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A STOCHASTIC APPROACH TO THE PHARMACOTHERAPEUTIC MANAGEMENT OF CHRONIC MODERATE ADULT ASTHMA

by

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September, 1995

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The therapies compared were: 1) inhaled beta$_2$-agonist agent and inhaled cromolyn; 2) inhaled beta$_2$-agonist agent and an inhaled corticosteroid agent; 3) inhaled beta$_2$-agonist agent and sustained-release theophylline.

The combined therapy of an inhaled beta$_2$-agonist agent and an inhaled corticosteroid agent had the lowest cost-effectiveness ratio of the three treatments indicating it should be the therapy of choice when associated hospital costs are included. Even though the inhaled beta$_2$-agonist agent and sustained-release theophylline protocol had the lowest maintenance medication costs, it also had the highest cost-effectiveness ratio, suggesting it is the least desirable therapy when associated hospital services are included in the costs.

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A STOCHASTIC APPROACH TO THE PHARMACOTHERAPEUTIC MANAGEMENT OF CHRONIC MODERATE ADULT ASTHMA

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ABSTRACT

This thesis demonstrates stochastic modelling techniques for the quantitative evaluation of the effects of three different pharmacotherapy protocols of chronic moderate adult asthma on hospital services (emergency room use and hospitalizations).

The therapies compared were: 1) inhaled beta$_2$-agonist agent and inhaled cromolyn; 2) inhaled beta$_2$-agonist agent and an inhaled corticosteroid agent; 3) inhaled beta$_2$-agonist agent and sustained-release theophylline.

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EXECUTIVE SUMMARY

Asthma is a chronic illness of reversible airway hyperactivity that currently affects an estimated 10 million people in the United States. Recent evidence suggests that the prevalence and severity of asthma in the United States has risen alarmingly. Although asthma is a highly treatable condition when properly managed, 43 percent of its economic impact is associated with emergency room use, hospitalization, and death.

Health care planners and physicians should not only be concerned with the clinically proven effectiveness of the pharmacotherapy of asthma but also with the impact the therapy has on hospital services. This thesis demonstrates stochastic modelling techniques for the quantitative evaluation of the effects of different pharmacotherapy protocols of chronic moderate adult asthma on hospital services, thus providing useful information for the planning of effective asthma management strategies. Cost effectiveness ratios were calculated for three different therapies, where the costs include not only the medication costs, but also the hospital and emergency room costs associated with each treatment. The effectiveness measure for each treatment was the time the asthmatic spent well (or more accurately, not seeking treatment for an attack or adverse drug reaction).

The stochastic models for the three different therapies were based on probabilities estimated from a meta-analysis of the literature. For each variable in the models, sensitivity analysis was performed which varied the distribution of that variable through a clinically reasonable range. The three treatments compared were:

1. **Treatment 1:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and inhaled cromolyn *(two puffs fours times daily)*,
2. **Treatment 2:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and an inhaled corticosteroid agent *(two to four puffs twice daily)*,

3. **Treatment 3:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and sustained-release theophylline *(dosage must be individualized).*

Treatment 1 had an average estimated expected present value of 9270.71 dollars over a five year time horizon, Treatment 2 had an average estimated expected present value of 6236.35 dollars, while Treatment 3 had an average estimated expected present value of 21324.18 dollars.

Patients receiving Treatment 1 spent an estimated average of 98.8 percent of the time "well", those receiving Treatment 2 spent an estimated average of 98.9 percent of the time "well", while Treatment 3 patients spent an estimated average of 96.35 percent "well".

Treatment 2 has the lowest cost-effectiveness ratio of the three treatments indicating it is the therapy of choice when associated hospital costs are included. Treatment 3, even though it has the lowest maintenance medication costs, has the highest cost-effectiveness ratio suggesting it is the least desirable therapy when associated hospital services are included in the costs.

Given the apparent equivalent therapeutic efficacy of the three pharmacotherapy strategies for moderate adult chronic asthma, analysis indicates that a beta$_2$-agonist and a corticosteroid (Treatment 2) is the preferable pharmacotherapy of adult chronic moderate asthma when utilization of associated hospital services is considered. A beta$_2$-agonist agent and sustained-release theophylline (Treatment 3) is preferred when associated hospital services are not considered. The results are sensitive to the probability of an emergency room visit and/or hospitalization associated with each treatment.

The models presented make contributions to two fields. To the modelling audience, they represent the results of an attempt to synthesize important medical and economic factors which play crucial roles in the treatment/cost of a chronic disease. To the clinician, the models yield valuable information on the comparative cost/effectiveness of therapy combinations. In addition, the modelling techniques invite a number of sensitivity analyses which may provide new insights concerning the treatment of asthma.

The methods presented are not intended to provide a definitive answer, but rather to demonstrate, within the limitations of any probabilistic model, the effects of important parameters on the costs and effectiveness of medical treatment plans. The techniques outlined here can be easily applied to other diseases such as epilepsy and diabetes.

As resources available for health care become increasingly limited, difficult choices among competing uses of health care dollars must be made. Currently, the standard of care for medical conditions is influenced by published clinical trials, consensus among clinicians, and formal peer review of medical strategies. Analyses such as those presented herein could be included as an additional factor in establishing the standard of care.

I. INTRODUCTION

A. BACKGROUND

Asthma is a chronic illness of reversible airway hyperactivity that currently affects an estimated 10 million people in the United States (Schoenborn and Marano, 1989). Recent evidence suggests that the prevalence and severity of asthma in the United States has risen alarmingly (Evans *et al.,* 1987). Between 1980 and 1987, the occurrence of asthma among the general population increased 29 percent. During this same period, the asthma hospitalization rate increased six percent, and the mortality rate increased 31 percent (Centers for Disease Control, 1990).

The reason for the rise in asthma morbidity and mortality remains elusive. However, the physical and emotional toll that asthma takes is becoming increasingly clear. A study of the impact of asthma found that during 1985, adults with asthma missed three million work days, had 4.9 million contacts with medical doctors, and required 350,000 hospitalizations (Weiss *et al.,* 1992).

In addition to the human toll, the economic impact of asthma is enormous. The cost of asthma in the United States in 1990 was estimated to be $6.2 billion. An estimated 1.81 million people required emergency room services for asthma, 52.2 percent of the visits involved persons 18 years old and older. Inpatient hospital services represented the largest direct medical expenditure, accounting for $1.6 billion, 66 percent of which were for persons 18 years or older. The estimated impact on production resulting from lost school or work days was the largest single indirect cost, approaching $1 billion. Although asthma is a highly treatable condition when properly managed, 43 percent of its economic impact was associated with emergency room use, hospitalization, and death (Weiss *et al.,* 1992). The pressing need for more efficient allocation of resources in health care has stimulated interest in operations research methods.

B. LITERATURE REVIEW

A Medline search (1966-1995) was conducted for publications offering analyses of asthma health care interventions. Medline is an online database maintained by the National Library of Medicine in Bethesda, Maryland. Several combinations of the following entries were used: asthma, costs, cost-analysis, cost-effectiveness, Markov, outcomes, model, evaluation, treatment.

There are hundreds of clinical trials of pharmaceuticals used in asthma care that examine outcomes critical to establishing clinical efficacy (*i.e.,* changes in pulmonary function), as well as a number of studies of the cost-effectiveness and cost-benefit of asthma education programs. However, only one published study of the cost-effectiveness of asthma pharmacotherapy was found, even though this is the main intervention in asthma. Rutten-van Molken *et al.* reported on the relative cost-effectiveness of the use of an inhaled beta$_2$-agonist plus an inhaled corticosteroid versus an inhaled beta$_2$-agonist plus a placebo (Rutten-van Molken *et al.*, 1993). This study suggests that the patient-year savings were seen both in relation to improvements in pulmonary function as well as in symptom-free days with the use of an inhaled beta$_2$-agonist plus an inhaled corticosteroid in children. Only one study by Ross *et al.* studied the cost-effectiveness of asthma therapy in terms of the reduction in the number of emergency room visits and hospitalizations (Ross *et al.*, 1988). In this study, a retrospective chart review was undertaken to estimate the costs of treating asthma in patients whose treatment plan included cromolyn sodium and those whose treatment plan did not include cromolyn (Ross *et al.,* 1988).

In 1983, Beck and Pauker described the use of Markov models for deciding prognosis in medical applications (Beck and Pauker, 1983). Since that introduction, Markov models have been applied in the medical field with increasing frequency.

Several Markov models examining the clinical strategies for managing patients with chronic diseases have been formulated in recent years. A 1994 study by Disch *et al.* developed a Markov model comparing the risks and benefits of warfarin, quinidine, and amiodarone (pharmacotherapy strategies) for managing patients with chronic atrial fibrillation (Disch *et al.,* 1994). Estimates for each parameter in the model were extracted from the medical literature. The study shows that cardioversion followed by low-dose amiodarone to maintain normal sinus rhythm appears to be a safe and effective treatment for patients with chronic atrial fibrillation. (Disch *et al.,* 1994) Similarly, a 1991 study by Podrid *et al.* examined the cost-effectiveness of quinidine, procainaimide and mexiletine in the treatment of ventricular arrhythmias (Podrid *et al.,* 1991). This study suggests that mexiletine is a cost-saving alternative therapy for ventricular arrhythmias when adverse reactions are considered in addition to pharmaceutical costs and treatment efficacy. (Podrid *et al.,* 1991)

A 1990 study by Edelson, Tosteson and Sax used a Markov model to research the cost-effectiveness of misoprostol for prophylaxis against nonsteroidal anti-inflammatory drug-induced gastrointestinal tract bleeding (Edelson *et al.*, 1990). The model compares prophylaxis treatment with no prophylaxis treatment with outcomes of five degrees of gastrointestinal tract bleeding. Again, estimates for the parameters were obtained from a review of the medical literature. The study found that misoprostol is costly as the primary prophylactic therapy for nonsteroidal anti-inflammatory drug-induced gastrointestinal tract bleeding, but may be cost-effective as a secondary prophylactic therapy in patients with a proven history of gastrointestinal tract bleeding. (Edelson *et al.*, 1990)

C. PROBLEM DEFINITION

In recent years operations analysis techniques have become increasingly important in the medical community to guide hospital administrators and health care providers in the allocation of scarce medical resources. The National Institutes of Health (NIH) has published specific guidelines on the management of asthma in which several pharmaceutical choices for management exists.

Specifically, for the management of moderate adult asthma, the recommended therapy is (NIH expert panel,1991):

1. **Treatment 1:** Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and inhaled cromolyn (*two puffs four times daily*),
2. **Treatment 2:** Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and an inhaled corticosteroid agent *(two to four puffs twice daily)*,
3. **Treatment 3:** Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and sustained-release theophylline *(dosage must be individualized)*.

The Medline search revealed that numerous studies have been conducted which determine that the above therapies significantly improve pulmonary function and are effective in the treatment of asthma, but no comparative studies have been conducted to determine the impact of each of the strategies on emergency room use or hospitalizations as a measure of effectiveness.

The objective of this thesis is to develop stochastic models to help determine which of the above pharmacotherapy strategies is the most cost-effective for the asthma management process among adults with chronic moderate asthma. The costs for the models are to include daily costs of maintenance medication and the expected costs associated with hospital services utilization. Then, using the amount of time spent *well* (or more accurately, the time not seeking treatment for an attack or adverse drug reaction) as a measure of effectiveness, a cost/effectiveness ratio can be calculated for each of the three strategies.

D. ORGANIZATION OF THE THESIS

There are five chapters in this thesis. Chapter I provides the background, selective literature review, and problem definition. Chapter II describes the disease and its treatment. Chapter III addresses the methodology and model formulations. Chapter IV examines the results and Chapter V discusses the conclusions. Appendix A contains a glossary of terms.

II. THE DISEASE AND TREATMENT

A. ASTHMA

Asthma is characterized by reversible airflow obstruction and airway hyperresponsiveness, a condition manifested by an exaggerated bronchoconstrictor response to many physical changes and chemical/pharmacologic agents. Asthma patients develop clinical symptoms such as wheezing and dyspnea after exposure to allergens, irritants, viral infections, cold air, or exercise. Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms. Exacerbations are characterized by decreases in expiratory airflow. Bronchial smooth muscle contraction is the primary obstructive abnormality in asthma, causing the airways to narrow. However, bronchospasm, mucosal edema, and mucous plugging also contribute to the narrowing of the airways. Air is trapped behind occluded or narrowed small airways causing the asthmatic to breathe close to his/her total lung capacity leading to hyperventilation. (NIH expert panel, 1991)

B. PHARMACOTHERAPY

Asthma therapy has several integral components: patient education, environmental control, and pharmacotherapy, as well as the use of objective measures to monitor the severity of disease and the course of therapy (NIH expert panel, 1991). The focus of this thesis is on the pharmacotherapy of adult moderate asthma. Medications for the pharmacotherapy of asthma are ones which reverse and prevent airflow obstruction, namely, anti-inflammatory agents and bronchodilators. Anti-inflammatory agents interrupt the development of bronchial inflammation and have a prophylactic and suppressive action. Bronchodilators act principally to dilate the airways by relaxing bronchial smooth muscle. Although bronchodilators reverse and/or inhibit bronchoconstriction and related symptoms of acute asthma, they do not reverse bronchial inflammation and hyperresponsiveness. (NIH expert panel, 1991)

Since asthma is a disease of the airways, inhalation treatment is generally preferable to systemic or oral treatment. The advantage of inhalants is that a higher concentration of drug can be delivered more effectively to the airways, and systemic side effects are usually avoided. The anti-inflammatory agents examined in this thesis are corticosteroids and cromolyn sodium and the bronchodilators are beta$_2$-agonists and theophylline. (NIH expert panel, 1991)

Pulmonary function tests are essential for diagnosing asthma and assessing the severity of asthma in order to make appropriate therapeutic recommendations. In analyzing lung function, the *vital capacity* is the most important volume in assessing the severity of the disease. To determine the reduction in vital capacity, flow rates are obtained. The volume of air expired in one second from maximum inspiration is the *forced expiratory volume one second (FEV_1).* Although FEV_1 is the single best-known measure of pulmonary function, correct techniques and calibrated equipment limit its use primarily to the physician's office. An alternate measure is the *peak expiratory flow rate (PEFR),* defined as the maximum flow rate that can be generated during a forced expiratory maneuver. The PEFR provides a simple, quantitative, reproducible measure of airway obstruction that can be obtained at home using inexpensive, portable peak flow meters. Individuals 18 years old or older who have more than two acute asthma exacerbations per week with a PEFR or FEV_1 decreasing twenty to forty percent from their personal best, are considered to have moderate asthma. (NIH expert panel, 1991)

As mentioned in Chapter I, when treating adult moderate asthma the physician has three choices for therapy:

1. **Treatment 1:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and inhaled cromolyn (*two puffs four times daily)*,

2. **Treatment 2:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and an inhaled corticosteroid agent *(two to four puffs twice daily)*,

3. **Treatment 3:** Inhaled beta$_2$-agonist agent *(as needed or up to three to four times daily)* and sustained-release theophylline *(dosage must be individualized).*

All three therapies include a beta$_2$-agonist. Beta$_2$-agonists are the therapy of choice for the treatment of acute exacerbations of asthma and for the prevention of exercise- induced asthma. They can be used either intermittently to control episodic airway narrowing or chronically to aid in the control of persistent airway narrowing. Although beta$_2$-agonists are commonly used continuously, a 1990 study by Sears, Taylor, Print, *et al.*, questions whether regular therapy with a specific beta$_2$-agonist may be associated with deterioration of control of asthma in some patients (Sears *et al.*, 1990). A study by Tashkin, Conolly, and Deutsch suggests that a potential reason for increased asthma symptoms during prolonged therapy with inhaled beta$_2$-agonists may be a result of the development of tolerance or subsensitivity from down-regulation of beta-adrenergic receptors (Tashkin *et al.*, 1982). Adverse drug reactions involving the cardiovascular system may also occur as a result of inhaled beta$_2$-agonists.

To avoid frequent fluctuations in PEFR and asthma symptoms, as well as the overuse of beta$_2$-agonists, additional therapy is needed. As previously specified there are three choices: inhaled corticosteroids, cromolyn sodium, or sustained-release theophylline. Inhaled corticosteroids are steroidal anti-inflammatory drugs effective for the treatment of reversible airflow obstruction. Systemic adverse effects of long-term oral steroids are significant and limit their use. Adverse effects include Cushing syndrome, cataracts, osteoporosis, hypertension and, in rare instances, impaired immune mechanisms. Delivering corticosteroids via the airways dramatically reduces the adverse effects. However, long-term follow-up studies on the effects of long-term high dose regimens of inhaled corticosteroids continue. Inhaled cromolyn sodium is a non-steroidal anti-inflammatory drug that produces only minimal side effects (occasional coughing and dry throat), but its effectiveness in asthma is less predictable than that of inhaled corticosteroids. Theophylline is an oral bronchodilator that, when given as a sustained-release preparation, has a long duration of action. It may augment respiratory muscle contractility, reducing respiratory muscle fatigue and possibly possesses some degree of anti-inflammatory activity. However, it has the potential for significant adverse effects (nausea, vomiting, tachycardia, arrhythmias, seizures and death) and has numerous interactions with other drugs which can either decrease or increase the blood level concentration. Because of the severity of toxicity associated with theophylline frequent monitoring of serum concentrations (via a blood test) must be conducted at regular intervals which may be viewed as detriments to quality of life. (NIH expert panel, 1991)

Weighing the above competing risks, benefits, and effectiveness simultaneously is difficult and involves too many variables for clinical intuition alone. For this reason, stochastic models were developed to compare the cost-effectiveness of the three therapy choices.

III. METHODOLOGY AND MODEL FORMULATIONS

A. STOCHASTIC APPROACH

As Chapter I suggests, health care planners and physicians should not only be concerned with the clinically proven effectiveness of the pharmacotherapy of asthma but also with the impact the therapy has on hospital services. This thesis demonstrates stochastic modelling techniques for the quantitative evaluation of the effects of different pharmacotherapy protocols of chronic moderate adult asthma on hospital services, thus providing useful information for the planning of effective asthma management strategies. In this case it is desired to calculate cost effectiveness ratios for three different therapies, where the costs include not only the medication costs but also the hospital and emergency room costs associated with each treatment. The effectiveness measure is the time spent well (or more accurately, the time not seeking treatment for an attack or adverse drug reaction over a five year time period).

B. MARKOV MODELS

1. Discrete-Time Stochastic Model

Suppose that at any time t an asthmatic is in one of the following states:

0) *asthma well controlled (well):* asthmatics in the (well) state are experiencing no exacerbation or medication complication requiring medical treatment. Patients leave the (well) state when either an attack or adverse drug reaction necessitates medical attention,

1) *emergency room visit/attack:* asthmatics in the (ER/attack) state are seeking medical treatment for an asthma attack from the emergency room. Patients leave the emergency room visit/attack state via admission to the hospital or disposition home,

2) *emergency room visit/ADR:* asthmatics in (ER/ADR) state are seeking medical treatment for an adverse drug reaction (ADR) from the emergency room. Patients leave the emergency room

visit/ADR state via admission to the hospital or disposition home,

3) *hospital/attack:* asthmatics in the (hospital/attack) state are receiving medical treatment in the hospital for an asthma attack. Patients in the hospital/attack state transition to the (well) state (*i.e.*, are discharged home),

4) *hospital/ADR:* asthmatics in the (hospital/ADR) state are receiving medical treatment in the hospital for an adverse drug reaction. Patients in the hospital/ADR state transition to the (well) state (*i.e.*, are discharged home),

5) *minor adverse drug reaction:* asthmatics in the (minor/ADR) state are experiencing an adverse drug reaction that requires treatment but was discovered during a routine follow-up visit. All patients in the minor adverse drug reaction state transition to the (well) state.

The probability of death from an attack or adverse drug reaction is very rare among moderate adult asthmatics and therefore is neglected (NIH expert panel, 1991). As time progresses, the asthmatic moves from state to state with some conditional probability.

Now, assume that the conditional probability of the asthmatic's next state (*e.g.,* emergency room visit for an attack) given the entire state history only depends upon the present state (Markovian assumption). Further assume that the conditional probability of a state does not change over time (the probability of going to an emergency room today for an attack is the same as yesterday). The assumption of stationary transition probabilities is reasonable in this case for a time horizon of five years. However, after this time the overall health of the asthmatic could change, a drug tolerance could develop, and other factors are likely to occur which may change the conditional probabilities.

To formulate the discrete-time Markov chain model, let $X_t^{(k)}$ represent the state of the process at time t, when treatment k is used. The Markovian assumption above is formally stated as (Howard, 1971),

$$P(X_{t+1}^{(k)} = i_{t+1} \mid X_t^{(k)} = i_t,\ X_{t-1}^{(k)} = i_{t-1},\ .\ .\ .\ ,\ X_1^{(k)} = i_1, X_0^{(k)} = i_0) \qquad \textbf{(1)}$$
$$= P(X_{t+1}^{(k)} = i_{t+1} \mid X_t^{(k)} = i_t).$$

Define

$$P_{ij}^{(k)} = P(X_{t+1}^{(k)} = j \mid X_t^{(k)} = i) \qquad \textbf{(2)}$$

so that $P_{ij}^{(k)}$ is the probability that the asthmatic will be in a state j at time $t+1$ given an asthmatic on treatment k was in state i at time t. If the asthmatic moves from state i during one period to state j during the next period, a transition from i to j has occurred. Then, if the patient is in state i at time m, the probability that n periods later the patient will be in state j can be calculated using the n-step transition probabilities.

The $P_{ij}^{(k)}$'s are the *transition probabilities* for the Markov chain. The transition probabilities are displayed as an n x n transition probability matrix $P^{(k)}$.

$$P^{(k)} = \begin{bmatrix} P^{(k)}_{00} & P^{(k)}_{01} & P^{(k)}_{02} & P^{(k)}_{03} & P^{(k)}_{04} & P^{(k)}_{05} \\ P^{(k)}_{10} & P^{(k)}_{11} & P^{(k)}_{12} & P^{(k)}_{13} & P^{(k)}_{14} & P^{(k)}_{15} \\ P^{(k)}_{20} & P^{(k)}_{21} & P^{(k)}_{22} & P^{(k)}_{23} & P^{(k)}_{24} & P^{(k)}_{25} \\ P^{(k)}_{30} & P^{(k)}_{31} & P^{(k)}_{32} & P^{(k)}_{33} & P^{(k)}_{34} & P^{(k)}_{35} \\ P^{(k)}_{40} & P^{(k)}_{41} & P^{(k)}_{42} & P^{(k)}_{43} & P^{(k)}_{44} & P^{(k)}_{45} \\ P^{(k)}_{50} & P^{(k)}_{51} & P^{(k)}_{52} & P^{(k)}_{53} & P^{(k))}_{54} & P^{(k)}_{55} \end{bmatrix}. \qquad \textbf{(3)}$$

Given that the state at time t is i, the asthmatic must be somewhere in the state space at time $t+1$. This means that for each i, (0, 1, 2, ..., s),

$$\sum_{j=0}^{s} P_{ij}^{(k)} = 1. \qquad \textbf{(4)}$$

The discrete-time step should be selected which gives an adequate amount of information concerning the amount of time that the asthmatic remains in each state. For this model the time step of one day was chosen.

Since the model projects costs five years into the future, a present-value approach is necessary. Present-value analysis is a widely accepted method of weighing future dollars by a discount to make them comparable to present dollars. Even if all costs, present and future are adjusted for the rate of inflation, future costs still need to be discounted. The reason is that a dollar not spent now can be invested productively to yield a larger number of real dollars in the future (Weinstein and Stason, 1977).

To formulate the discrete-time cost/effectiveness model, let:

$C_i^{(k)}(\delta)$ = expected present-value of the cost of treatment k when the discount rate is δ, starting in state i.

δ = a discounting factor for future costs

$D_i^{(k)}$ = the expected cost of one day sojourn in health state i while on treatment k.

Then, using standard first-step analysis $C_i^{(k)}(\delta)$ can be written as (Howard, 1971):

$$C_i^{(k)}(\delta) = D_i^{(k)} + \delta \Sigma P_{ij}^{(k)} C_j^{(k)}(\delta) \qquad i = 0,\ldots,5. \tag{5}$$

Expression (5) represents a set of six linear equations that define the expected present value of treatment k over an infinite horizon. In matrix form the solution to Equation (5) can be written as:

$$C^{(k)}(\delta) = (I - P^{(k)})^{-1} D^{(k)} \tag{6}$$

where I is the identity matrix.

To find the expected present value of treatment k over a finite horizon ($EPV^{(k)}_{\text{finite}}$) the following equation is used:

$$EPV^{(k)}_{finite} = (I - \delta^N (P^{(k)})^N) C^{(k)}(\delta) \tag{7}$$

where N equals the number of time steps for a finite time horizon (*e.g.*, five years or 1825 days).

To estimate the amount of time spent in the (well) state the steady state probabilities, $\pi_0^{(k)}$, $\pi_1^{(k)}$, $\pi_2^{(k)}$, $\pi_3^{(k)}$, $\pi_4^{(k)}$, $\pi_5^{(k)}$ can be used. The steady state probabilities are the ij^{th} entry of the limit of the n-step transition probabilities defined as:

$$\pi_i^{(k)} = \lim_{n \to \infty} [(P^{(k)})^n]_{ij} \tag{8}$$

and can be determined by solving the following set of simultaneous equations for each treatment k, (Howard,1971):

$$\begin{gathered} \pi_j^{(k)} = \sum_{i=0}^{5} \pi_i^{(k)} P_{ij}^{(k)} \qquad j = 0,\ldots,5. \\ \sum_{j=0}^{5} \pi_j^{(k)} = 1. \end{gathered} \tag{9}$$

The quantity $\pi_j^{(k)}$ gives the fraction of the total amount of time for which the asthmatic on treatment k will occupy state j in the long run. Then, using the fraction of time the asthmatic occupies the (well) state as the measure of effectiveness and the $EPV^{(k)}_{finite}$ costs from Equation (7), a cost-effectiveness ratio can be calculated for each of the treatments.

2. Continuous-Time Stochastic Model

Since the asthmatic may be seeking treatment at any time, not just at the end of a day, a continuous-time model may more accurately represent the process.

Suppose that at any time t an asthmatic is in one of the states described above (well, ER/attack, ER/ADR, hospital/attack, hospital/ADR, minor). Let $Q_{ij}^{(k)}$ be the transition rate of the asthmatic from state i to j while on treatment k. Symbolically, if $X_t^{(k)}$ represents the state of the process at time t then (Howard, 1971),

$$P(X^{(k)}_{t+\Delta t} = j \mid X_t^{(k)} = i) = Q_{ij}^{(k)}\Delta t + o(\Delta t), \quad j \neq i \ . \tag{10}$$

(The probability of two or more state transitions is of the order of $(\Delta t)^2$ or higher and can be neglected if Δt is sufficiently small). The infinitesimal generator for treatment $Q^{(k)}$ has off-diagonal elements $Q_{ij}^{(k)}$ and diagonal elements (Howard, 1971):

$$Q_{ii}^{(k)} = -\sum_{i \neq j} Q_{ij}^{(k)} \ , i = 0, \ldots, 5. \tag{11}$$

Similar to the discrete-time Markov chain cost/effectiveness model define,

$D_i^{(k)}$	=	the cost per unit time incurred by being in state i while on treatment k,
$C_i^{(k)}(r)$	=	the expected present value (with continuous discounting) given the asthmatic starts in state i while on treatment k,
$T_1^{(k)}$	=	time of first transition of $\{X_t^{(k)}\}$ while on treatment k,
r	=	the (continuous) discounting factor.

Then conditional on $X_0^{(k)} = i$, T_1 and $X_{T_1}^{(k)}$ are independent with $(T_1 \mid X_0^{(k)} = i) \sim Exp(-Q_{ii}^{(k)})$ also,

$$P(X_{T_1}^{(k)} = j \mid X_0^{(k)} = i) = -\frac{Q_{ij}^{(k)}}{Q_{ii}^{(k)}} \tag{12}$$

thus, conditioning on the first transition state $X_{T_1}^{(k)}$:

$$C_i^{(k)}(r)=E\left[\int_o^{T_1} D_i^{(k)} e^{-rt}dt\right]+E\left[e^{-rT_1}\right]\sum_{i\neq j}\left(\frac{-Q_{ij}^{(k)}}{Q_{ii}^{(k)}}\right)C_j^{(k)}(r)$$

$$=\frac{D_i^{(k)}}{r}E\left[1-e^{-rT_1}\right]-\frac{Q_{ii}^{(k)}}{r-Q_{ii}^{(k)}}\sum_{i\neq j}\left(\frac{-Q_{ij}^{(k)}}{Q_{ii}^{(k)}}\right)C_j^{(k)}(r)$$

$$=\frac{D_i^{(k)}}{r}\left(1-\left(\frac{-Q_{ii}^{(k)}}{r-Q_{ii}^{(k)}}\right)\right)+\frac{1}{r-Q_{ii}^{(k)}}\sum_{i\neq j}\left(Q_{ij}^{(k)}\right)C_j^{(k)}(r)$$

$$=\frac{D_i^{(k)}}{r-Q_{ii}^{(k)}}+\frac{1}{r-Q_{ii}^{(k)}}\sum_{i\neq j}Q_{ij}^{(k)}C_j^{(k)}(r)$$

$$r\,C_i^{(k)}(r)-\sum_{i\neq j}Q_{ij}C_j^{(k)}(r) = D_i^{(k)}. \tag{13}$$

In matrix form,

$$\left(rI-Q^{(k)}\right)C^{(k)}(r)=D^{(k)},$$

and solving gives:

$$C^{(k)}(r)=\left(rI-Q^{(k)}\right)^{-1}D^{(k)}, \tag{14}$$

where $C^{(k)}(r)$ is the vector of expected present values of treatment k over an infinite horizon and I is the identity matrix. The expected present values of treatment k over a finite horizon $[0, s]$ is given by:

$$C^{(k)}(r)-e^{-rs}P^{(k)}(s)\,C^{(k)}(r)=\left(I-e^{-rs}P^{(k)}(s)\right)C^{(k)}(r) \tag{15}$$

where $P^{(k)}(s)$ is the transition matrix of $\{X_t^{(k)}\}$. Therefore,

$$EPV^{(k)}_{finite}=\left(I-e^{-rs}P^{(k)}(s)\right)\left(rI-Q^{(k)}\right)^{-1}D^{(k)}. \tag{16}$$

$P^{(k)}(t)$ may be found by the Chapman-Kolmogorov equations as follows. Consider the small time interval [t, $t + \Delta t$],

$$P_j^{(k)}(t+\Delta t) = P_j^{(k)}(t)(1-\sum_{i \neq j} Q_{ij}^{(k)} \Delta t) + \sum_{i \neq j} P_i^{(k)}(t) Q_{ij}^{(k)} \qquad j = 0,\ldots,5. \tag{17}$$

Substituting Equation (11) in (17) gives

$$P_j^{(k)}(t+\Delta t) = P_j^{(k)}(t)(1+Q_{ii}^{(k)}\Delta t) + \sum_{i \neq j} P_i^{(k)}(t) Q_{ij}^{(k)} \Delta t \tag{18}$$

or

$$P_j^{(k)}(t+\Delta t) - P_j^{(k)}(t) = \sum_{i=0}^{5} P_i^{(k)}(t)\, Q_{ij}^{(k)} \Delta t. \tag{19}$$

Dividing by Δt and taking the limit as Δt goes to zero yields

$$\frac{d}{dt} P_j^{(k)}(t) = \sum_{i=0}^{5} P_i^{(k)}(t)\, Q_{ij}^{(k)} \qquad j = 0,\ldots,5. \tag{20}$$

This is a set of six linear constant- coefficient differential equations that relate the state probabilities to the transition rate matrix $Q^{(k)}$. In matrix form Equation (20) can be written as:

$$\frac{d}{dt} P^{(k)}(t) = P^{(k)}(t) Q^{(k)}. \tag{21}$$

The solution to Equation (21) is $P^{(k)}(t) = e^{Q^{(k)} t}$ (Hirsch and Smale, 1974).

Analogous to the discrete-time case, the steady state probabilities are given by the solution to:

$$\sum_{i=0}^{5} \pi_i^{(k)} Q_{ij}^{(k)} = 0 \tag{22}$$

$$\sum_{i=0}^{5} \pi_i^{(k)} = 1.$$

Dividing Equation (16) by Equation (22) yields a cost/effectiveness ratio for each treatment k.

C. ALTERNATIVE FORMULATIONS

1. Marked Poisson Process Approximation

An alternative formulation of the process is to model non-well episodes as sequences of mutually independent random variables with times between episodes that are exponentially distributed (a Poisson process). The asthmatic experiences periods of continuous satisfactory health that end by a need for special medical treatment. During these periods the asthmatic is *well*. These periods often appear "random" ; note that the pattern of randomness may differ somewhat between patients on the same treatment, but for the present ignore this possibility and let it be modelled as a random variable $T_p^{(k)}$ that represents the time between successive events for patient p administered medication k, and let successive such times be independently and *exponentially* distributed:

$$P\left(T_p^{(k)} > t\right) = e^{-\lambda(k)t} \tag{23}$$

where $(\lambda(k))^{-1}$ is the mean time to a next event, following the termination of a state of special medical treatment that interrupts well states; call it the *mean inter-event time*; the parameter $\lambda(k)$ is also called *event rate* or *hazard rate*. This parameter is the same as $-Q_{00}^{(k)}$ in the continuous-time model.

It is assumed that the event rate or hazard rate $\lambda(k)$ is only dependent on the dosage of medication k. However, it is possible to quantify this effect, and also account for the effect of covariates or explanatory variables such as age, gender, exposure to asthma-attack agents, etc. One technique is to represent λ by a *log-linear* function:

$$\lambda = \lambda\left(x_k, g, a\right) = \exp[\beta_0 + \beta_1 x_k + \beta_2 a + \beta_3 g] \tag{24}$$

where x_k is the dosage per unit time of medication k, and g (= 1 if male, -1 if female, for instance) is a gender-indicator, and a denotes the age of the patient (*e.g.*, at the initiation of treatment). Interaction terms, like $\beta_4\ (x_k \cdot a)$ for treatment-level-age interaction, can also be introduced. This aspect is not pursued here, but could be fruitful.

There will also be an expense per unit time of using medication k during the well periods : $C^{(k)}_{(\text{well})}$. When a well-period-terminating event occurs it can be classified into one of the following event types:

An ER/attack event is defined as a visit to an emergency room for an attack. Suppose this event occurs with probability $p^{(k)}_{ER(attack)}$, when "on" medication k, independently of all other events or times. From the standpoint of time, the duration of an emergency room visit for an attack is on the order of hours (fraction of a day); let it have distribution $F_{ER(attack)}(t)$ with mean $\mu_{\text{ER(attack)}}$. Suppose the cost for a visit to an emergency room for a patient prescribed medication k is a random variable $C^{(k)}_{ER(attack)}$ with expected cost of $D^{*(k)}_{ER(attack)}$.

An ER/ADR event is defined as an emergency room visit for an adverse reaction. Let $p^{(k)}_{ER(ADR)}$ be the probability of such a visit occurring, when taking medication k given an event that terminates a well period; assume independence as before. Let the duration of an ER/ADR visit have distribution $F_{ER(ADR)}(t)$ with mean $\mu_{ER(ADR)}$. A visit to an emergency room for an adverse event has cost $C^{(k)}_{ER(ADR)}$ for a patient taking medication k ; let the mean cost $C^{(k)}_{ER(ADR)}$ be $D^{*(k)}_{ER(ADR)}$.

A Hospital/attack event is defined as a visit to a hospital for an attack. Suppose this event also occurs with probability $p^{(k)}_{Hosp(attack)}$ while on medication k , independently of all other events or times. The duration of a hospital visit for an attack is on the order of days; let it have distribution $F_{Hosp(attack)}(t)$ with mean $\mu_{Hosp(attack)}$. Suppose the cost for a visit to a hospital for an attack for a patient prescribed medication k is a random variable $C^{(k)}_{Hosp(attack)}$ with expectation $D^{*(k)}_{Hosp(attack)}$.

A Hospital/ADR event is defined as a hospital visit for an adverse reaction. Let $p^{(k)}_{Hosp(ADR)}$ be the probability of such a visit occurring when taking medication k, given an event that terminates a well period; assume independence. Let the duration of an Hospital/ADR visit have distribution

$F_{Hosp(ADR)}(t)$ with mean $\mu_{Hosp(ADR)}$. A visit to a hospital for an adverse reaction has cost $C^{(k)}{}_{Hosp(ADR)}$ for a patient taking medication k; let the mean of $C^{(k)}{}_{Hosp(ADR)}$ be $D^{*(k)}{}_{Hosp(ADR)}$.

A Minor/ADR event is defined as an adverse drug reaction discovered during a routine follow-up visit. Suppose this event occurs with probability $p^{(k)}{}_{M(ADR)}$ while on medication k, independently of all other events or times. Let it have distribution $F_{M(ADR)}(t)$ with mean $\mu_{M(ADR)}$. Suppose the cost for a Minor/ADR for a patient prescribed medication k is a random variable $C^{(k)}{}_{M(ADR)}$ with expectation $D^{*(k)}{}_{M(ADR)}$.

Since the asthma patient is typically in the well state for time periods which are quite long compared to times in other states described, and since any of the attack events take, and return, the patient to the well state, it is reasonable to simply ignore the durations of the attack events. Therefore, the events form a simple Poisson process, which are *marked* or *colored* to depict event types. Let r be a discounting factor and $j = 1, 2, 3, 4, 5$ represent each of the events described above, then, given n "events" occurring at times $T_1, \ldots, T_n$, they are distributed as n uniform [0, T] order statistics as:

$$E[C^{(k)}_{events}(r) \mid n\ events] = \sum_{j=1}^{n} E[e^{-rT_j}] \sum_{j=1}^{5} D_j^{*(k)} p_j^{(k)}, \tag{25}$$

where $T_j \sim$ uniform [0, T]. So,

$$\begin{aligned} E[C^{(k)}_{events}(r)] &= \sum_{n=0}^{\infty} E[C^{(k)}_{events}(r) \mid n\ events] \frac{(\lambda T)^n}{n!} e^{-\lambda T} \\ &= \frac{1}{rT}(1-e^{-rT})\left(\sum_{j=1}^{5} D_j^{*(k)} p_j^{(k)}\right)(\lambda T) \\ &= \frac{\lambda}{r}(1-e^{-rT})\left(\sum_{j=1}^{5} D_j^{*(k)} p_j^{(k)}\right). \end{aligned} \tag{26}$$

Then, adding the costs of using treatment k during the (well) periods, the expected discounted costs of treatment k over the period [0, T] is,

$$E[C^{(k)}(r)] = \frac{c_w^{(k)} + \lambda \sum_{j=1}^{5} D_j^{*(k)} p_j^{(k)}}{r} (1 - e^{-rT}). \tag{27}$$

Here D_j is the expected costs of all j events and is given by the solution to the following linear equations:

$$D_j^{(k)} = c_j^{(k)} + \sum_{i=1}^{5} P_{ji}^{(k)} D_i^{*(k)} \qquad j = 1,\ldots,5. \tag{28}$$

To find the expected time unwell (time in all states not zero), the first-passage time from state j to state zero (well) satisfies:

$$S_j^{(k)} = 1 + \sum_{i=1}^{s} P_{ji} S_j^{(k)} \quad j, i = 1,\ldots, s = 5, \tag{29}$$

which can easily be solved. In the special present case the problem can be solved in simple closed form. Now,

$$S^{(k)} = \sum_{i=1}^{s} p_j^{(k)} S_j^{(k)} \qquad j = 1,\ldots, s = 5, \tag{30}$$

is the duration of an arbitrary unwell period. Note that these alternate with well periods. By simple two-state renewal-process theory:

$$\begin{aligned} E[\mathit{Fraction\ of\ Time\ Well}] &= \frac{\frac{1}{\lambda^{(k)}}}{\frac{1}{\lambda^{(k)}} + S^{(k)}} \\ &= \frac{1}{1 + \lambda^{(k)} S^{(k)}} \\ &\approx 1 - \lambda^{(k)} S^{(k)} . \end{aligned} \tag{31}$$

As before, Equation (27) divided by Equation (31) gives a cost/effectiveness ratio for each treatment k.

2. Markov Decision-Analysis

Another formulation of the process is that used by Beck and Pauker. In 1983, Beck and Pauker described the use of Markov processes for deciding prognosis (outcome) in medical applications (Beck and Pauker, 1983). Their method (Markov decision-analysis) provides a convenient way of modelling outcomes for clinical problems with ongoing risk. Analogous to the Markov chain model in the previous section, the model assumes that the patient is always in one of a finite number of *Markov health states.* All events of interest are modelled as transitions from one state to another. Each state is assigned a cost or utility, and the contribution of this cost to the overall outcome depends on the length of time spent in that state. The time horizon of the analysis is divided into equal increments of time (cycles). During each cycle, the patient may make a transition from one state to another. The length of the cycle is chosen to represent a clinically meaningful time-interval.

Evaluation of the process yields the expected amount of time spent in each state. The cost that is associated with spending one cycle in a particular state is referred to as the *incremental cost.* Cost accrued for the entire process history is the total number of cycles spent in each state, (t_s) each multiplied by the incremental cost for that state (u_s):

$$\textit{Expected cost} = \sum_{s=1}^{n} t_s u_s. \tag{32}$$

The probability of making a transition from one state to another during a single cycle are the transition probabilities.

Sonnenberg and Beck devised a computational method called *cohort analysis* to analyze the model (Sonnenberg and Beck, 1993). Cohort analysis begins with 100 percent of a hypothetical population (the cohort) initially in the (well) state. For each cycle, the fraction of the cohort initially in each state is partitioned among all states according to the transition probabilities. This results in a new distribution of the cohort among the various states for the subsequent cycle. The cost accrued for the cycle is the *cycle sum* and is calculated by the formula:

$$Cycle\ sum = \sum_{s=1}^{n} f_s u_s, \tag{33}$$

where n is the number of states, f_s is the fraction of the cohort in state s, and u_s is the incremental cost of state s. The cycle sum is added to a running total which is the *cumulative cost*. The expected cost for the cohort at the end of the simulation (a simulated finite time horizon determined by the user) is equal to the mean cumulative cost at the end of the simulation divided by the size of the cohort.

The model used was constructed as a decision tree using a Markov cycle-tree representation to illustrate the process (Hollenberg, 1984), as shown in Figure 1. The square represents the decision node and its three branches represent the three therapy choices.

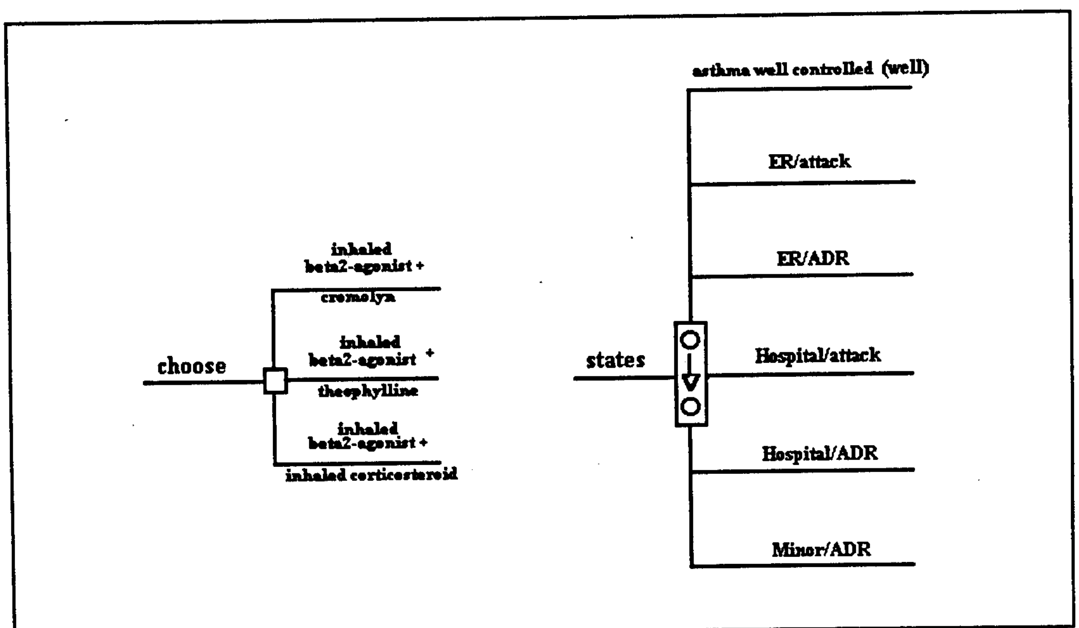

Figure 1 Decision and State Trees for the Model.

Each branch leads to the state tree representing the states. The model assumes that at all times a patient will be in one of these states and that the movement of the patients from one state to another is dependent only on the present state and is independent of past history (the Markovian assumption).

Each of the state branches leads to the probability tree which depicts all of the possible events that occur during a single cycle of the simulation. Figure 2 depicts the probability event tree for the (well) state. These events are: 1) exacerbation; 2) adverse drug reaction; 3) no event. An exacerbation

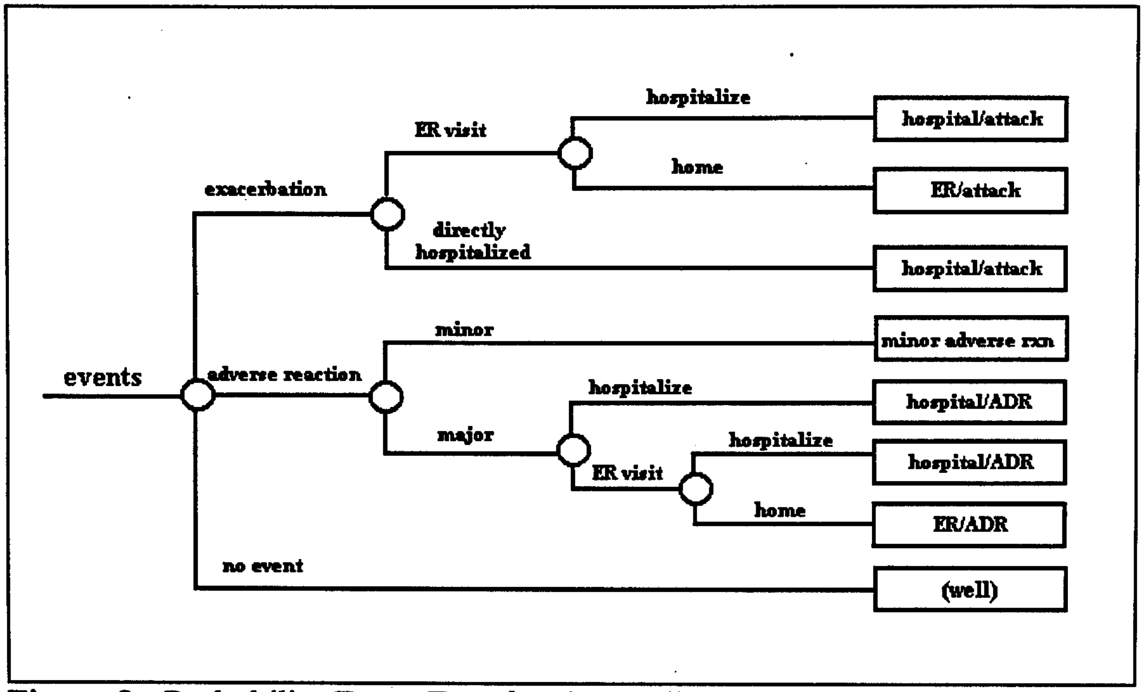

Figure 2 Probability Event Tree for the (well) state.

may lead to direct hospitalization or an emergency room visit. An emergency room visit may result in a hospitalization. If a patient has an adverse drug reaction it may be major (defined as requiring an emergency room visit, hospitalization, or both) or minor (defined as discovered during a routine follow-up appointment and requiring a cost to treat). Adverse reactions that do not incur a cost are not modelled. The label on each terminal branch of the cycle tree indicates the Markov health state in which the patient will begin the next cycle. For example, whether admitted directly or following an emergency room visit, patients admitted to the hospital for an attack will begin the subsequent cycle in the "hospital/attack" state. Patients seeking treatment for an adverse effect in the emergency room will begin the next cycle in the "ER/ADR" state. The model assumes all patients in any "hospital" state (*i.e.*, Hospital/attack and Hospital/ADR) are discharged home. The complete model is illustrated in Figure 3.

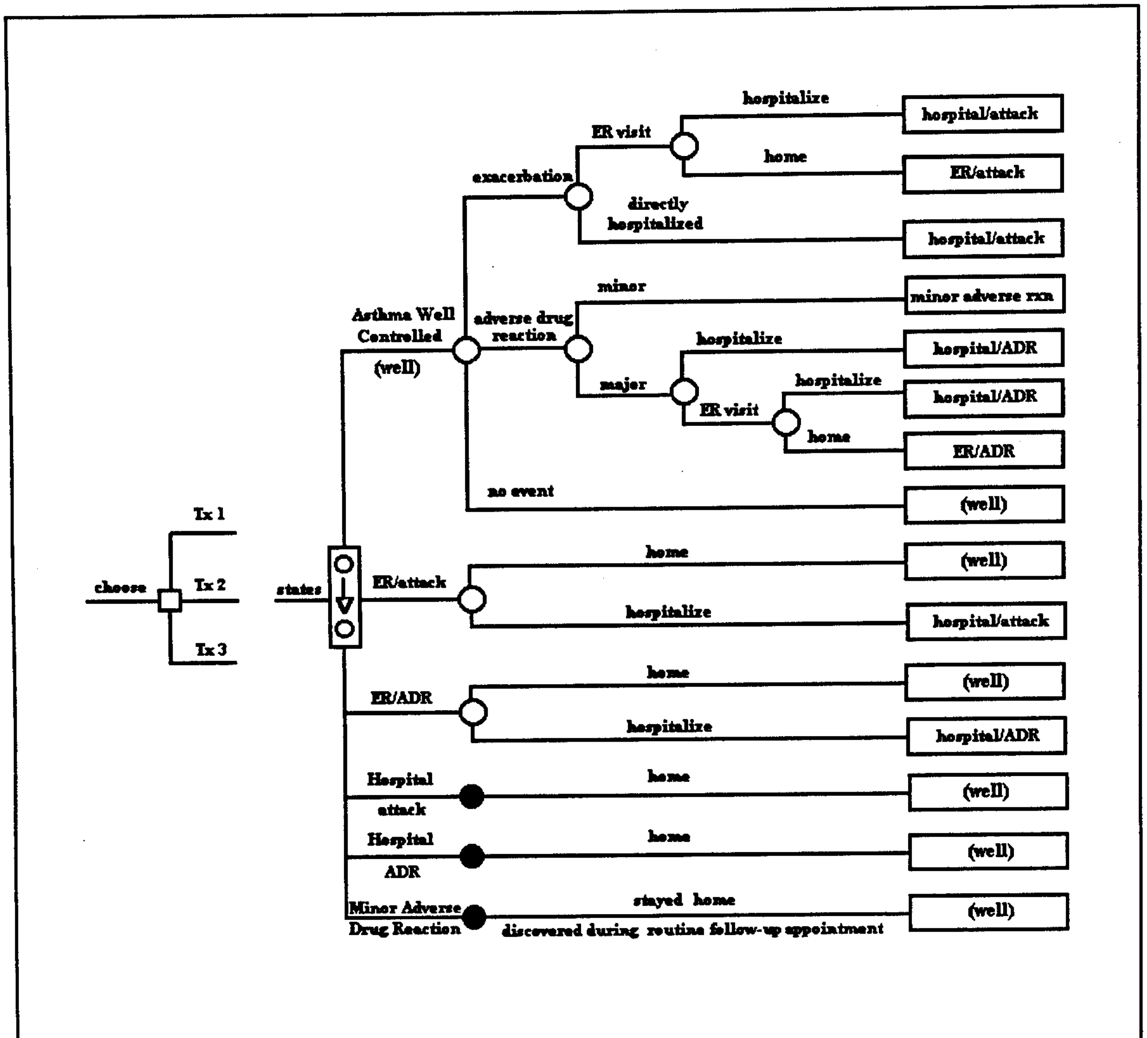

Figure 3 The Complete Model.

The costs for each state are weighted by the fraction of patients in that particular state and added to a *cumulative total*. The cumulative total cost at the end of the simulation (a simulated finite time horizon determined by the user) divided by the cohort size, is equal to the estimated expected cost of treating a patient for one time interval (day/week/month; determined by the transition probabilities). The effectiveness measure is defined in terms of a time interval without an exacerbation or therapy complication (herein referred to as a Complication Free Interval (CFI)). The effectiveness for each therapy is calculated by crediting patients one CFI during each cycle they are in the (well) state. When weighted by the fraction of patients in that state, this results in the estimated expected number of CFI's per patient for each therapy regimen. The cost-effectiveness for each therapy is computed by dividing the estimated expected cost by the estimated effectiveness. Measures of costs can be discounted to account for the decreasing present value of future costs.

D. DATA AND TRANSITION PROBABILITY ESTIMATES

The transition probabilities for all states are needed to evaluate the models. A retrospective chart review was conducted in an effort to obtain these probabilities.

Health charts from asthma patients receiving one of the three therapies were identified via a computerized search of pharmacy records at Naval Medical Center San Diego (NMCSD), a 600-bed teaching hospital.

To be included in the study, patients must have met the following criteria: (1) an adult eighteen years old or older; (2) moderate asthma is the only medical condition; (3) received health care only from NMCSD; (4) a non-smoker; (5) on one of the three treatment regimens for at least one year.

Several assumptions were made. First, although compliance is usually less than perfect, it was assumed that all patients complied perfectly with the prescribed treatment program. Second, all patients were prescribed medications to be taken on an as-needed (PRN) basis. It is not possible to ascertain from medical records how often patients use PRN medications. Therefore, after consultations with several pharmacists and physicians, it was assumed that all patients used PRN medications ten percent of the time. Third, since the study only includes adults, it was assumed that all patients were knowledgeable about their medications and used them correctly.

1. Study Sample

The review of eligible records yielded 81 qualifying patients, of whom 21 were in the Treatment 1 group, 30 were in the Treatment 2 group, and 30 were in the Treatment 3 group. Characteristics of the study sample by treatment groups are compiled in Table 1. The treatment groups did not differ significantly (statistically) in age or sex (ANOVA, p-value < 0.05). However,

	Tx 1 n=21	Tx 2 n=30	Tx 3 n=30	p-value
SEX				
Male	3	3	2	not signif.
Female	18	27	28	(p=0.94)
AGE (years)				
Mean	33.77	34.97	32.06	not signif.
Range	22-45	21-56	21-60	(p=0.47)
NUMBER OF ER VISITS *(per year per patient)*				
Mean	3.01	2.11	2.50	significant
Range	1-5	1-4	1-5	(p< 0.05)
NUMBER OF HOSPITALIZATIONS *(per year per patient)*				
Mean	0	0	0	
Range	--	--	--	
NUMBER OF ADVERSE REACTIONS *(per year per patient)*				
Mean	0	0 .13	0 .43	significant
Range	--	0-1	0-2	(p<0.05)

Table 1. Characteristics of the Study Sample.

the study sample contains a larger number of females than males. Epidemiologic data indicate that among children, boys are more likely to have asthma (Tager, *et al.*, 1987; Anderson *et al.*, 1987). Although the National Institute of Allergy and Infectious Diseases (NIAID) Task force concluded in 1979 that being male is a risk factor for asthma (NIAID, 1979), other reports suggest that asthma prevalence either does not differ between adult men and women (Broder *et al.*, 1974; Schachter *et al.*, 1984) or that adult women predominate in clinic populations (Pedersen and Weeke, 1981). There has been no satisfactory explanation of this apparent discrepancy between epidemiologic and clinical results. One possible explanation for the predominance of female subjects in this study is that military recruitment standards consider individuals with any history of asthma from birth to the present to be disqualified for military service (Department of Defense Directive, 1994). Since the Navy population is 88 percent male and only a small percentage of males are dependent spouses, this may account for the low male incidence count in the sample[1]. Other possible explanations are: a) females may seek medical treatment more frequently than males (Gijsbers van Wijk *et al.*, 1991), b) diagnostic discrepancies are possible between the sexes (Burrows, 1987).

2. Adverse Drug Reactions

There were no adverse drug reactions documented for any patient in the Treatment 1 group. A total of four adverse drug reactions were recorded in the charts for the Treatment 2 group. Oral candidiasis (a fungal infection of the mouth) was experienced once by three different patients. All three cases were treated in the emergency room. One patient complained of coughing during a routine follow-up visit. There were 13 adverse drug reactions associated with Treatment 3. Four patients presented to the emergency room with complaints of tachycardia. Three patients were treated in the emergency room for gastric irritation (dyspepsia / nausea / vomiting), and two patients were seen in the emergency room for severe headache (not migraine). Two patients reported nervousness, and two patients reported difficulty sleeping, during a routine follow-up visit. Table 2 summarizes the adverse drug reactions of the study sample.

3. Number of Emergency Room Visits

The 21 patients in the Treatment 1 group visited the emergency room 65 times. Patients in the Treatment 2 group had a total of 63 visits, and the

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[1] Percentages provided by the Navy Bureau of Personnel and include Training and Administration of Reserves (TAR).

	Tx 1	Tx 2	Tx 3
Oral Candidiasis	0	3	0
Coughing	0	1	0
Tachycardia	0	0	4
Gastric Irritation	0	0	3
Headache	0	0	2
Nervousness	0	0	2
Difficulty Sleeping	0	0	2
Total	0	13%	43%

Table 2. Adverse Reactions from Study Sample.

Treatment 3 group had a total of 75 emergency room visits. The months of March and December had the greatest number of emergency room visits among the three groups. These two months represent 26 percent of the emergency room visits for all three groups. During the month of December, 54 percent of the visits generated by the treatment groups occurred during the week of December 20 through December 27. The total number of emergency room visits by month are summarized in Figure 4. There is a remarkably common

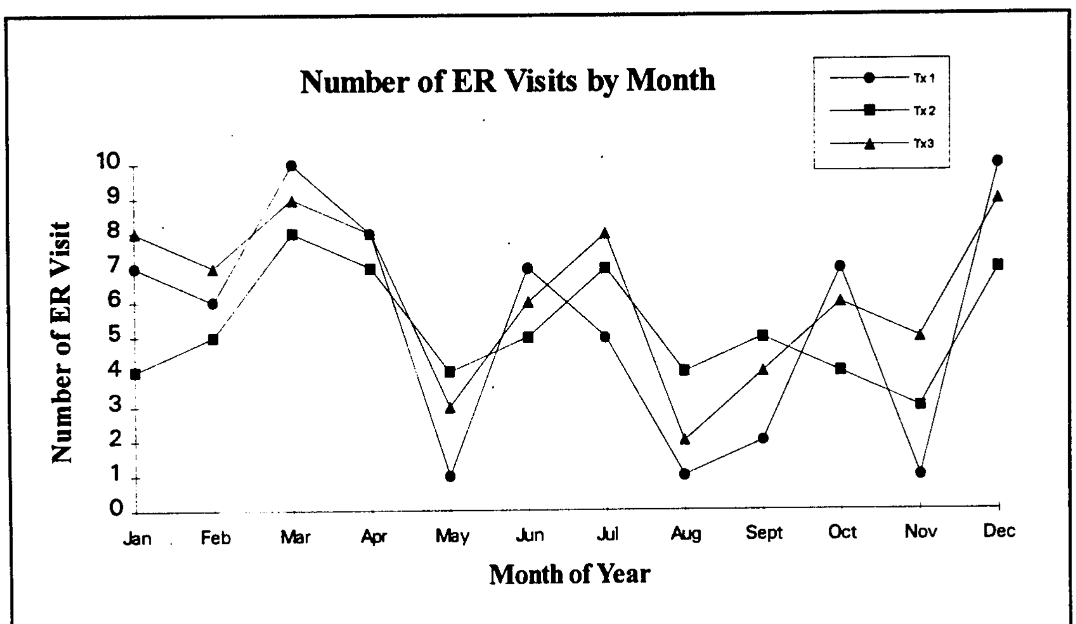

Figure 4. Number of ER Visits by Month.

monthly fluctuation of emergency room visits among all treatments. This is most likely attributed to the level of asthma-attack triggers (*e.g.*, pollens, molds, air pollutants, stress, etc.) during the month. For example, March is a month of high emergency room use; it also is a month where the chance of Santa Ana winds are high. Santa Ana winds are strong, hot, dry winds that blow off the mountains towards the Pacific Ocean and can last for days. Santa Ana winds also, typically, have higher levels of pollen, air pollution, dust and other irritants, that could lead to higher emergency room use by asthmatics. A similar association can be made with stress and the increased emergency room use during the month of December. No attempt has been made to incorporate effects of seasonality into the models that have been introduced, but this could be captured by a time-varying Markov model.

4. Number of Hospitalizations

There were no hospitalizations for any patient in any of the treatment groups.

5. Event Probability Estimates

Data extracted from the charts provide information on events as rates (*i.e.*, emergency room visit rate, adverse drug reaction rate). These rates can be converted to the corresponding transition probabilities by Equation (34); for any constant rate ρ, the probability of at least one event occurring over a time interval of t time units is:

$$P(t) = 1 - e^{-\rho t} . \tag{34}$$

Equation (34) can be easily understood by examining the survival curve for a process defined by a constant rate. The equation describing the survival curve is $f = e^{-\rho t}$, where f is the fraction surviving at time t and ρ is the constant transition rate. At any given time, the fraction that has experienced the event is equal to $1 - f$. Therefore the curve describing the probability that at least one event will occur in time t is simply $1 - f$, or $1 - e^{-\rho t}$ as in Equation (34). The probabilities estimated from the study sample are listed in Table 3.

	Tx 1	Tx 2	Tx 3
Daily probability ER visit for attack *Standard Error*	0.008 (0.0006)	0.005 (0.0005)	0.007 (0.0004)
Daily probability ER visit for ADR *Standard Error*	0	0.0004 (0.0002)	0.001 (0.0004)
Daily probability hospital admission for attack	0	0	0
Daily probability hospital admission for ADR	0	0	0
Daily probability of minor ADR	0	0	0

Table 3. Daily Probabilities Estimated from the Study Sample.

E. META-ANALYSIS

Since the transition probabilities are derived from a retrospective chart review there is a potential for bias. Patients are not randomly assigned to the three treatment groups so it is possible that differences in outcomes could be attributed to individual differences among the patients. Administrative policies, geographic location, and population uniqueness (military), also could impart bias. Besides "clinic patient bias", the data is extracted from patient charts, which is solely dependent on the quality of documentation. Furthermore, the small sample sizes may not properly represent the entire population. Because of these shortcomings, a meta-analysis of published data was conducted to estimate each of the variables in the model.

Meta-analysis refers to a collection of techniques whereby the results of two or more independent studies are statistically combined to yield an overall answer to a question of interest (Hunter and Schmidt, 1990). Two procedures were used to combine data from published clinical trials. The first is a method given by Fleiss (Fleiss, 1993). The procedure combines measures of treatment difference to an estimator of the common treatment effect. The method assumes that the measure of effect size given by each of the studies is the standardized difference between two means:

$$Y = \frac{x_1 - x_2}{s} \tag{35}$$

where x_1 and x_2 are the means in the two treatment groups and s is the square root of the pooled variance. Then an estimator using values Y_1, Y_2, . . ., Y_c from c studies is:

$$Y^* = \frac{\sum_{i=1}^{c} w_i Y_i}{\sum_{i=1}^{c} w_i} \tag{36}$$

where:

$$w_i = \frac{n_{i1} + n_{i2}}{n_{i1} + n_{i2}} \tag{37}$$

and n_{i1} and n_{i2} are the sample sizes in each treatment group for the i[th] study. The standard error of Y^* is given by:

$$SE(Y^*) = (\sum_{i=1}^{c} w_i)^{\frac{-1}{2}}. \tag{38}$$

Fleiss considers the problem of assessing whether the effect sizes from the different studies are homogeneous. The test statistic is:

$$Q = \sum_{i=1}^{c} w_i (Y_i - Y^*)^2. \tag{39}$$

The hypothesis of homogeneity is rejected if Q exceeds $\chi^2_{c-1,\,\alpha}$, the 100 (1-α) percentile of the chi-square distribution with c -1 degrees of freedom.

The second procedure used is the DerSimonian and Laird (D&L) method (DerSimonian and Laird, 1986). In this approach, the parameter of interest in each study is the difference between event rates in the treated and control groups and is similar to Fleiss. Let d_{ti} and d_{ci} be the number of events in the treated and control groups, respectively, and the corresponding sample size be n_{ti} and n_{ci}. The proportions of events in the treated and control groups are:

$$p_{ti}^* = \frac{d_{ti}}{n_{ti}} \tag{40}$$

and

$$p_{ci}^* = \frac{d_{ci}}{n_{ci}}, \tag{41}$$

and the rate difference in the i[th] study is:

$$\theta_i^* = p_{ti}^* - p_{ci}^*, \tag{42}$$

with variance estimated by:

$$V_i = \left[p_{ti}^* \frac{(1-p_{ti}^*)}{n_{ti}} \right] + \left[p_{ci}^* \frac{(1-p_{ci}^*)}{n_{ci}} \right]. \tag{43}$$

A test statistic of homogeneity is:

$$Q = \sum_{i=1}^{k} w_i (\theta_i^* - \overline{\theta}_w)^2 \tag{44}$$

where:

$$w_i = V_i^{-1} \quad \textit{and} \quad \overline{\theta}_w = \frac{\Sigma w_i \theta_i^*}{\Sigma w_i}. \tag{45}$$

To incorporate explicitly any among-study differences which may cause variability in treatment effects, such as patient populations, protocols, length of follow-up, etc., assume each study has its own treatment effect, θ_i. Let μ and τ^2 denote the mean and variance of the θ_i. A straightforward method of moments (MOM) estimate of the among-study variance is (DerSimonian and Laird, 1986),

$$\overline{\tau}^2 = \max \left[0, \frac{Q-(K-1)}{\Sigma w_i - \left(\frac{\Sigma w_i^2}{\Sigma w_i} \right)} \right]. \tag{46}$$

Given this estimate, the MOM estimate of the mean effect of treatment (the mean rate difference) is:

$$\bar{\mu} = \frac{(\Sigma w_i^* \theta_i^*)}{\Sigma w_i^*} \tag{47}$$

with standard error estimated by:

$$SE(\bar{\mu}) = (\Sigma w_i^*)^{-\frac{1}{2}} \tag{48}$$

where

$$w_i^* = (V_i + \bar{\tau}^2)^{-1} . \tag{49}$$

The results of the meta-analysis are summarized in Table 4. Because of the limited amount of published data, results from both adult and children studies were included.

F. SUMMARY OF STUDIES USED FOR META-ANALYSIS

1. Cromolyn

A retrospective record-based study by Ross *et al.*, to study the effects of the inclusion of cromolyn sodium in the regular treatment plan for asthmatic patients states that patients in the cromolyn sodium group made three visits to the emergency room, where as those in the control group made 54 such visits. The number of hospital admissions decreased to one in the cromolyn sodium group and seven in the control group (Ross *et al.*, 1988). An open drug trial of cromolyn in 19 asthmatic children by Mellon *et al.*, reports a reduction in emergency room visits from 24 visits reported by nine of the 16 patients to four visits reported by four patients out of 16. The study also reports a reduction in hospitalizations from three episodes documented for three patients out of 16 to zero episodes (Mellon *et al.*, 1982). A double-blind crossover study designed to test the effectiveness of cromolyn therapy in children with chronic asthma by Hyde *et al.*, claims a reduction in hospitalization for asthma exacerbations from 38 hospitalizations experienced by 13 patients out of 33 to 12

		Value	Range	SE	Reference
Daily probability Er visit for attack	Tx 1	.005	(.001-.050)	.057	Ross *et al.* Mellon *et al.*
	Tx 2	.003	(.001-.050)	.065	Tinkelman *et al.* VanEssen-ZandVliet *et al.*
	Tx 3	.010	(.001-.050)	.064	Wood *et al.*, Pierson *et al.*, Tinkelman *et al.*
Daily probability ER visit for ADR	Tx 1	.001	(.000-.050)	.014	Settipane *et al.*, Setcow *et al.*, Newth *et al.*, Shapiro *et al.*, Chen *et al.*, Hambleton *et al.*, McLean *et al.*, Blumenthal *et al.*
	Tx 2	.001	(.000-.050)	.058	Meltzer *et al.*, Gustafsson *et al.*, VanEssen-ZandVliet *et al.*, Tse and Bernstein, Sears *et al.*, Tinkelman *et al.*
	Tx 3	.005	(.000-.050)	.076	Meltzer *et al.*, Tinkelman *et al.*, Pierson *et al.*
Daily probability hospital admission for attack	Tx 1	.001	(.000-.010)	.063	Ross *et al.*, Mellon *et al.*, Mascia *et al.*, Hyde *et al.*
	Tx 2	.001	(.000-.010)	.024	Tinkelman *et al.* VanEssen-ZandVliet *et al.* Rutten-VanMolken *et al.*
	Tx 3	.005	(.000-.010)	.049	Hallas *et al.*, Wood *et al.* Tinkelman *et al.*
Daily probability hospital admission for ADR	Tx 1	.001	(.000-.010)	.014	Settipane *et al.*, Setcow *et al.*, Newth *et al.*, Shapiro *et al.*, Chen *et al.*, Hambleton *et al.*, McLean *et al.*, Blumenthal *et al.*
	Tx 2	.001	(.000-.010)	.058	Meltzer *et al.*, Gustafsson *et al.*, VanEssen-ZandVliet *et al.*, Tse and Bernstein, Sears *et al.*, Tinkelman *et al.*
	Tx 3	.003	(.000-.010)	.076	Pierson *et al.*, Tinkelman *et al.* , Meltzer *et al.*
Daily probability minor ADR	Tx 1	.001	(.000-.050)	.021	Settipane *et al.*, Setcow *et al.*, Newth *et al.*, Shapiro *et al.*, Chen *et al.*, Hambleton *et al.*, McLean *et al.*, Blumenthal *et al.*
	Tx 2	.002	(.000-.050)	.030	Meltzer *et al.*, Gustafsson *et al.*, VanEssen-ZandVliet *et al.*, Tse and Bernstein, Sears *et al.*, Tinkelman *et al.*
	Tx 3	.001	(.000-.050)	.068	Meltzer *et al.*, Pierson *et al.*, Tinkelman *et al.*

Table 4. Daily Probabilities Estimated from Published Data.

hospitalizations reported by seven of the 33 patients (Hyde *et al.*, 1973). In a long-term study by Mascia *et al.,* who analyzed 53 children with asthma who have been taking cromolyn continuously for up to three and one-half years found that cromolyn therapy reduced hospitalizations from 72 percent to 13 percent (Mascia *et al.*, 1976).

A study by Settipane *et al.*, evaluated adverse effects thought to be associated with cromolyn sodium in all asthmatic patients over a four year period (Settipane *et al.,* 1979). The study reports that the frequency of adverse reactions to cromolyn sodium in asthmatic patients was two percent (Settipane *et al.*, 1979). Setcow *et al.* compared the efficacy and safety of cromolyn versus theophylline in predominately young, mild to moderate asthmatics (Setcow *et al.*, 1983). In that study, no adverse reactions were reported by the cromolyn group (Setcow *et al.*, 1983). No adverse reactions to cromolyn were also reported by Newth *et al.*, Shapiro *et al.*, and Chen *et al.* A 1977 double-blind comparison of cromolyn and theophylline by Hambleton *et al.*, found that 26 percent of the asthmatics on the cromolyn therapy experienced mild adverse reactions (Hambleton *et al.*, 1977). However, none required treatment with another drug (Hambleton *et al.*, 1977). In a double-blind, placebo-controlled crossover trial of cromolyn, McLean *et al.* found that 15 percent of patients in the study reported side-effects to cromolyn (McLean *et al.*, 1973). Again, none of the reactions required treatment with another drug (McLean *et al.*, 1973). Blumenthal *et al.* conducted a double-blind study to determine the efficacy and safety of cromolyn sodium by metered-dose inhaler compared to placebo. Only one patient out of 46 (two percent) complained of an adverse reaction (minor throat irritation) related to cromolyn (Blumenthal *et al.*, 1988).

2. Corticosteroids

In a multi-center, double-blind, randomized, controlled trial by Tinkelman *et al.*, to compare the benefits and adverse reactions of theophylline and beclomethasone in children with mild to moderate asthma, it is reported that 4.9 percent of children in the beclomethasone group had one or more emergency room visits or hospitalizations for asthma (Tinkelman *et al.*, 1993).

A randomized double-blind multicenter clinical study of the effects of corticosteroids and/or beta$_2$-agonists by Van Essen-Zandvliet *et al.*, states that 14 percent of the patients in the beta$_2$-agonist and corticosteroid group visited an emergency room for an asthma exacerbation and that there were no hospitalizations for asthma exacerbations (Van Essen-Zandvliet *et al.*, 1992).

In a cost-effective analysis of inhaled corticosteroid plus bronchodilator therapy, 3.4 percent of patients in the beta$_2$-agonist and corticosteroid group were hospitalized for asthma (Rutten-van Molken *et al.*, 1993). A long-term comparison study of albuterol, theophylline, and beclomethasone by Meltzer *et al.*, found that 14 percent of patients treated with a beta$_2$-agonist and corticosteroid reported exacerbations of asthma (Meltzer *et al.*, 1992). In a randomized double-blind cross-over study comparing the effects of increasing the dosage of inhaled corticosteroids in adults with mild to moderate asthma by Sears *et al.*, found that 23 patients out of 32 experienced a total of 70 asthma exacerbations while on a beta$_2$-agonist and corticosteroid during the study (Sears *et al.*, 1992).

A study by Gustafsson *et al.*, designed to compare the efficacy and safety of two inhaled corticosteroids, reports 47 percent of patients receiving beclomethasone had adverse events (Gustafsson *et al.*, 1993). Of those patients experiencing adverse reactions, 1.5 percent presented with oral candidiasis (Gustafsson *et al.*, 1993). A review article of corticosteroid aerosols by Tse and Bernstein states that beclomethasone causes major adverse reactions in about five percent of patients (Tse and Bernstein, 1984). In a randomized double-blind cross-over study comparing the effects of increasing the dosage of inhaled corticosteroids in adults with mild to moderate asthma by Sears *et al.*, found that 6.2 percent of the patients experienced oral candidiasis (Sears *et al.*, 1992). A study of the effects of corticosteroids and/or beta$_2$-agonists by Van Essen-Zandvliet *et al.*, states that 28 percent of the patients in the beta$_2$-agonist and corticosteroid group reported an adverse effect but none were serious (Van Essen-Zandvliet *et al.*, 1992). In a multi-centered, double-blind, randomized, controlled trial by Tinkelman *et al.*, to compare the benefits and adverse reactions of theophylline and beclomethasone in children with mild to moderate asthma, it is reported that 43.5 percent of patients taking beclomethasone experienced adverse reactions (Tinkelman *et al.*, 1993). Of those patients who reported adverse drug reactions, 21.3 percent experienced headache, 6.5 percent experienced gastric irritation, and 1.9 percent reported oral candidiasis (Tinkelman *et al.*, 1993). A long-term comparison study of albuterol, theophylline, and beclomethasone by Meltzer *et al.*, found that 41 percent of adverse reactions associated with a beta$_2$-agonist and corticosteroid treatment were for headache, 16 percent for nervousness, eight percent for vomiting, and 16 percent for sleeping difficulties (Meltzer *et al.*, 1992).

3. Theophylline

In a study by Hallas *et al.*, four out of 11 patients (36 percent) taking a beta$_2$-agonist and sustained-release theophylline were admitted to the hospital for an asthma attack (Hallas *et al.*, 1992). Wood *et al.* conducted a study on compliance with theophylline therapy among asthmatic children (Wood *et al.*, 1979). In their paper it is reported that compliant patients had a mean of 14.5 emergency visits and 2.4 hospital admissions in the past year (Wood *et al.*, 1979). A long-term, double-blind comparison of controlled-release albuterol versus sustained-release theophylline in adolescents and adults with asthma by Pierson *et al.*, states that 19 percent of the patients in the theophylline group experienced at least one exacerbation that required a short course of oral corticosteroids (Pierson *et al.*, 1990). A long-term comparison study of albuterol, theophylline, and beclomethasone by Meltzer *et al.*, found that 33 percent of patients treated with a beta$_2$-agonist and theophylline reported exacerbations of asthma (Meltzer *et al.*, 1992).

In a multi-centered, double-blind, randomized, controlled trial by Tinkelman *et al.*, to compare the benefits and adverse reactions of theophylline and beclomethasone in children with mild to moderate asthma, it is reported that 65.7 percent of patients taking theophylline had adverse reactions (Tinkelman *et al.*, 1993). Of those patients experiencing adverse reactions, 31.4 percent reported headaches, and 30.4 percent reported gastric irritation while taking theophylline (Tinkelman *et al.*, 1993). A long-term, double-blind comparison of controlled-release albuterol versus sustained-release theophylline by Pierson *et al.*, reports that 23 percent of patients taking theophylline exhibited at least one adverse reaction during the study (Pierson *et al.,* 1990). The Pierson *et al.* study also found that eight percent of the patients reported occurrences of headache, 3.2 percent reported nervousness, and 12.9 percent reported gastric irritation (Pierson *et al.*, 1990). A long-term comparison study of albuterol, theophylline, and beclomethasone by Meltzer *et al.*, found that 44 percent of adverse reactions associated with a beta$_2$-agonist and theophylline treatment were for headache, 15 percent for nervousness, 21 percent for vomiting, and 10 percent for sleeping difficulties (Meltzer *et al.,* 1992).

G. TRANSITION PROBABILITY MATRICES

Substituting the probabilities extracted from the literature into Equation (3) yields the daily transition probability matrices[1] for each of the treatments.

$$P^{(1)} = \begin{bmatrix} .991 & .005 & .001 & .001 & .001 & .001 \\ .999 & 0 & 0 & .001 & 0 & 0 \\ .999 & 0 & 0 & 0 & .001 & 0 \\ .370 & 0 & 0 & .630 & 0 & 0 \\ .530 & 0 & 0 & .470 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$P^{(2)} = \begin{bmatrix} .992 & .003 & .001 & .001 & .001 & .002 \\ .999 & 0 & 0 & .001 & 0 & 0 \\ .999 & 0 & 0 & 0 & .001 & 0 \\ .370 & 0 & 0 & .630 & 0 & 0 \\ .530 & 0 & 0 & .470 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

[1]Probabilities for Hospital/attack and Hospital/ADR states based on mean 2.69 and 1.89 day hospital stay respectfully, during FY94, extracted from the Retrospective Case-Mix Analysis System (RCMAS).

$$P^{(3)} = \begin{bmatrix} .976 & .010 & .005 & .005 & .003 & .001 \\ .999 & 0 & 0 & .001 & 0 & 0 \\ .999 & 0 & 0 & 0 & .001 & 0 \\ .370 & 0 & 0 & .630 & 0 & 0 \\ .530 & 0 & 0 & .470 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

H. COSTS

Costs are counted in the model by associating a specific cost with each state. The cost for each state is:

0) Well: cost of one day supply of medication
1) ER/attack: MEPRS[1] cost of an ER visit for NMCSD
2) ER/ADR: MEPRS cost of an ER visit for NMCSD
3) Hospital/attack: MEPRS cost of mean 2.69 day hospital stay[2]
4) Hospital/ADR: MEPRS cost of mean 1.89 hospital stay[2]
5) Minor/ADR: expected cost of one day supply of medications to treat reaction.

Table 5 lists the costs per day used in the models.

[1]Medical Expense and Performance Reporting System (MEPRS). A computer based program designed to reflect all costs of services including personnel, direct expenses, and depreciation.

[2]Mean hospital stay based on fiscal year 1994 data extracted from the Retrospective Case-Mix Analysis System (RCMAS).

	Tx 1	Tx 2	Tx 3
Well	2.16	0.60	0.26
ER/attack	140	140	140
ER/ADR	140	140	140
Hospital/attack	557	557	557
Hospital/ADR	529	529	529
Minor/ADR	0.83	0.83	0.83

Table 5. Daily Costs used in the Models.

IV. RESULTS

A. MODEL INPUTS

All models were evaluated according to the transition probabilities estimated in Chapter III from a meta-analysis of the literature. The discount rate used was five percent and the length of time was five years (1825 days). All calculations except for the cohort analysis were performed with the assistance of *MAPLE V Release 3* computer software and the cohort analysis was programmed using *Turbo Pascal for DOS version 7.0* computer software.

The cohort analysis was started with 1000 hypothetical patients in the Asthma Well Controlled (well) state. Every day (one cycle for the analysis) the patients are newly re-distributed among the six states (Well, ER/attack, ER/ADR, Hospital/attack, Hospital/ADR, Minor/ADR) according to the transition probabilities estimated in Chapter III from a meta-analysis of the literature.

For each variable in the models, sensitivity analysis was performed which varied the distribution of that variable throughout the range listed in Table 4 and the analysis was repeated for each value within that range.

B. OUTCOMES

Table 6 displays the estimated expected present value of Treatments 1, 2, and 3, for each of the models. All four models resulted in nearly identical values with

	Discrete Time	Continuous Time	Marked Poisson	Cohort Analysis	Avg	Std Error
Tx 1	9141.68	9141.04	9258.54	9141.59	9170.71	29.27
Tx 2	6217.56	6217.12	6293.09	6217.63	6236.35	18.91
Tx 3	21125.21	21123.73	21922.69	21125.08	21324.18	199.50

Table 6. Estimated Expected Present Value Over a Five Year Period.

Treatment 1 (a $beta_2$-agonist and a corticosteroid) as the therapy with the lowest estimated expected present value costs when associated hospital services are included.

Table 7 lists the estimated effects of Treatment 1, Treatment 2, and Treatment 3 on the proportion of time spent "well" for each of the models. All four models again gave nearly identical numerical values with Treatment 1 accumulating a slightly higher proportion of time in the "well" state over a five year time horizon.

	Discrete Time	Continuous Time	Marked Poisson	Cohort Analysis	Avg	Std Error
Tx 1	0.988	0.988	0.988	0.988	0.988	0
Tx 2	0.989	0.989	0.989	0.989	0.989	0
Tx 3	0.964	0.964	0.961	0.965	0.9635	0.00086

Table 7. Estimated Proportion of Time Spent "well".

Dividing the daily expected present value by the proportion of time spent "well" yields the cost/effectiveness ratio. The cost/effectiveness ratios for each of the treatments are summarized in Table 8.

	Discrete Time	Continuous Time	Marked Poisson	Cohort Analysis	Avg	Std Error
Tx 1	5.069	5.069	5.135	5.069	5.085	0.0165
Tx 2	3.445	3.445	3.486	3.445	3.449	0.0102
Tx 3	12.000	12.000	12.499	11.995	12.123	0.1251

Table 8. Cost-Effectiveness Ratios.

Treatment 2 has the lowest cost-effectiveness ratio of the three treatments indicating it is the therapy of choice when associated hospital costs are included. Treatment 3, even though it has the lowest maintenance medication costs, has the highest cost-effectiveness ratio suggesting it is the least desirable therapy when associated hospital services are included in the costs.

The estimated present value costs of each treatment were compared to the estimated present value if costs associated with the emergency room use and hospitalizations were excluded. A summary of the comparison is illustrated in Figure 5.

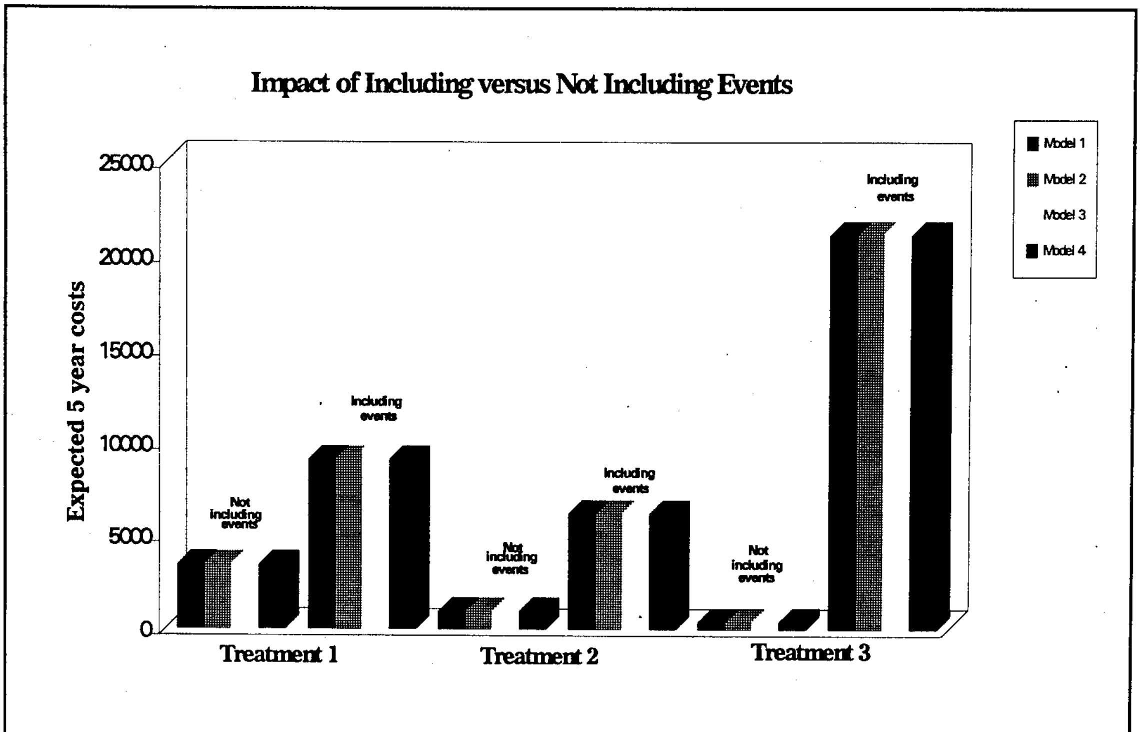

Figure 5. Impact on Costs of Including/Excluding Events.

C. SENSITIVITY ANALYSIS

The analysis results in a higher cost-effectiveness ratio for Treatment 1 than Treatment 2. However, the maintenance costs of Treatment 1 are 3.5 percent higher than Treatment 2. It is of interest to examine if reducing the maintenance costs associated with Treatment 1 would reduce its cost-effectiveness ratio to a point where it would become the preferred treatment. The maintenance costs (costs of a 30 day supply of medication) for Treatment 1 were reduced by five percent to 50 percent incrementally by five percent, and the cost-effectiveness ratios re-calculated. Figure 6 displays the results.

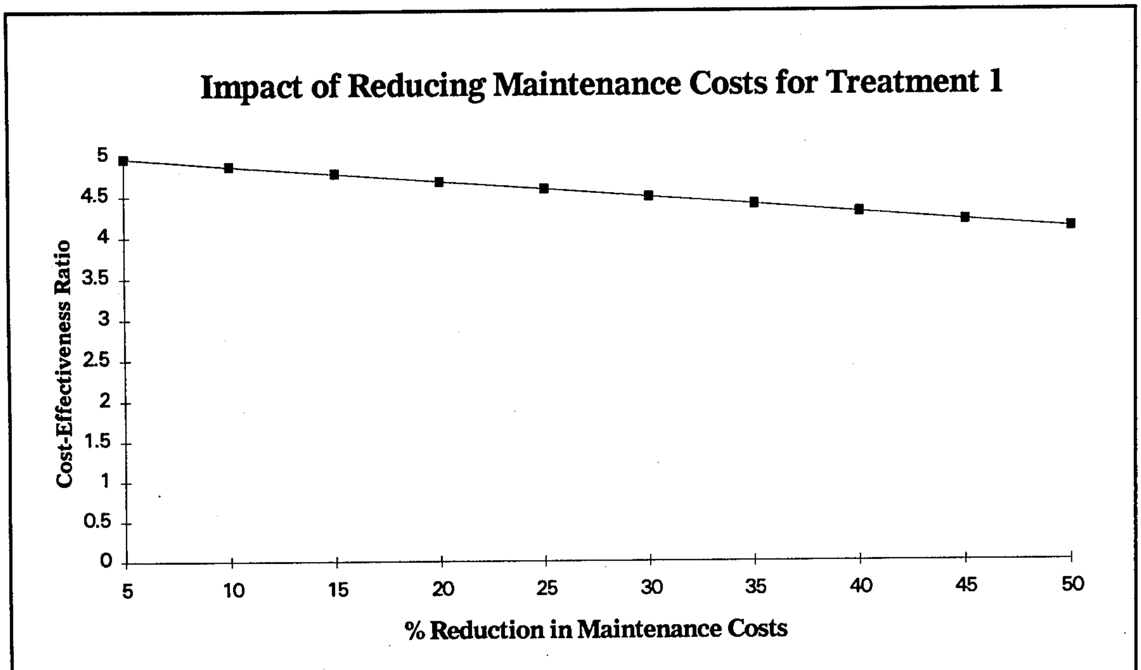

Figure 6. Impact of Reducing Maintenance Costs of Treatment 1.

Although reducing the maintenance costs for Treatment 1 by 50 percent lowers its cost-effectiveness ratio to 4.11, it is still higher than the 3.44 cost-effectiveness ratio of Treatment 2.

In an effort to determine the contribution of the cost of each individual event to the cost-effectiveness ratio, analysis was performed separately with each individual costs in turn set to zero, thus removing that cost from the model. The combined analysis found that regardless of which event had the cost removed from the model, Treatment 2 remained the preferred therapy. Treatment 2 also remained the preferred therapy when the discount factor was varied from five percent to 25 percent. However, cost-effectiveness ratios were sensitive to the probability of an emergency room visit or hospitalization. Therefore, the cost-effectiveness ratios were re-calculated varying the probabilities for emergency room visits/hospitalizations.

The probability of visiting an emergency room for an attack while on Treatment 2 was varied from zero to five percent and the cost-effectiveness ratios re-calculated. The results are shown in Figure 7. When the probability for an ER visit for an attack is 2.5 percent, the cost-effectiveness ratio for Treatment 2 increases to 6.18, which is

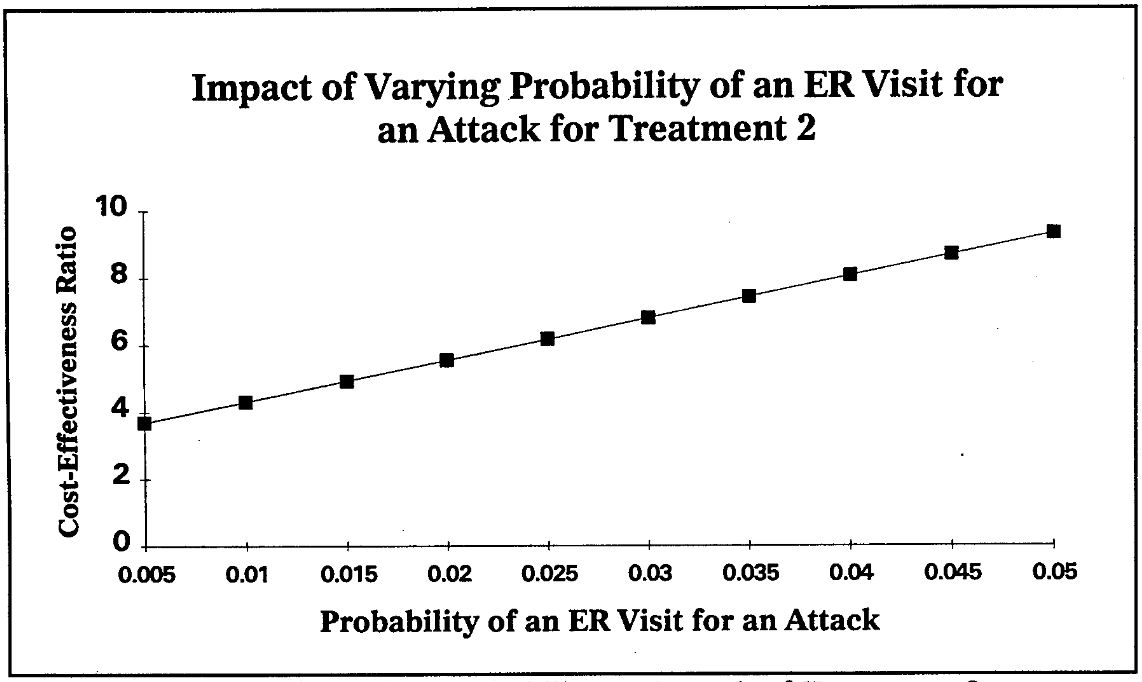

Figure 7. Impact of Varying Probability ER/Attack of Treatment 2.

greater than the cost-effectiveness ratio for Treatment 1 (5.06). Therefore, if the daily probability of a visit to the ER for an attack while on Treatment 2 is 2.5 percent then, keeping all else the same, Treatment 1 would be the preferred treatment. The probability for an ER visit for an adverse reaction for Treatment 2 was also varied from zero to five percent. Results yielded a cost-effectiveness ratio of 6.43 when the probability is increased to 2.5 percent. Accordingly, if the probability of an ER visit for an adverse reaction were 2.5 percent for Treatment 2, then Treatment 1 would be the preferred treatment.

Increasing the probability of a hospitalization for an attack while on Treatment

2 from 0.001 to 0.003 yields a cost-effectiveness ratio of 6.09. Therefore, if the daily probability of a hospitalization for an attack is 0.003 for Treatment 2, then Treatment 1 would be the preferred treatment. Increasing the probability of a hospitalization for an adverse reaction while on Treatment 2 from 0.001 to 0.003 yields a cost-effectiveness ratio of 5.61. Accordingly, if the probability of a hospitalization for an adverse reaction were 0.003 for Treatment 2, then Treatment 1 would be the preferred treatment. The results of varying the probability of a hospitalization for an attack from zero to 0.5 percent are illustrated in Figure 8.

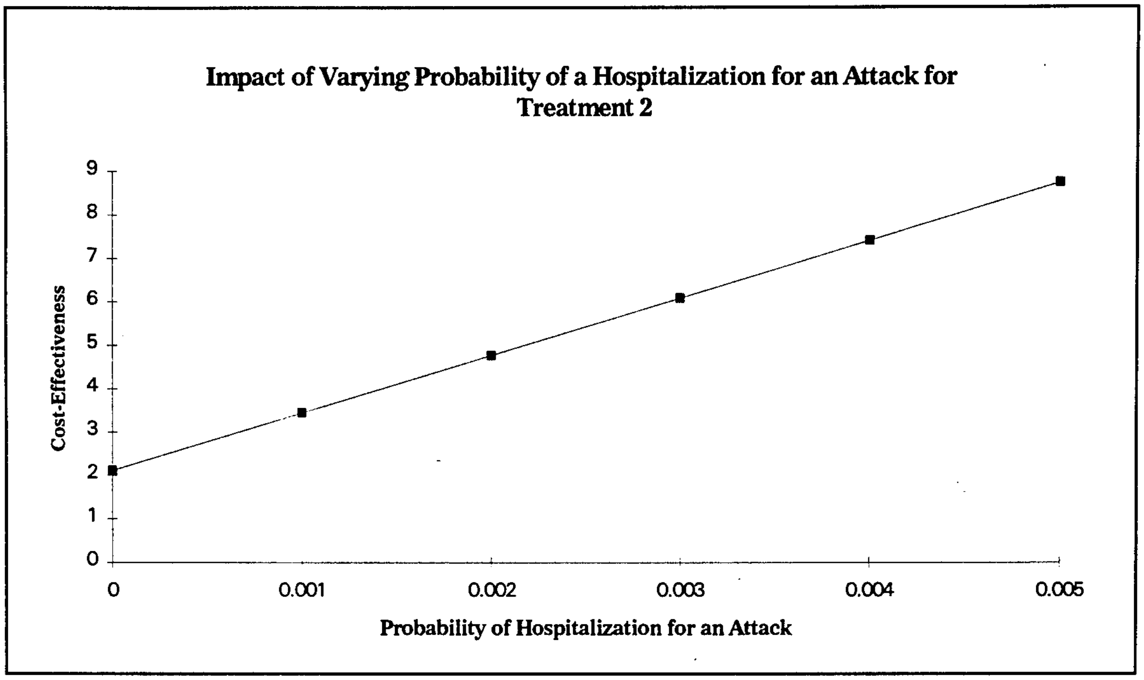

Figure 8. Impact of Varying Probability Hospital/Attack of Treatment 2.

V. DISCUSSION

A. CONCLUSIONS

Given the apparent equivalent therapeutic efficacy of the three pharmacotherapy strategies for moderate adult chronic asthma, the analysis presented in Chapter III indicates that a beta$_2$-agonist and a corticosteroid (Treatment 2) is the preferable pharmacotherapy of adult chronic moderate asthma when utilization of associated hospital services is considered. A beta$_2$-agonist agent and sustained-release theophylline (Treatment 3) is preferred when associated hospital services are not considered. The results are sensitive to the probability of an emergency room visit and/or hospitalization associated with each treatment.

B. VALIDITY

To accept these results, the validity of the models must be considered. Certainly, the models presented here are simple and require several assumptions: the time horizon of the process is five years; only one event can occur each day; probabilities remain constant; and additional factors such as allergies, pollen levels, seasonality effects, concomitant diseases, and patient preferences are not modelled. Nevertheless, the models are a reasonable approximation of the major cost factors associated with moderate adult chronic asthma.

Any analysis must consider the validity of the data upon which it is based. The probabilities used here are the result of meta-analysis. Meta-analysis methods are not universally accepted. The reviewer must make judgements as to which studies are appropriate to include in the review. As a result, meta-analysis has been criticized for mixing studies that measure "apples" with those that measure "oranges", so that no meaningful results can be obtained. Some of the studies summarized in Table 4 were not as well-controlled as others and dealt with highly selected patients from both children and adult populations. The selected studies themselves may be biased.

Published clinical trials may prevail in favor of "significant" or "promising" results. Clinical trials which fail to show any treatment differences are less likely to be published. Consequencely, conclusions of treatment effects based on a review of only published papers may be misleading. However, given that the retrospective chart review at Naval Medical Center San Diego (NMCSD) yielded a small sample with no data on hospitalizations, a meta-analysis of the literature was felt to be superior to *ad hoc* approaches such as, "impressionistic" or "expert opinion".

Data on costs for the models are also imperfect. While data on costs for the medications are readily available, costs associated with an emergency room visit are not identifiable at the individual patient level within Navy Medical Treatment Facilities (MTF's). That is, if an asthmatic reports to the emergency room for an attack, costs for laboratory, X-ray, medications, etc., are not recorded in an individual account, but are "pooled" into the Medical Expense and Performance Reporting System (MEPRS), designed to reflect all costs of services including personnel, direct expenses, and depreciation for "any" emergency room visit. The MEPRS cost of an emergency room visit for NMCSD of $140.00 was used for all treatments for both the "ER/attack" and "ER/ADR" states/events. This is not necessarily an accurate reflection of the costs associated with the different treatments. For example, an asthmatic prescribed Treatment 3 may require more laboratory tests, rescue medication, etc., than an asthmatic prescribed Treatment 2 or Treatment 1, but presently there is no method of retrieving this information from MTF's.

A similar problem exists with the costs of hospitalizations. MEPRS costs of inpatient services are aggregated by specialty of care. For example, there is an associated cost with the number of occupied bed days of the Internal Medicine Ward, Cardiology Ward, Oncology, etc., While it is possible to ascertain the length of stay and costs of a hospital admission by the Diagnostic Related Group (DRG) through the Retrospective Case-Mix Analysis System (RCMAS), it not known if the patient spent one day in the Intensive Care Unit (ICU) and another day in the Allergy Unit. Furthermore, if an asthmatic is admitted to the hospital, the treatment plan the patient was prescribed is not recorded in RCMAS. The RCMAS cost at NMCSD associated with DRG code 097 (Bronchitis or Asthma >17 years old without complication) of $557 per day was used for the "Hospital/attack" state/event for all treatments. This does not capture possible differences in lengths of stay/costs associated with each of the treatments. However, sensitivity analysis revealed that the models are insensitive to changes in single event costs. Therefore, uncertainty about the true costs should not impact the models' results. Nevertheless, it is recognized that the differences in the cost/effectiveness ratios could be the result of imperfect data rather than superior strategies.

Despite the unreliability of the input parameters, the models presented make contributions to two fields. To the modelling audience, they represent the results of an attempt to reasonably synthesize important medical and economic factors which play crucial roles in the treatment/cost of a chronic disease. To the clinician, the models yield valuable information on the comparative cost/effectiveness of therapy combinations. In addition, the modelling techniques applied here invite a number of sensitivity analyses which may provide new insights concerning the treatment of asthma.

C. SUMMARY

The objective of this thesis was to develop modelling tools for the quantitative evaluation of the impact of three different pharmacotherapy protocols of chronic moderate adult asthma on hospital services. The methods presented are not intended to provide a definitive answer, but rather to demonstrate, within the limitations of any probabilistic model, the effects of important parameters on the costs and effectiveness of medical treatment plans. The techniques outlined here can be easily applied to other diseases such as epilepsy and diabetes.

As resources available for health care become increasingly limited, difficult choices among competing uses of health care dollars must be made. Currently, the standard of care for medical conditions is influenced by published clinical trials, consensus among clinicians, and formal peer review of medical strategies. Analyses such as those presented herein could be included as an additional factor in establishing the standard of care.

APPENDIX A. GLOSSARY OF TERMS

Asthma: A disease characterized by reversible airflow obstruction and airway hyperresponsiveness.

Attack: Also termed "exacerbation". Acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms.

Complication Free Interval (CFI):
The measure of effectiveness for each of the therapies defined as a month without an exacerbation or therapy complications requiring medical attention.

Exacerbation:
Also termed "attack". Acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms.

Forced Expiratory Volume one second (FEV_1):
The volume of air expired in one second from maximum inspiration.

Major Adverse Drug Reaction:
An unwanted medication effect resulting in an emergency room visit or hospitalization to treat.

Minor Adverse Drug Reaction:
An unwanted medication effect discovered during a routine follow-up appointment resulting in a cost to treat.

Moderate Adult Asthma:
Individuals eighteen years old or older who have more than two acute asthma exacerbations per week with a PEFR or FEV_1 decreasing twenty to forty percent from their personal best.

Peak Expiratory Flow Rate (PEFR):
The maximum flow rate that can be generated during a forced expiratory maneuver.

Treatment 1 (Tx1):
Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and inhaled cromolyn (*two puffs four times daily)*.

Treatment 2 (Tx 2):

Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and an inhaled corticosteroid agent *(two to four puffs twice daily).*

Treatment 3 (Tx 3):

Inhaled $beta_2$-agonist agent *(as needed or up to three to four times daily)* and sustained release theophylline *(dosage must be individualized).*

APPENDIX B. SAMPLE MAPLE WORKSHEETS

Results for Treatment ONE (Discrete-Time Discounting Model)

```
>

> with(linalg);
>

> p:=matrix([[.991,0.005,.001,.001,.001,.001],
> [.999,0,0,.001,0,0],
> [.999,0,0,0,.001,0],
> [.37,0,0,.63,0,0],
> [.53,0,0,.47,0,0],
> [1,0,0,0,0,0]]);
>
```

$$p := \begin{vmatrix} .991 & .005 & .001 & .001 & .001 & .001 \\ .999 & 0 & 0 & .001 & 0 & 0 \\ .999 & 0 & 0 & 0 & .001 & 0 \\ .37 & 0 & 0 & .63 & 0 & 0 \\ .53 & 0 & 0 & .47 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{vmatrix}$$

```
> discount:=(.95^(1/365));
>
```

$$discount := .9998594803$$

```
> evalm(ident[6]);
```

$$\begin{vmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

```
>
> ident[6]:=evalm(matrix(6,6,0) +1);
```

$$ident_6 := \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

```
>
> A:=inverse(evalm(ident[6] - (p*discount)));
```

$$A := \begin{bmatrix} 7032.154070 & 35.15582957 & 7.031165914 & 28.03060177 & 7.038196090 & 7.031165912 \\ 7031.163247 & 36.15087615 & 7.030175231 & 28.02935397 & 7.037204416 & 7.030175229 \\ 7031.163674 & 35.15087829 & 8.030175658 & 28.02792360 & 7.038204703 & 7.030175656 \\ 7029.484025 & 35.14248122 & 7.028496244 & 30.72201501 & 7.035523750 & 7.028496244 \\ 7029.911170 & 35.14461665 & 7.028923329 & 29.29144939 & 8.035951263 & 7.028923328 \\ 7031.165917 & 35.15088950 & 7.030177900 & 28.02666293 & 7.037207088 & 8.030177898 \end{bmatrix}$$

```
> costs:=([2.16,140,140,557,529,.83]);
```

$$costs := [2.16, 140, 140, 557, 529, .83]$$

```
>
>
> EPVinfinite:=evalm(A*costs);
```

$EPVinfinite :=$

$$[40437.71895 \quad 40573.52615 \quad 40573.25988 \quad 41927.41040 \quad 41661.09327 \quad 40432.86667]$$

```
> p1825:=evalm(p^1825);
```

$p1825 :=$

[.9881532567 , .004940766281 , .0009881532566 , .003940514825 , .0009891414096 , .0009881532566]

[.9881532564 , .004940766279 , .0009881532563 , .003940514824 , .0009891414093 , .0009881532563]

[.9881532564 , .004940766279 , .0009881532563 , .003940514824 , .0009891414093 , .0009881532563]

[.9881532565 , .004940766280 , .0009881532564 , .003940514824 , .0009891414094 , .0009881532564]

[.9881532566 , .004940766280 , .0009881532565 , .003940514825 , .0009891414095 , .0009881532565]

[.9881532568 , .004940766281 , .0009881532567 , .003940514825 , .0009891414097 , .0009881532567]

```
>
```

```
>
> B:=evalm(p1825 *(discount^1825));
>
```

$B :=$

[.7646141532 , .003823070764 , .0007646141531 , .003049095255 , .0007653787670 , .0007646141531]
[.7646141529 , .003823070762 , .0007646141529 , .003049095254 , .0007653787668 , .0007646141529]
[.7646141529 , .003823070762 , .0007646141529 , .003049095254 , .0007653787668 , .0007646141529]
[.7646141530 , .003823070763 , .0007646141529 , .003049095254 , .0007653787669 , .0007646141529]
[.7646141531 , .003823070763 , .0007646141530 , .003049095255 , .0007653787670 , .0007646141530]
[.7646141532 , .003823070764 , .0007646141532 , .003049095255 , .0007653787671 , .0007646141532]

```
> F:=evalm(ident[6] - B);
```

$F :=$

[.2353858468 , -.003823070764 , -.0007646141531 , -.003049095255 , -.0007653787670 , -.0007646141531]
[-.7646141529 , .9961769292 , -.0007646141529 , -.003049095254 , -.0007653787668 , -.0007646141529]
[-.7646141529 , -.003823070762 , .9992353858 , -.003049095254 , -.0007653787668 , -.0007646141529]
[-.7646141530 , -.003823070763 , -.0007646141529 , .9969509047 , -.0007653787669 , -.0007646141529]
[-.7646141531 , -.003823070763 , -.0007646141530 , -.003049095255 , .9992346212 , -.0007646141530]
[-.7646141532 , -.003823070764 , -.0007646141532 , -.003049095255 , -.0007653787671 , .9992353858]

```
> PVfinite:=evalm(F*EPVinfinite);
```

PVfinite :=

[9141.685641   9277.492855   9277.226584   10631.37710   10365.05996   9136.83336]

```
> CostEffectiveness:=(PVfinite[1]/1825)/(p1825[1,1]);
```

CostEffectiveness := 5.069196284

```
>
```

Results for Treatment ONE (Continuous-Time Discounting Model)

```
> with(linalg);
>

> p:=matrix([[.991,0.005,.001,.001,.001,.001],
> [.999,0,0,.001,0,0],
> [.999,0,0,0,.001,0],
> [.37,0,0,.63,0,0],
> [.53,0,0,.47,0,0],
> [1,0,0,0,0,0]]);
>
```

$$p := \begin{vmatrix} .991 & .005 & .001 & .001 & .001 & .001 \\ .999 & 0 & 0 & .001 & 0 & 0 \\ .999 & 0 & 0 & 0 & .001 & 0 \\ .37 & 0 & 0 & .63 & 0 & 0 \\ .53 & 0 & 0 & .47 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{vmatrix}$$

```
> discount:=(.95^(1/365));
> b:=evalm(-log(discount));
```

$$discount := .9998594803$$

$$b := .0001405295738$$

```
> ident[6]:=evalm(matrix(6,6,0) +1);
> evalm(ident[6]);
```

$$ident_6 := \begin{vmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

$$\begin{vmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

```
> Q:=evalm( p - ident[6] );
```

$$Q := \begin{bmatrix} -.009 & .005 & .001 & .001 & .001 & .001 \\ .999 & -1 & 0 & .001 & 0 & 0 \\ .999 & 0 & -1 & 0 & .001 & 0 \\ .37 & 0 & 0 & -.37 & 0 & 0 \\ .53 & 0 & 0 & .47 & -1 & 0 \\ 1 & 0 & 0 & 0 & 0 & -1 \end{bmatrix}$$

```
> rl:=evalm(b*ident[6]);
>
```

$$rI := \begin{bmatrix} .0001405295738\,,0\,,0\,,0\,,0\,,0 \\ 0\,,.0001405295738\,,0\,,0\,,0\,,0 \\ 0\,,0\,,.0001405295738\,,0\,,0\,,0 \\ 0\,,0\,,0\,,.0001405295738\,,0\,,0 \\ 0\,,0\,,0\,,0\,,.0001405295738\,,0 \\ 0\,,0\,,0\,,0\,,0\,,.0001405295738 \end{bmatrix}$$

```
> costs:=([2.16,140,140,557,529,.83]);
```

$$costs := [2.16, 140, 140, 557, 529, .83]$$

```
>
> m:=evalm(rl-Q);
> y:=inverse(m);
> EPV(infinite):=evalm(y*costs);
>
```

$m :=$

$$\begin{bmatrix} .009140529574 & -.005 & -.001 & -.001 & -.001 & -.001 \\ -.999 & 1.000140530 & 0 & -.001 & 0 & 0 \\ -.999 & 0 & 1.000140530 & 0 & -.001 & 0 \\ -.37 & 0 & 0 & .3701405296 & 0 & 0 \\ -.53 & 0 & 0 & -.47 & 1.000140530 & 0 \\ -1 & 0 & 0 & 0 & 0 & 1.000140530 \end{bmatrix}$$

$$y := \begin{bmatrix} 7031.658660 & 35.15335321 & 7.030670639 & 28.02862787 & 7.037700324 & 7.030670638 \\ 7030.667971 & 36.14825994 & 7.029680089 & 28.02738021 & 7.036708783 & 7.029680087 \\ 7030.668398 & 35.14840258 & 8.029540005 & 28.02595005 & 7.037708929 & 7.029680514 \\ 7028.988979 & 35.14000667 & 7.028001332 & 30.71966295 & 7.035028350 & 7.028001330 \\ 7029.416067 & 35.14214181 & 7.028428361 & 29.28929833 & 8.035315294 & 7.028428359 \\ 7030.670640 & 35.14841380 & 7.029682758 & 28.02468956 & 7.036711455 & 8.029542246 \end{bmatrix}$$

$\mathrm{EPV}(\mathit{infinite}) :=$

$$[40434.87070 \quad 40570.65878 \quad 40570.39253 \quad 41924.35281 \quad 41658.07308 \quad 40430.01906]$$

```
>
```

```
>

>
> PS:=exponential(Q,1825);
```

$PS :=$

[.9881534515 , .004940767258 , .0009881534515 , .003940515605 , .0009891416050 , .0009881534515]

[.9881534516 , .004940767258 , .0009881534515 , .003940515605 , .0009891416050 , .0009881534515]

[.9881534516 , .004940767257 , .0009881534515 , .003940515605 , .0009891416050 , .0009881534515]

[.9881534517 , .004940767259 , .0009881534518 , .003940515441 , .0009891416053 , .0009881534518]

[.9881534517 , .004940767260 , .0009881534517 , .003940515483 , .0009891416053 , .0009881534517]

[.9881534516 , .004940767258 , .0009881534515 , .003940515605 , .0009891416050 , .0009881534515]

```
> rs:=b*1825;
> beta:=(discount^1825);
> e:=evalm(beta*PS);
> a:=evalm(ident[6]-e);
> PV(finite):=evalm(a*EPV(infinite));
>
>
>
```

$$rs := .2564664722$$

$$\beta := .7737809373$$

$e :=$

[.7646143039 , .003823071520 , .0007646143039 , .003049095858 , .0007653789182 , .0007646143039]

[.7646143040 , .003823071520 , .0007646143039 , .003049095858 , .0007653789182 , .0007646143039]

[.7646143040 , .003823071519 , .0007646143039 , .003049095858 , .0007653789182 , .0007646143039]

[.7646143041 , .003823071521 , .0007646143041 , .003049095731 , .0007653789185 , .0007646143041]

[.7646143041 , .003823071521 , .0007646143041 , .003049095764 , .0007653789185 ,

.0007646143041]

[.7646143040 , .003823071520 , .0007646143039 , .003049095858 , .0007653789182 , .0007646143039]

$a :=$

[.2353856961 , -.003823071520 , -.0007646143039 , -.003049095858 , -.0007653789182 , -.0007646143039]

[-.7646143040 , .9961769285 , -.0007646143039 , -.003049095858 , -.0007653789182 , -.0007646143039]

[-.7646143040 , -.003823071519 , .9992353857 , -.003049095858 , -.0007653789182 , -.0007646143039]

[-.7646143041 , -.003823071521 , -.0007646143041 , .9969509043 , -.0007653789185 , -.0007646143041]

[-.7646143041 , -.003823071521 , -.0007646143041 , -.003049095764 , .9992346211 , -.0007646143041]

[-.7646143040 , -.003823071520 , -.0007646143039 , -.003049095858 , -.0007653789182 , .9992353857]

PV(*finite*) :=

[9141.036002 9276.824076 9276.557828 10630.51812 10364.23838 9136.18436]

```
> CostEffectiveness:=(PV(finite)[1]/1825)/(PS[1,1]);
```

CostEffectiveness := 5.068835051

```
>
```

Marked Poisson Process Approximation (Treatment 1)

```
>
> with(linalg);
> r:=evalm(-log(.9998594803));
> ert:=exp(-r*1825);
>
```

$$r := .0001405295738$$

$$ert := .7737809373$$

```
> DTx:={D1=140+(.001*D3),D2=140 + (.001*D4),D3=557+(.63*D3),
> D4=529+(.47*D3),D5=.83};
```

$DTx :=$

$$\{D2 = 140 + .001\ D4, D3 = 557 + .63\ D3, D4 = 529 + .47\ D3, D1 = 140 + .001\ D3, D5 = .83\}$$

```
> solve(DTx,{D1,D2,D3,D4,D5});
```

$$\{D4 = 1236.540541, D1 = 141.5054054, D3 = 1505.405406, D2 = 141.2365405, D5 = .83\}$$

```
> DP1:=((.005*141.50)+(.001*141.23)+(.001*1505.40)+(.001*1236.54)+(.001*.83));
>
>
```

$$DP1 := 3.59150$$

```
> M1Costs:=((2.16+DP1)/r)*(1-ert);
>
```

$$M1Costs := 9258.541842$$

```
> psub:=matrix([[0,0,.001,0,0],[0,0,0,.001,0],[0,0,.63,0,0],[0,0,.47,0,0],[0,0,0,0,0]]);
```

$$psub := \begin{vmatrix} 0 & 0 & .001 & 0 & 0 \\ 0 & 0 & 0 & .001 & 0 \\ 0 & 0 & .63 & 0 & 0 \\ 0 & 0 & .47 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{vmatrix}$$

```
>

> evalm(ident[5]);
> ident[5]:=evalm(matrix(5,5,0) +1);
```

$$\begin{vmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

$$ident_5 := \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

>
> s:=evalm(ident[5] - psub);
>
> si:=evalm(1/s);
>
>

$$s := \begin{bmatrix} 1 & 0 & -.001 & 0 & 0 \\ 0 & 1 & 0 & -.001 & 0 \\ 0 & 0 & .37 & 0 & 0 \\ 0 & 0 & -.47 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

$$si := \begin{bmatrix} 1. & 0 & .002702702702 & -.4255319148\ 10^{-12} & 0 \\ 0 & 1. & .001270270270 & .0009999999998 & 0 \\ 0 & 0 & 2.702702702 & -.4255319148\ 10^{-9} & 0 \\ 0 & 0 & 1.270270270 & .9999999998 & 0 \\ 0 & 0 & 0 & 0 & 1. \end{bmatrix}$$

> prob:=vector([.005,.001,.001,.001,.001]);

$$prob := [.005 \quad .001 \quad .001 \quad .001 \quad .001]$$

>
> dprob:=evalm(prob/.009);

$$dprob := [.5555555555 \quad .1111111111 \quad .1111111111 \quad .1111111111 \quad .1111111111]$$

> Sdays:=innerprod(si,dprob);
>

$$Sdays := [.5558558558 \quad .1113633633 \quad .3003003002 \quad .2522522522 \quad .1111111111]$$

> a:=Sdays[1];
>

$$a := .5558558558$$

> b:=Sdays[2];
>

$$b := .1113633633$$

> c:=Sdays[3];
>

$$c := .3003003002$$

```
> d:=Sdays[4];
>
```

$$d := .2522522522$$

```
> e:=Sdays[5];
>
```

$$e := .1111111111$$

```
> Edays:=a+b+c+d+e;
>
```

$$Edays := 1.330882883$$

```
> Tdays:=Edays*.009;
>
```

$$Tdays := .01197794595$$

```
> ptime:=1-Tdays;
```

$$ptime := .9880220541$$

```
>
>
> CostEffectiveness:=(M1Costs/1825)/ptime;
>
```

$$CostEffectiveness := 5.134676490$$

```
>
>
```

APPENDIX C. TURBO PASCAL PROGRAMMING CODE

```
(* Title       : CohortAnalysis
   Author      : Lynda M. Race
   Date        : 7/12/95
   System      : 486/66 with math coprocessor and MS DOS v6.2
   Compiler    : TURBO PASCAL for DOS v 7.0
   Description : Program designed to calculate cohort analysis

______________________________________________________________*)

program CohortAnalysis;

uses crt;

type screentype = array[0..3999] of byte;

var screen            : screentype absolute $B800:0000; {for intro screen}
   x, offset          : integer;      {to tell intro screen where to go }
   patient_num        : integer;
   N_days             : integer;
   p_No               :   real;
   p_Ex               :   real;
   p_ExHosp           :   real;
   p_ExEr             :   real;
   p_ExErHosp         :   real;
   p_ExErHome         :   real;
   p_ADR              :   real;
   p_ADRMin           :   real;
   p_ADRMaj           :   real;
   p_ADRMajHosp       :   real;
   p_ADRMajEr         :   real;
   p_ADRMajErHosp     : real;
   p_ADRMajErHome     : real;
   Press              :   char;
   UHOME              :   real;
   UErAttack          :   real;
   UErADR             :   real;
   UHospAttack        :   real;
   UHospADR           :   real;
   UMinor             :   real;
   C_Sum              :   real;
   C_Util             :   real;
```

```
  {$L help.obj}
procedure IMAGEDATA; external;


procedure TREE1DATA; external;


(*------------------------------INTRO----------------------------------*)

procedure INTRO;
 begin
  move (pointer(@imagedata)^,ptr($B800,0)^,4000);   {call intro screen}
  CRT.textbackground(0);CRT.textcolor(14);
  gotoXY(1,24);
  write('                                                              ');
  textbackground(0);textcolor(14);
  gotoXY(1,25);
  write('                    Press any key to continue . . .                    ');
  Press:= readkey;
  textbackground(1);textcolor(14);
  clrscr;
 end;

(*---------------------------GET DATA--------------------------------*)

procedure Get_Data;
 begin
  repeat
   clrscr;
   {$L tree1.obj}
    move (pointer(@tree1data)^,ptr($B800,0)^,4000);  {call tree screen}
    textbackground(1);textcolor(14);
    gotoXY(1,25);
    textcolor(11);
    gotoxy(15,6);
    write('?: ');
    readln(p_Ex);
    gotoXY(30,4);
    write('?: ');
    readln(p_ExEr);
    gotoXY(30,9);
    write('?: ');
    readln(p_ExHosp);
    gotoXY(51,3);
    write('?: ');
```

```
    readln(p_ExErHosp);


    gotoXY(51,6);
    write('?: ');
    readln(p_ExErHome);
    gotoXY(15,14);
    write('?: ');
    readln(p_ADR);
    gotoXY(29,12);
    write('?: ');
    readln(p_ADRMin);
    gotoXY(29,17);
    write('?: ');
    readln(p_ADRMaj);
    gotoXY(43,15);
    write('?: ');
    readln(p_ADRMajHosp);
    gotoXY(43,19);
    write('?: ');
    readln(p_ADRMajEr);
    gotoXY(56,18);
    write('?: ');
    readln(p_ADRMajErHosp);
    gotoXY(56,21);
    write('?: ');
    readln(p_ADRMajErHome);
    gotoXY(17,24);
    write('?: ');
    readln(p_No);
    gotoXY(23,25);
    write('    Is this correct?  (Y/N): ');
    readln(Press);
  until Press in ['Y','y'];
repeat
  clrscr;
  textcolor(14);
  writeln;
  writeln;
  writeln;
  writeln;
  write('     Please enter NUMBER OF PATIENTS to simulate:            ');
  readln(Patient_Num);
  writeln;
  write('     Please enter NUMBER OF DAYS to simulate:                ');
  readln(N_days);
```

```
    writeln;
    write('     Please enter COST of state HOME:                              ');
    readln(UHOME);


    writeln;
    write('     Please enter COST of state EMERGENCY ROOM/attack:     ');
    readln(UErAttack);
    writeln;
    write('     Please enter COST of state EMERGENCY ROOM/ADR:     ');
    readln(UErADR);
    writeln;
    write('     Please enter COST of state HOSPITAL/attack:                ');
    readln(UHospAttack);
    writeln;
    write('     Please enter COST of state HOSPITAL/ADR:                   ');
    readln(UHospADR);
    writeln;
    write('     Please enter COST of state MINOR:                              ');
    readln(UMinor);
    writeln;
    writeln;
    writeln;
    write('                    Is this Correct?   (Y/N):                          ');
    readln(Press);
  until Press in ['Y','y'];
end;

(*--------------------------Power Function------------------------------*)
function XtotheY(x:real; Y:integer):real;
   var count:integer;
      delta:real;

      begin
       delta:=1;
       for count:=1 to Y do
         delta:=delta*X;
         XtotheY:=delta;
         end;

(*------------------------------SHOW DATA--------------------------------*)
Procedure Results(var P_Num:integer;Util_Sum_Home3:real;
             Cum_Util4:real;Pt_Cycle_Sum4:real; CFI4:real;
             N_days3:integer);

  var cost:real;
```

```
   eff :real;
   ce  :real;
 begin
  GOTOXY(11,14);
  textbackground(2);textcolor(15);


  COST:=Cum_Util4 / Pt_Cycle_Sum4 * N_days3;
  EFF:=CFI4/PT_Cycle_Sum4;
  writeln('╔══════════════════════╗');
  GOTOXY(11,15);
  writeln('║        COST:         ║');
  GOTOXY(11,16);
  writeln('║ ', cost:13:2,'       ║');
  GOTOXY(11,17);
  writeln('╚══════════════════════╝');
  Textbackground(1);
  GOTOXY(48,14);
  textbackground(2);textcolor(15);
  writeln('╔══════════════════════╗');
  GOTOXY(48,15);
  writeln('║   EFFECTIVENESS:     ║');
  GOTOXY(48,16);
  writeln('║ ', eff:13:5,    '    ║');
  GOTOXY(48,17);
  writeln('╚══════════════════════╝');
  Textbackground(1);
  CE:=(COST/N_days3)/EFF;
  GOTOXY(3,20);
  textbackground(4);textcolor(14);
 writeln('╔═════════════════ ════════════════════════════════════════════╗')
  GOTOXY(3,21);
  writeln('║     COST/EFFECTIVENESS RATIO:  ',CE:27:2,'
  GOTOXY(3,22);
 writeln('╚══════════════════════════════════════════════════════════════╝')
  textbackground(1);
 end;


Procedure ShowData(var P_Num3:integer;I3:integer;Home3:real;ErAttack3:real;
                 ErADR3:real;HospAttack3:real;HospADR3:real;Minor3:real;
                 Util_Sum3:real;Cum_Util3:real;
                 Util_Sum_Home2:real;Pt_Cycle_Sum2:real;
                 CFI2:real;N_days2:integer);
```

```
 begin
  Textbackground(4);Textcolor(14);
  GOTOXY(3,2);

writeln('╔══════════════════════════════════════════════════════════════════════════╗');
  GOTOXY(3,3);
  writeln('║ Cycle',' Home',' ER/Attack',' ER/ADR',' Hosp/Attack','
Hosp/ADR',' Minor ║');
  GOTOXY(3,4);
 writeln('╟──────────────────────────────────────────────────────────────────────────╢');
  GOTOXY(3,5);
  writeln('║ start ', P_num3:7,'                              ║');
  GOTOXY(3,6);
  writeln('║', I3:6, Home3:8:0 ,ErAttack3:10:0 ,ErADR3:11:0,
HospAttack3:12:0,HospADR3:13:0,Minor3:11:0,' ║');
  GOTOXY(3,7);
 writeln('╟──────────────────────────────────────────────────────────────────────────╢');
  GOTOXY(3,8);
  writeln('║                                                     ║');
  GOTOXY(3,9);
  writeln('║      Patient Cum Sum:              Cum Cost:       ║');
  GOTOXY(3,10);
  writeln('║'      ,Pt_Cycle_Sum2:21:0 ,           Cum_Util3:38:0,'      ║');
  GOTOXY(3,11);
  writeln('║                                                     ║');
  GOTOXY(3,12);
 writeln('╚══════════════════════════════════════════════════════════════════════════╝')
  textbackground(1);textcolor(14);
  results(P_num3,Util_Sum_Home2,Cum_Util3,Pt_Cycle_Sum2,CFI2,N_days2);
 end;


(*--------------------------------CYCLE--------------------------------*)

 Procedure Cycle(var P_num:integer;N_days1:integer;
           pEx:real;pExEr:real;pExHosp:real; pExErHosp:real;
           pExErHome:real; pADR:real;pADRMin:real;
           pADRMaj:real;pADRMajHosp:real;
           pADRMajEr:real;pADRMAjErHosp:real;pADRMajErHome:real;
           pNo:real; U_Home:real;U_ErAttack:real;U_ErADR:real;
```

```
            U_HospAttack:real;U_HospADR:real; U_Minor:real;
            C_Sum1:real;C_util1:real);

    var Home2:real;
        ErAttack2: real;
        ErADR2:real;
        HospAttack2:real;
        HospADR2:real;
        Minor2:real;
        Util_Sum2:real;
        Util_Sum_Home:real;
        Util_Sum_Home1:real;
        Cum_Util2:real;
        I: Integer;
        Home:real;
        ErAttack:real;
        ErADR:real;
        HospAttack:real;
        Minor:real;
        HospADR:real;
        Home_1:real;
        ER_1ADR:real;
        Er_1attack:real;
        Hosp_1ADR:real;
        Minor_1:real;
        Hosp_1attack:real;
        Pt_Cycle_Sum:real;
        PT_Cycle_Sum1:real;
        CFI:real;
        CFI1:real;
        discount:real;
  begin
   textbackground(1);textcolor(14);
   I:=0;
   CFI1:=0;
   Pt_Cycle_Sum1:=0;
   Util_Sum_Home1:=0;
   C_Util1:=0;
   discount:=0;
   Home:=P_num*pNo;
   ErAttack:=P_num*pEx*pExEr*pExErHome;
   HospAttack:=(P_num*pEx*pExHosp) + (P_Num*pEx*pExEr*pExErHosp);
   Minor:= P_num*pADR*pADRMin;

HospADR:=(P_num*pADR*pADRMaj*pADRMajHosp)+(P_num*pADR*pADRMaj*
```

```
pADRMajEr*pADRMajErHosp);
ErADR:=(p_num*pADR*pADRMaj*pADRMAjEr*pADRMAjERHome);
    for I:=1 to N_days do begin
      Home2:=Home;
      ErAttack2:=ErAttack;
      HospAttack2:=HospAttack;
      Minor2:=Minor;
      HospADR2:=HospADR;
      ErADR2:=ErADR;
      discount:=XtotheY(0.9998594803,I);
      Util_Sum2:=  (Home2*U_Home)*discount +


                    (ErAttack2*U_ErAttack)*discount +

                    (HospAttack2*U_HospAttack)*discount +
                    (Minor2*U_Minor)*discount +

                    (HospADR2*U_HospADR)*discount +

                    (ErADR2*U_ErADR)*discount;

      Cum_Util2:=  (Util_Sum2 + C_Util1);
      Util_Sum_Home:=(Home2*U_Home) + Util_Sum_Home1;
      Pt_Cycle_Sum:=(Home2) + (ErAttack2 ) +
      (HospAttack2 ) + (Minor2 ) +
       (HospADR2 ) + (ErADR2) + Pt_Cycle_Sum1;
      CFI:=Home2 + CFI1;
      Home_1:=Home2;
      Er_1Attack:=ErAttack2;
      Hosp_1Attack:=HospAttack2;
      Minor_1:=Minor2;
      Hosp_1ADR:=HospADR2;
      Er_1ADR:=ErADR2;
      Home:=(Home_1*pNo) + (Er_1Attack*pExErHome) +
            (Er_1ADR*pADRMajErHome)
            + (Hosp_1ADR*0.53) + (Hosp_1Attack*0.37) + (Minor_1);
      ErAttack:=(Home_1*pEx*pExEr);
      ErADR:=(Home_1*pADR*pADRMaj*pADRMajEr);
      HospADR:=(Home_1*pADR*pADRMaj*pADRMajHosp)+
                 (Er_1ADR*pADRMAjHosp);
      HospAttack:=(Home_1*pEx*pExHosp) +
                   (Er_1Attack*pExERHosp)+(Hosp_1Attack*0.63)
                   + (Hosp_1ADR*0.47);
      Minor:=(Home_1*pADR*pADRMin);
      C_util1:=Cum_util2;
```

```
      Util_Sum_Home1:=Util_Sum_Home;
      Pt_Cycle_Sum1:=Pt_Cycle_Sum;
      CFI1:=CFI;
      clrscr;

ShowData(P_Num,I,Home2,ErAttack2,ErADR2,HospAttack2,HospADR2,Minor2,Uti
l_Sum2,
            Cum_Util2,Util_Sum_Home1,Pt_Cycle_sum1,CFI1,N_days1);
     end;
  end;

(*----------------------------MAIN PROGRAM------------------------------*)

  begin  {main program}
    clrscr;

    INTRO;
    repeat
      textbackground(1);textcolor(14);
      Get_Data;
      Cycle(Patient_num,N_days,
          p_Ex,p_ExEr,p_ExHosp,p_ExErHosp,p_ExErHome,p_ADR,
          p_ADRMin,p_ADRMaj,p_ADRMajHosp,p_ADRMajEr,p_ADRMajErHosp,
          p_ADRMajErHome,p_No,UHome, UErAttack,UErADR,UHospAttack,
          UHospADR,UMinor,C_sum,C_util);
      textbackground(1);textcolor(15);
      GOTOXY(16,24);
      write('Do you want to run another simulation?  (Y/N): ');
      readln(Press);
        case Press of
          'y' , 'Y' :
            begin
              clrscr;
            end;
        end;
      until Press in ['N','n'];
    clrscr;
  end.
```

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