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A Probabilistic Cost-Effectiveness Analysis of Asthma Management

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Abstract

Asthma is a chronic-episodic disease characterised by acute, symptomatic episodes of varying severity. We report the development of a Markov model that can be used to estimate the cost-effectiveness of alternative asthma treatments. From an economic perspective, asthma exacerbations ('attacks') are of key importance when they require intervention by a health care professional due to the costs incurred. Due to the undoubted clinical and economic importance of exacerbations, this was a central consideration in the development of the model. Treatment success is assessed as asthma control, a composite measure based on goals defined in world-wide asthma management guidelines. Transition probabilities have been derived from observed clinical trial data and costs were estimated from resource profiles defined for each of the model states. A key aspect of the model is the use of probabilistic sensitivity analysis techniques to examine the uncertainty in the cost-effectiveness results. Distributions were fitted to transition probabilities and to cost input parameters and values were sampled at random from these distributions using a second order Monte Carlo simulation technique. This produced a distribution for incremental cost-effectiveness that was employed to construct 95% quasi-confidence intervals and to construct cost-effectiveness acceptability curves. Finally we present a tentative cost-utility analysis based on attaching utilities to the Markov model states.

1. Introduction

Asthma is a disease that has a considerable economic impact on the patient, healthcare system and society as a whole (Weiss et al, 1992). A disproportionate amount of this burden is a consequence of sub-optimal control (Barnes et al, 1996) which can result in symptoms, exacerbations and a reduction in the health-related quality of life of patients. Treatment strategies that improve asthma control have the potential to improve the quality of life of patients and may reduce the burden of the disease by reducing costs of managing treatment failure.

In order to determine whether asthma treatments are an appropriate use of scarce health care resources, it is necessary to evaluate the benefits of competing treatments in light of their associated costs by undertaking economic evaluations such as cost-effectiveness analysis.

An increasingly common approach to assess the cost-effectiveness of treatment interventions is to use economic modelling techniques. Economic models can be used to extrapolate from clinical efficacy data to assess the economic value of treatments in cohorts of patients. As well as simulating clinical care, economic models provide a framework in which assumptions underlying the analyses can be easily tested, through changes to the input parameters. Importantly, economic models also provide an opportunity to comprehensively explore uncertainty in the results through sensitivity analysis techniques.

Although clinical trial based cost-effectiveness analyses have been widely reported in the literature, there are no widely accepted economic models of asthma. We report on the development of such a model with an emphasis on making the model fully probabilistic in order to capture the effect of important uncertainties in the input parameters.

To illustrate the functionality of the model, results are generated using data from a clinical trial that compared a newly developed asthma treatment, Seretide™ with a well

established alternative treatment option, the inhaled steroid fluticasone propionate. Seretide™ is a combination of fluticasone propionate and a long acting beta-2 agonist, salmeterol.

2. Management of Asthma

2.1 Background

The purpose of an economic model is to accurately and credibly simulate the cost and consequences of a disease and investigate the impact of treatments on these outcomes. In order to develop a model of a disease it is first necessary to understand its natural course, the health states that occur (from a clinical and a health economic perspective) and the potential treatment options that exist.

Asthma is a common, chronic-episodic disease that is characterised by acute, symptomatic episodes of varying severity. Commonly experienced symptoms include wheeze, chest tightness, breathlessness, cough and nocturnal awakening. These symptoms are often accompanied by reduced lung functioning. Many patients feel relatively well between attacks or will have symptoms that whilst troublesome, can be self-managed. From an economic perspective, asthma exacerbations ('attacks') are of key importance when they require intervention by a health care professional due to the costs incurred. Although relatively rare, inpatient hospitalisations are of considerable economic importance due to their high cost. Severe exacerbations requiring hospitalisation are also important from a clinical management point as they are indicative of poor disease control. From the perspective of patients, such events are likely to be distressing and will have implications for their quality of life that may last beyond the acute exacerbation itself.

Due to the undoubted clinical and economic importance of exacerbations, this was a central consideration in the development of the model. From an economic perspective, the clinical setting in which the exacerbation is managed is also of key importance as well as being an indicator of the clinical severity of the event. Hospitalisations for asthma

exacerbations, for example, are more severe events than primary care managed exacerbations.

When patients are not experiencing moderate or severe exacerbation, at any given point in time, they are either likely to be adequately controlled or to be symptomatic at a level that does not require intervention by a health care professional.

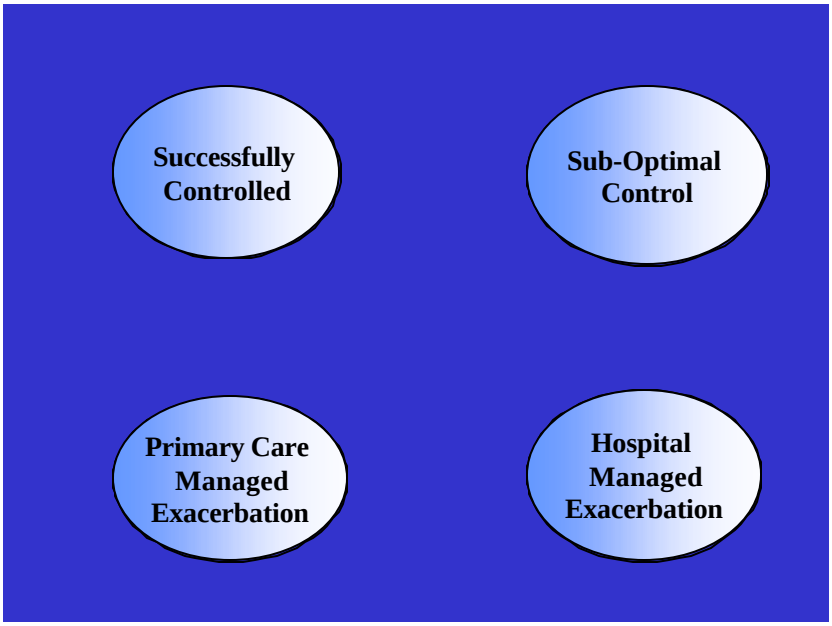
This clinical profile of asthma forms the basis for the framework of health states that are defined in this model, which was developed using Microsoft Excel 97.

2.2 Markov Model for Asthma

2.2.1 Model Health States

In this model, four distinct and mutually exclusive health states have been defined. It is possible for an asthma patient to be in any one of these states at a given point in time. These states (defined below) are Successfully Controlled, Sub-Optimal Control, Hospital Managed Exacerbation and Primary Care Managed Exacerbation (Figure 1)

Figure 1: Asthma Markov Model Health States



Successfully Controlled

Asthma control, which is based on a composite set of criteria that reflect the goals of asthma management, is a key measure of therapeutic outcome. This economic model uses a definition of asthma control that has been established by the Global Initiative for Asthma (GINA). In the GINA asthma management guidelines (GINA, 1998), the level of asthma control is defined in terms of whether patients achieve predefined improvements in a range of measures of treatment efficacy. In this model, the term used to describe the achievement of all GINA criteria is referred to as 'total control'

A second definition of asthma control has also been developed which is termed 'well controlled'. This definition relies on the same parameters that are assessed for total control, but the criteria for success have been relaxed slightly. Use of two definitions of control in this model is important as it is currently unclear whether total control is both realistic or indeed attainable for some patients. It is also possible that some decision-makers may perceive 'well controlled' to be a desirable outcome when determining the value of competing treatments (in other words they may perceive that total control is unnecessary).

As the cycle length for this model is one week, the health state based on treatment success in this model has been termed a 'successfully controlled week'. In order for patients to have their week classified as 'successfully controlled', the following criteria must be satisfied: -

'Total control' will be defined as meeting the following criteria, assessed on a weekly basis:

All of the following criteria:

- no symptoms
- no rescue salbutamol use
- $\geq$ 80% predicted am PEF every day
- no night-time wakening due to asthma
- no emergency visits

- no exacerbations
- no treatment related adverse effects enforcing a change in asthma therapy

'Well-controlled' asthma will be defined as meeting the following criteria, assessed on a weekly basis:

1. **Two** or more of the following criteria:
   - symptoms on no more than two days with a symptom score of greater than 1
   - no more than 2 days of rescue salbutamol use, up to a max. of 4 occasions (8puffs) per week
   - ≥ 80% predicted am PEF every day **AND**

2. all of the following criteria:
   - no night-time wakening due to asthma
   - no emergency visits
   - no exacerbations
   - no treatment related adverse effects enforcing a change in asthma therapy

Cycle length is an important consideration in a Markov model. The chosen cycle length should represent a realistic timeframe in the disease under study, during which potential changes in a patient's clinical status may occur. Although cycle times of months or years may be applicable in some diseases, the chronic-episodic nature of asthma demands a much shorter cycle as patients typically deteriorate over a relatively short space of time and may improve equally as quickly. In this model, the cycle length was chosen to be one week as it was felt that a patients clinical status can realistically change from week to week, whilst it is unlikely for example that a patient would require two discreet hospitalisations for asthma within the same seven day period.

Hospital Managed Exacerbation

This health state is defined by the need for patients to be admitted to hospital as an inpatient for the management of an asthma exacerbation. Patients who have an exacerbation requiring inpatient management remain in this health state for the entire week before they are able to transition to other potential health states

Primary Care Managed Exacerbation

This health state is defined as the need for patients to be managed by a health care professional for the treatment of an asthma exacerbation in an outpatient setting. As this is designed to be an international model, the exact setting for the management of this exacerbation will vary. In the UK for example, the most likely management setting is General Practice, whereas in other countries, such management may be more commonly undertaken in hospital outpatient clinics.

Sub-Optimal Control

In any given week, patients may be in a health state that is neither 'successfully controlled' nor will they be experiencing an exacerbation as defined in this model. These asthma patients will fail one or more of the criteria described above that are required for a patient to be classified as 'controlled'. These patients are classified in the model as 'sub-optimally controlled' for that particular week.

Hierarchy of Health States

It is theoretically possible for a patient to be in more than one state in any given week. For example, a patient who has a hospitalisation for asthma will undoubtedly be 'sub-optimally controlled' also. Therefore, it is necessary to set up a hierarchy of states so that where more than one state occurs in any given week, it is clear to which health state that patient is assigned. Exacerbations are the most important events in terms of asthma control and costs and their occurrence is of prime importance. The hierarchy has therefore been determined to be: -

Hospital exacerbation > Primary Care Exacerbation > Unsuccessfully treated > Successfully treated.

Consideration of an Absorbing State

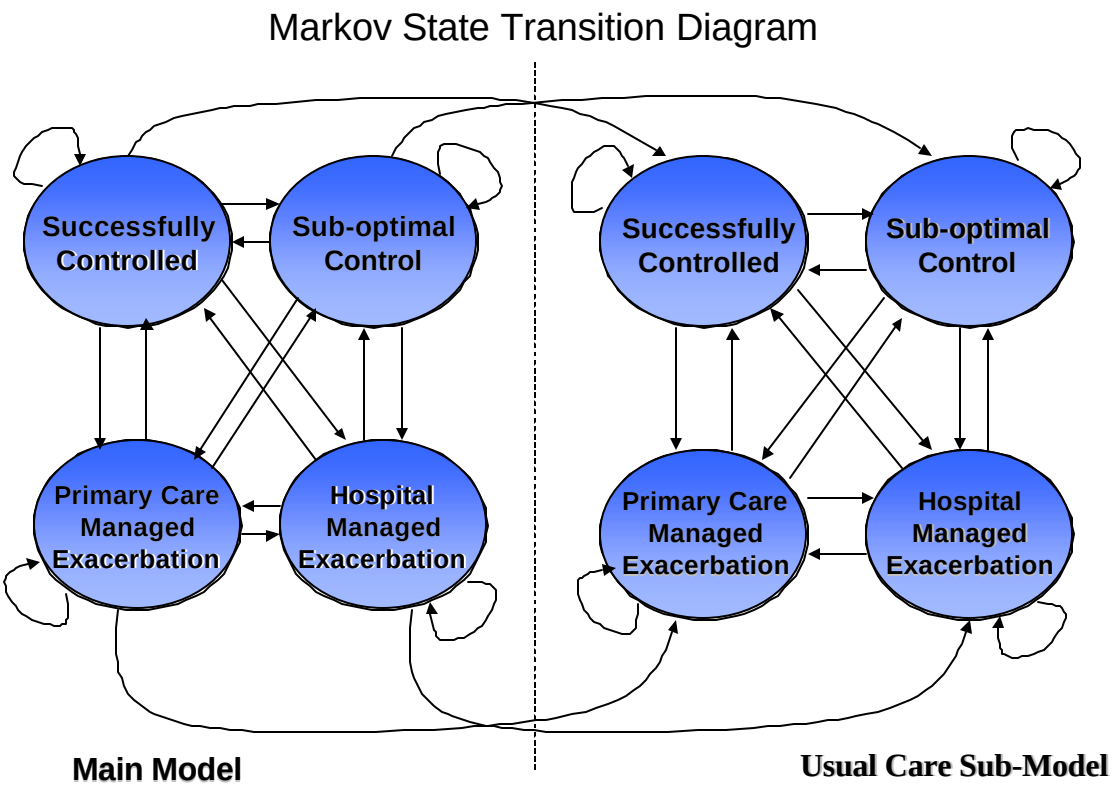
Many Markov models have an absorbing state, which once entered into, patients cannot return from (for example 'death'). Inclusion of an absorbing death state is not relevant to this model for two reasons. Firstly, the underlying level of asthma-related mortality is

extremely low and it is controversial to suggest that asthma-related mortality increases with age. Secondly, this model evaluates cost-effectiveness over a short term period and so asthma-related deaths are extremely unlikely during the time-frame under study. Although this model does not have an absorbing state, it does allow for patients to discontinue treatment ('treatment failure'). This is similar to an absorbing state in that once patients enter 'treatment failure' they cannot return to the original treatment. Reasons for treatment failure could include repeated exacerbations, lack of satisfaction with the level of control and adverse events.

When patients discontinue treatment it is important to recognise that they do not simply disappear but will receive other asthma treatments and continue to accrue costs and benefits. From an economic perspective, these patients cannot be ignored and should be accounted for in the calculation of cost-effectiveness. As a result, in this model, 'treatment failure' is essentially a 'virtual' health state. Patients entering 'treatment failure' immediately enter a 'usual care' submodel, from which they cannot return to the main model. This is identical to the main Markov model in terms of health states, but the transitions between these health states will be determined by their new treatment. The assumption is that once asthma patients enter 'usual care' they remain there until the end of the evaluation period and are not allowed further drop out. Patients re-enter the usual care submodel in the same state they were in prior to drop-out. Thus, if people were in the primary care exacerbation health state in the cycle prior to dropping out of the model by entering the treatment failure state, they are assigned to the primary care exacerbation health state in the submodel.

The potential transitions of patients through the Markov model is illustrated in the state transition diagram (Figure 2).

Figure 2. Asthma Markov Model State Transition Diagram



2.2.2 Model Transitions

Movement between the different Markov health states illustrated in Figure 2 are determined by the natural course of the disease and the ability of the treatment to influence this course. Transitions between health states will be determined by transition probabilities and it is these probabilities that will differ according to the treatment taken.

Transition probabilities currently used to populated the model have been derived from observed clinical trial data. In order to calculate transition probabilities, the study data are chronologically separated into weekly blocks for each patient in each treatment arm. For each week, patients are assigned to one of the four possible health states according to the hierarchy described above.

Firstly, it was determined whether a patient suffered an exacerbation that required management as an inpatient in hospital in each week. This data was routinely collected in the trials, either in the resource utilisation section of the trial case report form or in the serious adverse event form. If there is evidence of a hospitalisation, the patient was assigned to the hospital exacerbation health state for that week.

If no hospitalisation was identified in a given week, it was determined whether the patient had suffered an exacerbation managed in primary care. These data were again collected as part of the clinical trial. During those weeks in which a primary care exacerbation was identified, patients were assigned to the primary care managed exacerbation health state.

Assuming that no exacerbations were recorded in a given week, the weekly level of asthma control was established using the definition of control outlined in Section 2.2.1. All data necessary to establish control were collected in the trial. Symptoms, lung function, nocturnal awakenings and use of rescue salbutamol were captured in the daily diary card, whilst exacerbations and need for change in treatment were collected in the case report form. Patients who met all criteria for asthma control were classified as 'successfully controlled' for that week. If any criteria were not met, then the week was classified as 'sub-optimally controlled'.

Finally, it was necessary to determine whether a patient had 'treatment failure' in any given week. Transition probabilities for 'treatment failure' were determined by examining whether patients prematurely withdrew from the trial and discontinued study treatment. If patients were withdrawn prior to the end of the study, they were immediately entered into the usual care sub-model.

By applying these decision rules, it was possible to profile each patient's health states during each week of the trial. From these individual patient profiles it is straightforward to establish the transitions from the existing health state to the other potential health states in the model. Across each treatment arm, it is possible to produce counts of the transitions that occurred between the health states in the model across the trial (Table 1).

Table 1. Tabulation of Clinical Trial Transitions*

To From	Health State A	Health State B	Health State C	Total
Health State A	Xa	Xb	Xc	Xt = Xa+Xb+Xc
Health State B	Ya	Yb	Yc	Yt =Ya+Yb+Yc
Health State C	Za	Zb	Zc	Zt = Za+Zb+Zc

*Variables Xa to Zc are the counts of transitions observed in the clinical trial

These observed data are used to calculate the transition probabilities as illustrated in Table 2.

Table 2. Transition Probability Matrix

To From	Health State A	Health State B	Health State C	Total*
Health State A	Xa/Xt	Xb/Xt	Xc/Xt	1
Health State B	Ya/Yt	Yb/Yt	Yc/Yt	1
Health State C	Za/Zt	Zb/Zt	Zc/Zt	1

*probability of transitions from health states must = 1

As well as reporting transition probabilities based on observed data, the standard errors of the probabilities were also calculated for sensitivity analyses. Observed transitions and the probabilities derived from study data are presented in Tables 3 to 6. Transition probabilities were obtained from a 12 week, randomised, double-blind, double-dummy parallel group clinical trial of Seretide™ (a combination of fluticasone propionate 100mcg and salmeterol 50mcg) in a single dry powder inhaler (Diskus™) and fluticasone propionate 100mcg via a Diskus™ inhaler. For the purpose of this illustration, costs and transition probabilities for the fluticasone propionate arm are used in the 'usual care' sub-model due to the lack of good data with which to estimate 'usual care' transition probabilities. We also use the assumption that economic evaluations of new treatments

should be compared to the standard of care. Here, fluticasone propionate is considered to be the current standard of care.

Table 3. Observed Transitions with Fluticasone Propionate

To From	Successfully Controlled	Sub-optimal control	Primary care exacerbation	Hospital exacerbation	Treatment failure
Successfully cont.	85	19	0	0	3
Sub-optimal cont.	29	759	0	5	19
Primary care exac.	0	0	0	0	0
Hospital exac.	0	4	0	1	0
Treatment failure*	0	0	0	0	156

*denotes entry into usual care sub-model

Table 4. Observed Transitions with Seretide™

To From	Successfully Controlled	Sub-optimal control	Primary care exacerbation	Hospital exacerbation	Treatment failure
Successfully cont.	252	40	0	1	1
Sub-optimal cont.	69	638	0	4	13
Primary care exac.	0	0	0	0	0
Hospital exac.	0	4	0	0	1
Treatment failure*	0	0	0	0	81

*denotes entry into usual care sub-model

Table 5. Fluticasone Propionate Transition Probabilities

To From	Successfully Controlled	Sub-optimal control	Primary care exacerbation	Hospital exacerbation	Treatment failure
Successfully cont.	0.7944 (0.039)	0.1776 (0.037)	0	0	0.0280 (0.016)
Sub-optimal cont.	0.0357 (0.007)	0.9347 (0.009)	0	0.0062 (0.003)	0.0234 (0.005)
Primary care exac.	0	0	0	0	0
Hospital exac.	0	0.8000 (0.179)	0	0.2000 (0.179)	0
Treatment failure	0	0	0	0	1.0000

figures in brackets are standard error values

Table 6. Seretide™ Transition Probabilities

To From	Successfully Controlled	Sub-optimal control	Primary care exacerbation	Hospital exacerbation	Treatment failure
Successfully cont.	0.8571 (0.020)	0.1361 (0.020)	0	0.0034 (0.003)	0.0034 (0.003)
Sub-optimal cont.	0.0953 (0.011)	0.8812 (0.012)	0	0.0055 (0.003)	0.0180 (0.005)
Primary care exac.	0	0	0	0	0
Hospital exac.	0	0.8000 (0.179)	0	0	0.2000 (0.179)
Treatment failure	0	0	0	0	1.0000

figures in brackets are standard error values

It is clear from these data that there are problems associated with calculation of a number of probabilities. Straight conversion of the observed data would yield a probability of zero for a number of potential transitions. To illustrate this problem, based on the above data, the model would not allow any patients to pass from a primary care exacerbation health state to successfully controlled. In the real world, this transition is certainly possible, as are all the other potential combinations described above.

We are currently considering possible solutions to this problem. The first option would be to assume that each potential transition will have at least one occurrence during the model evaluation period. Therefore all zero data in tables 3 and 4 (with the exception of 'treatment failure' transitions to the 'usual care' sub-model) would be given a default value of 1. This will yield non-zero probabilities for all potential transitions. The impact of entering non-zero data on the model outputs will be evaluated prior to taking a decision on the validity of this approach. One potential problem with defaulting the observed transitions to 1 is that the probability resulting from this transition will vary across the health states. In model health states that see relatively few transitions such as hospital exacerbations, assuming one observed transition will produce a higher transition probability than in more commonly populated health states such as successfully controlled. Whether this is a critical driver of the results remains to be seen.

Another potential approach that is being investigated is to supplement missing data with expert opinion. Respiratory physicians would be asked to estimate the probability of transitioning between health states and their values used to complete the transition

matrix. This process could also potentially be carried out using observational data from databases, although it remains to be seen whether any potential sources contain the richness of information that would be required for this exercise.

2.2.3 Health Outcomes

The measure of health outcome in this model is the proportion of successfully controlled weeks in each treatment arm (as defined above). The three other health states in the model are, by their definition, assigned zero benefit for the purpose of the cost-effectiveness analysis.

2.2.4 Resource Use and Costs

All four of the Markov model health states have an associated resource utilisation and hence healthcare cost associated with them. Costs are considered from the perspective of the healthcare system. Each patient will incur the cost associated with their current health state for each cycle of the model. The exact resource use and cost components of each state, together with their values are described below in Table 7.

Table 7: Resource Use and Costs Associated with Model Health States

Health State	**Resource Use**	**Seretide™ weekly health state cost (£)**	**Fluticasone propionate weekly health state cost (£)**
Successfully Controlled Week	Study and rescue asthma medication utilisation	8.52	3.03
Sub-optimally controlled week	Study and rescue asthma medication utilisation	728.52	723.03
Hospital Managed Exacerbation	Asthma drug utilisation plus inpatient hospitalisation for asthma exacerbation	20.52	15.03
Primary Care Managed Exacerbation	Asthma drug utilisation plus physician consultation	8.52	3.03

3. Probabilistic Evaluation of Asthma Management

3.1 Background

In order to ensure the credibility of the model, it is essential that a comprehensive set of sensitivity analyses are undertaken to test the robustness of results to underlying assumptions and to examine the distribution of the results around the point estimate cost-effectiveness analysis. Markov models provide an excellent framework in which to explore uncertainty in the data through the use of simulation techniques. The primary method of handling uncertainty in this model is Probabilistic Sensitivity Analysis (PSA) using a second-order Monte Carlo simulation technique (Critchfield et al. 1986; Doubilet et al. 1985; Briggs, 2000).

Using this methodology, it is possible to simultaneously and randomly vary the plausible ranges of multiple model parameters and to test the impact of variability in these values on model results. By sampling from the plausible range of parameter values and repeating the technique a large number of times the distributions of cost and outcome values are obtained. Subsequently, the distribution of the cost-effectiveness ratios can be presented and quasi 95% confidence intervals constructed. In order to carry out the PSA it is necessary to identify the distribution of model parameters, from which the PSA can sample. Model parameters that require fitting of distributions are the transition probabilities and health state costs.

3.2 Fitting Distributions

3.2.1 Transition Probabilities

Although transition probabilities used in this model are derived from observed data, there is uncertainty surrounding the true values for these parameters. In order to fit a distribution to the transition probabilities it is necessary to understand the nature of the parameter. Transition probabilities must be positive and are continuous parameters

constrained between zero and one. As a result transition probabilities from one state of the model to another were assumed to follow a beta distribution.

In order to fit the parameters of the beta distributions the method of moments technique was used (Pratt et al. 1995). The observed proportions and standard errors from the clinical trial transitions (see Tables 5 & 6) were matched to the formulae for the mean and standard error of the beta distribution and the resulting equations were solved simultaneously for the parameters.

3.2.2 Costs

In this model, there is a degree of uncertainty around the costs of managing exacerbations in primary and secondary care and so it is necessary to fit a distribution to these variables to permit random sampling in the PSA. By contrast, drug costs are fixed by the manufacturers price and together with the dosing strategies these costs are the intervention under evaluation. Therefore, it makes no sense to fit distributions to these parameters and they are instead treated as given.

Costs of primary and secondary care exacerbations are assumed to follow a gamma distribution as they are constrained at the lower limit by zero and must be a positive value. The costs from Table 7 were assumed to represent mean values. No standard errors were available, so we made the assumption that all costs have a coefficient of variation (ratio of the standard error to the mean) of 0.1. Method of moments was then used to obtain the parameters of the Gamma distribution.

4. Presenting Results

4.1 Markov Model Results

Using baseline parameters, Markov model results indicate that Seretide™ results in a higher proportion of successfully controlled weeks (32% vs. 16%) and higher mean

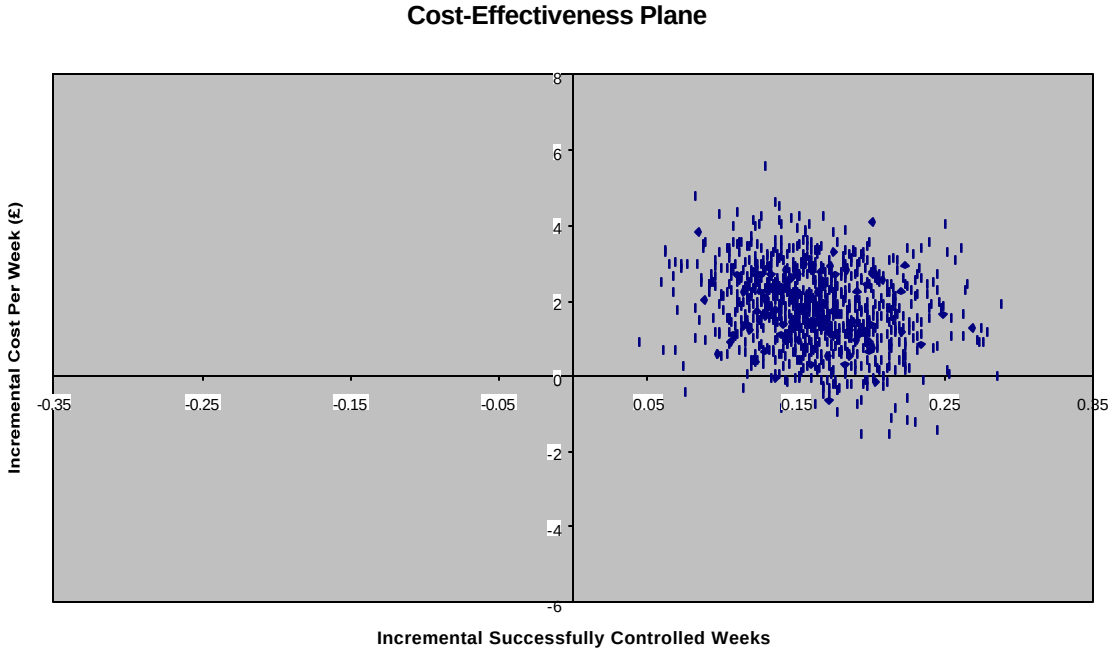
weekly direct asthma management costs (£10.82 vs. £8.87). The average incremental cost per successfully controlled week with Seretide™ was £11.85.

This point-estimate result gives no indication of the uncertainty around this result, therefore, using the methodology outlined in section 3, a Monte Carlo simulation was undertaken to probabilistically explore uncertainty around the incremental cost-effectiveness ratio.

4.2 Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis are graphically represented in Figure 3, which shows the results of 1000 simulation on the cost-effectiveness plane. The results show that for the majority of simulations there is an incremental increase in cost as well as incremental benefits associated with Seretide™.

Figure 3. Monte Carlo Simulations

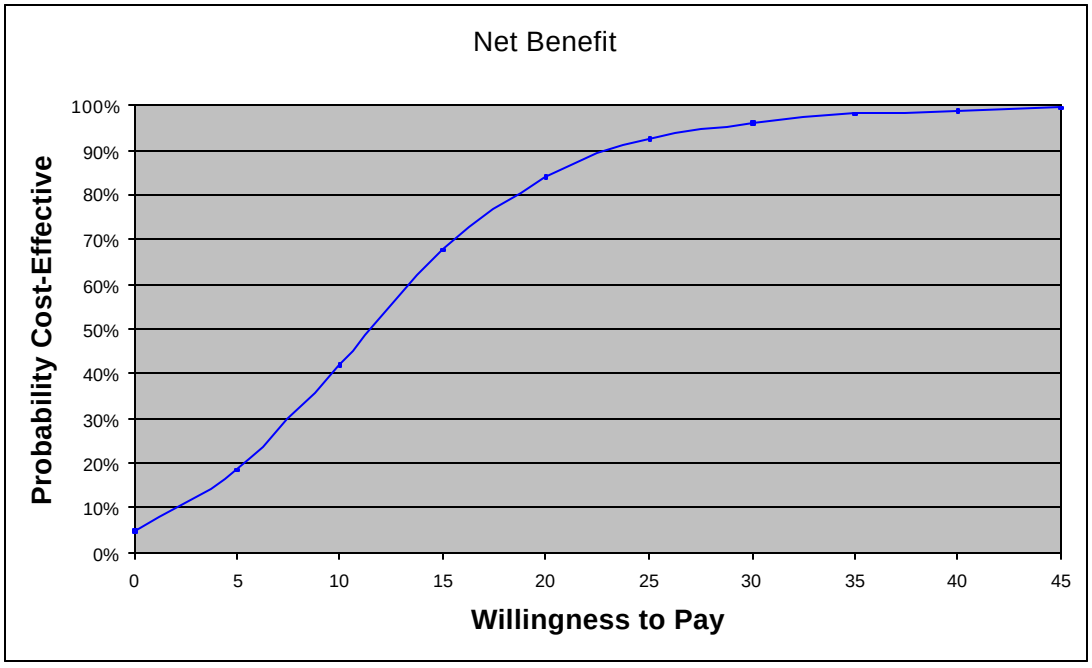


Whilst the majority of simulations are found in the top right hand quadrant of the cost-effectiveness plane, a small proportion fall below the x-axis into the bottom right hand quadrant which would indicate dominance for Seretide™ compared to fluticasone propionate. The importance of these simulation are realised when quasi-95% confidence intervals are calculated for the incremental cost-effectiveness ratio.

By taking the 97.5th and 2.5th percentiles of the 1000 simulations, the non-parametric confidence intervals can be calculated. These will vary slightly each time the Monte Carlo simulation is run, but based on the results from these simulations the 95% CIs are £32.97 to -£1.22. This indicates that the upper estimate of the ICER is an additional £33 per asthma controlled week with Seretide™, whilst the lower limit indicates that Seretide™ is the dominant strategy.

To further understand the uncertainty around the point-estimate incremental ratio, the model calculates a net benefit statistic for each of the 1000 simulations. The decision-maker willingness to pay value (λ) can be varied in the model, allowing a cost-effectiveness acceptability curve (van Hout et al. 1994; Stinnett and Mullahy, 1998) to be calculated (Figure 4).

Figure 4. Cost-effectiveness Acceptability Curve



The cost-effectiveness acceptability curve indicates that we can be 90% certain that Seretide™ is the most cost-effectiveness strategy if decision-makers are willing to pay approximately £23 per additional asthma controlled week. The flexibility of the model means that the implications of any changes to the assumptions or values of the input parameters on the cost-effectiveness results can be easily evaluated. The ability to present the cost-effectiveness plane and calculate both quasi-95% confidence intervals and a net benefit curve means that this model can comprehensively explore uncertainty in the estimation of the cost-effectiveness of alternative asthma treatments.

6. A Tentative Cost Utility Analysis

As stated in the introduction, more effective asthma treatments have the potential to maximise societal health gain and improve the health-related quality of life of asthma patients. A current limitation of the model is that quality of life based outcomes are not included in the model. As an acknowledgement of the potential value of such outcomes from both a decision-making and therapeutic point of view, we present here a 'tentative' cost-utility analysis based on the clinical trial data used in this paper. This data is provided purely as an illustration of the future applicability of the model.

To attain an incremental cost per QALY, two approaches were used. Firstly, an EQ-5D mapping exercise was used, whereby an author of this paper (MP) who has clinical experience of asthma completed the questionnaire so as to represent the expected health status of patients for each day within a given health state. The mean utility value across each day in each health state, derived from EQ-5D scores has been used as the valuation of the four health states in the model (Table 8).

Table 8. Tentative EQ-5D Health State Valuations

Health State	Mean Health State Utility Value
Successfully Controlled Week	1.00
Sub-Optimally Controlled Week	0.88
Primary Care Exacerbation	0.78
Hospital Exacerbation	0.62

Using this approach, the mean incremental cost per QALY for Seretide™ treatment compared to fluticasone propionate was calculated to be £4,035 (Table 9). Although this figure is tentative, in terms of generally accepted thresholds for QALY gains, Seretide™ would appear to be a highly cost-effective intervention.

Table 9. Tentative Incremental Cost per QALY (EQ-5D)

Treatment	Cost per patient per year (£)	QALY	Incremental cost (£) per QALY
Seretide™	562	0.91	4035
Fluticasone propionate	461	0.88	

The second approach taken was to use the only published data that has attempted to calculate utility values for asthma health states (Stahl et al, 1999). Using a rating scale, asthma patients were asked to rate three health states: -

- **Severe exacerbation**: Requirement of oral steroids or the feeling that lung function had decreased a lot.
- **Mild exacerbation**: Increased use of rescue medication, night time awakenings and a small decrease in lung functioning
- **Asthma status today**

Clearly there are problems with directly mapping values from this study to the model health states, primarily because the exacerbation definitions used by Stahl et al. are

milder than similar states defined in this model. However, as an illustration, the utility value for 'severe exacerbation' (0.26) was used for the hospital managed exacerbation, the utility value for 'mild exacerbation' (0.62) was used for the primary care managed exacerbation' whilst the asthma status today value (0.81) was used for sub-optimal control. Asthma control was assigned a utility of perfect health (1.0). Using these values the incremental cost per QALY for Seretide™ compared to fluticasone propionate was £2719 (Table 10).

Table 10. Tentative Incremental Cost per QALY (Rating Scale Approach)

Treatment	Cost per patient per year (£)	QALY	Incremental cost (£) per QALY
Seretide™	562	0.86	2719
Fluticasone propionate	461	0.82	

This analysis illustrates the potential to demonstrate the cost-effectiveness of asthma treatments using preference based measures of health, although credible valuations of these health states and an understanding of the distribution of the data are required if this is to be achievable, particularly within the frame work of a probabilistic sensitivity analysis. Nevertheless, the mechanics of the model have the potential to allow easy valuation of health gain associated with competing asthma treatments so as to better inform health care decision-making.

5. Discussion/ Future Directions

This model represents one of the first probabilistic sensitivity analyses of alternative asthma treatments and is a framework within which cost-effectiveness of asthma management strategies and the inherent uncertainty within the results can be evaluated.

Currently, transition probabilities have been directly derived from short-term clinical trials. This can be considered both as a strength and a weakness of the model. It is a

strength in as much as the probabilities in the model are based on directly observed data and the fact that probabilities derived from short term trials are acceptable in a disease that is chronic-episodic rather than a gradually deteriorating health status leading to death that is more typical of chronic diseases. Transition probabilities based on observed data have more credibility than those derived from expert opinion or by extrapolation from literature values. Derivation of transition probabilities in this manner could also be considered a weakness is so far as clinical trials do not adequately reflect real world conditions. This is an acknowledged limitation and in the future, attempts will be made to populate the model with data from real world source such as observational databases.

Another area requiring further research is a better understanding of the value decision-makers place on improvements in asthma outcomes. At present, decision-maker willingness to pay for improvements in asthma control are unknown and only technical efficiency questions can be answered. By using a generic measure of effectiveness such as quality adjusted life-years, the model could be used to answer questions concerned with allocative efficiency, which have more applicability for health care decision-makers since asthma treatments can be compared directly with other uses of scare health care resources. Once more information has been obtained on potential utility values for the health states of the model it should be possible to specify distributions for those utitilty values and provide a fully probabilistic cost-utility model.

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