-effectiveness plane makes it very difficult to tell whether tiotropium was more cost-effective than a placebo as there is huge variability and uncertainty as most of the points are spread across all the four quadrants.

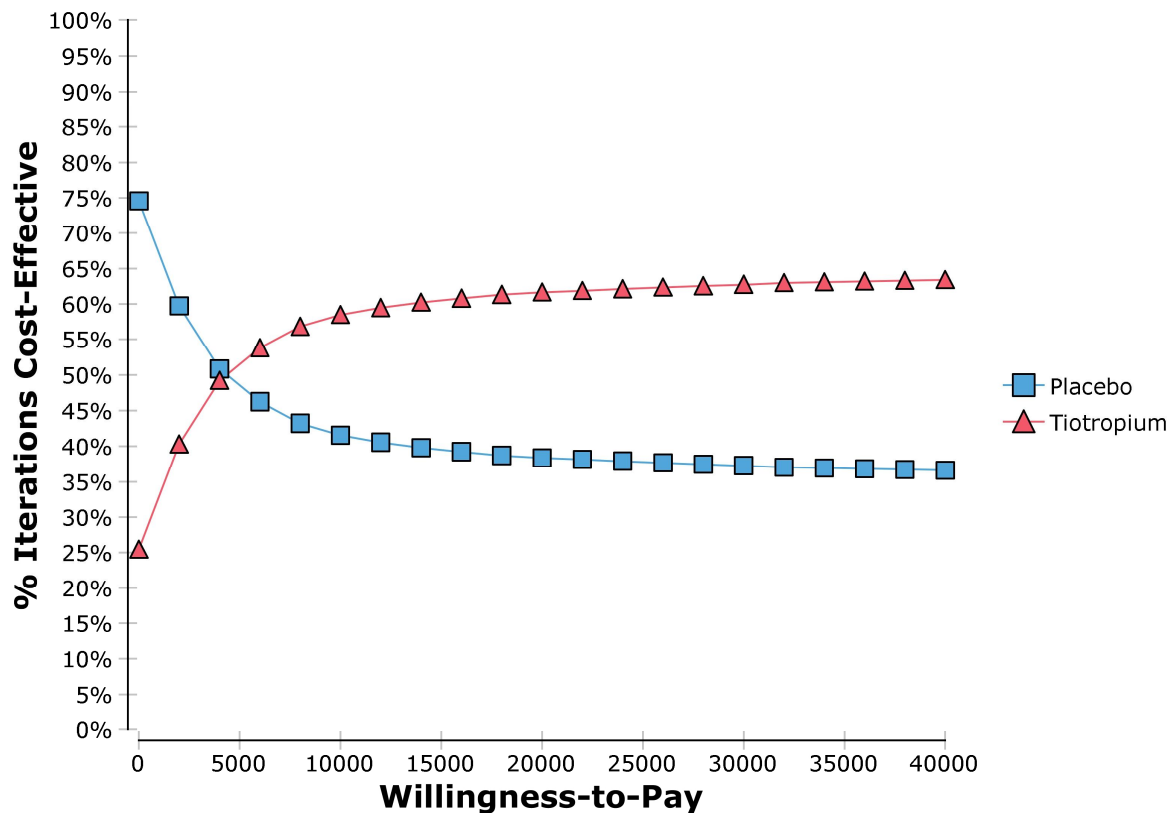
By contrast, Figure 8 displays joint distribution of cost and effects for QALY. Similar to Figure 7, it seems to be quite fairly spread out as almost 74% of the joint distribution was spread out on the northeast and northwest quadrants. So, in terms of incremental effect, almost 65% of the joint distribution fell on the northwest (48%) and southwest quadrants (17%) indicating that there may be dominance or benefit of tiotropium (either higher cost and higher effectiveness or lower cost and higher effectiveness). Although there is some variability detected in the QALYs, it was not as large in comparison to the exacerbations outcome. The value of the ICERs produced from the aggregated PSA simulation results varied widely compared to the base-case results with \$12,896 cost per exacerbation avoided per year and \$4,655 cost per QALY gained.

A cost-effectiveness acceptability curve (CEAC) is presented in Figures 9 and 10. The y-axis indicates the probability that tiotropium is cost-effective compared to a placebo, given a range of willingness-to-pay threshold values from \$0 to \$40,000 (on the x-axis). At a willingness-to-pay threshold of \$0 per exacerbation avoided, the probability of tiotropium being cost-effective compared to a placebo was 25%. The CEAC, however, showed that the probability of tiotropium being cost-effective increased as the willingness-to-pay for exacerbation avoided per patient increased. When the willingness-to-pay threshold increased to \$5,000, the probability of tiotropium being cost-effective compared to placebo increased to 47%. At the same willingness-to-pay threshold, the probability of placebo being cost-effective was 53% but decreased as the threshold increased. A much larger impact of the value of the ceiling ratio was observed in the acceptability curves regarding quality-adjusted

life years. The probability for tiotropium to be cost-effective increased from 25% when the ceiling ratio was set to \$0, and then to 60% when the ceiling ratio was set to \$15,000. Placebo had the highest expected net benefit for values of the ceiling ratio below ~\$5,000, whereas tiotropium had the highest probability of being cost-effective for all threshold values above that ratio suggesting that tiotropium might be the preferred treatment in terms of cost per QALYs gained.



**Figure 9: Cost-effective Acceptability Curve (Exacerbations avoided)**



**Figure 10: Cost-effective Acceptability Curve (Quality-adjusted life years)**

### 5.3.2 ONE-WAY SENSITIVITY RESULTS

The one-way sensitivity analysis has been summarised in Table 12 and presented as tornado diagrams in Figures 11 and 12. The results highlight the key variables that influenced the ICERs. As presented in Table 12, the ICERs for the cost per exacerbation avoided per year and cost per QALY gained per year ranged from -\$38,733 to \$33,124 and -\$17,648 to \$28,187 respectively. Interestingly, the ICERs remained less than \$30,000 (within the WHO cost effectiveness threshold) (Blakely et al., 2012). More attractive ICERs were highly influenced by the probability of developing a severe or moderate exacerbation. This is consistent with current literature examining tiotropium among COPD patients.

**Table 12: One-way sensitivity results (ICER in NZD 2016)**

Variable of interest	Input range	ICER (cost per exacerbation avoided per year)		ICER (cost per QALY gained per year)	
		Low	High	Low	High
Average number of exacerbations (Placebo)	1.01 to 1.45	-2149	12896	NA*	NA*
Average number of exacerbations (Tiotropium)	0.97 to 1.43	-1954	12896	NA*	NA*
Quality of life weight for those taking tiotropium	0.8 to 0.98	NA*	NA*	-5125	28187
Quality of life weight for those taking placebo	0.79 to 0.97	NA*	NA*	-17648	6044
Probability of developing a severe exacerbation (Tiotropium)	0.0061 to 0.077	-1346	9897	3826	25399
Probability of developing a moderate exacerbation (Placebo)	0.51 to 0.72	-1466	33124	-3948	5387
Probability of developing a moderate exacerbation (Tiotropium)	0.48 to 0.68	-1632	12896	-4575	4655
Probability of developing a severe exacerbation (Placebo)	0.0019 to 0.06	-38733	5767	-3814	5262



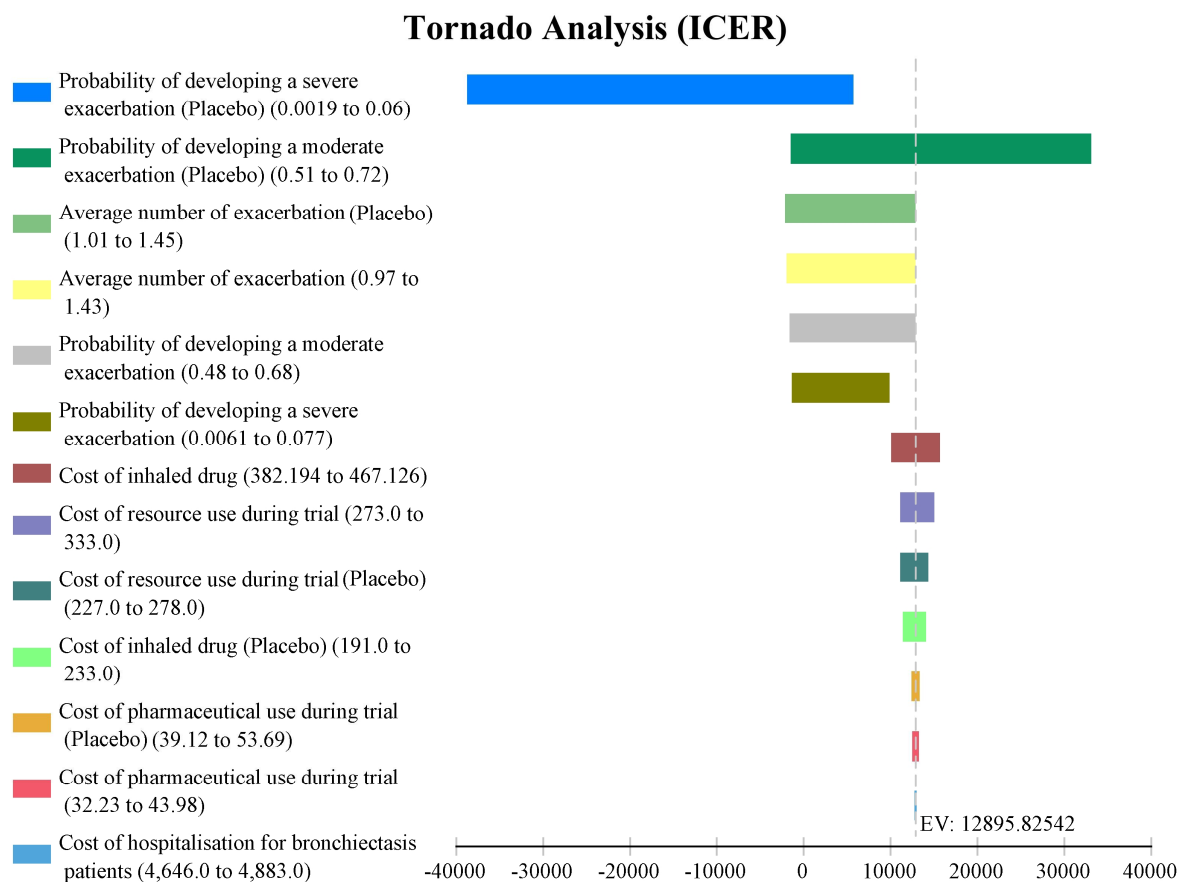
Variable of interest	Input range	ICER		ICER	
		(cost per exacerbation avoided per year)		(cost per QALY gained per year)	
		Low	High	Low	High
Cost of inhaled drug (Tiotropium)	382.194 to 467.126	10090	15702	3642	5668
Cost of resource use during trial (Tiotropium)	273.0 to 333.0	11112	15076	4011	5442
Cost of resource use during trial (Placebo)	227.0 to 278.0	11113	14360	4012	5184
Cost of inhaled drug (Placebo)	191.0 to 233.0	11432	14105	4127	5092
Cost of pharmaceutical use during trial (Placebo)	39.12 to 53.69	12432	13360	4488	4823
Cost of pharmaceutical use during trial (Tiotropium)	32.23 to 43.98	12507	13284	4515	4795
Cost of hospitalisation for bronchiectasis patients	4,646.0 to 4,883.0	12764	13026	4608	4702

\*NA (Non-Applicable)

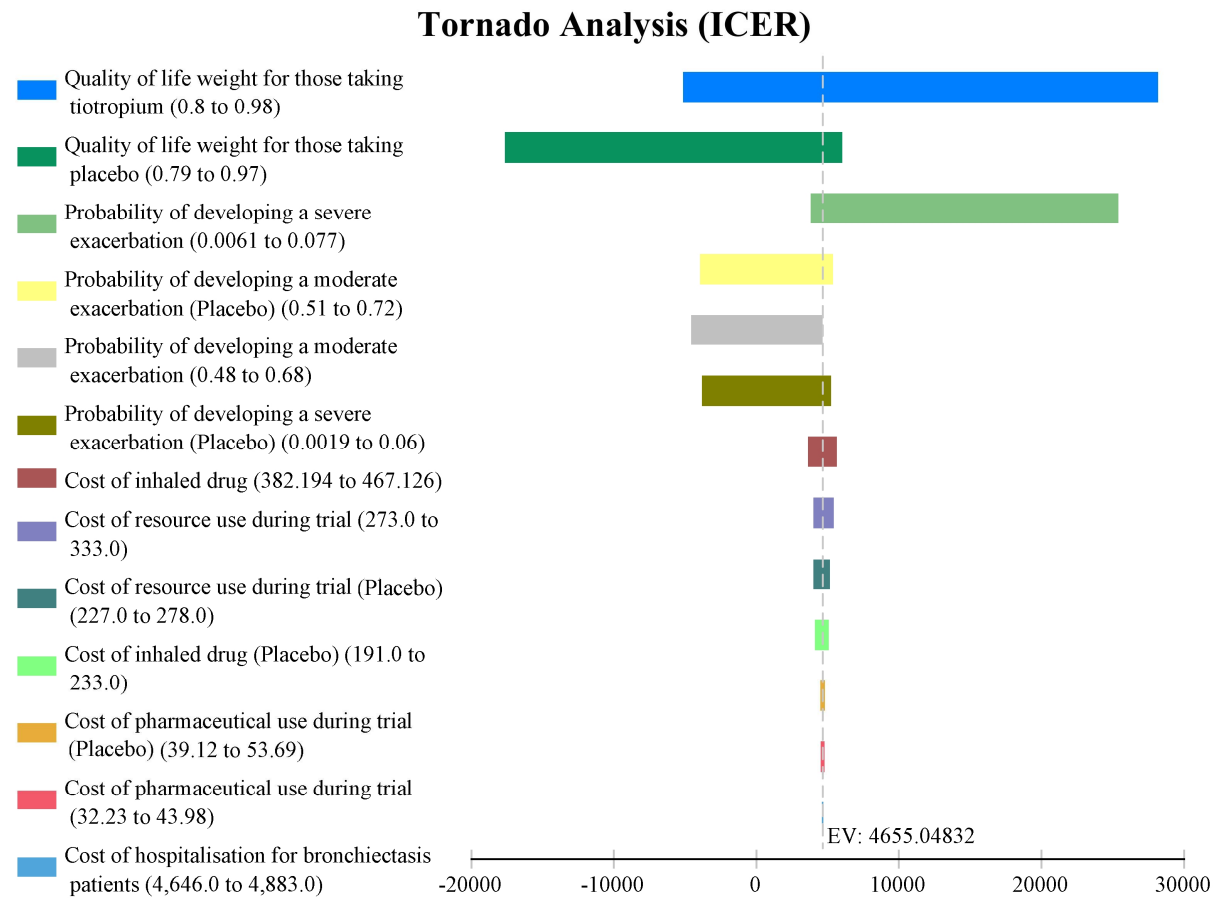
Similarly, the tornado diagrams, also indicated the impact of the parameters which had the greatest impact on both ICERs, were the number of exacerbations, QALYs, risk of getting severe exacerbations or moderate exacerbations associated with both treatment groups and the cost of the inhaled drug for tiotropium. The ICERs change little when the cost of medication use, resource use and cost of hospitalisation change.

Lowering the risk of moderate exacerbation in placebo increased the ICER for cost per exacerbation avoided by >\$30,000 and was way above the base-case results, whereas lowering the risk of severe exacerbations produced ICERs lower than base-case results. Also, increasing the risk produced negative ICERs leading to negative values in favour of a placebo. Higher probability of moderate exacerbations or higher number of exacerbations under tiotropium produced similar base-case ICERs of \$12,896 for cost per exacerbation avoided. Using the lower or upper limit values for the cost of the inhaled drug and resources use still produced ICERs in favour of tiotropium but well below the WTP threshold.

The parameters that impacted the most for ICERs for cost per QALY gained were the utilities weight values for tiotropium and placebo and the risk of getting severe or moderate exacerbations. So, applying the upper limits for QALYs (0.98) and the risk of severe exacerbations (0.077) for tiotropium increased the ICERs to \$28,187 and \$25,399 respectively compared to the base case results, but still remained to be cost-effective at the current willingness-to-pay threshold (~ \$40,000). Whereas increasing the risk of moderate exacerbations from 0.58 to 0.68 still produced the same base-case results, but using the lower limit resulted in negative ICERs in favour of a placebo. In terms of costs for inhaled drug and resource use, using the lower limit produced smaller ICERs than base-case results and using higher limits increased ICERs but was well below the threshold in favour tiotropium.



**Figure 11: Tornado diagram ICER on cost per exacerbation avoided per year**



**Figure 12: Tornado diagram ICER on cost per QALYs gained per year**

### 5.3.3 SCENARIO RESULTS

#### 5.3.3.1 BEST CASE SCENARIO

Best case scenarios input in Table 9; both models A and B inputs which resulted in producing negative ICERs compared to base-case analysis for both outcomes. The ICERs from model B indicate that tiotropium has a cost saving of \$1,064 per exacerbation avoided and \$2,593 per QALY gained, yielding the most favourable situation.

**Table 13: Summary of ICER under best-case scenarios**

Best scenarios	Group	Cost(\$)	Effectiveness	QALY	ICER (per Exacerbation avoided per patient per year)	ICER (QALY gained per year)
Model A	Placebo	578	1.12	0.76		
	Tiotropium	567	0.78	0.61	Dominant (cost savings)	Dominant (cost savings)
Model B	Placebo	2519	1.45	1.13		
	Tiotropium	1976	1.96	1.34	Dominant (cost savings)	Dominant (cost saving)

#### 5.3.3.2 WORST CASE SCENARIO

The results from Table 14 indicated that in both the worst case scenarios, tiotropium costs more and resulted in poorer outcomes compared to a placebo. This suggests that new treatment should be rejected based on the inputs used in the worst case. It shows that the

number of exacerbation events, the probability of getting severe or moderate exacerbations, the cost of an inhaled drug and resource use cost determines tiotropium cost-effectiveness.

**Table 14: Summary of ICER based under worst case scenarios**

<b>Worst scenarios</b>	<b>Group</b>	<b>Cost(\$)</b>	<b>Effectiveness</b>	<b>QALY</b>	<b>ICER (per Exacerbation avoided per patient per year)</b>	<b>ICER (QALY gained per year)</b>
Model A	Placebo	349	0.80	0.53		
	Tiotropium	604	0.57	0.47	Ineffective	Ineffective
Model B	Placebo	1625	1.48	0.99		
	Tiotropium	1894	0.97	0.80	Ineffective	Ineffective

## CHAPTER 6. DISCUSSION

### 6.1 SUMMARY OF KEY FINDINGS

The primary objective of this study was to assess the cost-effectiveness of tiotropium compared to a placebo in bronchiectasis patients relevant to the NZ setting from a funder payer perspective. Based on the results from the decision tree/Markov modelling analysis using the parent data, the tiotropium treatment might be cost-effective compared to a placebo in improving quality adjusted life years, but may not be in terms of reducing exacerbations. There was very little substantial difference in exacerbation events, but there was a moderate difference in QALYs between the treatment groups in this 1-year model. However, the results were not statistically significant due to the large variability based on the sensitivity analyses.

From the base-case results in the decision tree/Markov model, the expected effectiveness in terms of exacerbation avoided per patient per year for tiotropium vs. a placebo was 0.84 vs. 0.83 and the expected utility in terms of QALYs gained for tiotropium was 0.62 vs. 0.59. There was very little difference in the expected number of exacerbation events between the two groups and some difference in QALYs. This small difference could also be due to the fact that the patients who presented with severe exacerbations were very few across the two arms and could be based on the model driven by disease severity as defined by lung function (Oostenbrink, Rutten-van Mölken, Monz, & FitzGerald, 2005). The expected costs were also higher under the tiotropium arm due to the fact that cost of the inhaled drug and resource use were higher than the placebo, but in terms of medication use there was not much difference. The higher cost could also be associated with having severe or moderate exacerbations. Even though the ICERs produced indicated an additional cost of \$12,896 per exacerbation avoided and \$4,655 per QALY gained when treated with tiotropium compared to placebo, it was much lower than the historical willingness-to-pay cut-off of \$40,000 (Blakely et al., 2012).

There were also other thresholds that were accepted in the 1900s where the cost-effectiveness ratios below US\$20,000-25,000/QALY (equates to ~\$27000-34000 in 2016) (Zaniolo, Iannazzo, Pradelli and Miravittles, 2012) were considered an appropriate way of using

society and health-care service resources. Another article by Kanis and Jonnson (2002) suggested that a value of US\$30,000 per QALY gained (~NZD 40,000) is a reasonable benchmark for developed countries. Also in the United Kingdom, £30,000/QALY (~ NZD 55,000) is considered a good cost-effectiveness threshold, according to NICE (National Institute for Clinical Excellence) recommendations (NICE, 2008).

There was variability in ICERs for cost per exacerbations avoided and cost per QALYs gained after the sensitivity analyses were performed. When the risk of getting severe or moderate exacerbations was increased with tiotropium, the cost per QALY and cost per exacerbation also increased but was still under the WTP threshold. But, based on the one-way sensitivity analysis results, the largest variability with the inputs for instance, was in exacerbation events, QALYs and probability of getting a severe or moderate exacerbation and cost of inhaled study drug and resource use. Costs of medication use and hospitalisation had less impact on the variability of the ICER. If the probability of getting severe or moderate exacerbation in tiotropium increased, it may be associated with more favourable cost-effectiveness ratios. If the probability decreased however, it would have less favourable cost-effectiveness ratios. Also, lowering the cost of inhaled drugs and resource use in tiotropium produced favourable ICERs lower than the base case results, and higher costs of the inhaled drug and resources used in tiotropium still produced favourable ICERs but higher than the base case estimate. The best-case scenario which involved altering the probability of getting severe or moderate exacerbations, exacerbation events and the cost of the inhaled drug, and resource resulting in negative ICERs – this suggests huge cost savings for both outcomes. This indicates that the tiotropium treatment would be cost-effective in terms of exacerbation events and QALYs, provided the exacerbation events for tiotropium were higher, and the probability of getting a severe exacerbation was higher compared to a placebo and the cost of the inhaled drug, and resource use was lower compared to a placebo. However, due to the huge variability with economic inputs, it is difficult to say that tiotropium is the preferred treatment for this patient population over a placebo. Depending on the parameter inputs, either drug could be viewed as favourable.

The probabilistic sensitivity analysis also reveals huge uncertainty surrounding the results of the cost-effectiveness analysis, which is considered important due to the variation in cost and effectiveness. The ICERs values produced from this analysis varied quite a lot compared to the base-case results. The cost-effectiveness planes in this study showed that most of the



uncertainty around the ratios was associated with the difference in effectiveness between tiotropium and placebo groups. The surface of the ellipses was mostly in the upper and lower-right quadrants for the QALY outcome but was quite spread out evenly for the exacerbation outcome. The simulation results are partly driven by the fact that the difference in exacerbation events were very small compared the QALY outcome (i.e., higher costs and high QALYs but lower exacerbation rates). This indicates a much better effectiveness for tiotropium in terms of QALYs rather than exacerbations avoided. So, tiotropium had the highest probability of being cost-effective when the ceiling ratio for avoiding an exacerbation was above \$15,000 and the ceiling ratio for gaining one QALY was at least \$25,000. The acceptability curves in our study showed that if the willingness-to-pay equalled zero, there was ~25% probability that tiotropium was cost-effective for both outcomes. Therefore the probability that tiotropium is cost-saving is about 25%. As the maximum acceptable ratio increased, the probability that tiotropium was cost-effective also increased. As the willingness-to-pay to avoid one exacerbation or to have one additional QALY gain is set at \$40,000, the probability that tiotropium is acceptable is 56% and 63% respectively. Additionally, 65% of cases in the simulation fall within the quadrant that indicates some effectiveness in terms of QALYs for tiotropium but not in terms of exacerbations, as only 56% of cases had higher effectiveness.

## 6.2 CONSISTENCY OF RESULTS WITH THE PREVIOUS ECONOMIC LITERATURE

Comparing the results to the previous economic literature, there are similar trends in terms of improving quality adjusted life years and reducing exacerbations. Some economic analyses conducted on tiotropium bromide in international settings provided results that compare quite well with those presented here (Oostenbrink, Rutten-van Mólken , Monz and FitzGerald ,2005; Maniadakis, Tzanakis, Fragoulakis, Hatzikou and Siafakas, 2006; Rutten-van Molken et al., 2007; Naik et al., 2010; Campbell et al., 2014 ) and some that do not (Costa-Scharplatz et al., 2015; ))\_as there were differences in terms of the cost-effectiveness ratios, total costs produced (i.e. whether the indirect cost was included) and difference in QALYS and exacerbation events for studies done in the Netherlands (Oostenbrink, Rutten-van Mólken , Monz and FitzGerald ,2005), Canada (Oostenbrink, Rutten-van Mólken , Monz and FitzGerald ,2005), US (Naik et al., 2010; Campbell et al., 2014), Spain (Rutten-van Molken et al., 2007; Eklund, Afzal ,Borgstrom, Ojanguren, Crespo and Baldwin , ,2015;

Hoogendoorn et al., 2013)), Italy (Zaniolo, Iannazzo and Padelli, 2012), Belgium (Hettle et al., 2012; Neyt, Devriese, Thiry and Van den Bruel, 2010), Greece (Maniadakis, Tzanakis, Fragoulakis, Hatzikou and Siafakas, 2006) and Sweden (Eklund, Afzal and Borgstrom, 2015; Costa-Scharplatz et al., 2015; ). The reason for this is that the proportion of patients who presented with severe or moderate exacerbations was very low for studies done in Sweden (Eklund, Afzal and Borgstrom, ) and Belgium (Hettle et al., 2012; Neyt, Devriese, Thiry and Van den Bruel, 2010) and hence this affects cost in terms of resource use and hospitalisation cost. The base-case ICER results when comparing tiotropium to usual care with those found in Hettle et al. were 10 times more than our base-case results. Hettle et al. estimated a cost per QALY gained of around £16,000 (~ NZD 28,000) in a UK setting in 2012. This huge variation is not surprising due to the fact that the maintenance cost and exacerbation cost were much higher considering the different cost structures and patient populations in the UK and Sweden, so this is expected. But comparing the incremental QALYs difference of 0.051 between tiotropium versus usual care is very similar to our base case result of 0.03.

Oostenbrink et al. (2005) looked at economic models evaluating tiotropium bromide, and compared its cost-effectiveness with ipratropium and salmeterol in the Netherlands and Canada. Oostenbrink et al. in 2004 estimated the ICER of tiotropium over ipratropium to be 667€ (~NZD 1,200) per exacerbation avoided, which is significantly lower than the ICERs for the same outcome in our study. For the similar study done in 2005, a Markov model was carried for a time horizon of one year which resulted in a mean difference in the number of exacerbations of 0.17 (-0.02 to 0.37) for tiotropium bromide vs. salmeterol, whereas the number of quality adjusted life months did not substantially differ between treatment groups. In another study by Maniadakis et al., (2006) the mean number of exacerbations per patient in one year was 0.92 in the tiotropium arm, and 1.1 in the salmeterol arm, resulting in 0.18 exacerbations avoided per patient and a cost difference of €85 leading to an ICER of € 472 (~NZD 840). Tiotropium was concluded to be cost effective, however, there was no statistically significant difference found between the treatments. In the Netherlands, tiotropium bromide was expected to dominate salmeterol; whereas in the Canadian context, the ICER of tiotropium bromide vs. salmeterol was about €150/QALY. In a Spanish adaptation of the same model, tiotropium bromide was associated with an ICER of just over €4,000/QALY vs. salmeterol over 5 years.

In another Spanish study by De Lucas et al., conducted in 2005 with a time horizon of one year and based on data from a real-world clinical trial, tiotropium bromide vs. a placebo determined an ICER of €320 per avoided exacerbation which is lower than our base-case results. In a cost-effectiveness analysis by Onukwugha, Mullins and DeLisle in 2008 based on data from a real-world sample of US veterans, tiotropium bromide was associated with an ICER of US \$2,360 per avoided exacerbation which is almost equivalent to the base-case ICERs in this study.

A cost-effectiveness analysis developed for the Swiss public health insurance system (Schramm, Hakke and Brandt, 2005) compared the use of tiotropium bromide, salmeterol and standard care for a one year time horizon, indicated dominance over the competing strategies. The higher acquisition cost of tiotropium bromide was adjusted by a fewer number of exacerbations. So based on some studies with economic evaluations of tiotropium which had some inconsistent findings due to the differences in the comparators used, the studies done in Belgium and the US concluded tiotropium had a favourable cost-effectiveness ratio, while those in Spain, and the United Kingdom found a less favourable cost-effectiveness ratio for tiotropium. This may be due to differences in the methods use, variation of QALYs based on population and different comparators for each study. The data gaps contribute to the difficulties in interpreting these various analyses. Intervention as cost increases substantially as disease severity moves from moderate to severe, the reduction in QALYs/exacerbation events and the cost involved in treating the respective events.

As discussed and mentioned in previous literature, there were a lot of studies using tiotropium in COPD but no studies done in the bronchiectasis population. Looking at other respiratory conditions, there was one study conducted in asthma patients. A study by Silva et al., 2015, used a 1-week cycle Markov model to estimate the cost per QALY for tiotropium as an add-on to usual care in patients with severe persistent asthma in Portugal. The results indicated that tiotropium enabled patients to live longer with controlled asthma and to suffer less exacerbation, thus allowing an incremental gain of 0.18 QALY (12.02 vs. 11.84). From the payers' perspective, tiotropium costs 7,038€ but savings made from follow-ups and exacerbations consist of an incremental cost of 459€. Therefore the cost per QALY is 2,576€ (~NZD 4,276; 2017). When compared to the cost of ICER per QALY gained in our study, tiotropium is considered a good alternative option for treatment. Based on the Silva study, tiotropium enhances the quality of life of patients with severe persistent asthma, as it allows a

better control of the disease and a reduction of exacerbation. This cost-utility analysis shows that, in the Portuguese setting, its use is cost-effective under the payers' perspective and dominant under the NHS perspective.

### 6.3 STRENGTH OF THE STUDY

One of the main strengths was the primary data source used in the model coming from the parent study which was the first RCT trial using tiotropium in bronchiectasis conducted in NZ and worldwide. Hence, the sources for the data inputs on health resource use, cost information and health outcomes that were collected prospectively over the study period and effectiveness outcomes will minimise incomplete and inaccurate information would otherwise result in retrospective data collection.

Another main advantage of this randomised cross-over trial study is that in the management of patients where information on health resource use was collected, records for any information of physician visits and other unscheduled visits were made. The model used in this study effectively incorporated the pathways patients with bronchiectasis undergo in response to treatment. The progression of the Markov model is in accordance to information obtained from published literature and inputs from expert opinion. This enabled us to create a stable economic model to evaluate the cost-effectiveness of tiotropium treatment in bronchiectasis.

### 6.4 LIMITATIONS

One of the limitations stems mainly from the key assumptions of the model. One assumption was that the mean number of exacerbations and mean QALY was the same across the three health states based which can lead to under or overestimation of bias expected QALYs or exacerbation events under both interventions. This approach taken was a pragmatic one as estimates were not reliable by severity due to low numbers in the parent study. Furthermore, as the primary data source came from a RCT trial; the sample size (n=90) was not large enough to detect the significant difference. Since this may be driven (in part) by the design of the ROBUST trial used to build the model, as the power of the study was not sufficient to detect the difference in exacerbations or QALYs. For instance, this was primarily based on

exacerbations rates from EMBRACE study (Wong et al., 2012) and hence not powered for economic end points or QALYs. So, as a result, no statistical significance was reached.

Secondly, obtaining accurate costs was quite challenging as cost by hospital location and region may differ. In the current study we assumed that the cost of hospitalisation for severe exacerbations was the same across the two treatment arms (Bibby, Milne and Beasley, 2015). However in real practice these estimates may vary thus leading to either an underestimation or overestimation of expected costs.

## 6.5 RECOMMENDATION

One of the future recommendations would be that the finding of the studies could be further verified through a larger RCT to investigate clinical efficacy of tiotropium for bronchiectasis patients and powered using both the clinical endpoints based on the ROBUST study. Secondly, a longitudinal observation study should supplement future RCTs to explore long-term effectiveness and cost effectiveness of the treatment drug. In turn, this will allow a life-time cost extrapolation in the model to see if any effect of long-term use of tiotropium in bronchiectasis as currently there is no evidence as most studies were performed on a short timeframe of between 1 to 5 years. Such analysis will inform future healthcare planning and resource allocation for treating patients with bronchiectasis. In the light of minor differences between the two treatments, further research studies and more evidence is needed to compare the efficacy of tiotropium since there have been so far no studies carried out worldwide.

The model was originally analysed from a funder perspective. Another area would be to look at the analyses from a societal perspective which includes both direct and indirect cost accounting for the productivity loss due to having the condition as well costs related to patient care provided by healthcare provider such as hospitals. The societal perspective measures all costs and effects associated with all the relevant stakeholders in society (Drummond et al., 2005). Such approach will be useful in illustrating social policy impact of the broader economic burden of disease in relation to other respiratory conditions. Further subgroup analysis is another aspect to be looked at based on severity (and other key risk-factors), especially those with moderate or severe exacerbations to check for any specific

treatment effect for a specific patient characteristic and to investigate the consistency of the trial conclusions among different subpopulations.

Since the proportion of those who dropped out was less than 10%, complete case analysis was carried out in this study. Thus, another recommendation to deal with the missing data would be to use nested imputation and bootstrapping in multiple imputations. This method imputes values that are sampled from patients who are comparable on demographic and baseline characteristics and also on costs and effects in previous periods. It also makes full use of the costs and effects the withdrawals had during the period. Above all, in contrast to other methods such as case deletion, the last value carried forward or mean imputation, multiple imputations take account of the extra uncertainty that results from the missing data, imputes multiple values for each missing value.

## 6.6 CONCLUSION

In summary, tiotropium may be cost-effective relative to a placebo as there is some indication of improving QALYs, but it has a very small effect in terms of reducing exacerbation events. The cost per exacerbation avoided and cost per QALY gained were well-below the willingness-to-pay threshold or New Zealand cost (~\$40,000). Based on the PSA results, there was huge variability for the ICERs per gained per exacerbation avoided and the parameter that had the most impact was increased exacerbation events, higher QALYs, and the risk of getting a severe or moderate exacerbation. This huge variability in the estimate could be due to the fact that majority of the patients were not very severe and most of them had no events, which resulted in low probability of getting either moderate or severe exacerbations.

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## GLOSSARY

ACC	Accident Compensation Corporation
ADHB	Auckland District Health Board
BDI	Baseline Dyspnea Index
BODE	Body-mass index, airflow Obstruction degree, Dyspnea and Exercise capacity
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CF	Cystic Fibrosis
CINAHL	Cumulative Index of Nursing and Allied Health
CMA	Cost-Minimisation Analysis
CMDHB	Counties Manukau District Health Board
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CUA	Cost-Utility Analysis
DALYs	Disability-Adjusted Life-Years
EQ-5D	Euroqol Five-Dimensions Questionnaire
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GDP	Gross Domestic Product
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRCT	High Resolution Computed Tomography
HRQoL	Health Related Quality of Life
HUI	Health Utilities Index
IBD	Inflammatory Bowel Disease
ICER	Incremental Cost-Effectiveness Ratio
ICERs	Incremental Cost-Effectiveness Ratios
MoH	Ministry of Health
NICE	National Institute for Health and Care Excellence
NZD	New Zealand Dollar
PSA	Probabilistic Sensitivity Analysis

PL	Placebo
TI	Tiotropium
PHARMAC	Pharmaceutical Management Agency
PB-FEV1	Post-Bronchodilator Forced Expiratory Volume
QALY	Quality-Adjusted Life-Year
QALYs	Quality-Adjusted Life-Years
SE	Standard Error
SF-36	Short Form 36 questionnaire
SGRQ	St. George's Respiratory Questionnaire
SOLQ	Seattle Obstructive Lung Disease Questionnaire
SVC	Slow Vital Capacity
RCT	Randomised Controlled Trial
RCTs	Randomised Controlled Trials
ROBUST	Reduction Of exacerbation in Bronchietasis USing Tiotropium
TDI	Transition Dyspnea Index
USD	United States Dollar
WHO	World Health Organization
WTP	Willingness-to-pay

## APPENDIX 1 SEARCH STRATEGY

**Table A-1. PubMed literature search strategy**

Search	Query	Hits
#1	Search (chronic obstructive pulmonary disease[MeSH Terms]) OR (COPD[MeSH Terms])	45004
#2	Search (chronic obstructive pulmonary disease[MeSH Terms]) OR (COPD[MeSH Terms]) AND [("cost effectiveness") OR ("cost benefit/analysis") OR ("cost utility")]	3840
#3	Search (chronic obstructive pulmonary disease[MeSH Terms]) OR (COPD[MeSH Terms]) AND [("cost effectiveness") OR ("cost benefit/analysis") OR ("cost utility")] AND [("tiotropium")]	37
#4	Search (chronic obstructive pulmonary disease[MeSH Terms]) OR (COPD[MeSH Terms]) AND [("cost effectiveness") OR ("cost benefit/analysis") OR ("cost utility")] AND [("tiotropium")] AND ("2000"[Date - Publication]: "2017"[Date - Publication]) AND ("English"[Language])	35

## **Table A-2. Cochrane Library search words**

There are **26** results from **1,055,253** records for your search on "tiotropium" in Title, Abstract, Keywords and "cost-effectiveness" in Title, Abstract, Keywords and "COPD" in Title, Abstract, Keywords, and Publication Year from 2000 to 2017 in ***Trials***.

**Table A-3. Details of paper selection in the literature review.**

<b>Study</b>	<b>Scope of Review</b>	<b>Reason for Exclusion</b>
MacIntyre (2004)	Title and Abstract	Not economic evaluation
Neil (2004)	Title and Abstract	Review
Oostenbrink & Rutten-van Mölken (2004)	Title and Abstract	Different methodology (empirical analysis)
Oostenbrink, Rutten-van Mölken, Al, Van Noord & Vincken (2004)	Title and Abstract	Different methodology (empirical analysis)
D'souza, Smith, Miller & Kavookjian (2006)	Title and Abstract	Review
Rutten-van Mölken, Oostenbrink, Tashkin, Burkhart & Monz (2006)	Title and Abstract	Not economic evaluation
Oba (2007)	Title and Abstract	Different methodology (empirical analysis using retrospective pooled analysis of different studies)
Onukwugha, Mullins & DeLisle (2007)	Title and Abstract	Different methodology (empirical analysis)
Najafzadeh et al. (2008)	Title and Abstract	Different methodology (empirical analysis) and combination of other drugs
Dalal, Roberts, Petersen, Blanchette & Mapel (2010)	Title and Abstract	Different study design (observational cohort study) and different methodology
Gani, Griffin, Kelly & Rutten-van Mölken (2010)	Title and Abstract	Different methodology (empirical analysis)
Kostikas & Bouros (2010)	Title and Abstract	Review
Mauskopf, Baker, Monz & Juniper (2010)	Title and Abstract	Review
Mittmann et al. (2011)	Title and Abstract	Different methodology used and

Study	Scope of Review	Reason for Exclusion
		combination of another treatment budesonide/formoterol was added to tiotropium
Sun et al. (2011)	Title and Abstract	Combined with another treatment (roflumilast)
Chong, Karner & Poole (2012)	Title and Abstract	Review
Hoogendoorn, Kappelhoff , Overbeek, Wouters & Rutten- van Mólken (2012)	Title and Abstract	Different methodology (empirical analysis)
Jose Antonio Vinagre et al. (2012)	Title and Abstract	Not economic evaluation
McKeage (2012)	Title and Abstract	Different treatment (Indacaterol)
Neyt & Van Den Bruel (2012)	Full paper	Review (Commentary)
Nieslen et al. (2012)	Title and Abstract	Combined with another treatment (budesonide/formoterol )
Rutten-van Mólken & Goossens (2012)	Title and Abstract	Review
Cazzola, Bardaro & Stirpe (2013)	Title and Abstract	Different study and looking at role of other treatment indacaterol
Gillespie et al. (2013)	Title and Abstract	Different alternative intervention using structured education pulmonary rehabilitation programme (no tiotropium)
Nieslen et al. (2013)	Title and Abstract	Combined with another treatment (budesonide/formoterol )
Ismaila, Robert, Puneekar and O'Leary (2014)	Title and Abstract	Different methodology (the study used a model which implemented a linked-equation model to estimate COPD progression)
Kew, Dias & Cates (2014)	Title	Review
Li, Zhou, Chen, Zheng, Zhong	Title and Abstract	Review of Study Protocol (no

<b>Study</b>	<b>Scope of Review</b>	<b>Reason for Exclusion</b>
& Ran (2014)		data presented)
Saylan, Beykoz & Keskinaslan (2014)	Title and Abstract	Looked at other outcomes like FEV1, Transition Dyspnea Index and Saint Georges Respiratory Questionnaire but not QALYs and Exacerbations events
Geitona et al. (2015)	Title and Abstract	Different methodology (microsimulation)
Puker, Roberts, Ismaila & Leary (2015)	Title and Abstract	Different methodology (used model which implemented a linked-equation model to estimate COPD progression)
Miravitlles et al. (2016)	Title and Abstract	Different methodology instead (the study used model which implemented a linked-equation model to estimate COPD progression)
Tebboth, Ternouth & Gonzalez-Rojas (2016)	Title and Abstract	Combined with another treatment (olodaterol )
van Boven, Kocks & Postma (2016)	Title and Abstract	Combined with another treatment (olodaterol )
Hoogendoorn et al. (2017)	Title and Abstract	Different study methodology (empirical analysis)