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Economic Evaluation

Broadening the Perspective of Cost-Effectiveness Modeling in Chronic Obstructive Pulmonary Disease: A New Patient-Level Simulation Model Suitable to Evaluate Stratified Medicine

Martine Hoogendoorn, PhD [1,], Isaac Corro Ramos, PhD [1], Michael Baldwin, BSc, MBA [2], Nuria Gonzalez-Rojas Guix, MSc [2], Maureen P.M.H. Rutten-van Mölken, PhD [1]*

[1]*Institute for Medical Technology Assessment/Erasmus School of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands;* [2]*Boehringer Ingelheim International GmbH, Ingelheim, Germany*

ABSTRACT

Objectives: To develop a health economic model that included a great diversity of patient characteristics and outcomes for chronic obstructive pulmonary disease (COPD), which can be used to inform decisions about stratified medicine in COPD. **Methods:** The choice of patient characteristics and outcomes to include in the model was based on 3 literature reviews on multidimensional prognostic COPD indices, COPD phenotypes, and treatment effects in subgroups. A conceptual model was constructed including 14 patient characteristics, 7 intermediate outcomes (lung function, physical activity, exercise capacity, symptoms, disease-specific quality of life, exacerbations, and pneumonias), and 3 final outcomes (mortality, quality-adjusted life-years [QALYs], and costs). Regression equations describing the statistical associations between the patient characteristics and intermediate and final outcomes were estimated using the longitudinal data of 5 large COPD trials (19,378 patients). A patient-level simulation model was developed in which individual patients from the baseline population of the 5 trials are sampled and their outcomes over lifetime are predicted based on the regression equations. **Results:** The base-case analysis (single-arm simulation representing treatment with tiotropium) showed that patients had a mean lung function decline of 43 mL/year, 0.62 exacerbations/year, a worsening of their physical activity and quality of life with 1.48 and 1.10 points/year, a life expectancy of 11.2 years, 7.25 QALYs, and total lifetime costs of £24,891. Results for a selection of treatment scenarios and subgroups were shown to demonstrate the potential of the model. **Conclusions:** We developed a unique patient-level simulation model that can be used to evaluate COPD treatment options for a variety of subgroups.

Keywords: chronic obstructive pulmonary disease, discrete event simulation model, costs, personalized medicine, quality-adjusted life-years

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease of the respiratory system characterized by progressive airflow limitation and symptoms such as shortness of breath, cough, and sputum production.[1] Because COPD is one of the most prevalent and costly diseases worldwide,[2] payers and policy makers are increasingly searching for innovative treatments to release the pressure of COPD patients on primary care, hospital care, and drug budgets while increasing patients' quality of life. In the search for treatments that are more effective and cost-effective than the ones currently available, it is expected that COPD treatments will increasingly be tailored to individual patients' characteristics.[3] New medications that are currently under development, such as biologics, will only be targeted to and reimbursed for specific subgroups of patients in which the added value needs to be established.[4]

Stratified medicine in COPD refers to an approach in which treatment is tailored to specific phenotypes of patients, such as patients with frequent exacerbations, with rapid lung function decline, with increased levels of inflammatory biomarkers, or with certain metabolic phenotypes.[5] Stratified medicine also includes the recognition of other COPD comorbidities, such as asthma, heart failure, or depression.[6]

* *Address correspondence to*: Martine Hoogendoorn, PhD, Institute for Medical Technology Assessment, Erasmus University Rotterdam, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.

E-mail: hoogendoorn@imta.eur.nl

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To assess the cost-effectiveness of stratified treatment approaches in COPD over a lifetime, new patient-level health economic models are needed. Most of the previously published COPD models are in essence Markov models that classify COPD severity by level of airflow obstruction only and assign COPD-exacerbation rates, costs, and utilities to these severity states.[7–9] In addition, these models can report only on a limited number of outcomes mainly relevant for evaluating pharmaceutical treatment options (ie, lung function, number of exacerbations, QALYs, and costs).[7–9] In the past decade nonpharmacological treatment options for COPD focusing on other outcomes, such as physical activity level, exercise capacity, level of symptoms, and disease-specific quality of life, became important as well.[1] To be able to compare the cost-effectiveness of different treatment strategies, such as reducing the lung function decline in "rapid" decliners, reducing the number of exacerbations in patients with frequent exacerbations, improving the physical activity level in inactive patients, or reducing symptoms in high-symptomatic patients, new comprehensive patient-level health economics models are needed that include a large number of patient characteristics and include a greater diversity of (intermediate) outcomes.

The aim of the current study was to develop a unique health economic patient-level simulation model for COPD that is able to estimate the incremental costs and effects of different treatments for many subgroups of patients. The current article describes the structure and input data of the new model and a selection of possible subgroup and treatment scenarios analyses to show the potential of the model.

Methods

Literature Review and Conceptual Model Construction

Three literature reviews were performed in PubMed to identify patient and disease characteristics currently considered important for COPD treatment allocation and prognosis (see Appendix I in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008). The first review focused on multidimensional indices in COPD and resulted in an overview of patient characteristics included in more than one of the indices. The second review investigated which COPD phenotypes were reported in the literature. In the third review, we searched for studies that reported the results of subgroup analyses in large randomized controlled trials evaluating both pharmacological and nonpharmacological COPD treatments. In addition, the Cochrane database was checked for subgroup results in reviews on COPD treatments. In the next step a draft conceptual model was constructed, which was discussed with 7 clinical and epidemiological COPD experts. Based on their feedback, the final conceptual model was drafted. In total, 14 patient characteristics were included in the final conceptual model: sex, age, body mass index (BMI), current smoking status, the number of pack-years smoked, history of heart failure, history of other cardiovascular disease (CVD), presence of asthma, bronchodilator responsiveness, diabetes, history of depression, diagnosis of emphysema, eosinophil count, and use of inhaled corticosteroids (ICS; Table 1). Intermediate outcomes included were exacerbations, pneumonias, lung function, exercise capacity, physical activity, symptoms (breathlessness and cough/sputum), and disease-specific quality of life (Table 1). Final outcomes included were death, quality-adjusted life-years (QALYs), and costs (Table 1). The final conceptual model consisted of a graph showing the associations between patient and disease characteristics and all outcomes (Fig. 1) and a set of conceptual equations describing the associations between baseline characteristics, intermediate outcomes, and final outcomes over time in mathematical terms (see Appendix II in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008).

Starting Population of the Model

The starting population of the model consisted of patients who participated in 5 large trials evaluating tiotropium: UPLIFT, EXACTT, POET, TIOSPIR, and TONADO.[10–14] Patient-level data from the trials were provided by the manufacturer of tiotropium, Boehringer Ingelheim. In total, the baseline population consisted of 35,341 patients. Because the 5 trials used rather homogeneous inclusion criteria, the patient populations across trials were deemed comparable (see Appendix III in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008).

Model Structure

The model can be described as a patient-level model based on discrete event simulation. The simulation starts with a random draw (with replacement) of a patient from the starting population of the model. Next, the time to first event for the selected patient, which can be an exacerbation, a pneumonia, or death, is simulated. This is done by filling in the baseline values of the selected patient into regression equations used to describe the statistical association between all patient and disease characteristics and the time to event. The event with the lowest predicted value (time) is considered to happen first. Because events are assumed to have a direct impact on the health status of a patient (Fig. 1), all intermediate and final outcomes are updated at the time the event is happening by calculating their new value using regression equations that describe the associations between the progression of time, patient and disease characteristics, and the outcomes. First, the updated value for lung function is calculated (Fig. 1) by filling in time since start of the simulation and values for all characteristics into the equation for lung function. The updated value is then used in the equation for exercise capacity to calculate the updated value for this outcome. Both updated values are then used to predict the new value for physical activity and so on until all outcomes are updated (Fig. 1). Based on the updated values for the intermediate outcomes, new estimates for the time to exacerbation, pneumonia, and death are calculated. The simulation continues until the patient dies, which is assumed to occur when the predicted event is death or the lung function drops below 0.20 liters. Retrospectively, the values for all intermediate and final outcomes are also updated when the time until the first event or between events is predicted to be more than 1 year. The whole process is repeated by randomly drawing 5000 patients from the total available starting population and simulating their individual disease progression over time. By combining the data of all simulated patients, the average value for the number of events, the intermediate outcomes, and final outcomes is calculated. The model was implemented in R using RStudio (version 1.1.383).

Equations Describing Disease Progression

Longitudinal data from the tiotropium trials (UPLIFT, EXACTT, POET, TIOSPIR, and TONADO[10–14]) were used to estimate the time-to-event equations and the regression equations describing the associations between patient characteristics and outcomes over time. Because only the longitudinal data of patients in the tiotropium arms of the trials (19,378 patients) were used to estimate the equations, the outcomes of the model were deemed representative for a patient population treated with tiotropium (comparator). In total, 13 different equations were estimated for the following outcomes: time to exacerbation (equation 1A), probability that the exacerbation is severe [i.e., leads to a hospital admission (1B)], time to pneumonia (2A), probability that the pneumonia results in hospitalization (2B), time to death (3), lung function (4), exercise capacity (5), physical activity (6), probability of having breathlessness (7A), probability of having cough/sputum (7B), disease-specific quality of life (8), number of visits to the

Table 1 – Definition of parameters in the model.

Parameter	Definition
Stable baseline characteristics	
Female	Female = 1, male = 0
Body mass index (BMI) class	BMI was calculated as weight/height^2. Class 1 (reference): low BMI was defined as BMI <21 based on the GOLD guidelines and BODE index; class 2: normal BMI was defined as 21 < BMI < 30; class 3: high BMI as BMI >30 kg/m^2
Smoking status	Smoker = 1, ex-smoker = 0
Number of pack-years	(Number of cigarettes per day/20) × number of years smoked
Presence of heart failure	Standardized MedDRA Query (SMQ) cardiac failure
Presence of other cardiovascular disease	History of myocardial infarction (SMQ myocardial infarction [broad]) OR history of cardiac arrhythmia (HLGT cardiac arrhythmias) OR history of stroke (PV stroke without MPT TIA) OR history TIA (MPT TIA)
Presence of asthma/rhinitis	SMQ asthma/bronchospasm (broad) OR HLT atopic disorders of SOC immune system disorders OR MPT rhinitis allergic OR MPT rhinitis perennial OR MPT rhinitis seasonal
Bronchodilator responsiveness	Postbronchodilator FEV_1 in liter/prebronchodilator FEV_1 × 100 Postvalue measured after administration of study drug and ipratropium + salbutamol (60 minutes later) + waiting 30 minutes
Presence of depression	SMQ depression excluding suicide
Presence of diabetes	SMQ hyperglycemia/new onset diabetes mellitus (narrow)
Emphysema	Question in CRF: diagnosis of emphysema? Yes = 1, No = 0
Eosinophil level	High: ≥4%; low: <4%, measured in blood
Concomitant ICS use	Inhaled corticosteroid (ICS) use at baseline and continued during the simulation; Yes = 1, No = 0
Intermediate time-dependent outcomes	
Moderate exacerbations	Increase in or new onset of more than one respiratory symptom lasting for at least 3 days and requiring treatment with antibiotics and/or oral steroids
Severe exacerbations	As above, but requiring hospitalization
Pneumonia	Pneumonia as defined by the treating physicians in the trials
Lung function	Postbronchodilator forced expiratory volume in the first second (FEV_1) in liters
Exercise capacity	Endurance time in a constant exercise test at 90% of the maximum work rate (treadmill) in seconds
Physical activity	St. George's Respiratory Questionnaire (SGRQ), activity subscore (score from 0 to 100, with higher scores indicating a lower level of physical activity)
Symptoms: breathlessness	SGRQ question on shortness of breath, Yes = 1 (most or several days per week), No = 0 (a few days per month, only with chest infections, not at all)
Symptoms: cough/sputum	SGRQ question on cough and sputum, Yes = 1 (most or several days per week), No = 0 (a few days per month, only with chest infections, not at all)
Disease-specific quality of life	SGRQ total score (score from 0 to 100, with higher scores indicating a worse quality of life)
Final outcomes	
Mortality	All-cause mortality
Utilities/QALYs	No data available; the SGRQ total score is converted into utilities using the published equation of Starkie et al[15]
Costs	Treatment costs: costs associated with the treatment under evaluation (= tiotropium for the base case). Maintenance costs: costs for general practitioner and specialist visits, influenza vaccination, spirometry, and ICS use. Exacerbation costs: cost for a moderate and severe exacerbation. Pneumonia costs: cost for pneumonia treated outside or inside the hospital.

BMI indicates body mass index; BODE, BMI Obstruction Dyspnea Exercise index; CRF, Case Report Form; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HLGT, High Level Group Term; MPT, Meddra Preferred Term; PV, pharmacovigilance; QALY, quality-adjusted life year; SGRQ, St. George's Respiratory Questionnaire; TIA, transient ischemic attack.

general practitioner (9A), and number of visits to the respiratory specialist (9B). In addition to equation (3), an additional mortality risk was applied at the occurrence of a severe exacerbation (6.3%) or a pneumonia requiring hospitalization (8.1%) (more details in Appendix II). For all time to event equations, a Weibull survival regression model was fitted. Generalized linear mixed-effects models with binomial family were estimated to derive probabilities. To describe continuous outcomes over time, linear mixed-effects models with random effect for the intercept were used. Visits to healthcare providers were based on negative binomial generalized linear models. In Appendix II, the estimated coefficients and other details of the equations can be found. It was not possible to estimate an equation for utilities because none of the trials included longitudinal data on utility values. Therefore, a previously published mapping algorithm was used to convert the St. George's Respiratory Questionnaire (SGRQ) total scores predicted at different time points into utilities.[15]

Resource Use and Costs

The model distinguishes between costs related to the intervention/medication of interest, costs for maintenance treatment, costs related to exacerbations, and costs related to pneumonias. Costs on maintenance treatment included COPD-related number of visits to the general practitioner and medical specialist, which were predicted based on equations and therefore dependent on patient characteristics. In addition, maintenance costs for the annual number of spirometries and influenza vaccination were

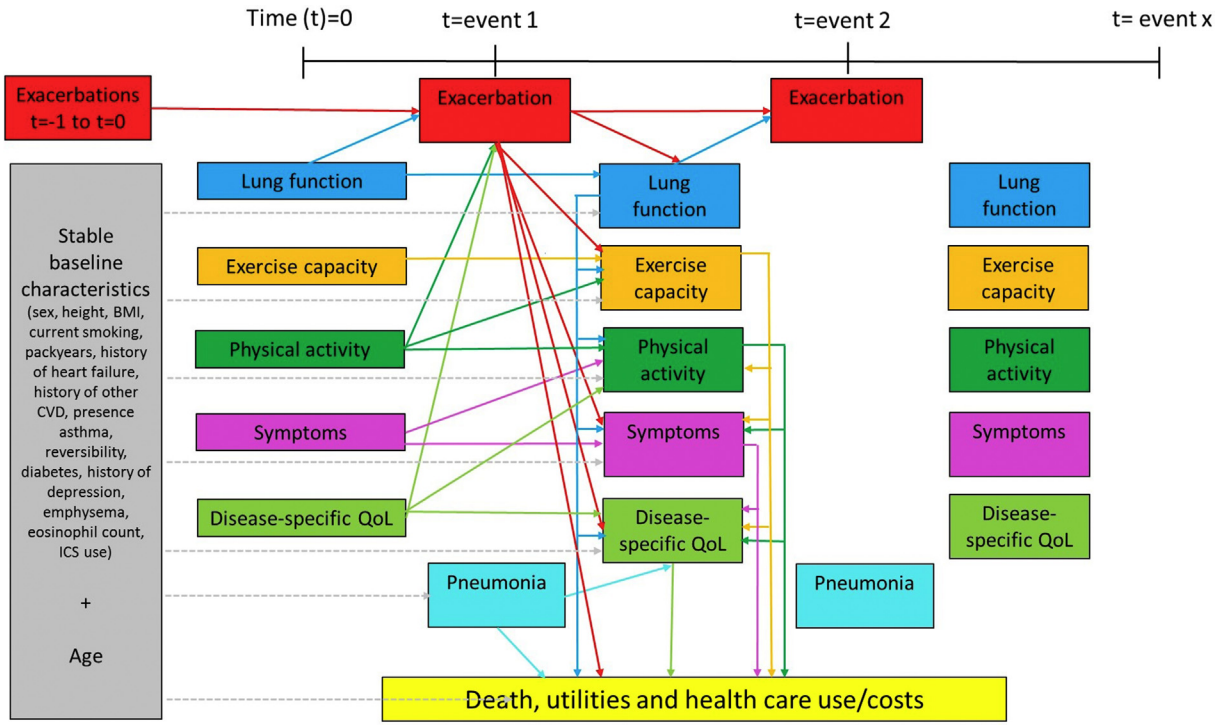

Fig. 1 – Conceptual model.

included for all patients, and costs for ICS were included for patients using ICS at baseline. These 3 types of costs were assumed constant for all patients. Costs for exacerbations covered the costs of physician visits, hospital days, emergency room visits, ambulance rides, medication costs, travel costs, and productivity loss. Costs for pneumonias were assumed to be the same as for exacerbations. For the analyses presented in the current article, costs were calculated for the year 2015 using the UK healthcare perspective (see Appendix IV in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008).[16–21]

Model Outcomes

The main model outcomes are the annual number of (severe) exacerbations and pneumonias, the annual decline in lung function, the annual change in exercise capacity, physical activity and disease-specific quality of life, the proportion of days with symptoms, the remaining life expectancy since start of the simulation, the total number of QALYs, and the total (healthcare) costs.

Base-Case Analysis (Comparator)

For the current analysis, results were based on 5000 simulated patients. Simulating different sets of 5000 patients gave comparable results, and therefore 5000 patients were deemed sufficient to get stable results while keeping the running time reasonable. The time horizon used was lifetime. The base-case analysis in which all patients used tiotropium served as the comparator when calculating the cost-effectiveness of the treatment scenarios.

Treatment Scenarios

Several treatment scenarios were run by assuming a change in intermediate outcomes associated with a hypothetical treatment. To illustrate the potential of the model, the following 4 scenarios addressing key targets of COPD treatment [1] are shown in this article: 1) 20% reduction in annual decline in lung function, 2) 30% increase in time to an exacerbation, 3) 4 points improvement in physical activity level (SGRQ activity score), and 4) 20% reduction in probability to have breathlessness plus 20% reduction in the probability to have cough/sputum. The assumed effectiveness was based on the range of effect sizes observed in clinical COPD trials or the minimal clinically important difference.[22,23] Treatment scenarios were run for the same 5000 patients used for the base-case analysis. Model outcomes for the treatment scenarios were compared with the base-case results to estimate the difference in QALYs and total costs associated with the hypothetical treatment. In addition, the incremental cost-effectiveness ratio (ICER) was calculated. For all treatment scenarios an increase in treatment costs of 20% over and above the costs of tiotropium was assumed, and future effects and costs were discounted with 3.5% according to UK guidelines.[24]

Subgroup Analysis

Subgroup analyses were performed by randomly drawing (with replacement) 5000 patients with the characteristics that define the subgroup. Results for 3 subgroups are shown as example: patients with a low BMI (<21 kg/m^2), patients with a history of a severe exacerbation (≥1 hospitalization for an exacerbation in the year before baseline), and patients with a low physical activity level (defined by the highest quartile of the baseline SGRQ activity score).

Probabilistic Sensitivity Analysis

Besides patient heterogeneity owing to the variation in the patient population at baseline, the model includes the following 2 types of uncertainty: 1) stochastic uncertainty, which is the uncertainty related to drawing random values from probability distributions during the simulation (Appendix II), and 2) parameter uncertainty,

which is the uncertainty associated with the coefficients of the equations describing disease progression and with the treatment effect parameters. The probabilistic sensitivity analysis was implemented as a double loop: an inner loop, in which a number of patients were sampled with replacement from the baseline population, and an outer loop, in which values of the input parameters of the model were randomly drawn. For the current analyses, the model was run for 500 different sets of randomly drawn input parameters with a sample size of 100 patients per set. This was sufficient to get stable results according to the formulas presented in the article of O'Hagan et al[25] (see Appendix V in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008). The resulting 500 differences in QALYs and costs between the hypothetical treatment and the base case were plotted in cost-effectiveness planes. The information in the cost-effectiveness plane was summarized in cost-effectiveness acceptability curves, which show the probability that the treatment evaluated is cost-effective at certain threshold values for the ICER.[26]

Results

Base-Case Analysis

The second column in Table 2 shows the characteristics of the 5000 patients at the start of the simulation. These were comparable to those of the total available model population. Table 3 shows the mean model results per patient over lifetime. Patients experienced on average 0.62 exacerbations per year. The mean life expectancy was 11.2 years. Figure 2 shows the individual progression of lung function over time for a subset of patients. In general, the lung function of patients worsened over time, with on average about 43 mL per year (Table 3). On average, physical activity (SGRQ activity score) and disease-specific quality of life (SGRQ total score) worsened by 1.5 and 1.1 point per year, respectively. Total lifetime QALYs and costs from a healthcare perspective were 5.69 and £18,600, respectively. A breakdown of the costs is shown in Figure 3.

Treatment Scenarios

Results for the scenarios assuming hypothetical effects and intervention costs showed that a scenario assuming a 20% reduction in breathlessness and cough/sputum did not have much impact on the different intermediate outcomes and resulted in 0.10 QALYs gained (Table 3). A 4-point improvement in physical activity score had a substantial impact on life expectancy and resulted in 0.53 QALYs gained (Table 3). The scenario analysis assuming a reduction in annual decline in lung function showed impact on a broad range of intermediate outcomes, and assuming a 30% increase in the time to exacerbation resulted in a decrease of the total lifetime costs (Fig. 3). The ICERs for the treatment scenarios ranged from being dominant to £5500/QALY (Table 3). The cost-effectiveness planes for the different interventions are shown in Appendix VI (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.008).

Table 2 – Patient and disease characteristics of the 5000 simulated patients at start of the simulation.

	Sample of 5000 randomly drawn patients			
	Base case and treatment scenario analysis	Subgroup: low BMI	Subgroup: history of a severe exacerbation	Subgroup: low level of physical activity
Total number of patients available in the model population	35,341	5,674	5,443	8,682
Female, %	27	29	18	42
Age (years)	64	64	63	64
FEV_1 (L)	1.35	1.17	1.19	1.02
FEV_1% predicted, %	49	43	42	40
Low BMI (<21 kg/m^2), %	16	100	26	19
Smoking, %	39	46	38	37
Pack-years (years)	44	42	42	50
Emphysema, %	49	80	65	66
ICS use, %	58	57	61	70
Asthma, %	5.4	4.7	3.4	11
Heart failure, %	6.4	4.8	21	13
Other CVD, %	14	10	16	17
Depression, %	6.7	4.4	3.7	14
Diabetes, %	12	1.6	11	15
High eosinophils, %	21	39	22	12
Bronchodilator responsiveness (%)	23	25	23	24
Previous exacerbations, %	60	61	100	62
Previous severe exacerbations, %	16	25	100	23
Exercise capacity (seconds)	346	342	338	327
Physical activity, SGRQ activity score (points)	60	61	64	75
Presence cough/sputum, %	68	66	74	82
Presence breathlessness, %	65	69	75	93
Disease-specific quality of life, SGRQ total score (points)	45	47	49	56

BMI indicates body mass index; CVD, cardiovascular disease; ICS, inhaled corticosteroids.

Table 3 – Model results for the base-case analysis, treatment scenarios, and subgroup analyses.

Average outcome per patient	Base-case analysis	Treatment scenarios				Subgroup analyses		
		20% Reduction in lung function decline	30% Increase in time to exacerbation	Four-point improvement in physical activity	20% Reduction breathlessness and cough/ sputum	Low BMI (<21 kg/m^2)	History of a severe exacerbation	Low physical activity level
Events								
Annual rate of moderate exacerbations	0.49 (0.41; 0.57)	0.49	0.36	0.46	0.49	0.46	0.56	0.61
Annual rate of severe exacerbations	0.13 (0.09; 0.18)	0.12	0.10	0.11	0.13	0.21	0.24	0.19
Annual rate of total pneumonias	0.035 (0.024; 0.050)	0.036	0.034	0.035	0.035	0.043	0.040	0.044
Life expectancy (years)	11.17 (9.81; 12.88)	11.65	11.51	11.89	11.23	7.85	9.16	9.05
Intermediate outcomes								
Decline in lung function (mL/year)	−42.6 (−46.7; −38.5)	−34.2	−42.7	−42.6	−42.6	−53.8	−40.1	−33.3
Change in exercise capacity (seconds/ year)	−3.8 (−10.2; +3.7)	−2.2	−3.2	−3.6	−3.8	−13.3	−4.9	−4.4
Change in physical activity (point/year)*	1.48 (1.19; 1.75)	1.33	1.42	1.20	1.43	1.72	1.51	1.08
Proportion of days with cough/sputum	0.59 (0.55; 0.69)	0.58	0.59	0.55	0.53	0.64	0.65	0.71
Proportion of days with breathlessness	0.59 (0.53; 0.67)	0.57	0.59	0.52	0.52	0.63	0.66	0.80
Change in disease-specific quality of life (points/year)*	1.10 (0.85; 1.35)	0.97	1.04	0.82	0.93	1.24	0.93	0.67
Final outcomes								
Total number of QALYs (undiscounted)	7.25 (6.37; 8.45)	7.63	7.46	8.02	7.39	5.11	5.64	5.25
Total number of QALYs (discounted)	5.69 (5.11; 6.45)	5.91	5.83	6.22	5.79	4.25	4.54	4.26
Total lifetime costs from a healthcare perspective (£) (undiscounted)	24,891 (20,352; 29,812)	26,125	24,027	26,131	25,627	22,584	27,078	24,794
Total lifetime costs from a healthcare perspective (£) (discounted)	18,567 (15,511; 21,354)	19,215	17,900	19,250	19,114	18,371	21,373	19,478
Incremental cost-effectiveness ratio (ICER) compared with the base-case analysis, cost per QALY gained (£) (discounted)	—	3,000	Dominant	1,300	5,500	—	—	—

BMI indicates body mass index; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SGRQ, St. George's Respiratory Questionnaire.

* Physical activity score = SGRQ activity score; disease-specific quality of life = SGRQ total score. An improvement in both scores indicates a worsening in physical activity level and disease-specific quality of life.

Subgroup Analysis

Results for the subgroup of patients with a low BMI are described below as example. Compared with the total population, the subgroup of patients with a low BMI had a lower lung function at start of the simulation and they were more likely to smoke, have emphysema, and have a history of a severe exacerbations (Table 2). Model outcomes for this subgroup showed a higher rate of severe exacerbations, a lower life expectancy, and a faster deterioration on other outcomes (ie, lung function, exercise capacity, physical activity, and disease-specific quality of life) compared with the base-case analysis for the total population (Table 3). Total lifetime costs for patients with a low BMI were lower (Table 3) because of their lower life expectancy (−3.3 years), but the average costs per year alive were higher (+£678) than for the total population. Results for the subgroups with a history of a severe exacerbation and a low physical activity level can be found in Tables 2 and 3 and Figure 3.

Model Validation

The prediction equations were validated by the expert panel and against the trial data used to estimate the equations (Appendix II). Validation of the model simulation outcomes showed that the estimated annual decline in lung function in the base-case analysis (43 mL/year) was in line with the UPLIFT trial[10] used to build the model, but somewhat higher than expected by the experts and the estimates found in the literature.[27] The average annual exacerbation rate of 0.62 met the expectations of the experts and was comparable with the rate in the studies used to estimate the equation for exacerbations[10–14] but were somewhat lower than rates reported in other large COPD studies.[22,28] The average remaining life expectancy predicted by the model was 11.2 years, resulting in an average expected age of death of 75 years. In both the United States and the European Union, the average life expectancy for the general population at age 65 years is 18 years for men and 21 years for women.[29,30] This implies that COPD patients in the model have a 7-year to 10-year lower life expectancy

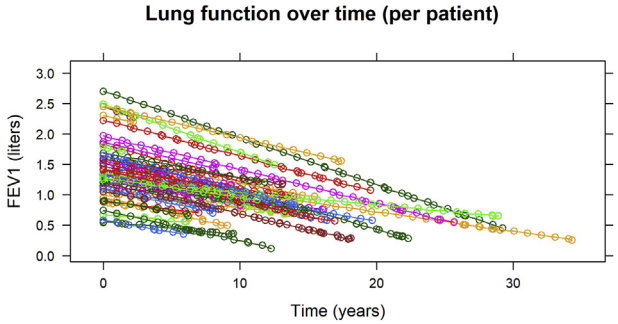

Fig. 2 – Individual progression of lung function over time (subset of 50 simulated patients).

compared with the general population at 65 years. Compared with a publication of Shavelle et al presenting life expectancies for COPD patients at the age of 65, our estimate of 11.2 years is about 1.8 years lower.[31] Validation of the 4-year mortality rate of the model with the observed 4-year mortality rate in the UPLIFT trial showed that the model resulted in a substantially higher rate, which could partly be explained by the additional mortality risk for a severe exacerbation and pneumonia that were added in the model. The expert panel on the other hand thought that the life expectancy predicted by the model was higher than expected. Estimates for the annual change in the SGRQ total score varied substantially in the literature, ranging from +0.24 to +3.2 points.[10,32,33] Our estimate of +1.10 was within this range.

Discussion

The current study aimed to develop a health economic patient-level simulation model for COPD that includes a great diversity of COPD patient characteristics and simulates annual changes in a wide variety of outcomes. By performing 3 different literature reviews, we aimed to identify a wide range of important factors for prognosis and treatment allocation. In total, 14 different patient and disease characteristics and 10 different outcomes were included in the model, enabling a broad description of the COPD population. This makes the newly developed COPD model unique because none of the previously published models included such a wide range of different patient and disease characteristics and outcomes.[7–9] Other innovative aspects of the model compared with standard Markov modes in COPD are the simulation of individual patients for whom time-to-events are modeled simultaneously with the annual change in continuous variables. Another strength of the model is that it was built using the combined data of 5 large COPD trials. The current model is also one of the first models to include pneumonias, which are commonly recognized as adverse events associated with use of inhaled corticosteroids.[34] Only one other recently developed COPD model included a wide range of patient characteristics and outcomes. This model was built using data from one single study and is less flexible because it is not a patient-level simulation model.[35–37]

Although our model includes a large number of patient characteristics, some important ones are still missing. Experts stressed the importance of factors such as socioeconomic status, marital status, coping skills, and self-efficacy of patients. All these factors could not be included in the current version of the model because no data on these parameters were available. A second limitation is that the conceptual model needed to be

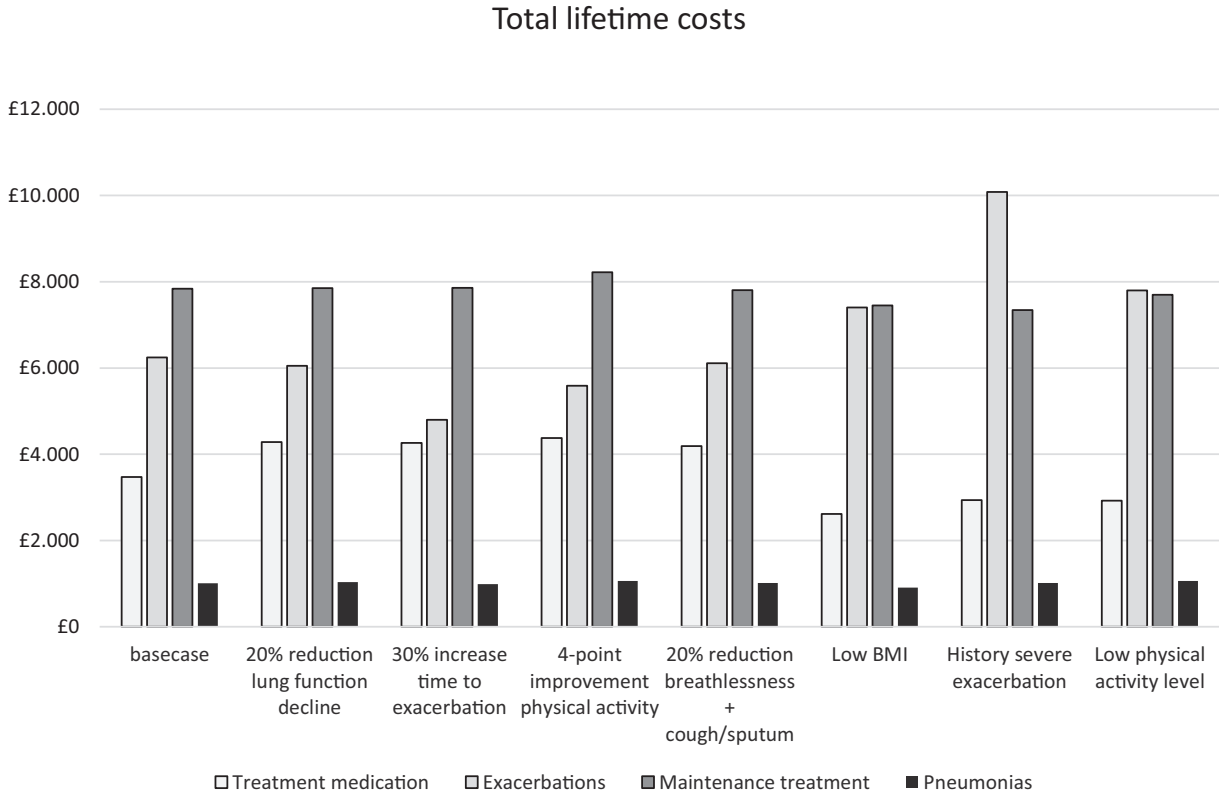

Fig. 3 – Lifetime discounted costs specified by type of costs using a healthcare perspective (costs in UK pounds).

operationalized into variables as measured in the 5 available clinical COPD trials. This involved using second-best options in some cases. For physical activity, for example, the number of steps per day was considered to be the best measurement by the clinical expert panel, whereas exercise capacity is preferably defined by the 6-minute walking distance. In addition, utilities to calculate QALYs were not directly measured but based on utility values that are derived from SGRQ total scores using a previously published algorithm.[15] Furthermore, although the model includes the most important costs drivers in COPD, some important cost categories are still missing (ie, costs for respiratory nurse, pulmonary rehabilitation, oxygen use). It would have been interesting to include non–COPD-related costs as well, especially because the model includes several comorbidities. If new data become available, these costs can be included in future versions of the model.

One of the challenges we were facing was the estimation of a consistent set of model regression equations using data from the 5 different tiotropium trials. Regression equations including all variables of the conceptual model could only be estimated for patients with complete data on all the defined variables, and none of the 5 trials provided data on all patient characteristics and outcomes together. Therefore values for missing variables in the baseline characteristics and the intermediate outcomes for each trial were predicted using the observed data in (one of) the other tiotropium trial(s) that did measure the variables. For each missing variable in each trial, a trial-specific prediction model was estimated by including as many observed covariates that the trial with the missing variable had in common with the trials with the observed variable. To assess the impact of predicting missing variables on the final model outcomes, 2 sets of model regression equations were estimated. The first set of equations was based on observed data only using data from the UPLIFT trial[10] because that was the trial that included almost all parameters in the model (with the exception of eosinophil count and exercise capacity). The second set of equations was based on both observed and predicted data using data from all 5 trials.[10–14] For the base-case analysis the differences between the 2 model versions were relatively small and the uncertainty intervals had substantial overlap. Therefore, the impact of using predicted data seemed small on a population level, and only results based on the second set of equations were presented in this article.

The model outcomes are representative for the group of patients who participated in the large tiotropium trials, which are mainly secondary care patients with moderate to severe airflow obstruction and no other life-treating diseases. This is relevant because this is the COPD patient population usually participating in clinical trials. In this way, early assessment of outcomes of new treatment options before clinical trials are even performed can be done in the same patient population as usually included in the trials. Nevertheless, it does limit the extrapolation of the results to the total COPD population because a large proportion of COPD patients has mild to moderate airflow limitation, is treated in primary care, and has a substantial number of co-morbidities.[38] Therefore, it would be interesting to re-estimate the model based on real-life data to see whether there are large differences in outcomes. Nevertheless, real-life databases usually do not include as many different parameters as our model does, and they often contain a lot of missing values, which makes it challenging to find a suitable database.

In conclusion, the newly developed COPD model is a unique patient-level simulation model that includes many of the patient and disease characteristics currently considered important for prognosis or treatment allocation in COPD patients. The model can be used to simulate annual changes in a range of outcomes for a wide variety of subgroups of patients. It can also provide valuable information to guide research and development of new treatment options in an early stage by showing the possible impact of new interventions on a large number of outcomes.

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Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.10.008.

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