A new economic model for COPD

Helen Starkie, Andrew Briggs and Mike Chambers

Contact details:
Helen Starkie
PhD student. Section of Public Health and Health Policy, 1 Lilybank Gardens, University of Glasgow, G12 8RZ Email: h.starkie.1@research.gla.ac.uk
or
Technical Analyst. National Institute for Health and Clinical Excellence
MidCity Place, 71 High Holborn, London, WC1V 6NA Email: helen.starkie@nice.org.uk

Abstract

Aim

To combine information on the natural history of COPD with treatment effects in a novel way in order to develop a new economic model for COPD. The model will aid better decision-making, as it is a generic disease model that can be used to appraise COPD therapies on the same platform.

Data

A Scottish prospective cohort (Renfrew/Paisley (MIDSPAN) study (n=15,402) followed up for over 30 years and a large (n=6112), multinational COPD trial (TORCH) were used.

Methods

A regression based model structure was employed. A series of regression equations were developed for: lung function; exacerbations; symptoms; EQ-5D utility; cost; and survival probability, using the MIDSPAN or the TORCH dataset. The equations were combined to form an economic model for COPD from a lifetime perspective, representing current treatment. A hypothetical treatment effect was applied to form a comparator arm.

Results

The regression equations were developed and predicted sensible results. The resulting model, models patients who, over time have: reduced lung function; an increasing rate and severity of exacerbations; and worsening symptoms, in line with the natural history of the disease. Interdependence exists between the different components of the model. The model allows for the incorporation of patient level heterogeneity so that different types of patients can be modelled including: people with different disease severities, smoking history and symptoms.

Conclusion

Data from an observational study and a trial were successfully used in a complementary manner to develop a new economic model for COPD based on the natural history of the disease.

Introduction

COPD is a lung disease that principally affects older people with a history of smoking. People with COPD initially complain of breathlessness and may have cough and increased sputum production, which tend to worsen over time. There are three important factors that impact quality and quantity of life, affect costs and influence mortality risk for people with COPD. These are: exacerbations, symptoms and lung function.

The role of treatment for COPD is important in designing a model as it has a bearing as to how manufacturers target their products and subsequently provides an insight into the potential effects of treatment. The role of treatment for COPD:

> "…in the absence of a disease cure, is to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance."(1)

Most of the published economic models for COPD are Markov models and have used lung function as the driver of progression through the model.(2-8) The models tend to incorporate either:r episodes of exacerbations which occur at a pre-defined rate within each health states, with increased frequency as disease severity worsens; or separate exacerbating states. Symptoms have not previously been modelled explicitly.

This paper presents the development and results of a new concept in economic modelling for COPD: a model that employs a series of regression equations to parameterise key drivers of cost effectiveness: lung function, symptoms and exacerbations and from these, informs regression equations for cost and effectiveness that predict cost and effect values per cycle. Values for a current treatment arm and a comparator arm are calculated separately and for each arm, costs and effects are summed over time to give cost effectiveness statistics.

The relationship between exacerbations, symptoms and lung function, and the relationship between these components of the model, and costs and QALYs are illustrated in figure 1. As shown in figure 1, the paths of effect between the components and HRQoL and cost are unlikely to be completely independent from one another: for example, as lung function becomes more limited, the severity and frequency of exacerbations tends to increase,(9-11) which in turn affects HRQoL. The relationship between the components and HRQoL is difficult to untangle, however one of the benefits of a regression based model is that this interdependence can be modelled explicitly because predicted scores from one regression

equation such as lung function, can be used as explanatory variables in regression equations that predict symptoms and exacerbation rates. Figure 1 additionally illustrates how four different interventions may work on the different components of COPD and how in turn these may impact upon costs and QALYs.

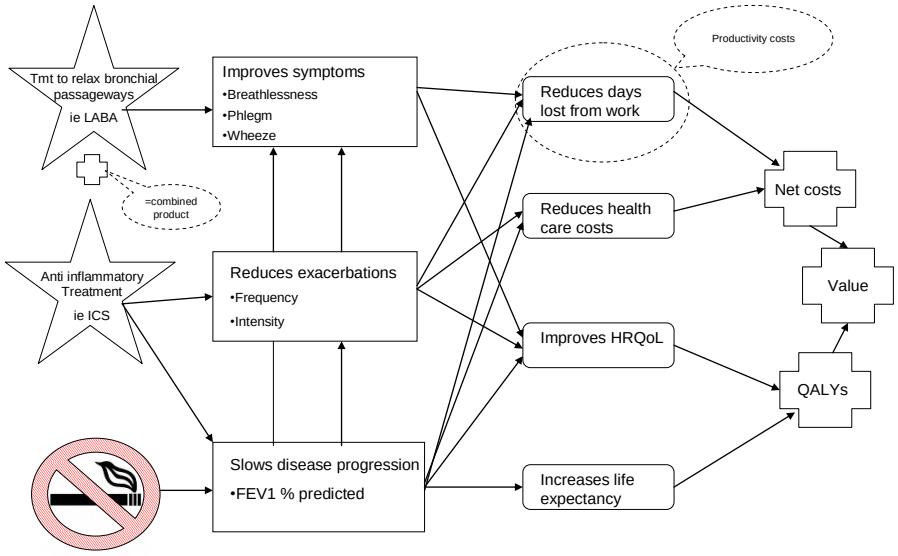

Figure 1 Conceptual COPD model

The aim of the study is to develop a model that represents the natural history of the disease for a range of COPD patients – based on a series of regression equations – and on top of that, layer in a treatment effect. This new COPD model will be flexible with regards to the type of intervention it will be employed for and the treatment effect will be dependent upon the intervention's mechanism of action. It will also be able to incorporate heterogeneity in the disease population.

Methods

Sources of data

Two datasets were used to develop the regression equations for the model. The first was a Scottish prospective cohort (Renfrew/Paisley (MIDSPAN) study) of 15 402 men and

women. Between 1972 and 1976, all residents aged between 45 and 64 years within the two towns of Renfrew and Paisley were asked to complete a health questionnaire and to attend a physical examination (78% participated) and since then, information on mortality in this cohort has been collected. Only people with GOLD diagnosed COPD,(1) were used to develop the model. The second study, the TORCH trial, assessed the efficacy of the combination product salmeterol/fluticasone compared to salmeterol, fluticasone and placebo in 6112 COPD patients over the course of three years. Inclusion criteria included that the subject had to have at least 10 pack years and FEV1 ≤60 % predicted. Outcome measures included: the EQ-5D, the SGRQ, rate of exacerbations and post bronchodilator FEV_1.(12) Measures were repeatedly collected throughout the trial period. Due to translations of the EQ-5D questionnaire being unavailable in some languages, the EQ-5D was administered to 4237 out of the 6112 respondents.

Development of the regression equations

Regression equations were developed predicting separately: FEV1, minor and major exacerbations, SGRQ symptoms score, survival, cost and utility. The development of each regression equation was carried out in either the TORCH or the Renfrew/Paisley (MIDSPAN) dataset. For each regression equation, potential explanatory variables were identified within the appropriate dataset, including: age, sex, disease severity at baseline, presence of symptoms and smoking as shown in table 1.

Table 1. Baseline user defined patient characteristics

Patient characteristics	Description
Age	years (>45 yrs)
Height	Cm
Disease severity (based on NICE COPD guidelines.(13))	FEV_1 % predicted (0-1 scale) possible (0): >=0.80, mild (1): 0.50-0.79, moderate (2): 0.30-0.49, severe (3) <0.30
Sex	0: men, 1: women
Ex-smoker	0: not ex-smoker 1: ex-smoker
Over 10 pack years	0: <10 1: ≥10
Respiratory symptoms	0: no symptoms 1: symptoms
UK	0: no 1: yes

Lung function was assumed to be the primary driver of the model affecting: the rate of exacerbations, symptoms, mortality, QALYs (through EQ-5D utility) and cost. In practical terms this means that the prediction equations for each of these components could potentially contain lung function as an explanatory variable. For the cost and utility equations, explanatory variables could also include symptoms and exacerbations (depending on statistical significance). The statistical package, STATA v11 was used to

develop the regression equations. The specific methods employed to develop each regression equation are detailed below.

Lung function

The Renfrew/Paisley dataset was chosen in preference to the TORCH dataset because of the wider range of lung function values recorded in the Renfrew/Paisley study. To develop the regression equation for FEV_1, the method of OLS was used with FEV_1 (litres) as the dependent variable, adjusted for user defined patient characteristics of: respiratory symptoms, over 10 pack years, being an ex-smoker, height, age and sex, with a categorical variable for disease severity at baseline in terms of: 0) $FEV_1 \geq 80\%$ predicted (used as the reference case); 1) $80 < FEV \geq 50\%$ predicted; 2) $50 < FEV \geq 30\%$ predicted; and 3) $FEV_1\%$ predicted <30% (depending on statistical significance).

An equation for FEV_1 % predicted was used within the model because COPD patients are frequently classified in terms of FEV_1 % predicted, rather than FEV_1. To calculate $FEV_1\%$ predicted from FEV_1, reference equations were used that predict expected FEV_1 for a 'healthy person' based on age, height and gender, as shown in equations 1 and 2 below:

Equation 1. Expected FEV_1 for men

$$FEV_1(l)\ in\ men = -1.859 - 0.029 \times age(yrs) + 0.037 \times height(cm)$$

Equation 2. Expected FEV_1 for women

$$FEV_1(l) in\ women = -0.225 - 0.029 \times age(yrs) + 0.024 \times height(cm)$$

To get to FEV_1 % predicted, the estimated FEV_1 as determined by the OLS regression equation was divided by the expected FEV_1 (for the same baseline characteristics) derived from equations 1 or 2 above (depending on gender), and multiplied by 100 (this was done for each cycle within the model).

Exacerbations

Exacerbations were said to occur when there is a worsening of respiratory symptoms requiring treatment with oral corticosteroids and/or antibiotics.(14) There were assumed to be two types of exacerbation which required different regression equations: minor and major exacerbations. A minor exacerbation is considered present when a subject is managed exclusively in primary care. A major exacerbation occurs when the worsening of symptoms require that the subject is hospitalised.(15). It was assumed that the rate of exacerbations was related to lung function, which in turn was expected to affect symptoms, QALYs (via EQ-5D utility) and cost. Exacerbations were incorporated into the model as an annual rate. The TORCH dataset was used to derive the prediction equations for rates of

mild and rates of major exacerbations. In developing the regression model for rate of exacerbations, an assumption was made that previous exacerbations have no impact on future exacerbations. Potential explanatory variables included: age, FEV_1 % predicted, ex-smoker, sex and a UK variable. FEV_1 % predicted was calculated for each observation within the TORCH dataset, using the prediction equation described above. Because the exacerbation data in the TORCH study are count data, the Poisson distribution was employed. A goodness of fit test was used to check for over-dispersion (where the sample variance is greater than the sample mean) in order to decide whether a Poisson regression model or a negative binomial model was appropriate for modelling the data.

Symptoms

The TORCH dataset was used to develop the prediction equation for symptoms. The SGRQ symptoms domain of the SGRQ was used as a surrogate measure for measuring symptoms, and was the dependent variable in the regression equation. The prediction equation for SGRQ symptoms was adjusted for a range of potential explanatory variables including: sex, age, ex-smoker and breathless at baseline. Because symptoms were *a priori*, expected to be influenced over time by exacerbations and by lung function, variables for major exacerbation rate and FEV_1 % predicted were also included within the model. GLM regression models were used in order to identify a model that fit the data well.

EQ-5D utility

The TORCH dataset was used to develop the prediction equation for EQ-5D utility. EQ-5D utility at one year time periods were used together with information on events and experiences occurring within the previous year to predict EQ-5D utility. Explanatory variables assessed for incorporation into the EQ-5D utility prediction model included: SGRQ symptoms; FEV_1 % predicted; breathless at baseline, sex, UK, ex-smoker, age and major exacerbations within the last year (where 0=no, 1=yes). The prediction equation for EQ-5D utility was developed using GLM models. The equation was estimated on the utility decrement scale (1-EQ-5D utility), in order to allow greater flexibility in identifying the appropriate family for the GLM model, and converted back for reporting.

Cost

Costs are modelled as those accruing to the NHS as a result of the disease. Costs were split into two types: treatment costs and all 'other costs', which includes the cost of hospitalisation, GP contacts and costs associated with adverse events. The two types were dealt with in different ways.

Based on prescribing practice before recent COPD therapies entered the market (Seretide, Spiriva and Symbicort), it was assumed that a person with mild (NICE diagnosed) COPD

would be prescribed ipratropium and salbutamol at an annual cost of £102 ($167) and for treating people with moderate COPD, that beclomethasone would been added to the treatment mix, so treatment might be: beclomethasone, ipratropium and salbutamol, with a one year cost of £183 ($299). As pharmacological costs are fixed, given the quantity prescribed, they are entered into the model as a user defined value that occurs every cycle.

For 'other costs', a regression equation was developed to predict cost based on patient events and experiences. The cost equation for 'other costs' was developed within the TORCH dataset. The cost equation was estimated using GLM regression methods. 'Other costs' was the dependent variable and explanatory variables offered to the model included: major exacerbations, minor exacerbations, SGRQ symptoms, sex, UK, FEV % predicted, breathless at baseline, age and ex-smoker.

Survival

People with respiratory symptoms, airflow obstruction and over 10 pack years, have been shown to have a higher mortality risk than people with no COPD, or people with GOLD defined COPD. It was also seen that people with more severe disease had a higher mortality risk than those with less severe disease, for all cause and COPD mortality and so a survival model was developed. The GOLD defined COPD cases in the MIDSPAN dataset were used to develop the regression model on survival. Potential explanatory variables included sex, FEV % predicted at baseline, age at baseline and dummy variables for: fewer than/over 10 pack years, ex-smoker and respiratory symptoms. The survival function was modelled using a Weibull regression.

Development of the model

Using the regression equations, the model was populated in cycles where each cycle represents one year. For the first cycle, the model runs as shown in figure 2. User defined patient characteristics (as shown in table 1): age, sex, symptoms, disease severity, were entered into the model as explanatory variables for FEV_1 (step 1) to get a regression equation for FEV_1 (step 2). Predicted values for FEV_1 and patient characteristics were inputted as explanatory variables into the equation for exacerbations (step 3). Step 4 uses the exacerbation rate from the model in step 3 with predicted values for FEV_1 and values for patient characteristics as explanatory variables into the equation from symptoms. Predicted values from these equations (step 5) are used as explanatory variables for the cost and EQ-5D utility equations (step 6) to allow for the interdependence of the various components of the disease on one another. The cost equation, and the EQ-5D utility equation are each multiplied by the survival probability (step 7) to give survival-adjusted cost and survival adjusted utility for the cycle (step 8).

In subsequent cycles, the model is populated in a similar way to the first cycle with the prerequisite that that the user defined patient characteristics remain the same as for the first cycle, with the exception of age which increases by one each cycle. As time increases, the survival probability, which is a function of time, decreases.

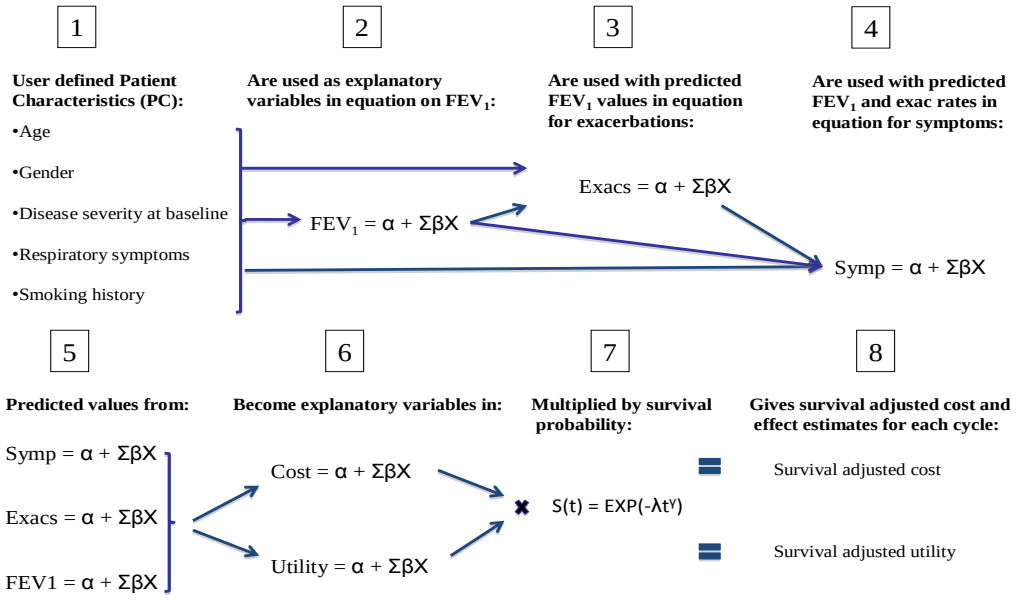

Figure 2 Populating the model

To get costs and QALY estimates, the survival-adjusted cost and utility from each cycle are summed and the mean value derived (once discounting has occurred). Once all these steps are completed, a fully operational model exists that represents the natural history of COPD for a defined patient population on current treatment: ie a current treatment arm. A 'new treatment' arm is developed in exactly the same way as described above. There were two differences between the 'new treatment' and the current treatment arms; the first is the incorporation of a treatment effect on lung function using the new treatment and the second is different treatment costs are applied to the different arms. The model was run with a lifetime perspective and costs and utility were summed over the duration of the study. A discount rate of 3.5% was applied to both costs and utility.

Treatment effects in the model could be applied to any of the components, nonetheless, a treatment affecting lung function is focussed on within this paper as some treatments for COPD have been shown to affect the decline in lung function.(16) For example one study reported a 10% increase in pre-bronchodilator FEV_1 (≈150ml) over a one year trial.(17) In the new treatment arm of the model, it was assumed that the new treatment caused an immediate and sustained increase in FEV_1 over time of 150ml. This one off increase in lung function was incorporated into the 'new treatment' arm of the model as a dummy variable into the equation for FEV_1. The duration of this effect was investigated, in order to assess the implications on cost effectiveness of a shorter treatment effect.

Treatment costs were estimated based on the expected prescribing of COPD patients following the entrance of the most recent COPD therapies (Seretide, Spiriva and Symbicort) to the market. A mild COPD patient is likely to be prescribed salbutamol and tiotropium at a cost of £493 ($808) per annum. Treatment for moderate COPD is likely to include: salbutamol, tiotropium and Seretide at a cost of £1240 ($2032) per annum. Cost effectiveness statistics (ICERs) were calculated for a cohort containing men aged 55 years with mild COPD at baseline by taking the difference between costs and QALYs in the 'current treatment' arm and those in the 'new treatment' arm. Treatments have different mechanisms of action that may impact on one or more of the components of COPD (lung function, exacerbations, symptoms). The treatment effect on lung function applied to the model was used to check for any spill over effects onto the other components within the model, for example on reducing exacerbations and/or improving symptoms.

The ICER was found by calculating the difference between the costs and QALYs in the 'new treatment' arm to those in the 'current treatment' arm. Deterministic analyses were conducted around the user defined characteristics of: age, sex, symptoms,treatment duration and disease severity, keeping all else the same and for each, ICERs were calculated. Age entering the model was changed from 55 years to 65 years; symptoms was changed to no symptoms; sex was changed from male to female (accordingly height was changed from 175 cm to 162 cm); disease severity was changed from mild to moderate; and the impact of a three year treatment duration was assessed. In this final analysis, 'new treatment' costs were assumed to occur for the first three years, after which time they returned to 'current treatment' cost. The model was built in the software package, Microsoft Excel™.

Results

Regression Equations

Lung function

The coefficients from the OLS regression on FEV_1 are shown in equation 3. All of the explanatory variables offered to the model were statistically significant ($p<0.001$) with the exception of over 10 pack years and ex-smoker, which had large p-values of 0.610 and 0.383 respectively ($R^2=0.89$). Whilst statistically insignificant, these explanatory variables were retained so that a NICE COPD cohort could be defined within the economic model. The equation shows that for each year that passes, and as age increases by one, FEV_1 declines by 20ml. Women have a lower lung function than men by, on average 380ml, *ceteris paribus*. People with respiratory symptoms have, on average, 50ml less lung capacity than those without respiratory symptoms. Disease severity at baseline is a categorical value. Compared to people with FEV_1 % predicted ≥80, the equation shows that those with mild COPD had a smaller lung function by 0.6 litres, those with moderate COPD by 1.2 litres less and those with severe COPD by 1.6 litres.

Equation 3 Prediction equation for FEV_1

$$FEV1(l) = -0.016 + 0.022 \times height - 0.022 \times age - 0.381 \times sex - 0.005 \times over10 + 0.009 \times exsmoker - 0.050 \times symptoms - 0.594 \times mild\ COPD - 1.173 \times moderate\ COPD - 1.610 \times severe\ COPD$$

Exacerbations

Major Exacerbations

The negative binomial model was found to be more appropriate for modelling major exacerbations, than the Poisson model: the probability these data would be observed conditional on alpha being 0 (assumption for Poisson model) is close to zero with a $\chi^2=$ 193.87, and an alpha value within the equation of 3.4. The coefficients from the negative binomial model are shown in equation 4. The variables ex-smoker and sex were not statistically significant in predicting the rate of major exacerbations and were therefore excluded from the analyses. The rate of exacerbations from the negative binomial model is equal to the exponential of the linear equation plus the offset term as shown in equation 4. As the cycle lengths are one year, the value for the offset term is one.

Equation 4. Prediction equation for rate of major exacerbations

$$Rma = e^{(-5.286+0.023\times age+0.599\times breat\ hless-1.524\times FEV1\%\ predicted\ +0.621\times UK+1)}$$

Minor Exacerbations

The prediction equation for minor exacerbations was developed in the same way as the prediction equation for major exacerbations. In the equation for minor exacerbations, age was found to be statistically insignificant in the prediction of minor exacerbations and so was excluded. The remaining explanatory variables: breathless, FEV_1% predicted and UK were seen to be statistically significant ($p<0.001$) and are shown below in equation 5.

Equation 5. Prediction equation for rate of minor exacerbations

$$Rmi = e^{-1.983+0.451\times breat\ hless-1.552\times FEV1\%\ predicted\ +0.880\times UK+1}$$

Symptoms

A GLM model with Gaussian family and identity link (OLS) was found to fit the data well. The prediction equation from the regression is shown in equation 6 below. Major exacerbations, sex, FEV_1 % predicted, being an ex-smoker, based in the UK and having breathlessness at baseline were all statistically significant in the prediction of SGRQ symptoms score. The equation shows that: a major exacerbation increases the symptoms score by 6.1 points; a 1% increase in FEV_1% predicted lowers the SGRQ symptoms score by -0.21 (FEV_1% predicted scale is 0-1); females have a higher symptoms score by on average 2.4; being an ex-smoker compared to a smoker lowers the symptoms score by 7.9 and a person with breathlessness has a higher SGRQ score by 7.4, compared to somebody without breathlessness. Age was excluded from the equation.

Equation 6 Prediction equation for symptoms

$$SGRQ\ symptom = 68.435 + 6.10 \times major\ exac + 2.382 \times sex - 21.301 \times FEV_1\%\ pred - 7.041 \times exsmoker + 7.870 \times UK + 7.365 \times breathless$$

EQ-5D utility

The GLM prediction equation for EQ-5D was fit with a Gaussian family and identity link. Equation 7 shows the resulting model. Major exacerbations within the last year, FEV_1 % predicted, SGRQ symptoms scores, breathlessness at baseline, UK and sex were all found to be statistically significant in the prediction of EQ-5D utility. Age and being an ex-smoker at baseline were not found to be statistically significant and were excluded from the regression model. Because the analysis was conducted using EQ-5D decrement, in order to generate EQ-5D scores, the predicted score was subtracted from 1 as shown in the equation above. For each major exacerbation, EQ-5D utility decreases by 0.053, people with respiratory symptoms at baseline have worse EQ-5D utility and women tend to have worse utility scores than men.

Equation 7. Prediction equation for EQ-5D utility

$$\mathbf{1 - EQ - 5D = -0.003 + 0.053 \times major\ exac - 0.056 \times FEV_1\%\ predicted + 0.004 \times SGRQ\ symptoms + 0.049 \times UK + 0.087 \times breathless + 0.031 \times sex}$$

Cost

The Gaussian family and identity link were found to fit the data well for predicting cost. Major exacerbations, minor exacerbations, age, SGRQ symptoms score, FEV % predicted were statistically significant in the prediction of 'other costs'. From equation 8 it can be seen that a major exacerbation is estimated to cost $2498 and a minor exacerbation, $330. On average, increasing age was associated with an increasing cost burden of $5 year on year. For every one point increase in symptoms score (associated with deterioration in health) an extra $1.50 is added to the cost burden. A 1% increase in FEV_1% predicted is seen to be associated with a $267 reduction in 'other costs'.

Equation 8. Prediction equation for cost

$$Cost = -150.835 + 2497.836 \times major\ exac + 330.223 \times minor\ exac + 5.376 \times age + 1.480 \times SGRQ\ symptoms - 267.176 \times FEV_1\%\ predicted$$

Survival

The Weibull model for survival is shown below. Respiratory symptoms, a smoking history, FEV_1 % predicted, age, sex and ex-smoker were all found to be statistically significant in the prediction of survival ($p<0.001$). The natural log of lambda is the linear predictor of covariates as shown in equation 9. This enters the survival function using equations 10, where gamma (=1.823) was given from the output of the model.

Equation 9. Prediction equation for survival

$$ln\lambda = -9.700 - 0.362 \times sex - 0.008 \times FEV_1\%\ predicted + 0.078 \times age + 0.455 \times over10 - 0.276 \times exsmoker + 0.263 \times symptoms$$

Equation 10. Weibull survival model

$$S(t) = EXP(-\lambda t^{1.827})$$

Survival adjusted EQ-5D utility and cost

Survival adjusted EQ-5D utility and total costs were estimated using the Kaplan-Meier sample average estimator.(18) For each interval (one year within the model) the estimator calculates the mean cost and the mean EQ-5D utility for patients alive at the beginning of the interval, weighted by the probability of surviving to the beginning of the interval and sums these values over all the time intervals.(19) Survival adjusted total cost was

calculated for each time period by multiplying the cost by the survival function, and EQ-5D utility was calculated in the same way.

Model development: the 'current treatment' arm

The economic model for COPD was developed by combining the individual regression equations developed above, to predict values for lung function, exacerbations and symptoms and from these to predict costs and utility, which are weighted by survival and are discounted. An example of the resulting model is presented in table 2 for 55 year old men with NICE diagnosed mild COPD, undergoing current treatment. The model is presented in full over a lifetime perspective with specified patient characteristics including: ex-smoker, over 10 pack years, presence of respiratory symptoms and based in the UK.

From the table it can be seen that as age increases, FEV_1 decreases year on year, as does predicted FEV_1 and FEV_1 % predicted and lung function. FEV_1 % predicted was 66% at baseline, falling to 62% by 35 years of follow up. Symptoms are seen to worsen over time. Symptoms score was 62.9 at baseline, rising to 64.3 over the 35 year follow up. The rate of minor exacerbations increased slightly over time from 0.51 to 0.54 exacerbations per year. The rate of major exacerbations more than doubled from 0.06 to 0.14. EQ-5D utility was almost constant over time, starting at 0.64 and falling to 0.63 from the 19th year of the model. Treatment costs were assumed to be constant over time. 'Other costs' were seen to increase over time, with starting 'other costs' of $379, rising to $787. Total costs are equal to the sum of treatment cost and 'other costs'. The survival probability was 0.07 at 89 years. Costs and QALYs after discounting and survival adjustment, are shown in bold in the bottom right hand corner of table 2 and are: 7.72 QALYs and $7710.

Model development: the 'new treatment' arm

Applying a treatment effect and associated costs of a new treatment to the current treatment arm of the model gave the 'new treatment' arm of the model, and in table 3 is shown representing 55 year old men with mild NICE diagnosed COPD taking a 'new' treatment which affects lung function. The lifetime costs and QALYs for the new treatment are shown in the bottom right hand corner of table 3 and are $15 164 and 7.94. A new treatment which improves and sustains lung function by 150ml compared to current treatment leads to improved HRQoL in that more QALYs are gained compared to current treatment, but at higher cost. Compared to current treatment, the ICER is £22 888 ($34 300) per QALY in the mild group. Based on these ICERs, it is likely it is likely that the treatment would be accepted for use in the UK NHS for the management of mild (NICE diagnosed) COPD.

Table 2. Current treatment arm of the economic model, men aged 55 yrs with mild COPD

Time	Age	FEV	pred FEV1	FEV1% pred	Symp	Exac minor	Exac major	EQ-5D utilitys	Tmt cost	Other cost	Total cost	S(t)	S(t)* utility	S(t)*total cost
1	55	2.00	3.02	0.66	62.9	0.51	0.06	0.64	167	379	546	1.00	0.62	525
2	56	1.98	2.99	0.66	62.9	0.51	0.06	0.64	167	388	555	0.99	0.59	511
3	57	1.96	2.96	0.66	62.9	0.51	0.06	0.64	167	398	565	0.97	0.56	495
4	58	1.93	2.93	0.66	63.0	0.51	0.06	0.64	167	408	575	0.95	0.53	477
5	59	1.91	2.91	0.66	63.0	0.51	0.07	0.64	167	418	585	0.93	0.50	457
6	60	1.89	2.88	0.66	63.0	0.51	0.07	0.64	167	428	595	0.90	0.47	436
7	61	1.87	2.85	0.66	63.1	0.51	0.07	0.64	167	438	605	0.87	0.44	414
8	62	1.85	2.82	0.66	63.1	0.51	0.07	0.64	167	448	615	0.84	0.41	392
9	63	1.83	2.79	0.65	63.1	0.51	0.07	0.64	167	459	626	0.80	0.38	369
10	64	1.80	2.76	0.65	63.2	0.51	0.07	0.64	167	469	636	0.77	0.35	347
11	65	1.78	2.73	0.65	63.2	0.51	0.08	0.64	167	480	647	0.73	0.32	324
12	66	1.76	2.70	0.65	63.2	0.52	0.08	0.64	167	490	657	0.69	0.29	301
13	67	1.74	2.67	0.65	63.3	0.52	0.08	0.64	167	501	668	0.65	0.27	279
14	68	1.72	2.64	0.65	63.3	0.52	0.08	0.64	167	512	679	0.61	0.24	258
15	69	1.70	2.62	0.65	63.3	0.52	0.08	0.64	167	524	691	0.58	0.22	237
16	70	1.67	2.59	0.65	63.4	0.52	0.09	0.64	167	535	702	0.54	0.20	217
17	71	1.65	2.56	0.65	63.4	0.52	0.09	0.64	167	546	713	0.50	0.18	199
18	72	1.63	2.53	0.64	63.5	0.52	0.09	0.64	167	558	725	0.46	0.16	181
19	73	1.61	2.50	0.64	63.5	0.52	0.09	0.63	167	570	737	0.43	0.14	164
20	74	1.59	2.47	0.64	63.5	0.52	0.10	0.63	167	582	749	0.39	0.13	148
21	75	1.56	2.44	0.64	63.6	0.52	0.10	0.63	167	594	761	0.36	0.11	133
22	76	1.54	2.41	0.64	63.6	0.52	0.10	0.63	167	607	774	0.33	0.10	119
23	77	1.52	2.38	0.64	63.7	0.53	0.10	0.63	167	619	786	0.30	0.09	107
24	78	1.50	2.35	0.64	63.7	0.53	0.11	0.63	167	632	799	0.27	0.08	95
25	79	1.48	2.33	0.64	63.8	0.53	0.11	0.63	167	645	812	0.25	0.07	84
26	80	1.46	2.30	0.63	63.8	0.53	0.11	0.63	167	658	825	0.22	0.06	75
27	81	1.43	2.27	0.63	63.9	0.53	0.11	0.63	167	671	838	0.20	0.05	66
28	82	1.41	2.24	0.63	63.9	0.53	0.12	0.63	167	685	852	0.18	0.04	58
29	83	1.39	2.21	0.63	64.0	0.53	0.12	0.63	167	699	866	0.16	0.04	51
30	84	1.37	2.18	0.63	64.0	0.53	0.12	0.63	167	713	880	0.14	0.03	44
31	85	1.35	2.15	0.63	64.1	0.54	0.13	0.63	167	727	894	0.12	0.03	38
32	86	1.33	2.12	0.62	64.1	0.54	0.13	0.63	167	742	909	0.11	0.02	33
33	87	1.30	2.09	0.62	64.2	0.54	0.13	0.63	167	757	924	0.10	0.02	29
34	88	1.28	2.06	0.62	64.2	0.54	0.14	0.63	167	772	939	0.09	0.02	25
35	89	1.26	2.04	0.62	64.3	0.54	0.14	0.63	167	787	954	0.07	0.01	21
													7.72	**7710**

Table 3. New treatment arm of the economic model, men aged 55 yrs with mild COPD

Time	Age	FEV	pred FEV1	FEV1% pred	Symp	Exac minor	Exac major	EQ-5D utility	Tmt cost	Other cost	Total cost	S(t)	S(t)* utility	S(t)*total cost
1	55	2.15	3.02	0.71	61.8	0.47	0.06	0.65	808	341	1149	1.00	0.62	1106
2	56	2.13	2.99	0.71	61.8	0.47	0.06	0.65	808	350	1158	0.99	0.60	1066
3	57	2.11	2.96	0.71	61.8	0.47	0.06	0.65	808	359	1167	0.97	0.57	1023
4	58	2.08	2.93	0.71	61.9	0.47	0.06	0.65	808	368	1176	0.95	0.54	977
5	59	2.06	2.91	0.71	61.9	0.47	0.06	0.65	808	377	1185	0.93	0.51	929
6	60	2.04	2.88	0.71	61.9	0.47	0.06	0.65	808	386	1194	0.91	0.48	880
7	61	2.02	2.85	0.71	61.9	0.47	0.06	0.65	808	395	1203	0.88	0.45	829
8	62	2.00	2.82	0.71	61.9	0.47	0.07	0.65	808	405	1213	0.85	0.41	779
9	63	1.98	2.79	0.71	62.0	0.47	0.07	0.65	808	414	1222	0.81	0.38	728
10	64	1.95	2.76	0.71	62.0	0.47	0.07	0.65	808	424	1232	0.78	0.36	679
11	65	1.93	2.73	0.71	62.0	0.47	0.07	0.65	808	434	1242	0.74	0.33	630
12	66	1.91	2.70	0.71	62.0	0.47	0.07	0.65	808	444	1252	0.70	0.30	582
13	67	1.89	2.67	0.71	62.0	0.47	0.07	0.65	808	454	1262	0.67	0.27	537
14	68	1.87	2.64	0.71	62.1	0.47	0.08	0.65	808	464	1272	0.63	0.25	493
15	69	1.85	2.62	0.71	62.1	0.47	0.08	0.64	808	474	1282	0.59	0.23	451
16	70	1.82	2.59	0.71	62.1	0.47	0.08	0.64	808	484	1292	0.55	0.20	411
17	71	1.80	2.56	0.70	62.1	0.47	0.08	0.64	808	495	1303	0.51	0.18	373
18	72	1.78	2.53	0.70	62.1	0.48	0.08	0.64	808	505	1313	0.48	0.17	338
19	73	1.76	2.50	0.70	62.2	0.48	0.09	0.64	808	516	1324	0.44	0.15	305
20	74	1.74	2.47	0.70	62.2	0.48	0.09	0.64	808	527	1335	0.41	0.13	274
21	75	1.71	2.44	0.70	62.2	0.48	0.09	0.64	808	538	1346	0.38	0.12	245
22	76	1.69	2.41	0.70	62.2	0.48	0.09	0.64	808	549	1357	0.34	0.10	219
23	77	1.67	2.38	0.70	62.3	0.48	0.09	0.64	808	560	1368	0.31	0.09	195
24	78	1.65	2.35	0.70	62.3	0.48	0.10	0.64	808	572	1380	0.29	0.08	173
25	79	1.63	2.33	0.70	62.3	0.48	0.10	0.64	808	583	1391	0.26	0.07	153
26	80	1.61	2.30	0.70	62.3	0.48	0.10	0.64	808	595	1403	0.24	0.06	135
27	81	1.58	2.27	0.70	62.4	0.48	0.10	0.64	808	607	1415	0.21	0.05	119
28	82	1.56	2.24	0.70	62.4	0.48	0.11	0.64	808	619	1427	0.19	0.05	104
29	83	1.54	2.21	0.70	62.4	0.48	0.11	0.64	808	631	1439	0.17	0.04	91
30	84	1.52	2.18	0.70	62.5	0.48	0.11	0.64	808	644	1452	0.15	0.03	79
31	85	1.50	2.15	0.70	62.5	0.48	0.11	0.64	808	656	1464	0.14	0.03	69
32	86	1.48	2.12	0.70	62.5	0.48	0.12	0.64	808	669	1477	0.12	0.03	59
33	87	1.45	2.09	0.69	62.6	0.48	0.12	0.64	808	682	1490	0.11	0.02	51
34	88	1.43	2.06	0.69	62.6	0.48	0.12	0.64	808	695	1503	0.09	0.02	44
35	89	1.41	2.04	0.69	62.6	0.48	0.13	0.64	808	708	1516	0.08	0.02	38
													7.94	**15 162**

Although the improvement was applied purely to FEV_1, knock on effects are seen on most of the components within the model, reflecting the interdependence between lung function, symptoms, exacerbations and mortality. Comparing the mild COPD cohort receiving the new treatment (table 3) to those receiving current treatment (table 2), at 89 years of age, symptoms scores are more favourable (62.6 instead of 64.3), there are fewer minor and fewer major exacerbations (0.48 minor exacerbations and 0.13 major exacerbations as apposed to 0.54 minor exacerbations and 0.14 major exacerbations), EQ-5D utility is marginally higher (0.65 compared to 0.64) and other costs are lower ($708 instead of $787), but treatment costs are higher ($808 rather than $167). There is a slight survival advantage in the new treatment arm at age 89 years (0.08 instead of 0.07).

Table 4. Results from analyses on heterogeneity, mild COPD.

		Current treatment		New treatment	
	ICER $ (£)	Cost ($)	QALYs	Cost ($)	QALYs
Base case	34 300 (22 888)	7710	7.72	15 162	7.94
Aged 65 yrs	27 529 (18 371)	6334	5.61	11 784	5.81
Women	24 429 (16 302)	9180	8.04	17 214	8.37
No symptoms	34 125 (22 773)	6305	10.10	15 575	10.34
Tx for 3yrs	13 268 (8854)	7710	7.72	9506	7.86
Moderate	95 004 (63 396)	10 977	6.91	30 618	7.12

Analyses were conducted around the user defined patient characteristics analysis for treatment on lung function. As seen from table 4, there were considerable differences in the cost effectiveness of the same treatment, dependent on user defined patient characteristics. The ICERs for the mild population ranged between £8854 to £63 396 per QALY as shown in table 4. The analyses on women with mild COPD gave lower ICERs than for men, with an ICER of £16 302 compared to £22 888. Using a cohort with no reported respiratory symptoms at baseline slightly reduced the ICERs compared to the base case to £22 773. Restricting treatment duration to three years reduced the ICER per QALY by more than half, from £22 888 to £8854. Changing disease severity to moderate from mild (with expansion in treatment regimen and associated cost) increased the ICER to £63 396 per QALY.

Discussion

In this paper an economic model for COPD was developed, based around the key components of COPD. A model based on a conceptual framework was operationalised, which works and predicts sensible results. The model can be used to assess the cost effectiveness of different types of treatments, which is important because if different treatments can be assessed on the same platform then decisions around cost effectiveness can be standardised.

This model is unique within COPD and breaks the mould for modelling the disease as Markov models have traditionally been employed. It has a number of advantages over earlier models. A variety of people with COPD can be modelled using this model, including those with: mild, moderate and severe disease; presence/absence of respiratory symptoms; and different smoking histories at baseline. A range of different ages can be modelled and men and women enter the model separately. Therefore the uncertainty pertaining to patient level heterogeneity is minimised.

Because of this flexibility the resulting model can assist with the identification of subgroups in which a product is cost effective.

An important advantage of the model over others in COPD is that this is the first to include a specific component for symptoms. Symptoms have a major impact on HRQoL for people with COPD and many treatments for COPD have mechanisms of action that work specifically on alleviating respiratory symptoms. Thus it is important to incorporate symptoms explicitly into the model. The model developed in this chapter allows interdependence to exist between the different components of COPD and is novel in modelling COPD. Lung function, symptoms, exacerbations, survival, costs and utility are all intertwined so that a treatment which specifically works on one component, can have a knock on effect on the other components and this interdependence was clearly demonstrated.

This type of model is demanding in terms of the need for good quality real data on which to derive the regression equations. The availability of the TORCH and the MIDSPAN datasets was of huge importance in enabling this type of model to be pursued and to be developed. The MIDSPAN observational study and the TORCH RCT are complementary types of dataset each with their own strengths and limitations. The benefit of using both types to develop the model is that where one dataset may not provide the information required, such as on long term survival, the other does, so that the resulting model is built on reliable data and is well supported. Because of this, the use of observational data together with RCT data can enhance the external validity of the cost effectiveness study.(20) For model building, the combined usage of such datasets is the gold standard for developing economic models.

The regression models within this paper are developed using data from each of the treatment groups within the TORCH trial, not just the placebo group. This means that data from the treatment group (those randomised to Seretide) in TORCH were included to develop equations for the current treatment arm. Whilst it may be argued that only patients receiving the placebo should form the 'current treatment' arm, this goes against the recommendation that it is current treatment that forms the comparator. It is argued here that whilst at the present time, Seretide may be one of the newest products on the market, it is anticipated that newer products, will soon supersede this. In which case, benefits of new treatment will need to be compared to products currently on the market, which this model represents.

Conclusion

Within this paper, data from an observational study and a RCT were used in a complementary manner in order that equations predicting lung function, exacerbations, symptoms, cost, EQ-5D utility and survival could be obtained. The resulting equations were combined so that an economic model representing the natural history of COPD under current treatment was built. A hypothetical treatment effect was combined into a second arm of the economic model to give a new treatment comparator arm. Costs and effects of current treatment were compared to those from the new treatment to obtain cost effectiveness statistics.

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