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ABSTRACT

This thesis provides an economic and mathematical framework, and the computing tools to compare the effects, costs and incremental cost-effectiveness of acute or preventative interventions for cardiovascular disease. A Finite Space Markov Chain Decision Analysis Model is designed by integrating a Decision Trees Model and a Markov Chain Model. The model and Cost-Effectiveness Analysis are implemented by using SAS/IML both on a PC with one processor and on a machine with multiple processors of the High Performance Computing Virtual Laboratory. A sample case with four states and eight intervention policies is studied to illustrate the framework, which is composed of (1) life path simulation, (2) cost and effectiveness estimation, (3) cost-effectiveness analysis, (4) sensitivity analysis, and (5) performance analysis on different platforms. Solution of delay effects, correlation among risk factors, and fluctuation in discount rate are viewed as limitations of the thesis and rewarding areas for further research.

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Chapter 1. Introduction

1.1 Statement of the Problem

Cardiovascular Disease (***CVD***), including heart disease and stroke, is the leading cause of illness, disability and death in Canada and it exacts high personal, community and health care costs. In Canada, it claims 80,000 lives annually (Picard, 2003) and the estimated annual cost of ***CVD*** is $20 billion (Heart and Stroke Foundation of Canada, 1999). ***CVD*** will continue to be the leading cause of death and morbidity as the population ages, and the cost of ***CVD*** is escalating as new, more costly medical care become available (Delta Report, 2000).

It is well recognized that the economically disadvantaged are at particular risk of ***CVD*** (Nichol et al., 2002). Ontario researchers noted that people living in poorer neighborhoods tend to have less access to some of these services and are more likely to die following a stroke than those living in wealthier neighborhoods (Anonymous, 2002a). In both 1986 and 1996, Canadians living in the poorest 20% of urban neighborhoods demonstrated notably higher mortality rates for ***CVD***, cancer, diabetes, and respiratory diseases than those in higher income groups (Wilkins et al., 1989).

It is also recognized that this large ***CVD*** burden has given rise to immense biomedical innovation aimed at improving survival or quality of life (Nichol et al., 2002). "However, medical care has been surprisingly limited in its ability to alter the national health profile." "Available estimates generally indicate that medical care has been accountable for only about 10% to 15% of the decline in premature deaths that have occurred in the twentieth century —the reminder attributable to factors that have helped prevent illness and injury

from occurring." (see Page vii Gold et al., 1996) This relatively modest improvement has come at a disproportionately high cost. For instance, in the United States 99% of health expenditures go to individually targeted medical care, leaving little for public health and prevention programs that bring benefit to the entire population (Gold et al., 1996).

Decision makers need to understand the implications of different preventive and acute interventions in terms of changes in population mortality, morbidity and in other benefits and costs before they choose whether to adopt them. The development of a common framework for the evolution of preventive interventions to forestall ***CVD*** in vulnerable populations and of acute interventions to treat ***CVD*** in the health care sector will assist decision makers in deciding which interventions provide the greatest benefit at the least cost (Nichol et al., 2002).

The Canadian Cardiovascular Outcomes Related to Economics (***CCORE***) Policy Model being developed by Drs. Nichol and Wells is a such common framework that will integrate quantitative relationships between socioeconomic risk factors and outcomes in patients with the results of ongoing effectiveness and economic evaluations to yield reliable and valid estimates of the long-term costs and effects for health interventions for patients with ***CVD*** or without ***CVD***, and for interventions targeted at economically disadvantaged individuals who are at high risk for ***CVD*** (Nichol et al., 2002).

The ***CCORE*** Policy Model will be embedded in a computer simulation model that will represent the long-term prognosis of individuals by using a series of monthly state transitions in a ***Markov*** Model. Within each one-month period, the simulated individuals can either experience a clinical event and change their health state, remain in their current health state, or die of other causes (Nichol et al., 2002).

Most individuals go through more than two states over the course of their life, and these individuals are subjected to different interventions on different health states. To properly describe the long-term prognosis of individuals, we need to consider not only an intervention on one state but also interventions on all possible states, i.e., we should consider the combinations of interventions depending on the health state of the individual. Even if there are only ten health states, and each state has three intervention options, an individual may have $3^{10} = 59049$ combinations of interventions over his/her lifetime. The ***CCORE Policy Model*** faces a grand computational challenge (Wilkinson and Allen, 1999) if it seeks to describe a large number, e.g. 100,000, individuals and the comparative costs and effects of multiple interventions over a lifetime of up to 50 years.

1.2 Research Objective and Goals

The research objective of this thesis was to provide the modeling and cost-effectiveness analysis framework that will support healthcare researchers in addressing the objectives of ***CCORE Policy Model***, i.e., to compare the effects, costs and incremental cost-effectiveness of prevention interventions versus those of acute clinical interventions for the clinical management of ***CVD***, and to develop a comprehensive Canadian ***CVD*** policy model that can be used on an ongoing basis to determine the population-based effects, costs and incremental cost-effectiveness of interventions to prevent and treat ***CVD*** in Canada (Nichol et al., 2002). More specifically, this objective was achieved in this thesis by realizing the following goals:

(1) Rapidly simulated the evolution of health states for each individual in a given large population over a long time period under different intervention policies.

(2) Automated the economic evaluation of various intervention programs based on the simulation data of health states.

(3) Compared the SAS/IML simulation program across different platforms, such as PC and High Performance Computing Virtual Laboratory (***HPCVL***) (see www.HPCVL.org) and developed a friendly user interface for non-expert users.

(4) Measured uncertainty in decision modeling and cost—effectiveness analysis arising from sampling uncertainty and parameter uncertainty.

1.3 Background and Constraints

1.3.1 Simulation of Life Paths

In the most general case, each individual has a life path that consists of moving through different health states over time until death. For the same individual, under different preventive or acute interventions he/she may face different life paths. To accurately assess the outcomes of various interventions, both quality and quantity of life should be taken into account, not just whether he/she is alive or dead. A simulation of the evolution of health states for each individual in the target population provides the basis for doing cost-effectiveness analysis.

There are two approaches to simulating life paths. One is to simulate the overall evolution of health states over a given cohort over time. For each month, we would state what fraction of the cohort is found in each health state. Transition rates would be applied to these fractions without regard to individual health histories. The result is an average over the representative sample of individuals of their health status (Naimark et al., 1997; Grover et al., 1999). The advantage is that this method is easy to implement; its disadvantage is that the

result does not represent individual life paths, and cannot yield life expectancy. Another approach is to simulate the life path for each individual. For each individual the same transition rate is used and compared to a random number drawn in the unit interval to see whether that individual dies (Wolfson, 1992; Weinstein et al., 1987). The result is an age at death for each individual. If a large number of individuals' expectancies are simulated, it is clearly far more computationally intensive than the cohort simulation approach.

In this thesis, an intervention policy was defined as the combination of interventions on all possible states that each individual may go through. Each individual's possible life paths under different intervention policies were simulated. For each individual a different transition rate was used, which was determined by the status of the individual's risk factors and the intervention policy, and compared to a random number drawn in the unit interval to see whether that individual died or reached age 85. The simulation results recorded both health status and the corresponding durations over time.

1.3.2 Economic Evaluation

Economic evaluation is defined as the comparative analysis of alternative courses of action in terms of their costs and consequences (Drummond, 1987). Therefore, the basic tasks of any economic evaluation are to identify, measure, value, and compare the costs and consequences of the alternatives being considered. The identification of various types of costs and their subsequent measurement in dollars is similar across most efficiency evaluations; however, the nature of the consequences stemming from the alternatives being examined may differ considerably. Basic types of economic evaluation include the following (Drummond, 1987):

- ***Cost-Minimization Analysis (CMA),*** *where the consequences of two or more alternatives are examined alongside costs, and shown to be equivalent.*
- ***Cost-Effectiveness Analysis (CEA),*** *where both the costs and consequences of health programs or treatments are examined. The incremental cost of a program is compared to the incremental health effects of the program, where the consequences of programs are measured in the most natural or physical units, such as lives saved, life-years gained. The results are usually expressed as a cost per unit of effect.*
- ***Cost-Utility Analysis (CUA)*** *is a form of economic appraisal that focuses particular attention on the quality of the health outcome caused or averted by health programs or treatments. In* ***CUA****, the incremental cost of a program, from a particular viewpoint, is compared to the incremental health improvement attributable to the program, where the health improvement is measured in quality-adjusted life-years* ***(QALYs)*** *gained.* ***QALYs*** *incorporate simultaneously both the increase in the quality of life (reduced mortality) and the increase in the quality of life (reduced morbidity). The results are usually expressed as a cost per* ***QALYs*** *gained.*
- ***Cost-Benefit Analysis (CBA)*** *is potentially a broad form of economic evaluation, where the consequences of program are measured in money terms, so as to make them commensurate with the costs. However, measurement problems usually mean that the range of benefits valued in money terms is fairly limited. Thus, while in theory it is a broad form of evaluation, in practice* ***CBA*** *is usually more restrictive than* ***CEA*** *and* ***CUA*** *and is limited to a comparison of those costs and consequences that can easily be expressed in money terms.*

To take account of both quality and quantity of life gained for different programs or treatments, the ***CUA*** approach is adopted in this thesis. The consequences are measured in ***QALYs***, and all the future costs and ***QALYs*** are stated in terms of "present value". Because of the similarities between ***CEA*** and ***CUA***, some authors do not distinguish between the two. Particularly, most health economic analyses involved ***QALYs*** appear under ***CEA*** instead of ***CUA*** (Gold et al., 1996; Weinstein et al., 1987). To be consistent with the mainstream in health care economic evaluation, in this thesis we also use term ***CEA*** to represent ***CUA.***

1.3.3 Implementation

By providing estimates of ***QALYs*** and costs, ***CEA*** shows the tradeoffs involved in choosing among programs or treatments. Those with the lowest cost per ***QALYs*** are the most efficient ways of improving health, but they may not be selected by decision makers. ***CEA*** only provides a useful guide to achieving better health; additional factors are almost always involved in selecting the final programs or treatments. A decision maker needs to be accurately and timely informed on ***CEA*** results as part of his/her decision process.

As the first step of ***CEA***, the simulation of individual's life path under a variety of intervention policies is far more computationally intensive than the simulation of average life expectancy of a given cohort, especially when the simulation time may be as long as 50 years and the transition period may be as short as one month. This huge repetitive computation on a large amount of data cannot be resolved in a reasonable time period with today's standard personal computer (***PC***).

One way of increasing computational speed is by using multiple processors operating together on a single problem. The overall problem is split into parts, each of which is performed by a separate processor in parallel. Writing programs for this form of computation

is known as parallel programming (Wilkinson and Allen, 1999). SAS/IML is a powerful and flexible programming language and can take advantage of multiple parallel processors. The new MP CONNECT tools in SAS/CONNECT software enable us to perform parallel computation by coordinating the data processing power of the SAS System running simultaneously on multiple servers (Anonymous, 1999a). In this thesis, the desired parallel program was written in SAS/IML language and implemented by using SAS/CONNECT on ***HPCVL*** at the University of Ottawa, which can make the computational speed much greater than existing models. Our choice of platform and language was dictated by availability. Details will be provided in Chapter 4.

In addition to increasing the computational speed, the simulation program was also built to be user friendly with a simple interface so that decision makers or analysts would be able to modify the parameters of the model or redefine the policies or treatments to be evaluated without processing expertise in SAS programming and Parallel programming.

1.3.4 Uncertainty Assessment

Economic evaluations, to some extent, always involve uncertainty that relates to a number of components of the analysis. There are different ways to identify uncertainty. For example, uncertainty is identified in four broad areas—variability in sample data, the generalisability of results, the extrapolation of results and the analytical methods employed (Briggs et al., 1994). Another example is that uncertainty is identified in three sources—sampling uncertainty, parameter uncertainty, and modeling uncertainty (Maria et al., 1998).

The methods to handle uncertainty vary from the use of sampling techniques and conventional statistical methods to sensitivity analysis, or from parametric approaches (Doubilet et al., 1985) to nonparametric bootstrap method (Maria et al., 1998). The

variability in sample data can be expressed using confidence intervals around the mean. A clear limitation to the use of statistical methods in economic evaluation occurs, however, when sample data are not available for a particular parameter (Briggs et al., 1994). Sensitivity analysis can deal with the various types of uncertainty by using the advantage of current computing power to simulate the results of repeated samples.

Sensitivity analysis, contrary to popular impression, is not a single approach, and it is distinguished into four types that can be used to handle different types of uncertainty (see Page 99-101 Briggs et al., 1994).

> *The most common form is **Simple Sensitivity Analysis** where one or more parameters of evaluation is varied across a plausible range. The use of simple sensitivity analysis can improve the generality of a study. For example, uncertainty about capital costs is a frequent problem with regard to generality. Simple sensitivity analysis can also play an important role in coping with uncertainty in some forms of analytical method.*
>
> *The second type of sensitivity is **Threshold Analysis** concerned with identifying the critical value of parameter(s) above or below which the conclusion of a study will change (Pauker and Kassirer, 1980). A limitation of threshold analysis is that it can only be used to deal with uncertainty in continuous variables, which would normally mean that it is useful only for dealing with uncertainty in data inputs.*
>
> *Another form of sensitivity analysis is **Analysis of Extremes** that involves undertaking a base-case analysis, incorporating the best estimated of inputs and then generating alternative analyses that look at extreme estimates. If an intervention is preferred under base case assumptions, high cost/low effectiveness (pessimistic) assumptions and low cost/high effectiveness (optimistic) assumptions, the analyst can be confident in the conclusions of the study.*

*The last type is **Probabilistic Sensitivity Analysis** that permits the analyst to assign ranges and distributions to uncertain variables within evaluations that are being modeled using decision analytical techniques. At the extreme, the distributions may be uniform ones if only range information is known. Monte Carlo simulation simultaneously selects values, at random, from each of the specified distributions and records the outcome of the analysis for a large number of hypothetical patients. It is then possible to record the proportion of patients for which one of the interventions under evaluations is preferred over its comparator(s); proportions near to 100% suggest that the intervention is nearly always preferable under a range of conditions. In addition, the expected value and variance of decision variables in the analysis can be estimated.*

In this thesis, by using the advantage of current computing power these approaches were built into the framework to handle uncertainty raised from different components of analysis at different steps of simulation and evaluation processes.

1.4 Contribution of this Thesis

The contribution of this thesis lies in the methodologies and techniques it presents. First, we combine a Decision Trees Model (Allan et al., 1997; Sox et al., 1988) with a State-transition Model (Naimark et al., 1997; Briggs and Sculpher, 1998; Sonnenberg and Beck, 1993) to construct a Finite State Markov Chain Decision Analysis Model to simulate the evolution of health status for each individual at different transition rate over a long time period. The framework presented here is illustrated on a simple 4-state ***CVD*** disease model, but could easily accommodate a more complex Markovian model of ***CVD*** diseases. Second, the framework provided the tools to measure uncertainty in epidemiological and economic data by using a statistical approach and various sensitivity analyses, particularly a Monte

Carlo simulation method (Nichol et al., 2002; Critchfield and Willard, 1986). Although policy models usually provide only point estimates of the benefit or cost of an intervention, it is increasingly recognized that such outputs are stochastic rather than deterministic (Gregory and Keith, 1986). Third, cost-effectiveness analysis (***CEA***) approach was used to evaluate tradeoffs for different scenarios to determine efficient and affordable intervention policies across a range of possible alternatives. We emphasized graphical tools for policy comparison. Fourth, the computational framework has been implemented by using SAS/IML language at the High Performance Computational Virtual Laboratory (***HPCVL***) at the University of Ottawa. This necessitated the development of a user interface for the input of model parameters, of parallel processing code, and an automated result report. This entire project was undertaken in close collaboration with the research team of Drs Nichol and Wells, and reflects their input.

The thesis was organized as follows. In Chapter 2, we briefly reviewed literature in this field and summarized the relevant part of ***CCORE*** project. In Chapter 3, we presented methodologies for the Finite State Space Markov Chain Medical Decision Analysis Model, Cost-effectiveness Analysis, and Measuring Uncertainty. A case study implementing the SAS/IML simulation framework of ***CEA*** on ***CVD*** appeared in Chapter 4. Finally, we presented conclusions, implications, and further research areas.

Chapter 2. Review of Literature and Summary on CCORE

2.1 Reviews on Cardiovascular Disease Policy Modeling

Decision makers need to understand the implications of possible prevention and treatment policies in terms of their effectiveness and affordability, and a number of simulation models have been developed to support and inform this process. Weinstein et al. (1987) developed a state-transition Coronary Heart Disease Policy Model (***CHDPM***) to describe the societal costs and effects of ***CHD.*** From page 7 of Nichol et al. 2002,

> *Investigators have used the **CHDPM** to evaluate the impact of risk factor reduction and improvements in treatment on population health (Hunink et al., 1997), as well as the economics of cholesterol-lowering diet (Tosteson et al., 1997), smoking cessation (Tosteson et al., 1990), cholesterol-lowering therapy (Prosser et al., 2000; Goldman et al., 1989; Goldman et al., 1999), hypertension (Edleson et al., 1990), beta-blocker therapy (Philips et al., 2000) and interventions to reduce homocysteine (Tice et al., 2001).*

The impact of congestive heart failure or a revascularization procedure was not considered in the model.

The ***POHEM model*** (Wolfson, 1992; 1994) at Statistics Canada is a Population Health Model that is used to estimate life expectancy adjusted for variations in health status during the course of individuals' lifetimes. It takes advantage of the power of modern computing to synthesize the data in the population array by using Monte Carlo simulation

techniques. For each individual the same transition rate is used and compared to a random number drawn in the unit interval to see whether that individual dies. This process is completed 100,000 times, and the simulation result of each time is an individual's life history and age at death. ***POHEM*** takes account of how healthy people are during their lives by assigning a value in the [0,1] interval to various health states. Then, from this sample an average age at death and the health status adjusted life expectancy are estimated. The transition probabilities have been estimated for the four main Framingham study (Babad et al., 2002) coronary heart disease risk factors: obesity, smoking, blood pressure, and cholesterol. It concerns more the impacts of health determinants on life expectancy rather than the effects of prevention and treatment policies.

Mui's cardiovascular disease policy model (1999) for the Australian population is concerned with prevention rather than treatment. Bensley (1995) has developed a population model of coronary events and revascularisation but it only follows patients through one event or one set of events and is not concerned with their long-term survival. Discrete Event Simulation model also was widely used in CVD studies (Davis, 1994; Cooper at al., 2002; Babad et al., 2002), which concerns the modeling of a system as it evolves over time by representing the changes as separate events. This is the opposite of Continuous Simulation where the system evolves as a continuous function (differential). Davies (1994) used a discrete event simulation model to evaluate revascularisation that was hospital, rather than population based. Cooper et al. (2002) developed a discrete event simulation model to simulate the progress of patients with stable angina, unstable angina or myocardial infarction, through their treatment pathways and subsequent coronary events. Babad et al. (2002) used a discrete event simulation model to simulate the impact on benefits and costs of

different primary prevention strategies, the purpose of primary prevention being to prevent or delay ***CHD*** through action to change known risk factors.

2.2 Reviews on Economic Evaluation in Health Care Sector

With limited resources, decision makers have to know how to determine the best way to allocate those resources among alternative uses. There are numerous books and articles addressing economic evaluation in the health care sector. The book edited by Frank A. S. (1995) summarizes the current state of the art in cost-effectiveness/cost-benefit analyses as they are applied to medical problems and discusses aspects of these methods, such as measuring quality of life, costs, discounting, downstream treatment effects, and the sensitivity of findings to underlying assumptions. In this book, cost-effectiveness and cost-benefit analyses are considered as formal economic evaluation methods, and the term "cost-utility analysis" has been used to describe a subset of cost-effectiveness where effectiveness expressed as utilities e.g. quality-adjusted life years (***QALYs***). The six basic steps in cost-effectiveness/cost-benefit analysis are given as—define the intervention, identify relevant costs, identify relevant benefits, measure costs, measure benefits, and account for uncertainties.

The book edited by Gold et al. (1996) focuses on the application of ***CEA*** methods to interventions that occur within the medical care and public health sectors. The reasons that motivate this emphasis on ***CEA*** in the health sector are: first, the health sector has traditionally favored economic analyses that assess cost per unit of health effect, resisting the use of ***CBA***, where both costs and effects of programs and interventions are valued in dollars, as ***CBA*** adds an additional difficulty in that it presumes to put a dollar figure on the value of human life and uses controversial methods to do so; second, ***CBA***'s primary valuation

method is *willingness to pay* (***WTP***), an approach whose difficulty lies in its intrinsic favoring of the programs and diseases of the affluent over those of the poor. ***CUA*** here is considered as a special subset of ***CEA***, where effectiveness is measured in ***QALYs***. This book provides the framework on conducting ***CEA,*** such as identifying, valuing and estimating the outcomes of programs; discounting future effects and costs; evaluating the uncertainty of study results.

Some other books, such as that written by Drummond (1987) and the book written by John et al. (1998) cover all the three methods—***CBA, CEA,*** and ***CUA***—used in the health sector, and distinguish the difference between ***CUA*** and ***CEA*** when effectiveness is measured in ***QALYs.*** In particular John et al. (1998) have defended the ***QALYs*** approach, and situated it within a broadly utilitarian framework, and in this sense have defended a particular concept of the good: maximizing quantity and quality of life or, more broadly, utility. As this approach can simultaneously capture gains from reduced morbidity (quality gains) and reduced mortality (quantity gains), and integrate these into a single measure, it is widely used in economic evaluations in health sectors, but most of them are under the term of cost-effectiveness analysis.

In 1972, Weinstein et al. (1972) developed the basic cost-effectiveness model in health care context, in which for a given budget the optimal resource allocation is to rank order the programs according to their cost-effectiveness ratios (***C/E***) and to select them from the highest to the point where the resource budget is exhausted. The decision rule for using the ***C/E*** ratio as a criterion for resource allocation depends on the existence of a decision-making entity with well-defined budget constraint and a well-defined objective. However, ***C/E*** ratio in practice can also be applied more broadly in economic evaluation from the societal perspective (Weinstein, 1990). For most economic analyses, results are also

expressed in terms of an incremental cost-effectiveness ratio (***ICER***) (Andrew and Bernie, 1999; Briggs and Sculpher, 1998; O'Brien et al., 1994; Van et al., 1994). The ***ICER*** has been the main focus of interest and various methods for computing confidence intervals have been proposed and discussed in the recent health economic literature (Lothgren and Zethraeus, 2000).

2.3 Reviews on Uncertainty Assessment

The paper written by Briggs et al. (1994) reviews the types of uncertainty that exist in economic evaluation and argues that some forms of uncertainty are not amenable to statistical methods. It categorizes sensitivity analysis into different forms—simple sensitivity analysis, threshold analysis, analysis of extremes, and probabilistic sensitivity analysis—and reviews each form with indication of its strengths and weaknesses in relation to the different types of uncertainty in economic evaluation.

Maria et al. (1998) identified three sources of uncertainty in decision modeling and *CEA*—sampling uncertainty, parameter uncertainty, and modeling uncertainty, and used a nonparametric bootstrap method (Efron and Tibshirani, 1993) to estimate the joint distribution of mean incremental cost-effectiveness gained. Gregory and Keith (1986) described methods for modeling uncertainty in the specification of decision tree probabilities and utilities by using Monte Carlo simulation techniques to perform a one-way sensitivity analysis. Doubilet and Begg (1985) described a practical method for probabilistic sensitivity analysis by using Monte Carlo simulation, in which uncertainties in all values are considered simultaneously.

As ***ICER*** is one of the most important results in economic evaluation, there are numerous articles in the recent literature outlining and comparing various approaches for

dealing with the uncertainty of the ***ICER*** (Andrew and Bernie, 1999; Briggs and Fenn, 1998; Lothgren and Zethraeus, 2000; O'Brien et al., 1994; Van et al., 1994.). Hutubessy et al. (2001) introduced stochastic league tables to present the uncertainty surrounding costs and effectiveness to decision-makers. It presented the probability that each intervention is included in the optimal mix of interventions for various levels of resource availability. The most likely optimal mix will be one that contributes the most to maximizing population health for the level of resources, given uncertainty. Risk-neutral decision-makers would choose the most likely combination of interventions. O'Brien et al. (2000) suggested a portfolio approach that characterizes health care resource allocation as a risky investment problem by adopting the concepts from financial economics. This approach provides the optimal intervention mix given the decision-makers' explicit preferences concerning risk and return.

2.4 Brief Summary of the CCORE Policy Model

As this research was conducted as part of the implementation of the ***CCORE*** Policy Model and was to develop a modeling and cost-effectiveness analysis framework, this section is extensively drawn from the original ***CCORE*** proposal (Nichol et al., 2002), and provides the general development background of the framework.

Following section 6.2.3 on page 7 of the ***CCORE*** proposal, we can note the rationale behind this research.

> *Evidence from clinical trials demonstrates that death due to **AMI** may be deferred by: primary or secondary prevention in high-risk groups (Larosa et al. 1999) early diagnosis and therapy (Anonymous, 1994), cardiac rehabilitation (Jolliffe et al., 2001), drug therapy or revascularization techniques (Anonymous, 1999b; Anonymous, 2000). Death due to **SCD** may be deferred by primary or*

secondary prevention as above, or implantable cardioverter defibrillators ***(ICD)*** *(The antiarrhythmics versus implantable defibrillators (AVID) investigators., 1997; Connolly et al., 2000). At the time of* ***SCD****, death may be deferred by early access to 911, early cardiopulmonary resuscitation, defibrillation or advanced life support (Nichol et al. 1999).*

Therefore,

It is important to determine whether prevention or acute interventions offer the greatest benefit at the least cost so that clinical and health services can be expanded efficiently. If prevention is more efficient than primary care, screening programs and other methods of prevention should be expanded. If not, then limited resources should be invested in acute interventions.

It, however, remains unclear how to allocate health care resources between preventive and acute interventions in ***CVD.*** The development of ***CCORE Policy Model*** will resolve this question. This thesis provides the tools for this development.

The ***CCORE Policy Model*** was developed as a population-based simulation model, which integrates quantitative relationships between socioeconomic risk factors and outcomes in patients with the results of ongoing economic evaluations to yield reliable and valid estimates of the long-term costs and effects for health interventions for patients with ***CVD***, and for interventions targeted at economically disadvantaged individuals who are at high risk for ***CVD***. Section 6.2.4 on page 7 of the ***CCORE*** proposal presents the methods used to construct ***CCORE*** Policy Model.

CCORE *Policy Model will be constructed using a conceptual framework similar to the Coronary Heart Disease Policy Model (Weinstein et al., 1987)* ***(CHDPM)*** *created at the Harvard School of Public Health, but considers the broader target disorder of* ***CVD.*** *It describes the long-term prognosis of*

individuals by using a series of cycles in a Markov model by integrating three sub-models: the ***demographic-epidemiological sub-model****, the* ***bridge sub-model****, and the* ***disease history sub-model*** *(Naimark et al., 1997). During each one-month period, the simulated individuals can either experience a clinical event and change their health state, remain in their current health state, or die of other causes. The probability of transition from one health state to another will be derived from epidemiological and effectiveness data. The states and events that will be considered in these sub-models are summarized in Figure 1. The ovals represent the states; the arrows represent the events or allowable transitions between states.*

The ***demographic-epidemiological sub-model*** *will describe the incidence of* ***CVD*** *and non-****CVD*** *mortality among individuals aged 35 to 84 years without* ***CVD****. The risk function for incidence of* ***CVD*** *will be based on the major coronary risk factors: age, gender, diastolic blood pressure, low-density lipoprotein (****LDL****) cholesterol level, high-density (****HDL****) cholesterol level and smoking status. The risk function for non-coronary heart disease mortality will be based upon age, gender, diastolic blood pressure and smoking status. After a hypothetical individual in the model develops* ***CVD****, she enters the* ***bridge sub-model****. This describes the initial cardiac event, as well as the sequelae in the first 30 days after the event. Events that occur at least 30 days after the initial* ***CVD*** *event are described by the* ***disease history*** *sub-model. For simplicity and clarity, the events within the* ***disease history sub-model*** *are illustrated with a single large arrow. Patients who do not experience an event within the* ***disease history sub-model*** *remain in the previous state.*

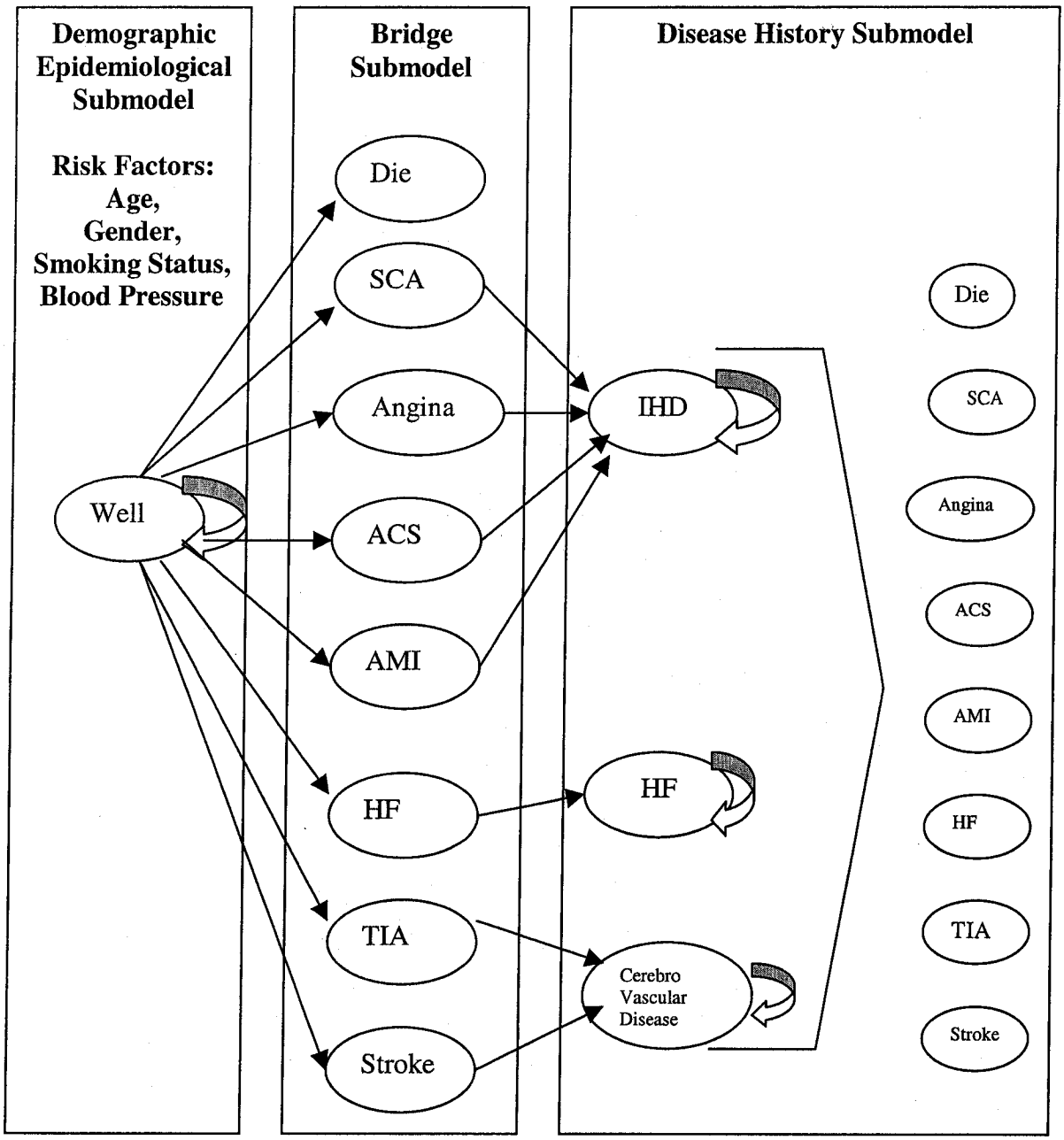

Figure 1 Framework for ***CCORE*** Policy Model Quoted from page 15 of the ***CCORE*** proposal

These paragraphs and subsequent discussions with the researchers involved determined the Markov model that was embedded into computer code as part of this thesis. For developmental purposes, the exact model implemented here is much simpler than the one envisaged by ***CCORE***. The eventual improvement in the model is straightforward given the

programs described here. The following paragraphs drawn from page 8 and 9 on the ***CCORE*** proposal present the methods on data collection, analysis perspective, interventions evaluated, outcomes, and analysis of uncertainty.

> *Relevant Canadian* ***demographic-epidemiological data*** *will be obtained from the Canadian Heart Health Survey, which defines the distribution of coronary risk factors in the population (Personal communication, 2001). These include age, gender, serum cholesterol, smoking status, diabetes and other factors. These data were obtained by using a stratified multistage probability design to survey representative samples in each province.*

Although the programs developed here are eventually to be used for population data acquired as described above, for developmental purposes the population characteristics used for our test cases were highly simplified and only generally realistic. Again, modification of the main program to accommodate more general models of population risk factors is straightforward. Again from Nichol et al. (2000),

> *The primary analysis will adopt the* ***perspective*** *of the Ministry of Health. A secondary analysis will adopt a societal perspective as suggested by current standards for economic evaluation (Wilkins et al., 1989; Canadian Coordinating Office for Health Technology Assessment 1997). All costs will be converted to 2001 Canadian dollars, using the medical care component of the Consumer Price Index as appropriate. Future effects and costs will be discounted to present value at a rate of 3% per annum (Gold et al., 1996).*
>
> *The* ***cost of care*** *will be calculated by using the following steps: a) itemize the resources used to provide care, b) cost each of these resources, and c) calculate the total cost by multiplying the amount of each resource by its unit cost and adding the results. Identification of the resources associated with*

individual interventions is not feasible due to the retrospective nature of this study. Therefore, ***CCORE*** *group will combine primary data by using bootstrapping to estimate the cost associated with either intervention (Maria et al., 1998; Efron and Tibshirani, 1993).*

Outcomes *will include: life expectancy, quality-adjusted life expectancy, lifetime costs and incremental cost-effectiveness ratios* ***(ICER)****. As clinical trials are frequently underpowered to simultaneously detect a significant difference in costs and effect, recent developments in economic theory suggest that economic evaluation should focus on estimation of the joint density of cost and effect differences, and the quantification of uncertainty about the* ***ICER*** *(Briggs and O'Brien, 2000). The* ***ICER*** *for candidate interventions will be illustrated by using cost-effectiveness acceptability curves (Briggs and Fenn., 1998; Lothgren and Zethraeus, 2000; Van et al., 1994), which is a cumulative conditional probability plot showing the proportion of the observed incremental cost-effectiveness density that lies below a threshold ratio (λ)—the monetary value of a unit of health gain. The plot is conditional on λ, and therefore the decision maker can interpret the data in light of their threshold willingness to pay (****WTP****) for the health outcome. Comparison of the observed* ***ICER*** *to the elicit* ***WTP*** *can be used to determine whether adoption of specific cardiovascular interventions is rational from a societal perspective.*

Costs of care are computed over each life path, collected and evaluated in this thesis in accordance with the above general directions. Plots of QALYs and ICER are provided to the user. This thesis makes no attempt to define what constitutes an intervention in the management of ***CVD***. This is described in Nichol et al. (2000) as follows.

Evaluated Interventions *will include current clinical management of coronary heart disease. For the purpose of this analysis, primary prevention will be defined as prescription drug or risk factor modification used before the onset*

*of symptomatic **CVD;** secondary prevention will be defined as similar interventions used after the onset of symptomatic **CVD.** The effectiveness of each intervention will be identified by using a structured literature search of **MEDLINE** and **EMBASE** with the keywords "cardiac arrest"/EXP or "acute myocardial infarction"/EXP combined with the Cochrane Collaboration's search strategy (Dickersin et al., 1994). The Cochrane Library will also be audited to identify effectiveness data. If available, effectiveness data from meta-analyses will be used, since meta-analyses and randomized trials may yield discordant results (Lelorier et al., 1997; Cappeleri et al., 1996; Ioannidis et al., 1998), and meta-analyses provide results that are closer to the truth than the results of individual randomized trials (Lau et al., 1995). In the absence of a meta-analysis of the effectiveness of a drug therapy (e.g. spironolactone), effectiveness data obtained from large randomized trials (n>1000) will be used.*

This thesis departs from the ***CCORE*** treatment of sensitivity analysis. Here we adopt a more numeric approach to the issue, whereas they described a more statistical one involving the calculation of confidence intervals for key parameters in population models and other features. Our more simple approach is more appropriate for the study of the stability of the program itself.

Chapter 3 Methodologies

3.1 Finite State Markov Chain Decision Analysis Model (MCDAM)

As stated on page 69 of Gold et al. (1996),

> *The conceptual or schematic model serves as a guide to the conduct of a cost-utility analysis, which outlines an "event pathway" stemming from the use of the program or treatment (or affected by the intervention) and linking the intervention to health outcomes. It reflects how the intervention is used and the manner in which it affects the course of disease of interest and health status of the target population and other affected individuals.*

Decision tree models and state-transition models are different but related mathematical methods that represent the unfolding of events that occur over time (Allan et al., 1997; Sox et al., 1988).

3.1.1 Decision Tree Models

Decision tree models represent a sequence of chance events and decisions over time (Raiffa, 1968; Sox et al., 1988; Weinstein et al., 1980). Each chance event is assigned a probability, often estimated from data in clinical studies. Each path through the decision tree represents one possible sequence of chance and decision events, and is associated with a consequence, which is valued in terms of a utility. Then, the net value of each alternative is calculated by multiplying the chance of each outcome by its value and adding the results. For economic evaluation of health programs or treatments, the favored alternative is whichever offers the greatest utility at a reasonable cost. Decision analysis models have been used extensively in medical literature (Gold et al., 1996)—for example, to estimate gains in life

expectancy from vaccines (Lieu et al., 1994) and from screening elderly women for breast cancer (Mandelblatt et al., 1992).

Decision analysis models offer several advantages over clinical trials or observational studies (Allan et al., 1997; Sox et al., 1988). First, it extends the time horizon beyond the duration of study follow-up to estimate the risk or benefit of therapy over the lifetime of a patient. Second, decision analysis provides more generalized estimation of effectiveness than that of clinical trials, by adjusting for any differences between the characteristics of the target population and the study population of the trial. Third, decision analysis may be used to compare therapies which have not been evaluated in head to head trials. Also, it may be used to adjust for the effect of combinations of therapies or non-adherence with therapy. Finally, it may be used to adjust for the morbidity associated with adverse effects of therapy. This is important when considering interventions for ***CVD***, where treatments can have a dramatic effect on a patient's Health-Related Quality of Life ***(HRQL)***.

However, decision tree models are not well suited to representing recurrent events that repeat over time. In chronic disease, such as ***CVD,*** the probability and utility variables often change with the time and conventional decision tree models do not easily capture this dynamic quality (Gold et al., 1996).

3.1.2 State-Transition Model: Markov Chains

State-transition models can allocate, and subsequently reallocate, members of a population or an individual into one of several categories, or health states (Gold et al., 1996). Transitions occur from one state to another at defined recurring time intervals according to transition probabilities. The transition probability can be made dependent on population characteristics, such as age, sex, and ***CVD*** disease related risk factors. Through simulation,

the average life expectancy of a cohort or the life path of an individual can be estimated or simulated. State-transition models have been used to estimate outcomes in a large number of cost-utility studies (Gold et al., 1996), such as coronary heart disease prevention (Weinstein et al., 1987), breast cancer screening (Eddy, 1989), and prostate cancer screening (Karhan et al., 1989).

Markov Chains are a special type of state-transition models, in which the transition probabilities depend only on the current state. A finite-state Markov chain is defined as a stochastic process {Xt} (t=0, 1, ...) that has the following properties (McDonald, 1995):

- A finite number of states.
- The Markovian property.
- Stationary transition probabilities: $p_{ij} = p\{X_{t+1} = j | X_t = i\} = p\{X_1 = j | X_0 = i\}$
- A set of initial probabilities $p_{ij} = p\{X_1 = j | X_0 = i\}$.

Markovian property is stated as the conditional probability of any future "event," given any past "event' and the present state $X_t = i$, is independent of the past event and depends only upon the present state of the process. The conditional probabilities $p_{ij} = p\{X_{t+1} = j | X_t = i\}$ are called transition probabilities.

There are two kind different Markov Chains of interest here. If all the transition probabilities are assumed to be constant over time, then the chain is called time-independent or homogeneous. Its analytical advantage is that the probability of being in a particular state at a particular point in time can be calculated simply by raising the transition matrix to the power of the appropriate cycle. However, the assumption of constant transition probabilities may be too restrictive for many potential applications in the health field. More general Markov chains, where transition probabilities can vary over time, are known as time-

dependent or non-homogeneous Markov processes. These are less convenient to represent in terms of matrix algebra, but are much more flexible with regard to the modeling of chronic disease (Naimark et al., 1997).

3.1.3 Finite State Markov Chain Decision Analysis Model

In this thesis, by integrating decision tree models with Markov chains a Finite State Markov Chain Decision Analysis Model was constructed, which incorporates the capabilities of both decision tree models and Markov models (Sonnerberg and Beck, 1993).

3.1.3.1 Defining Markov States

To construct such a model, the first task was to define the disease in terms of health states representing, clinically and economically, important events in the disease process. Based on the proposal of ***CCORE*** policy model, ***CVD*** diseases were defined in nine health states. These states are mutually exclusive since one of the requirements of a Markov chains is that patient cannot be in more than one state at any one time.

Supposing there are only two intervention options for each state: doing-nothing and doing-something, the illustrative Finite State Markov Chain Decision Analysis Model ***(MCDAM)*** of ***CVD*** progression is presented in Figure 2. States are shown by the ovals, choice nodes are rectangular, chance nodes are circles, and transition events are shown by the arrows. The model starts from the 'Well' state, indicating that an individual is at a ***CVD*** free state. At each state, this person may take no intervention: do-nothing or may take intervention: do-something to prevent or treat ***CVD,*** which leads to different transition probabilities to other states or remaining at current state.

Transitions are assumed to take place for each cycle, which may be defined as one month or three months per cycle. For each cycle, all possible transitions between those 9 states are given by two 9 x 9 matrices, one with do-nothing intervention, another with do-something intervention. The do-nothing transition probabilities are denoted as $\mathbf{P}^k_{ij}$ and do-something transition probabilities are denoted as $\mathbf{Q}^k_{ij}$, where k represents the number of cycle, i represents the transition starting state, j represents the transition ending state.

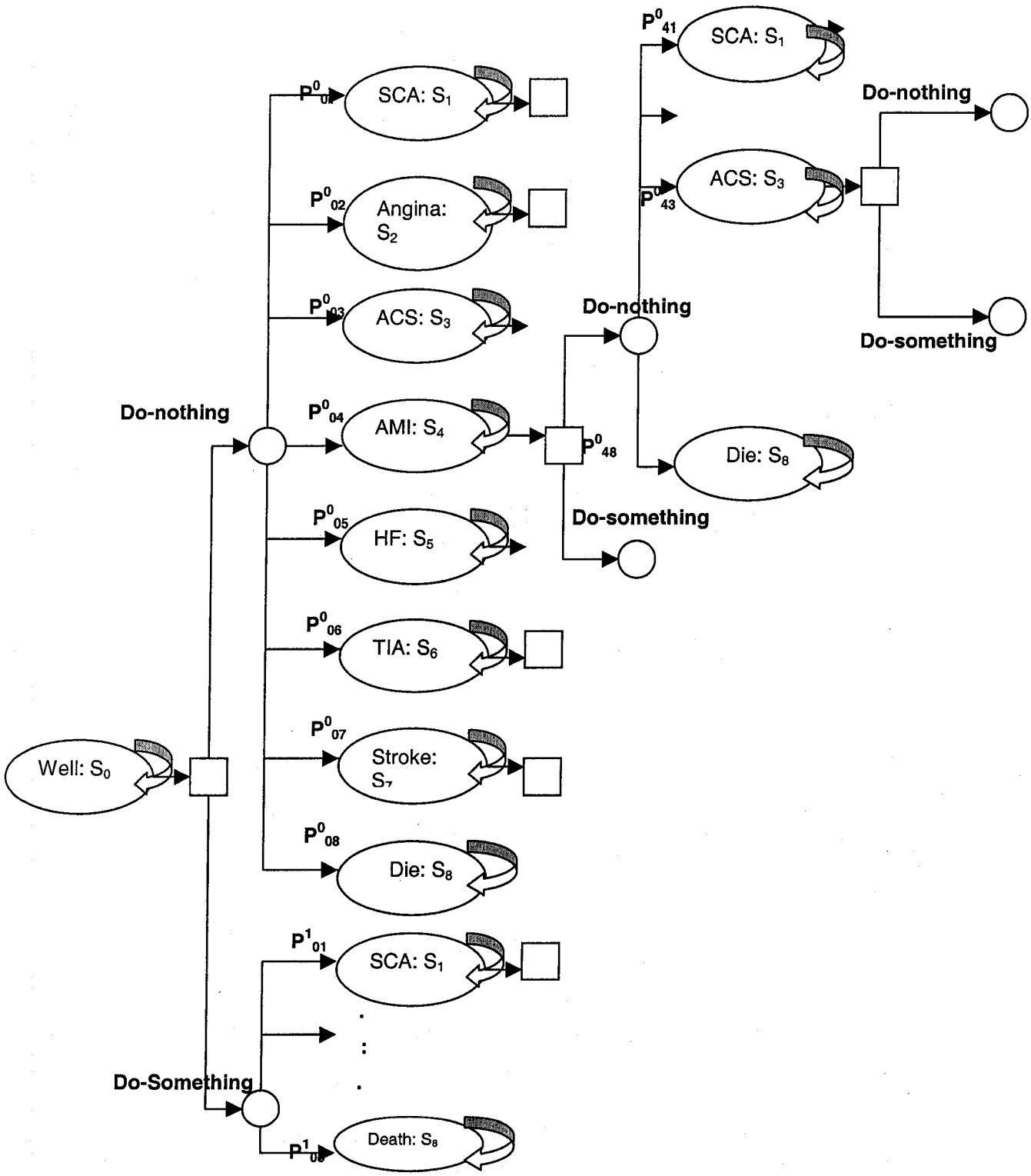

Figure 2: Illustrative ***MCDAM*** of ***CVD*** progression States are shown by the ovals, choice nodes are rectangular, chance nodes are circles, and transition events are shown by the arrows. P^k_{ij} right above the arrows are the transition probabilities, where i represents the starting states, j represents ending state, and k represents the number of cycle.

When i equals to j, it represents the probability that the person remains at the current state. Once an individual enters 'Death', he/she cannot go anywhere, only stay in the 'Death' state, which means $\mathbf{P}^{k}_{8j}$ and $\mathbf{Q}^{k}_{8j}$ both equal zero, where j=0, 1, ...,7; and $\mathbf{P}^{k}_{88}$ and $\mathbf{Q}^{k}_{88}$ are both equal to one. States from which it is impossible to leave are known as 'absorbing states' in Markov models. The most common example of an absorbing state is 'Death' (Fig.2). Furthermore, we assumed that an individual will not recover from any ***CVD*** diseases, so $\mathbf{P}^{k}_{i0}$ and $\mathbf{Q}^{k}_{i0}$ both equal zero, for i=1,2, ..., 8.

Because of the Markovian property of Markov chains, the transition probability is independent of any past event and depends only upon the present state of the process. This 'memoryless feature' must be considered in constructing models. To take account of an individual health history, we distinguished the initial ***CVD***-related disease states from the same but post ***CVD*** disease states, and the transitions are unidirectional from the initial to post. The simplified transitions among states are given in Figure 3.

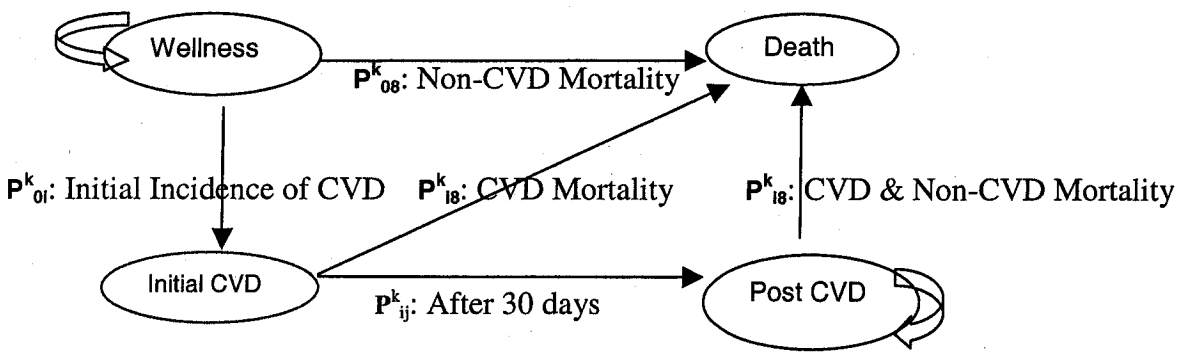

Figure 3: Illustrative simplified transitions among states of ***MCDAM***. Health states are represented by ovals, but state of Initial CVD and state of Post CVD represents a group of states from S_1 to S_7 in figure 2. Possible transitions under no intervention-Do-nothing-between those states are shown by arrows. P^k_{ij} adjacent to the arrows are the transition probabilities, where i represents the starting states, j represents ending state, and k represents the number of cycle.

3.1.3.2 Estimating Transition Probabilities

The second task in constructing the Finite State Markov Chain Decision Analysis Model is to estimate the transition probabilities under different intervention alternatives. For generality, suppose there are n+1 possible states for each person's health: S_0, S_1, ..., S_n. S_0 represents wellness, S_n represents death, and all the other states represent each of the distinct CVD-related diseases. Specifically, states from S_1 to S_m represent the initial ***CVD*** diseases; states from S_{m+1} to S_{n-1} represent the post ***CVD*** diseases. All possible transitions under each intervention at one cycle between those states were given by a following (n+1) x (n+1) matrix, where P means no intervention, and k is the number of transition cycle.

$P^{k}_{(n+1)\times(n+1)}$ =

	S0	**S1**	**S2**	**...**	**Si**	**...**	**Sn**
S0	P00	P01	P02	...	P0i	...	P0n
S1	P10	P11	P12	...	P1i	...	P1n
S2	...						
.							
.							
.							
Si	Pi0	Pi1	Pi2	...	Pii	...	Pin
.							
.							
.	...	...	...	...	...	...	...
Sn	0	0	0	...	0	...	1

In practice, as unidirectional transition and absorbing states exist, many elements in the transition matrix may be set to 0. For example, $P^{k}_{ij} = 0$, where $i = S_{m+1}, \ldots, S_{n-1}$ and $j = S_1, \ldots, S_m$, as individuals can not move back from the post ***CVD*** disease states to the initial ***CVD*** disease states. For the same reason $P^{k}_{i0} = 0$ when $i = S_1, \ldots, S_{n-1}$, as individuals can not recover from any CVD disease state to the 'wellness' state. $P^{k}_{0j} = 0$ when $j = S_{m+1}, \ldots, S_{n-1}$, as individuals cannot transit to 'the post CVD diseases' state directly. Another example mentioned above is $P^{k}_{nj} = 0$, when $j = S_1, \ldots, S_{n-1}$ and $P^{k}_{nn} = 1$, as S_n (representing 'Death') cannot go to any other states except remaining in the 'death' state. Other transition

probabilities, such as, P^k_{0j}, j = S_1, ..., S_m, represents the initial incidence of ***CVD;*** P^k_{0n} represents non-***CVD*** mortality; P^k_{in}, where i = S_1, ..., S_{n-1}, represents the mortality of individuals at initial ***CVD*** and post ***CVD*** disease states; P^k_{ij}, where i, j = S_1, ..., S_{n-1}, represents the transition probability between any two ***CVD*** diseases.

The high prevalence rate of the major risk factors– smoking, physical inactivity, high blood pressure, dyslipidemias, obesity, and diabetes - continues to contribute to the epidemic of heart disease and stroke in Canada. Differences in risk factors exist among men and women, various age groups and individuals living in different regions of the country (Picard, 2003). The mathematical relationship between the transition probabilities and the risk factors, age, and gender are modeled by the survivor function (Collett, 1994). For the ***i***'th individual, the survivor probability, i.e. the probability to remain at the current state, is given by

$$S_i(t) = [S_0(t)]^{\exp(\beta X_i)}$$

where $t_{(k)} \le t \le t_{(k+1)}, k = 1,2,\ldots,r$, $S_0(t)$ is the estimated value of the baseline survivor function, X_i is a vector of an individual's explanatory variables, i.e., risk factors, age and gender, β is a vector of coefficients corresponding to the explanatory variables, and k is the number of transition cycles. This conditional survivor function derives from the Cox proportional hazards model for survival data as described in Section 2.3.2 of Kalbfleisch and Prentice (1980). One can estimate the conditional survivor functions from data as given in Chapter 4 of that book.

Estimation of those coefficients and baseline survival values relies of the results on clinical trials and observational studies, which is beyond the resources and time available to the author and was not covered in this thesis. Instead, a set of hypothetical coefficients and

survival baseline values were used to illustrate the simulation process. Recall that there are two kinds of Markov Chains: time-independent and time-dependent. (See 3.1.2 Markov Chains) As 'age' is an explanatory variable, the transition probability matrix is not constant over time, but dependent on time. Therefore, the transition probabilities have to be updated after each cycle.

3.2 Cost Effectiveness Analysis (CEA)

CEA is a method used to evaluate the outcomes and costs of interventions designed to improve health (Gold et al., 1996). The results of an analysis are usually summarized in a series of cost-utility ratios that show the cost of achieving one unit of health outcome. By providing estimates of outcomes and costs, *CEA* shows the tradeoffs involved in choosing among interventions or variants of an intervention. Those with the lowest cost per year or per case are the most efficient ways of improving health; the ratios show which interventions produce the most years of life, or prevent the most cases of disease, for a given expenditure. Additional factors are almost always involved in selecting the final set of interventions, but *CEA* provides a useful guide to achieving a central objective, better health.

3.2.1 Framing the Cost-Effectiveness Analysis

"Framing a study involves making a series of decisions that collectively define and describe the study to be undertaken" (see Page 54 of Gold et al., 1996)

3.2.1.1 Perspectives of the Analysis

> ***CEA*** *can be undertaken from a number of different perspectives. The choice of the study perspective is an important methodological decision because it determines what costs and effects to count and how to value them. The*

appropriate perspective depends upon the objective of the study. The broadest is the comprehensive societal perspective, which incorporates all costs and all health effects regardless of who incurs the costs and who obtains the effects. This perspective assures that all resource costs are included in the analysis, even when shifted among hospitals, insurers, patients, and other parties—as is often the case in health care (see Page 60 of Gold et al., 1996).

By contrast, ***CEA*** from other perspectives can reasonably omit some outcomes and costs if they are not interest to the decision maker. For example, a ***CEA*** done for Ministry of Health might not include patient and caregiver time missed from work as costs (Nichol et al., 2002).

3.2.1.2 Target Population for the Intervention

The target population is the population for whom the program is intended. Depending on the program, this may be individuals of a given age and sex, individuals living in a particular region, those with specific disease, those with a certain risk profile, or groups defined by combinations of these characteristics. The target population can have a dramatic effect on the result of Cost-utility of an intervention (see Page 62 of Gold et al., 1996).

In general, there are two ways to get the risk factors for each individual in the target population. One way is through primary survey to get these characteristics of each member. Assume we consider the following risk factors and ranges: age from 35 to 84 in one year intervals, gender status (1-Female, 2-Male), diastolic blood pressure with 3-levels (1-High, 2-Normal, 3-Low), low-density lipoprotein (LDL) with 3-levels (1-High, 2-Normal, 3-Low), cholesterol level with 3-levels (1-High, 2-Normal, 3-Low), high-density (HDL) cholesterol level with 3-levels (1-High, 2-Normal, 3-Low), and smoking status with 2-status (1-Smoker,

2-Non-Smoker), then the population will be maximally stratified into a total of (50*2*3*3*3*3*2=) 16200 groups.

Another way, since in most cases we cannot get the risk factor status of each individual, is to take a large number, i.e., 100,000 of imaginary individuals randomly generated by the distributions of these factors drawn from the sample of primary survey or second hand resources. This basically assumes that these factors are expressed independently in individuals. In either case we have to have the data structure of the target population as in Table 1 before doing a Cost-effectiveness analysis.

Person	Age	Gender	Blood_P	LDL	HDL	Smoking	State 1	...	State N
1	35	1	1	1	2	1	1	...	0
2	37	2	1	2	1	2	1	...	0
3	48	1	2	1	2	1	1	...	0
:	:	:	:	:	:	:	:	...	:
N-1	78	2	1	1	2	1	1		0
N	84	2	3	1	1	2	1	...	0

Table 1 Data Structure of the Target Population in Individual

3.2.1.3 Lifetime Health Paths

Each individual may have a different lifetime health path that consists of moving through health states until terminating at age 85 or at an earlier time of death. For example, consider a percutaneous coronary intervention designed to reduce the risk of acute myocardial infarction (***AMI***). From page 89 of Gold et al. 1996,

> *Without the intervention each individual has a possible path of states through life. With the intervention, the person may have a different, hopefully improved, lifetime path. In this study, we seek to evaluate preferences among the paths themselves, rather than among individual health states along the paths. This*

*task in its general form is extremely taxing, because each sequence of health states over a lifetime must be evaluated holistically. This is the reason that the Quality Adjust Life of Years (**QALY**) approach—which reduces the task to assigning values to individual health states—is so appealing.*

Indeed, this thesis develops the tools to compute the QALY for each simulated life path in the ***CCORE*** model, and generates plots that identify the improvement in QALY due to different interventions.

3.2.1.4 Defining the Interventions and Programs

The interventions and programs to be analyzed in the ***CEA*** must be clearly defined. In theory, the ideal approach would be to identify all possible program variations applicable to ***CVD*** and all possible comparator programs and their variations, including a "do-nothing" option.

For instance, suppose the target population with n states is simulated over life, and for each state S_i having w_i possible interventions where $i = 1, 2, \ldots, n$. Then, there will be N programs or policies, where $N = \prod_{i=1}^{n} w_i$. Costs and effects would be gathered on all of these programs. However, from page 64 of Gold et al. 1996,

In reality, resources for undertaking cost-effectiveness analyses are limited, and normally studies must be much less ambitious. As a rule and as a minimum, studies from the societal perspective should compare the policy to existing practice for addressing the health problem (the status quo).

The cost of complete studies for comparing policies is very high. The simulation-based approach of the ***CCORE*** model and this thesis provide an alternative where it is

possible to compare simultaneously hundreds of policies over a short time period, at the cost of substituting machine-generated cohorts for real populations.

3.2.1.5 Outcomes Measurement

Within the context of ***CEA***, health outcomes are the end result of the evaluated program and its alternatives with regard to the health status of a population from the time of the intervention until death or the end of the observation period, such as 85 years of age in this study. Health outcomes can range from intermediate outcomes, such as millimeters-of-mercury blood-pressure reduction, to more distal outcomes such as lives saved, life years gained or quality-adjusted life years (***QALYs***) gained. From page 84 of Gold et al. 1996,

> *In many cases, however, life years gained is an insufficient outcome measure in **CEA.** In order to capture health outcomes beyond simple survival it is necessary to obtain information on the Health-Related Quality of Life (**HRQL**) associated with different programs. Cost effectiveness analysis requires that **HRQL** be placed on a continuum and that changes on this continuum be followed for the duration of survival. This continuum, shown in **Figure 3**, is anchored at the top by an optimal level of **HRQL** assigned the value of 1.0 and at the bottom by a level of **HRQL** judged equivalent to death, assigned the value 0.0.*

"Optimal health" here is interpreted to mean "***CVD*** free state" here. The quality-adjustment weights are then multiplied by the individual's time in that state, and then summed over states to provide the quality adjusted life years (QALYs) for that simulate individual life history. The QALYs combines gains from reduced morbidity and from reduced mortality. In Figure 3, the area between the two curves is the QALYs gained by an intervention.

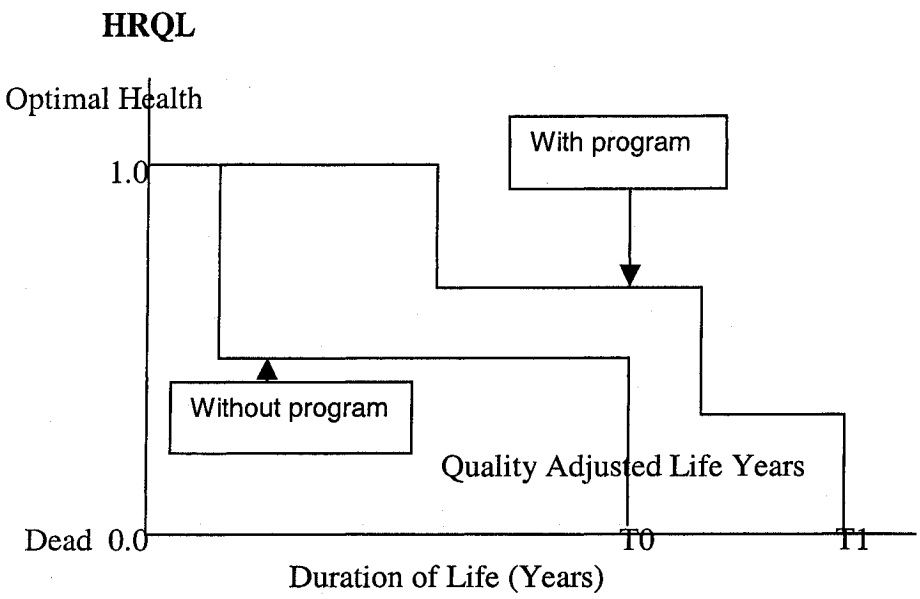

Figure 3 ***QALYs*** gained from an intervention redrawn from page 92 of Gold et al. (1996)

3.2.1.6 Time Horizon and Time Preference

> *The time horizon of the analysis for a Cost-effectiveness study should extend far enough into the future to capture the major health and economic outcomes—both intended effects and unintended side effects. (see Page 68 of Gold et al., 1996)*

In this study, the time horizon of ***CUA*** might be up to 50 years as an individual at age 35 entering the CCORE may live up to 84 years old before leaving ***CCORE***.

The future costs and health consequences should be stated in terms of their "present value" to the decision maker. Virtually all ***CEA*** in health to date have used some variants of the following "discrete-time" model. Let Ej(t) be the health consequence (QALYs) for a well-defined group of individuals who receive program j, and $E_0(t)$ be the health consequence expected for the group under the comparator (baseline) intervention. Let Cj(t) and Co(t) be the corresponding costs associated with these programs for period t. If the

programs were initiated at period 1 and continued through period T, then the present value of costs and health consequences can be calculated, respectively as

$$\Delta C = \sum_{t=1}^{T} [C_j(t) - C_0(t)]/(1+i)^{t-1} \qquad (1)$$

and

$$\Delta E = \sum_{t=1}^{T} [E_j(t) - E_0(t)]/(1+i)^{t-1} \qquad (2)$$

where i and r are the discount rates selected to convert future costs and ***QALYs*** to present value. Dividing Equation (1) by Equation (2) yields the Cost-effectiveness ratio for the program relative to the comparator (Gold et al., 1996).

There is consensus in economics that Equation (1) represents the appropriate vehicle for converting costs to present value, given the assumption of a constant discount rate over time. By contrast, there remains considerable controversy about precisely how to convert future health consequences—expressed in non-monetary terms—to present value (Krahn and Gafni, 1993; Cairns, 1992).

We will not explore these controversial issues in this study; instead, we will follow the mainstream practice in current ***CEA***s to discount health consequences to present value, as one would discount future monetary flows. Moreover the prevailing practice is to set r (the discount rate for health consequences) equal to i (the discount rate for cost).

3.2.2 Designing the Cost-effectiveness Analysis

> *Designing the study involves planning the approach to the analysis, including the types of data to be used and the means for incorporating these data into the **CEA**. Designing the data collection and analytic plan for the **CEA** involves three basic steps. First, the analyst must develop a conceptual model*

describing the intervention and its effects on health outcomes. Second, the analyst must determine how to collect the data on costs, health effects, and preferences for health effects for the intervention and the relevant comparators from the perspectives selected for the study. Finally, the analyst must develop the analytic methods to combine the information appropriately into a cost-effectiveness analysis (see Page 68-69 of Gold et al., 1996).

The conceptual model required by Gold has been presented here in section 3.1 and the last step described in the above paragraph is presented in section 3.3. The following paragraphs are drawn from pages 71-77 of Gold et al. 1996,

3.2.2.1 Data on Cost, Effectiveness

Ideally, data on the costs and effects of an intervention should both be collected from the same properly designed primary study. However, for a variety of reasons, this ideal is frequently not a feasible design for a Cost-effectiveness analysis given the goals of the analysis and the financial constraints for most studies. When a primary Cost-effectiveness study is not feasible, effectiveness and cost data can be gathered from separate sources. These sources may be primary or secondary, and they may employ a variety of study designs.

There are two main groups of ***primary study designs,*** piggyback trials and Cost-effectiveness trials. Piggyback trials are additions to studies designed for other purposes, such as clinical trials for safety or effectiveness, and suffer from small sample sizes or restrictive population criteria. Cost-effectiveness trials target a wider class, but are larger, more expensive and lengthier to run.

For technologies already in the inventory of health care, ***secondary research designs*** are designed to study ***CEA*** using existing data, which can be derived from a variety of

research designs, including ***RCTs***, observational (epidemiological) studies, databases, and synthesis methods. Often, cost and effect data or event probability data have to be obtained from more than one source.

It has several advantages. It is relatively inexpensive, and it can be done fairly quickly because the data are already available. It also maximizes external validity, since one is analyzing what actually transpired in the community settings. Its main problem, and can be a serious one, is selection bias: Those who received the intervention likely differ from those who did not, and this difference may not be completely correctable by statistical control. Also, the data may not be well suited for the Cost-effectiveness analysis, because they were initially gathered for other purposes. Finally, retrospective data will sometimes include only billing data rather than indicating the quantity of specific services consumed.

In addition to primary and secondary study designs, ***modeling design*** is an alternative to collecting data that is particularly useful when source data is scant, or when the analyst wishes to forecast future performance.

Such an epidemiologically based model employs risk factors and models the course of a disease such as ***CVD***. Clinical decisions are not modeled directly, but are represented through transition rates, average costs and other behavioral changes related to life expectancy. The choice of parameters and costs rely heavily on existing sources of primary or secondary data on costs and intervention effects relevant to the subject of stud, and even employ expert opinion in choosing values. Again, from Gold et al. (1996),

> *Model-based **CEAs** can be an inexpensive and quick way of estimating Cost- effectiveness when compared to alternatives requiring primary data collection. However, elaborate models are generally required to simulate an intervention's effects in a thorough and credible fashion, as required for*

publication. Models have clear limitations. Estimates incorporated into the analysis may be inaccurate, whether derived from data or based on expert opinion. Because of the complexity of many models, biases may not be readily apparent to reader of the study.

The ***CCORE*** model is of the most common ***CEA*** design option — a **combination design,** which combines the various methods discussed above. This design begins with primary data — for example, from the Framingham Heart Study --- which are sufficient to make certain inferences regarding health and economic impacts, but the model extends the analysis beyond the original setting and time frame to estimate ultimate patient outcomes and cost-effectiveness over their entire lifetimes.

3.2.3.2 Data on Preferences

Like data on costs and health effects, the preference weights used to QALYs in the denominator of the C/E ratio—can be obtained from primary or secondary sources. Preference weights can be obtained along with cost and effectiveness data from subjects in a clinical trial. ...

Analyst can also obtain preference weights for a Cost-effectiveness study from existing studies that have collected data on preferences for health states. ...

Another option that is being widely used in clinical trials consists of gathering primary prospective data on the health status of patients in the trial using a generic health state system (e.g., the Quality of Well-Being Index [Kaplan and Anderson, 1998] or the Health Utilities [Feeny et al., 1995; Torrance et al., 1995]) that already has preference weights available. ...

To examine the long-term effects of different programs reducing the occurrence of ***CVD*** in the target population, a combination design would be used. Cost-effectiveness analysis might include the clinical (and possibly economic) results from the primary study at

hand, results from other clinical research previously reported, and modeling for future health events and their costs (Nichol et al., 2002).

In this thesis, however, as we focused on developing the modeling and cost-effectiveness computational framework, for simplicity and illustration purpose instead of using primary and secondary data sources, we used hypothetical data on costs, health effects and preference weights on health states and combined modeling design method to perform ***CEA*** on different intervention.

3.3 Computing

3.3.1 Computing Module

The first task in simulating individuals' lifetime paths and performing cost-utility analyses is to construct the computational module and the simulation algorithm. The illustrative module of ***MCDAM*** integrating three sub-models: the ***demographic-epidemiologic sub-model***, the ***bridge sub-model***, and the ***disease history sub-model*** (See Chapter 2: Brief Summary of CCORE policy model) is presented in Figure 5.

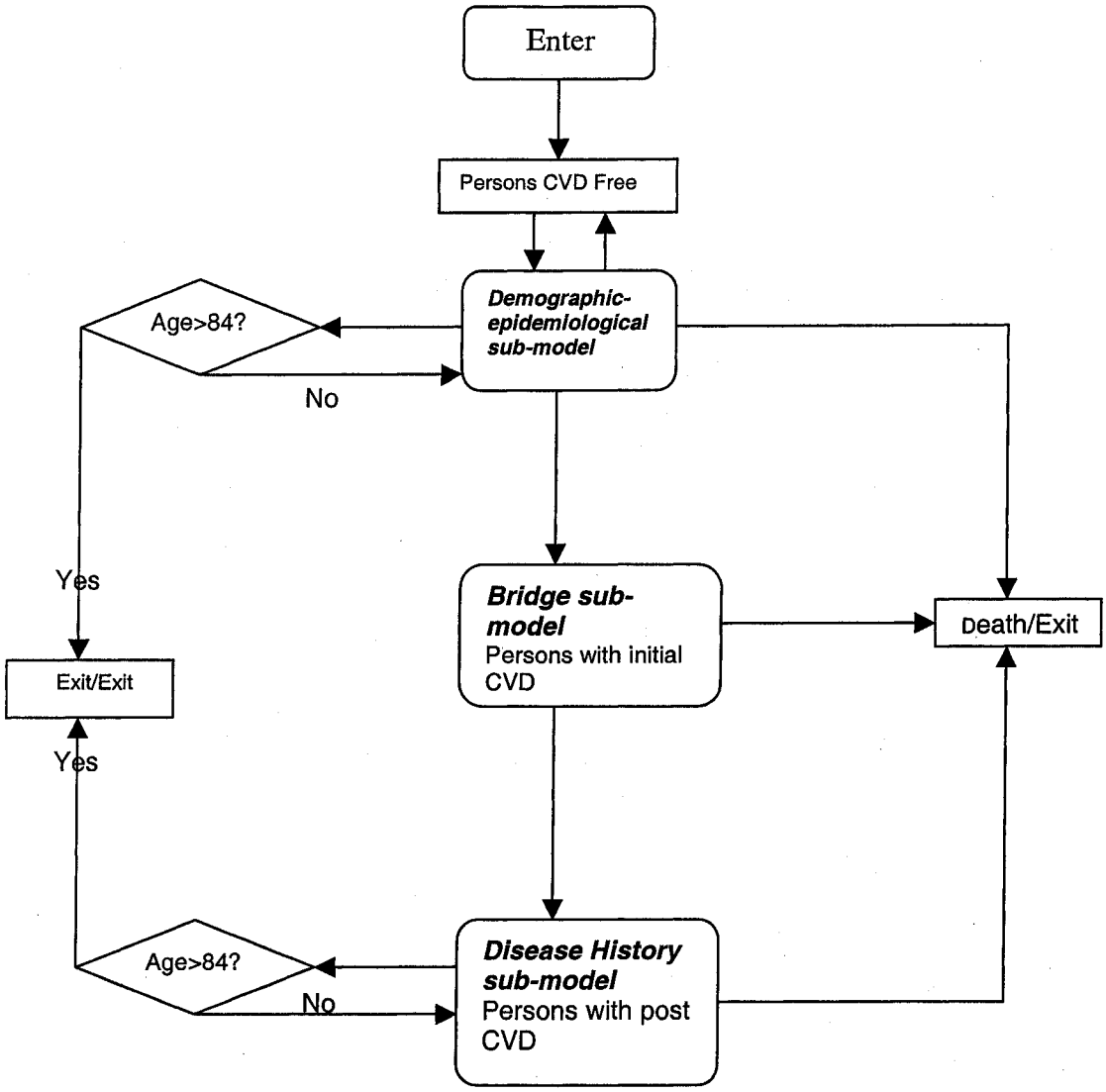

Figure 5 Computational module of ***MCDAM*** of ***CVD.*** Three sub-models are represented by squares and possible transitions are shown by arrows. The outcomes are exit with age more than 84 or death state. Once the individual is more than 84 years old or dead, he/she moves out the module.

The module starts with a cohort of hypothetical individuals aged 35 to 84 without *CVD*. Each individual would first go through the ***demographic-epidemiological sub-model (DE)*** that describes the incidence of ***CVD*** and non-***CVD*** mortality. The transition probabilities from ***CVD*** free (Well) state to the initial ***CVD*** disease states and to death state are functions of the major coronary risk factors, such as age, gender, blood pressure, cholesterol level, and smoking status as previously modeled. (See **3.1.3.2** Estimating

Transition Probabilities) After a hypothetical individual in ***DE*** model develops ***CVD,*** he/she enters the ***bridge sub-model.*** This describes the initial cardiac event as well as the sequalea in the first 30 days after the event. Events that occur at least 30 days after the initial ***CVD*** are described by the ***disease history sub-model.***

3.3.2 Computing Algorithm

The computing algorithm is shown in Figure 6, which is comprises the following steps:

(1) Creating a cohort of a large number of hypothetical individuals, i.e., 100,000, based on distributions of the risk factors, i.e., age, gender, blood pressure, low-density lipoprotein (LDL), cholesterol level, high-density (HDL) cholesterol level, and smoking status;

(2) Defining Intervention Programs (See **3.2.5** Defining the Interventions and Programs);

(3) Individuals enter the simulation process one by one. The transition probabilities of an individual who enters the simulation process were estimated based on the risk factors, intervention programs, and the function given at section **3.1.3.2** Estimating Transition Probabilities;

(4) Determining the state transition by assigning a uniform random value in the range of 0.0 and 1.0 and comparing the random value with the transition probabilities to determine which state to enter and record this state;

(5) If entering 'Dead' state, this individual will exit the simulation process, and the number of individual simulated N = N + 1;

(6) If N>100,000, i.e., all the hypothetic individuals lifetime paths in the cohort have been simulated, the simulation process will end; otherwise, another individual will enter the simulation process from step (3);

(7) If not entering 'Dead' state after step (4), the individual's risk factors will be updated, especially Age = Age + the length of cycle/12, where the length of cycle measured in months;

(8) If Age > 84, this individual will exit the simulation process, and the number of individual simulated N = N + 1, then go to step (6);

(9) If Age ≤ 84, the simulation process will go to another cycle, go to step (3) until this person exits the simulation process either at age more than 84 or entering 'dead' state;

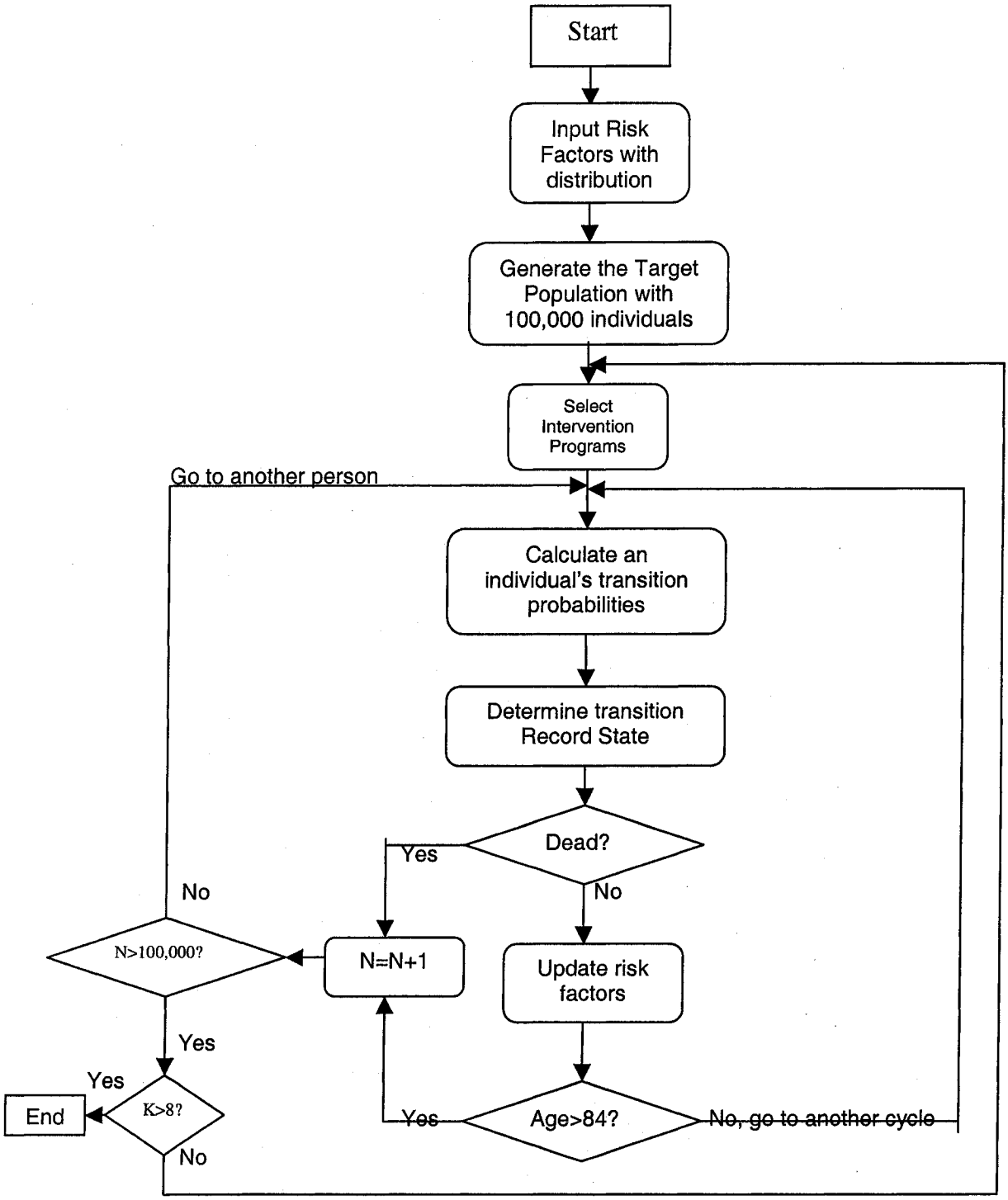

Figure 6 Computational Algorithm of ***MCDAM***. Calculations are represented by squares, comparisons are represented by diamonds, and possible transitions are shown by arrows. The outcomes are exit with age more than 84 or death state. Once the individual is more than 84 years old or dead, he/she exits the simulation process.

3.3.3 Computing Task and Results

The simulation results are arrays of lifetime paths—chains of health states—under different intervention programs for each individual. If there are ***n*** possible states and for each state S_i having w_i intervention alternatives, where ***i =1,2,...,n,*** there will be $N = \prod_{i=1}^{n} w_i$ programs or combinations of interventions. Each individual will have a number, ***N,*** of arrays of lifetime paths, which means for one individual, he/she will go through ***N*** times lifetime path simulation. In one lifetime path, a person at age ***T*** ($35 \le T \le 84$), maximally may go through $K = (12/l) * (84 - T)$ cycles, where l is the length of cycle in months. Thus, for one individual, there may be ***N*** x ***K*** simulation iterations. In total, if there are 8 states, each state with 2 intervention options, and the length of cycle is 1 month, approximately $\sum_{i=1}^{100000} N \times K_i \approx 100000 \times 2^8 \times 588 = 1.5 \times 10^{10}$ simulation processes will be executed. Correspondingly, the simulation result will be a matrix with 2.56×10^7 rows and 588 columns.

Based on the simulation results, the present values of cost and utility for each individual and each intervention program will be estimated. Then, the ratio of incremental cost and utility will be calculated and the distributions of cost, utility, and their incremental ratio will be analyzed to compare different intervention programs.

3.3.4 Computing Software and Platform/Parallel Computation

There are numerous computing softwares available. To choose which software to use mainly depends on the nature of the problem to be solved and the feature the software has.

As mentioned above, the problem to be solved in the thesis involved massive number of simulations, matrix computations and statistical analyses. SAS provides the tools to conduct simulations, matrix computation and statistical analyses, such as SAS/IML, this is a powerful and flexible programming language that can perform complex matrix computation. SAS/FSP can be used to build user-friendly interface to input or modify parameter and SAS/BASE can perform statistic analyses.

In years past, each computer had one central processing unit (CPU) and was not connected to another computer. SAS was created as a single-threaded application, which means the program executes in a top-down approach on one processor. Presently, a computer can have multiple processors, or be part of a network. The current SAS version and previous versions are still single-threaded applications, but the new MP CONNECT tools in SAS/CONNECT software enable us to perform parallel processing by coordinating the data processing power of the SAS System running simultaneously on multiple servers.

Parallel processing (also known as multiprocessing, or asynchronous processing) is the process of executing code simultaneously, whether that execution occurs on a local machine or on one or more remote machine. The purpose of parallel processing is to complete the computational task in less total elapsed time than it would take to complete the same job serially by taking advantage of multiple processors on a symmetric multi-processing (SMP) single machine or of each processor on a network of machines (Wilkinson and Allen, 1999).

Parallel programming involves dividing a problem into parts in which separate processors perform the computation of the parts. An ideal parallel computation is one that can be immediately divided into completely independent parts that can be executed simultaneously. This is called pleasantly parallel. Parallelizing these problems is obvious and

requires no special algorithms to obtain working solution. A truly pleasantly parallel computation suggests no communication between the separate processes; each process requires different (or the same) data and produces results from its input without any need from other processes. This situation will give the maximum possible speedup if all the available processors can be assigned processes for the total duration of the computation. The only constructs required here are simply to distribute the data and to start the process (Wilkinson and Allen, 1999).

In this thesis, the SAS program was written sequentially initially following the computing algorithm above and was implemented on a PC windows platform. As all the simulation processes are based on the status of individuals' risk factors, and it is reasonable to assume that the status of one individual's risk factors is independent from another one's. Furthermore, an individual's lifetime path or evolution of health states over time depends on his/her status of risk factors and intervention programs, but is independent from other individuals. We can divide the target cohort with 100,000 individuals into a number of completely independent sub-cohorts that can be executed simultaneously. Each process has its own data and there is no communication among those processes until all the simulation and estimation processes of lifetime paths, costs and utilities were completed. The parallel program was implemented on an AIX platform with 2 processors at the Department of mathematics and Statistics and on the HPCVL facility with 20 processors at the University of Ottawa.

3.4 Measuring Uncertainty

The real purpose of measuring uncertainty in the final ***CE*** or ***CU*** ratio (or net benefit) is to show how much uncertainty there is about the mean value that will drive the decision.

Uncertainty in decision modeling and cost-effectiveness analysis can arise from—sampling uncertainty, parameter uncertainty, and modeling uncertainty (Maria et al., 1998).

3.4.1 Sampling uncertainty

Sampling uncertainty is the uncertainty resulting from the actual realized outcomes of a strategy for a sample of patients (Maria et al., 1998). In terms of probabilistic sensitivity analysis, this may be considered as first-order uncertainty. In this thesis, no sample of patients enrolled in the health programs or treatments. Instead, a large number of, i.e., 100,000, hypothetical individuals were randomly generated by using the distributions of *CVD* risk factors. The methodology adopted here does provide an approach to capture the sampling uncertainty.

One way to deal with the sampling uncertainty is to perform a first-order Monte Carlo simulation in which each probability is simulated at the individual patient level (Maria et al., 1998), i.e., instead of a cohort's going through the model with 10% mortality at a particular health state, each individual has 10% mortality at that state. If he/she dies, that simulation stops, and new individual's simulation follows. In this thesis, each probability was simulated at the individual level based on an individual's risk factors, which means that each individual may have different mortality even when they are at the same health state.

3.4.2 Parameter uncertainty

Parameter uncertainty stems from uncertainty in the input parameters (Maria et al., 1998). This uncertainty may also be called to as second-order uncertainty. To deal with parameter uncertainty, on the top of first-order simulation, a second-order Monte Carlo simulation was performed (Maria et al., 1998). Instead of using the estimated distributions,

the hypothetical distributions of the transition probability model parameters were used and the model was run multiple times, each time taking random draws from these distributions. The variable value randomly drawn from the distributions was updated after each transition cycle. A second-order Monte Carlo simulation was also performed on costs associated with each cycle spent in a particular health state along an individual's life path. The values of costs spent in each health state were kept constant for the same health program or treatment and were updated randomly within its distribution once the health program or treatment changed.

3.4.3 Modeling Uncertainty

Modeling uncertainty stems from uncertainty in the model structure and the modeling process, e.g., not knowing the exact form of the underlying mathematical model (Maria et al. 1998). In our problem, what ***CVD*** risk factors should be included in the Survivor Functions and how to include these factors: using additive or multiplicative functions may be uncertain. The modeling process uncertainty arises from viewpoint of the decision maker, who or what group does the ***CEA*** modeling can introduce uncertainty about the result.

Although we did not measure the modeling uncertainty in this thesis, as part of ***CEA*** modeling how to deal with the model structure and process uncertainty were presented here. For model structure uncertainty (Gregory and Keith, 1986):

- *Compute a separate CEA/CUA under each different structural assumption;*
- *From each CEA/CUA, get a probability distribution over net benefit;*
- *Weight each of these with how likely you consider that assumption to be the correct one;*
- *Use a weighted average to combine the separate distributions into a final, average distribution.*

For model process uncertainty:

- *Have the whole CEA/CUA done by different modeling teams or different analyst.*

3.4.4 Sensitivity Analysis

There are four types of sensitivity analysis—simple sensitivity analysis, threshold analysis, analysis of extremes, and probabilistic sensitivity analysis—which can be used to handle different types of uncertainty (Briggs et al., 1994). It is generally the case that the more sophisticated the type of sensitivity analysis the more limited it is to certain contexts. If the uncertain parameters within an analysis are considered to be independent of each other, then a series of one-way simple sensitivity analyses may be the first choice for assessing sensitivity. If, however, it is not safe to assume such independence then a multi-way simple sensitivity analysis will increase the information available to potential decision makers. Probabilistic sensitivity analysis has the potential to be the most comprehensive way of dealing with some forms of uncertainty in economic evaluation. The extent to which the alternative types of sensitivity analysis are appropriate to deal with the different forms of uncertainty identified is summarized in Table 2.

Sensitivity analysis	Uncertainty			
	Data variability	Generalisability	Extrapolation	Analytical method
Simple sensitivity analysis	√	√	√	√
Threshold analysis	√	√	√	X
Analysis of extremes	√	o	√	X
Probabilistic sensitivity analysis	√	o	o	X

Table 2 √ = Generally useful; o = Potentially useful in certain contexts; X = Unlikely to be useful (Quoted from Briggs et al. 1994).

The most common form of sensitivity analysis is where one or more parameters of an evaluation are varied across a plausible range (Briggs et al., 1994). With one-way analysis, each uncertain component of the evaluation is varied individually, while the others retain their base-case specifications, in order to establish the separate effect of each component on the results of the analysis. A multiple-way simple sensitivity analysis involves varying more than two inputs at the same time, and studying the effect on outcomes.

In this thesis, rather than focusing on doing sensitivity analysis itself, we were focusing on constructing the tools to enable user to do sensitivity analysis by modifying the distributions of risk factors, values of parameters, cost, utility weights, and interest rate.

3.5 Summary

This chapter began by constructing a Finite State Markov Chain Decision Analysis Model, which was built by integrating a decision tree model and a Markov chain. Then, we presented basic concepts and assumptions for conducting Cost Utility Analysis (CUA). The third section was comprised of computation module, algorithm, parallel processing, and implementing software and platforms. Finally, we presented the methods to deal with sampling uncertainty, parameter uncertainty and modeling uncertainty.

Chapter 4 Implementation of the SAS CCORE Framework: A case study from beginning to end

In this chapter we present the implementation of a multiprocessor SAS simulation framework of the ***CCORE*** policy model (the ***SAS CCORE framework***) for modeling and cost-effectiveness analysis of acute or preventative interventions for cardiovascular disease on a sample case in four steps. First, the framework describes the long-term cardiovascular prognosis of a hypothetical cohort of individuals by using a series of cycles in a state-transition Markov model. The probability of transition from state to state was expressed as a function of risk factors, and modified by the effect of various interventions. During each cycle, individuals either experience a clinical event, or remain in their previous state, or die, or reach age 85. Second, this framework estimates the lifetime costs and effects (in life expectancy and quality-adjusted life expectancy) for each intervention under consideration of time preference and uncertainty. Third, sensitivity analyses were used to define which parameters or factors have more impact on the cost effectiveness analysis result. Finally, the performance of the framework on different platforms is evaluated.

4.1 Life path Simulation

4.1.1 Creating a Target Population

The target population is the population to whom the intervention program is intended. In general, there are two ways to obtain the risk factors for each individual in the target population. One way is through a primary survey to obtain the characteristics of each member. Another way, since in most cases we cannot obtain the risk factor status of each

individual, is that a large number, i.e., 100,000 of hypothetical individuals be randomly generated by the distributions of these factors drawn from the samples of primary survey or secondary sources.

For simplicity, we consider only four risk factors that are known to be highly correlated with the development and subsequent natural history of ***CVD***: age, gender, smoking status and blood pressure. We assume the distributions of these factors in the target population are statistically independent. Specifically,

(1). AGE, an integer value in the range from 35 to 84 years old;

(2). GENDER, an integer value 1 or 2: 1 represents 'MALE', 2 represents 'FEMALE';

(3). SMOKING STATUS, an integer value 1 or 2: 1 Smoker, 2 Non-smoker;

(4). BLOOD PRESSURE, an integer value in the range from 60 to 180 millimeters-of-mercury.

Instead of using the estimated distributions of these risk factors drawn from experimental or epidemiological samples, here we suppose that the marginal distributions of these determinants and the total fraction of individuals in the target population are already known. We designed a software interface that allows the user to select the distributions of age, gender, smoking status, and blood pressure, as well as the number of subjects.

For example, based on the Age Distribution of the Population of Canada July 1, 2003 (Statistics Canada, 2003) and discussions with members of the ***CCORE*** group, the default distribution of age between 35 and 84 was generated from a normal distribution with truncations at 35 and 84; the default distribution of blood pressure was assumed be a normal distribution with the mean at 90 and the standard deviation at 40; the default distributions of Gender, and Smoking Status were assumed to be binary with 50% FEMALE vs. 50% MALE and 20% SMOKER vs. 80% NON-SMOKER in the target population. All these assumptions

are used only for illustration purpose, which can be modified without modifying the framework.

With these assumptions, the framework can create a cohort of a given size, up to 100,000 hypothetical individuals, with the four randomly generated determinants. Table3 shows the data structure.

PERSON_N	INI_AGE	GENDER	SMOKING	BLOOD_P
441	54	2	1	98
442	43	1	2	89
443	45	1	2	87
444	44	1	2	115
445	61	1	2	129
446	60	1	1	133
447	41	2	2	128
448	49	1	2	80
449	67	2	1	150
450	44	1	2	73
451	42	1	2	80
452	46	2	2	132
453	41	2	2	130
454	49	1	2	128
455	53	1	2	114
456	58	1	2	68
457	41	1	2	99
458	72	2	2	120
459	61	2	2	123
460	35	2	1	105

Table3 Target Population with Four Risk Factors

4.1.2 Transition Probabilities Estimation

4.1.2.1 Defining Health States

The *SAS CCORE framework* can consider as many states as required, subject to available data and available computational resources. For simplicity, we assume there are only four health states:

(1). NON_CVD (S_1): cardiovascular disease Free State;

(2). INI_CVD (S_2): represents the state that is the first manifestation cardiovascular Disease;

(3). POST_CVD (S_3): represents the state after INI_CVD;

(4). DEATH (S_4): Dead state.

To take into account of an individual's health history, we distinguished between the initial CVD-related disease state and the post ***CVD*** disease state by defining INI_CVD and POST_CVD; and the transitions between them are unidirectional from INI_CVD to POST_CVD. The allowable transitions among these states were given in Figure 7.

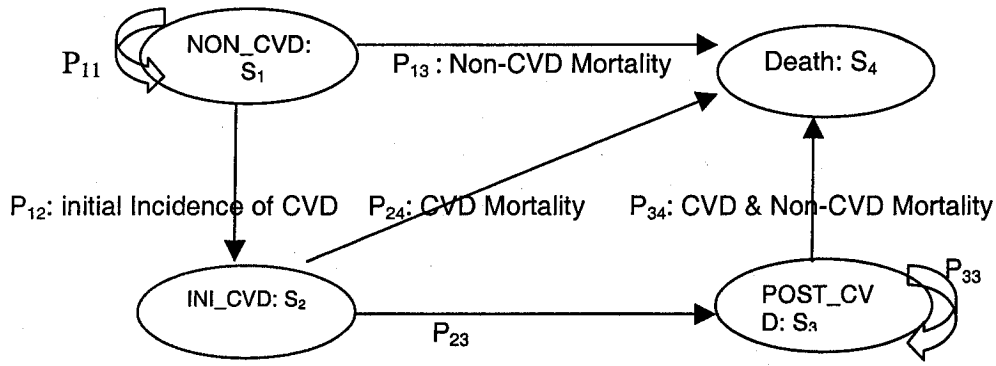

Figure 7: Illustrative allowable transitions among four states. Health states are represented by ovals, possible transitions are shown by arrows. P_{ij} adjacent to the arrows are the transition probabilities, where i represents the starting states, j represents ending state, and k represents the number of cycle.

4.1.2.2 Designing Intervention Programs or Policies

For management of chronic disease, the choice of initial intervention is only the first decision, and indeed, the effects of that choice depend strongly on how downstream decisions will be made. These later decisions have to be taken into account in evaluating the initial decision. The Bellman principle underlying dynamic programming states that each part of an optimal strategy must be optimal (Bellman, 1957). Thus, in deciding present optimal treatment, one should assume future decisions would be made optimally and back track from them to the present. Alternatively, one can pick strategies that decide all future decisions in advance in some reasonable way and "hardwire" those decisions into the model.

With discounting, differences in outcomes between future reasonable preset decisions and future optimal decisions may be small (Frank, 1995).

Here a policy is simply defined as the combination of interventions on the four states that an individual may experience. In this case study, there are four states, and we suppose there are two options for each state except Death: No-Intervention and Intervention, i.e., $w_i = 2$, i=1, 2, 3 and $w_4 = 1$. In sum, there are $N = \prod_{i=1}^{4} w_i = 2^3 = 8$ combinations or policies of these two intervention options in a four state model. These are represented in Table 4.

Policy Alternatives	**Intervention Option on State:**			
	NON_CVD	INI_CVD	POST_CVD	Death
POLICY_1	**O**	**O**	**O**	**O**
POLICY_2	**X**	**O**	**O**	**O**
POLICY_3	**O**	**X**	**O**	**O**
POLICY_4	**O**	**O**	**X**	**O**
POLICY_5	**X**	**X**	**O**	**O**
POLICY_6	**X**	**O**	**X**	**O**
POLICY_7	**O**	**X**	**X**	**O**
POLICY_8	**X**	**X**	**X**	**O**

Table 4 Feasible Combinations of Interventions in a Four-State Model: **X = intervention; O = no intervention**

As a policy is a combination of interventions on all possible states, it is reasonable to assume that the cost and effectiveness of any policy are independent of which other policies are adopted. Then, we can analyze separately the impact of each policy and the impact of

each intervention. For example, if we compare POLICY_2, POLICY_3, and POLICY_4 with POLICY_1 sequentially, we will be able to know the impact of each policy overall as well as the impact of each intervention on the state of NON_CVD, INI_CVD, and POST_CVD separately. Decision-makers will be informed both on the impact of particular intervention and of policies. They can make decisions not only on what intervention should be adopted on a particular state but also on how to implement these possible interventions in sequence on a particular individual or a specified group of individuals who are common on risk factors.

4.1.2.3 Define time horizon and cycle length

The sequence of events experienced by each hypothetical individual was assumed to be independent of those experienced by other individuals. The evolution was projected to age 84 or to the time that the individual died, whichever came first. As the minimum age in the target population is 35, the maximum time horizon for simulation is 49 years. Suppose the duration of each cycle is l months (= 1, 2, 3, 4, or 6), and the age of the individual at initial step is T, then, the maximum number of simulation cycles is

$$K = (12/l) * (84 - T). \qquad (3)$$

The default duration of each cycle is 6 months in this thesis, and the user can change it through the user interface.

4.1.2.4 Transition Probability

The transition probabilities from states: NON_CVD, INI_CVD, and POST_CVD to other states are estimated at each transition period by the Survivor Function for the i'th individual (Collett, 1994), which is given as:

$$S_i(t) = [S_0(t)]^{\exp(\beta X_i)} \quad (4)$$

where $t_{(k)} \le t \le t_{(k+1)}, k = 1,2,\ldots,r$, $S_0(t)$ is the estimated value of the baseline survival function, X_i is a vector of an individual explanatory variables (i.e., risk factors), β is a vector of regression coefficients corresponding to the explanatory variables, and k is the number of transition cycles.

As age continues to increase along an individual's lifetime, and the smoking status may be changed after an acute event, the values of individual's risk factors will be updated after each transition cycle. Here we simply suppose 30% smokers may cease smoking after they experience the initial CVD. The transition probability from state i to state j under the No-intervention option was denoted as P_{ij}; correspondingly under the Intervention option the transition probability was denoted as Q_{ij}.

For the No-Intervention policy, $S_0(t)$ and β are obtained from a series of Cox (survival) Regressions applied on the Framingham Cohort. $S_0(t)$ and β are independent. Different states will have different $S_0(t)$ and β, but for a particular transition (from state A to state B), $S_0(t)$ and β will be the same for all individuals. For the Intervention policies, the parameters will be obtained from similar regressions based on clinical trial or epidemiologic data.

For illustration purposes, in this thesis we used hypothetical $S_0(t)$ and β, which were shown in Table 5. To make it easy to modify these values later, our program was designed to input these means and standard deviations through the User' Interface.

N	S_{11}	S_{23}	S_{33}	B_{11}	B_{12}	B_{13}	B_{14}	B_{21}	B_{22}	...	B_{33}	B_{34}
1	0.9	0.3	0.6	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
2	0.99	0.3	0.6	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
3	0.9	0.8	0.6	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
4	0.9	0.3	0.9	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
5	0.99	0.8	0.6	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
6	0.99	0.3	0.9	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
7	0.9	0.8	0.9	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04
8	0.99	0.8	0.9	0.01	0.05	0.1	0.001	0.01	0.05	...	0.015	1E-04

Table 5 illustrates the hypothetical $S_0(t)$ and β under different policies on each state. For example, S_{11}, S_{23}, S_{33} represents the value of $S_0(t)$ on NON_CVD, INI_CVD, POST_CVD state respectively; B_{11}, B_{12}, B_{13}, and B_{14} are the elements of vector β corresponding to risk factors: Age, Gender, Smoking Status, and Blood Pressure on NON_CVD.

For each intervention policy, a Monte Carlo Simulation was started by computing each transition probability at the individual level. Each individual will have different transition probabilities even if they are in the same state and under the same intervention policy as the risk factors X may be different from individual to individual. With the same parameters of the survivor function but with different X_i, the transition probabilities will be different. Particularly under No-intervention option, the transition probabilities were obtained from:

- $P_{11}=S_i(t) = [S_0(t)]^{\exp(\beta X_i)}$ represents probability from NON_CVD to NON_CVD; the left part (1- P_{11}) may go to INI_CVD state or die due to ***CVD*** unrelated causes. At this point, as the NON_CVD mortality is unknown, so it is simply assumed that these individuals who can not remain at NON_CVD state will have 70% chance to go to INI_CVD state and 30% chance to die for any other causes. If the mortality of NON_CVD is known or

given, the transition probability from NON_CVD to INI_CVD will be easily obtained by 1- P_{11} - P_{13}.

- P_{12}=0.7*(1 – P_{11}) represents 70% of those not surviving from NON_CVD to NON_CVD will develop INI_CVD;
- P_{14}=0.3*(1 – P_{11}) represents 30% of those not surviving from NON_CVD to NON_CVD will die;
- $P_{23}= S_i(t) = [S_0(t)]^{\exp(\beta X_i)}$ represents probability from INI_CVD to POST_CVD;
- P_{24}=1 – P_{23} represents probability from INI_CVD to death;
- $P_{33}= S_i(t) = [S_0(t)]^{\exp(\beta X_i)}$ represents probability from POST_CVD to POST_CVD;
- P_{34}=1 – P_{33} represents probability from POST_CVD to death.

Table 6 shows a sample of the transition probabilities of individuals under No-intervention option on all states.

POLICY_N	PERSON_N	P_{11}	P_{12}	P_{13}	P_{23}	P_{24}	P_{33}	P_{34}
1	1	90.32%	6.78%	2.90%	31.23%	68.77%	61.03%	38.97%
1	2	88.08%	8.34%	3.58%	23.45%	76.55%	54.05%	45.95%
1	3	88.50%	8.05%	3.45%	24.76%	75.24%	55.30%	44.70%
1	4	86.87%	9.19%	3.94%	20.01%	79.99%	50.53%	49.47%
1	5	87.43%	8.80%	3.77%	21.54%	78.46%	52.13%	47.87%
1	6	87.49%	8.76%	3.75%	21.71%	78.29%	52.30%	47.70%
1	7	88.78%	7.86%	3.37%	25.66%	74.34%	56.15%	43.85%
1	8	83.86%	11.30%	4.84%	13.39%	86.61%	42.60%	57.40%
1	9	86.74%	9.28%	3.98%	19.69%	80.31%	50.18%	49.82%
1	10	85.93%	9.85%	4.22%	17.68%	82.32%	47.94%	52.06%
1	11	88.93%	7.75%	3.32%	26.15%	73.85%	56.60%	43.40%
1	12	90.31%	6.78%	2.91%	31.20%	68.80%	61.00%	39.00%
1	13	88.71%	7.90%	3.39%	25.45%	74.55%	55.96%	44.04%
1	14	85.16%	10.39%	4.45%	15.94%	84.06%	45.89%	54.11%
1	15	86.09%	9.74%	4.17%	18.05%	81.95%	48.37%	51.63%
1	16	89.14%	7.60%	3.26%	26.89%	73.11%	57.28%	42.72%
1	17	86.32%	9.58%	4.10%	18.61%	81.39%	49.00%	51.00%
:	:	:	:	:				
1	995	88.93%	7.75%	3.32%	26.15%	73.85%	56.60%	43.40%
1	996	89.86%	7.10%	3.04%	29.46%	70.54%	59.54%	40.46%
1	997	85.28%	10.30%	4.42%	16.21%	83.79%	46.21%	53.79%
1	998	90.29%	6.80%	2.91%	31.12%	68.88%	60.94%	39.06%
1	999	86.67%	9.33%	4.00%	19.50%	80.50%	49.97%	50.03%
1	1000	87.32%	8.87%	3.80%	21.25%	78.75%	51.83%	48.17%

Table 6 Transition probabilities of individuals under No-intervention option on all states

4.1.3 Finite State Markov Chain Decision Analysis Model (MCDAM)

The four state Markov Chain Decision Analysis Model is shown in Figure 8. By convention, states are shown as ellipses, choice nodes are rectangular, chance nodes are circles, and transition events are shown as arrows. Within each cycle, there is a choice node. The upper branch out of that choice node represents the "No-intervention" event taken from the current state; the lower branch represents the "Intervention" event taken.

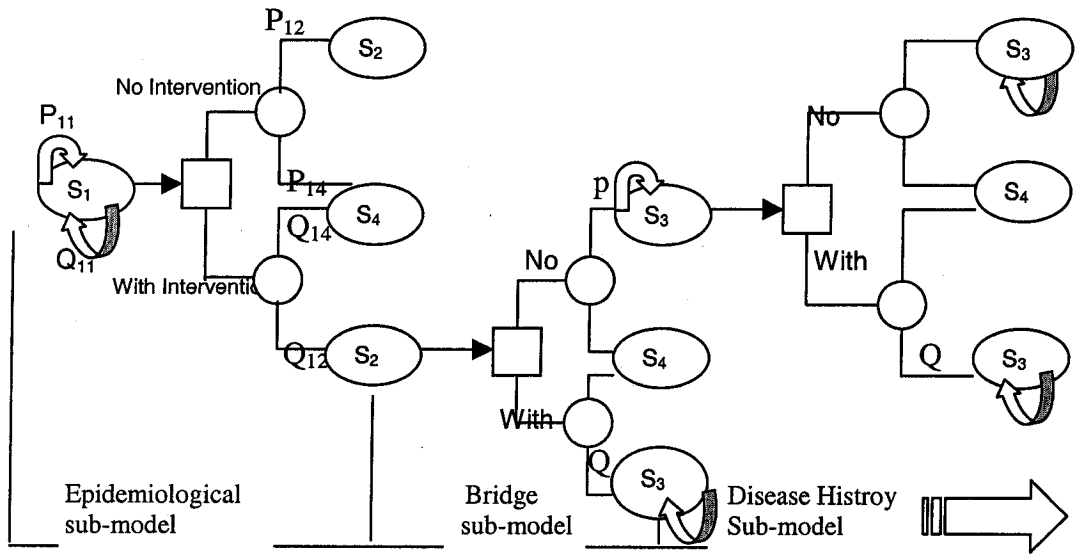

Figure 8 Simplified Illustrative ***MCDAM*** of ***CVD*** progression.

The first part represents an ***Epidemiological Sub-model*** representing the chances of a ***NON_CVD*** individual getting ***CVD***. The uncertainty of a "No-intevention" event and "Intervention" event are represented by chance nodes leading to states: S_1, S_2, or S_4 seperately, which means he/she may remain in a ***NON_CVD*** state, enter an ***INI_CVD*** state, or enter the ***DEAD*** state. The transition probabilities are denoted by P_{11}, P_{12}, and P_{14} for "No_intervention" events and denoted by Q_{11}, Q_{12}, and Q_{14} for the "With-intervention" events respectively.

Once an individual experiences ***INI_CVD***, he/she enters the ***Bridge Sub-model*** that describes what happens in the first thirty days after initially developing ***CVD***. Here we have another decision tree: a choice node leading to two branches: the upper one representing a "No-intervention" event taken from the current state, and the lower one representing a "With intervention" event taken from the current state; ecah branch having one chance node leading to two possible states: S_3 (***POST_CVD***) or S_4 (***DEAD***).

If the individual enters S_3 (***POST_CVD***) state, then he/she enters ***Disease History Sub-model*** that describes the rest of his (her) life. If he/she remains at S_3 (***POST_CVD***) state for a period: time t greater than the length of cycle l, he/she will experience more than one cycle. Within each cycle decision makers need to make a decision on taking intervention or not given the current state. This consists of a decision tree and the same structure as described above. The difference is that the destination states are either S_3 (***POST_CVD***) or S_4 (***DEAD***). Overall, the progrssion from the ***NON_CVD*** state to the ***Dead*** state over sucessive cycles comprises the Markov Chain and within each cycle there is a decision tree model, this describes the Finite State Markov Chain Decision Analysis Model that ws built in Chapter 3.

4.1.4 Life Path Simulation Algorithm

The evolution of health states or life path was simulated at individual level under different policies. The illustrative Life Path simulation algorithm is shown in Figure 9, which comprises the following steps:

1. Select a policy in the order from 1 to 8 to determine the values of $S_0(t)$ and β;
2. Select an individual in order from 1 to 100,000 to determine the value of the risk factors X;

3. All the individuals start from the ***NON_CVD*** state. Based on the formula in 4.1.2.4 Transition Probability and the chosen values of $S_0(t)$, β, X, specify P_{11}, P_{12}, and P_{14};
4. Apply a random device to generate a random value P in the range of 0.0 and 1.0;
5. If $P \leq P_{11}$, the individual will remain in the ***NON_CVD*** state
   - Update risk factors with Age = Age + $l/12$, where l is the length of cycle;
   - If Age ≥ 85, terminate this individual's life path simulation and N=N+1, where N is the number of individuals simulated, if $N \geq 100{,}000$, go to step 9; otherwise go to step 2;
   - If Age < 84, continue this individual's life path simulation and go to step 3;
6. If $P_{11} < P \leq P_{11} + P_{12}$, this individual will enter the ***INI_CVD*** state
   - Update risk factors with Age = Age + $l/12$, and 30% smokers will cease smoking after developing ***INI_CVD*** state;
   - If Age ≥ 85, terminate this individual's life path simulation and N=N+1, where N is the number of individuals simulated, if $N \geq 100{,}000$, all simulations terminate; otherwise go to step 2;
   - If Age $\leq$ 84, estimate P_{23}, and P_{24} as step 3;
   - Generate a random value P in the range of 0.0 and 1.0;
   - If $P \leq P_{23}$, this individual enters ***POST_CVD*** state and go to step 7;
   - If $P > P_{23}$, this individual enters ***DEAD*** state and go to step 8.
7. Once an individual enters ***POST_CVD*** state
   - Update risk factors with Age = Age + $l/12$;

- If Age ≥ 85, terminate this individual's life path simulation and N=N+1, where N is the number of individuals simulated, if N≥ 100,000, go to step 9; otherwise go to step 2;
- If Age ≤ 84,, estimate P_{33}, and P_{34} as method mentioned at step 3;
- Generate a random value P in the range of 0.0 and 1.0;
- If $P \leq P_{33}$, this individual remains at ***POST_CVD*** state and go to step 7;
- If $P > P_{33}$, this individual enters ***DEAD*** state and go to step 8.

8. If $P > P_{11} + P_{12}$, this individual enters ***DEAD*** state, terminate this individual life path simulation, and N=N+1, where N is the number of individuals simulated, if N≥ 100,000, go to step 9; otherwise go to step 2;
9. K = K + 1, where K is the number of policy simulated
   - If K ≤ 8, go to step 1 and reiterate all the steps above;
   - Otherwise terminating the life path simulation process.

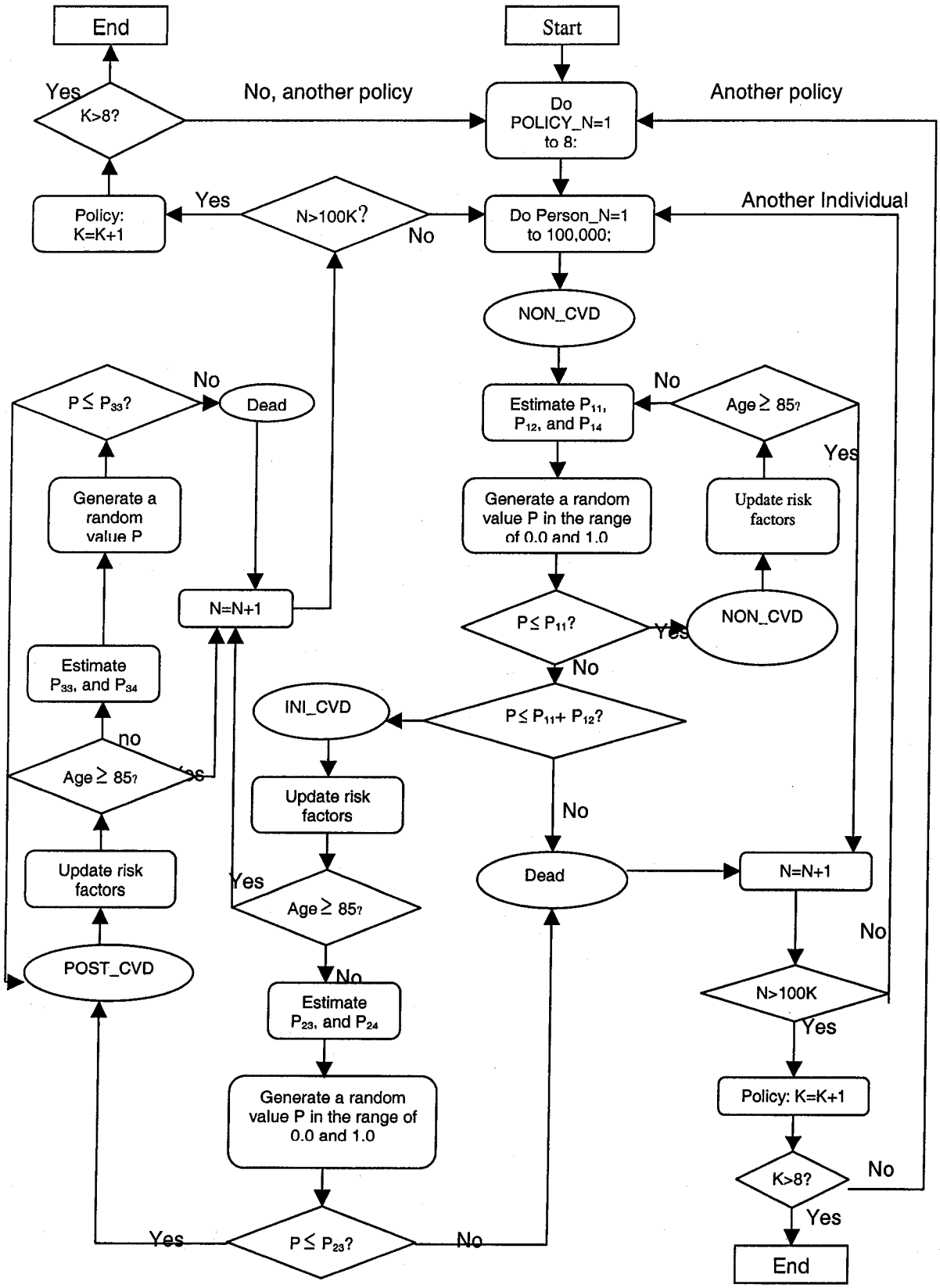

Figure 9 Illustrative Life Path Simulation Algorithm

4.1.5 Life Path Simulation Result

The life path simulation result is a matrix with K x N rows and 2 + (85-35) x 12/l columns. K is the number of policies under simulation; N is the number of individuals simulated, and l is the length of transition cycle in months. The first column recorded the number of individual whose life path was simulated; the second column recorded the number of policy under which the individual's life path was simulated; the first part of the subsequent columns record the health states for each cycle from starting state until the individual's age reaches 85 or enters the dead state. Afterwards, the remaining columns record nothing, i.e., blank, which implies no health states are recorded. The structure of the result matrix is illustrated in Table 7.

PERSON_N	POLICY_N	INI_AGE	STA_C0	STA_C1	STA_C2	STA_C3	STA_C4	STA_C5	STA_C6	... ...	STA_C98
981	4	44	1	1	1	1	1	1	1		
982	4	57	1	1	1	1	1	1	4		
983	4	70	1	1	1	1	1	1	1		
984	4	45	1	1	1	1	1	1	1		
985	4	36	1	1	1	1	1	1	2		
986	4	46	1	1	1	4					
987	4	59	1	1	2	4					
988	4	50	1	1	1	1	1	1	1		
989	4	46	1	1	1	1	1	1	1		
990	4	58	1	1	1	1	1	1	1		
991	4	42	1	1	1	1	4				
992	4	50	1	1	1	1	1	1	1		
993	4	66	1	1	1	1	1	1	1		
994	4	51	1	1	4						
995	4	36	1	1	1	1	2	4			
996	4	64	1	1	1	1	1	1	1		
997	4	56	1	1	1	1	1	1	2		
998	4	66	1	1	1	1	1	1	1		
999	4	49	1	1	1	1	1	1	1		
1000	4	52	1	1	1	1	1	1	1		

Table 7 Individuals' Life Paths under Policy 4 when transition length is six months. Column 3 records the initial age. STA_C0 records the initial health state. STA_Ci represents the health state at cycle I. The values in column STA_Ci: 1– ***NON_CVD***; 2 –***INI_CVD***; 3–***POST_CVD***; 4 –***DEAD***; and ' ' represents no health state recorded, which means either this life path already ended up in the **DEAD** state or at age more than 84.

4.2 Cost and Effectiveness Estimation

4.2.1 Cost and Effectiveness Measurement

4.2.1.1 Cost Measurement

Instead of using the real costs of different interventions, we assumed that we know their distributions through their mean values and the standard deviations. Further, we assume the cost of each intervention on the same health state over different cycles have identical independent distributions. Based on the health state at each cycle, a random value of the cost was drawn from the cost distribution of the corresponding intervention on that state; see Formula (5).

$$C_i^j(t) = U_i^j + S_i^j \times RANNOR(123); \qquad (5)$$

where j represents state; i represents the option of intervention on state j; U is the mean value of the cost distribution; S is its standard deviation; RANNOR(123) is a random device that generates a random value from a standard normal distribution.

Future costs are discounted to present values. The total cost of one policy over one life path is the accumulation of all the present values of costs at all cycles; see Formula (6).

$$C = \sum_{t=1}^{T} C(t)/(1+i)^{t-1} \qquad (6)$$

where C represents the total cost; C(t) represents the cost at cycle t; T is the number of total cycles; i is the interest rate in one cycle, which is derived from annual interest rate by Formula (7).

$$i = \frac{l}{12} \times r \qquad (7)$$

where l is the length of cycle in month; r is the annual interest rate.

4.2.1.2 Effectiveness Measurement

The effectiveness of an intervention policy was measured in Quality Adjusted Life Years (***QALYs***) gained, which can capture both quality and quantity of a survivor's lifetime.

First, we used the quality-adjustment weight for each health state multiplied by the time in the state to calculate the Health-Related Quality of Life ***(HRQL)*** for each state. The most current approaches have respondents assign weights to different health states on a scale ranging from 0 (for dead) to 1 (for wellness) (Sloan 1995). In this thesis, for illustration purposes we simply assigned 0.5 for the ***INI_CVD*** state, 0.7 for the ***POST_CVD*** state, and 1 for the ***NON_CVD*** state, although we can adopt here the same technique used to deal with cost, i.e., instead of using the point values of weights, using a distribution of weights to capture the variance of weights from different respondents.

Second, all the ***HRQLs*** were discounted to present values and summed to calculate ***QALYs*** gained for each life path; see Formula (5).

$$INCRE\_Q = \sum_{t=1}^{T} HRQL(t) / (1+i)^{t-1} \qquad (8)$$

where t is the number of cycle; T is the total number of cycles that has a value of health state; i is the interest rate in one cycle, which is derived from annual interest rate by Formula (7).

4.2.1.3 Incremental Cost—Effectiveness Ratios (*ICERs*)

Recent developments (Briggs and Fenn, 1998; Andrew and Bernie, 1999; Lothgren and Zethraeus, 2000; O'Brien et al., 1994; Van et al., 1994) in economic theory suggest that economic evaluation should focus on estimation of the joint density of cost and effectiveness differences, and the quantification of uncertainty about the ***ICERs*** (Nichol et al., 2002).

Incremental Cost-Effectiveness Ratios represents the additional cost of producing one more unit of ***QALYs*** achieved by the intervention ***S*** relative to its' comparator -**0**.

$$ICERs^{S} = \frac{C_S - C_0}{INCRE\_Q_S - INCRE\_Q_0} = \frac{\Delta C_{S\_0}}{\Delta U_{S\_0}} \qquad (9)$$

where C_s, C_0, $INCRE\_Q_s$, and $INCRE\_Q_0$ estimated by formula (6) and (8) represent the cost and ***QALYs*** gained under the scenario-***S*** and scenario-**0** respectively on individual basis.

4.2.2 Cost and Effectiveness Estimation

The default distributions of costs are normal distributions. The means and standard deviations of those distributions along with weights and annual interest rate were listed in Table 8. To make it easy for modifying these values later, the SAS program was designed to input these values through the User's Interface.

N	RATE	NON_ COST	INI_ COST	POST_ COST	NON_S TD	INI_ STD	POST_ STD	NON_Ut ility	INI_ Utility	POST_ Utility	LENGTH
1	5	0	0	0	0	0	0	1	0.5	0.7	6
2	5	1	0	0	0.1	0	0	1	0.5	0.7	6
3	5	0	100	0	0	14	0	1	0.5	0.7	6
4	5	0	0	10	0	0	2	1	0.5	0.7	6
5	5	1	100	0	0	14	0	1	0.5	0.7	6
6	5	1	0	10	0.1	0	2	1	0.5	0.7	6
7	5	0	100	10	0	14	2	1	0.5	0.7	6
8	5	1	100	10	0.1	14	2	1	0.5	0.7	6

Table 8 illustrates the hypothetical values for performing economic evaluation. **N** is the number of policies. **Rate** is the annual discount interest rate. **NON_COST, INI_COST, POST_COST, NON_STD, INI_STD, and POST_STD** represent the mean and standard deviation value for *COST* on the corresponding state under different policies. **NON_Utility, INI_Utility** and **POST_Utility** show the utility weight under on each state. **Length** is the duration of one cycle.

4.2.2.1 Economic Evaluation Algorithm

The illustrative cost and effectiveness estimation algorithm is shown in Figure 10, which comprises of the following steps:

(1) Read in all parameters on costs and effectiveness;

(2) Input the life path simulation result: life path matrix

(3) Read in a life path by selecting policy in the order from 1 to 8 and selecting an individual in the order from 1 to 100,000;

(4) From the first cycle to the last one, based on the Formula (5) – (8) estimate the total cost and ***QALYs*** gained for one life path;

(5) Reiterating step (3) – (4) to estimate the total cost and ***QALYs*** gained for all life paths.

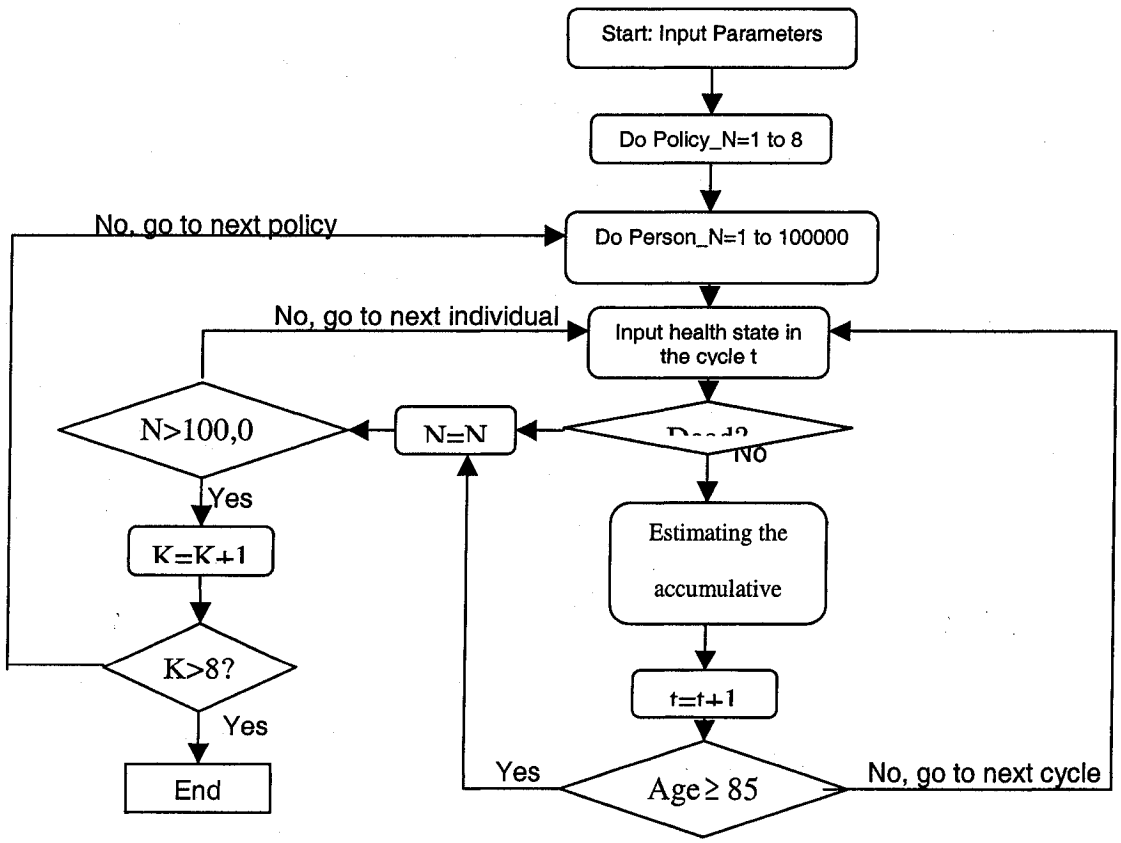

Figure 10 Illustrative cost and effectiveness estimation algorithm

4.2.2.2 Estimation Results

The estimation results are a number of matrices. One is with K x N rows and 6 columns with the structure shown in Table 9, where K is the number of policies; N is the number of individuals in the target population.

POLICY_N	PERSON_N	QALYS	INCRE-QALYS	COST	RATIO
2	1	54.117	8.1166383414	17.136	2.111
2	2	63.034	7.0344335469	14.511	2.063
2	3	62.325	2.3249546394	4.908	2.111
2	4	42.726	0.7260452746	1.03	1.419
2	5	48.488	0.4879500365	1.03	2.111
2	6	36.429	1.4288548331	3.017	2.111
.	.	...	...	.	.
2	17	48.374	6.373807686	13.099	2.055
2	18	58.952	4.9518105203	10.06	2.032
2	19	50.73	11.730044361	24.545	2.092
2	20	65.502	5.5024801995	11.617	2.111

Table 9 shows the estimation results of **Cost** and ***QALYs*** of the life path with policy 2 and individual from No.1 to No.20. The column 4 ***INCRE-QALYS*** recorded the ***QALYs*** gained in that life path since the individual entering the intervention program, which was estimated using the economic evaluation algorithm. ***QALYs*** were calculated by adding ***INCRE-QALYS*** to the initial Age that was the age when the individual was created at the beginning of the program. The last column ***RATIO*** was calculated by dividing ***COST*** by ***INCRE-QALYS***, representing the cost of a unit of ***QALYs*** gained under policy 2 for each individual.

The others show the ***incremental Cost***, ***QALYs*** and the ***Ratio*** of them for each individual and for each policy comparison. With 8 policies simulated there are 28 possible pairs of policy comparison, so there are 28 matrices showing the comparison results. For example, table 8 is the structure of one such matrix showing the comparison result between policy_6 and policy_4.

PERSON_N	POLICY_C	ΔC_{6_4}	ΔU_{6_4}	*ICERs*
1	64	-0.001	0.744	-0.001
2	64	12.534	-0.359	-34.914
3	64	15.281	2.259	6.764
4	64	24.165	11.004	2.196
5	64	9.194	0.275	33.433
6	64	43.153	5.305	8.134
7	64	19.214	7.273	2.642
8	64	12.747	1.537	8.293
9	64	21.652	7.019	3.085
10	64	9.905	1.568	6.317
11	64	11.636	3.782	3.077
12	64	15.591	7.038	2.215
13	64	21.341	5.129	4.161
14	64	9.11	2.033	4.481
15	64	8.296	-5.452	-1.522
16	64	11.437	3.177	3.6
17	64	-26.999	-7.944	3.399

Table 10 shows policy comparison results of incremental ***Cost, QALYs*** and the ***Ratio*** of them between Policy_6 and the comparator Policy_4 for individual from No.1 to No.17. The incremental cost and effectiveness ratio (*ICERs*) is estimated by using formula 6 on individual level.

4.3 Cost Effectiveness Analyses

4.3.1 The Basic Cost-Effectiveness Model

Cost-effectiveness analysis is based on the solution to a simple optimization problem. Given a budget constraint, an explicit objective such as ***QALYs*** and a set of alternative programs, such as treatments, that use resources (cost Ci) and contribute to the objective (effectiveness Ei), the optimal resource allocation is to rank order the programs according to their cost-effectiveness ratios (Ci/Ei) and to select them from the lowest to the highest to the point where the resource budget is exhausted. This allocation can be shown to yield the maximum total effectiveness, that is, ***QALYs*** gained, subject to the budget constraint (Weinstein et al. 1972). The cost-effectiveness ratio of the last program selected before the

budget is exhausted is especially important: it serves as the standard or cutoff against which programs that make claims against the budget can be judged (Frank, 1995).

4.3.2 Target Population Structure Analyses

Before doing any cost effectiveness analysis, decision makers need to know the structure of the target population. Based on the data set: COHORT created at 4.1.1 Creating Target Population, using **Proc gchart** we can create Figure 11 on the distributions of age, gender, smoking status, and blood pressure with N = 10,000 individuals.

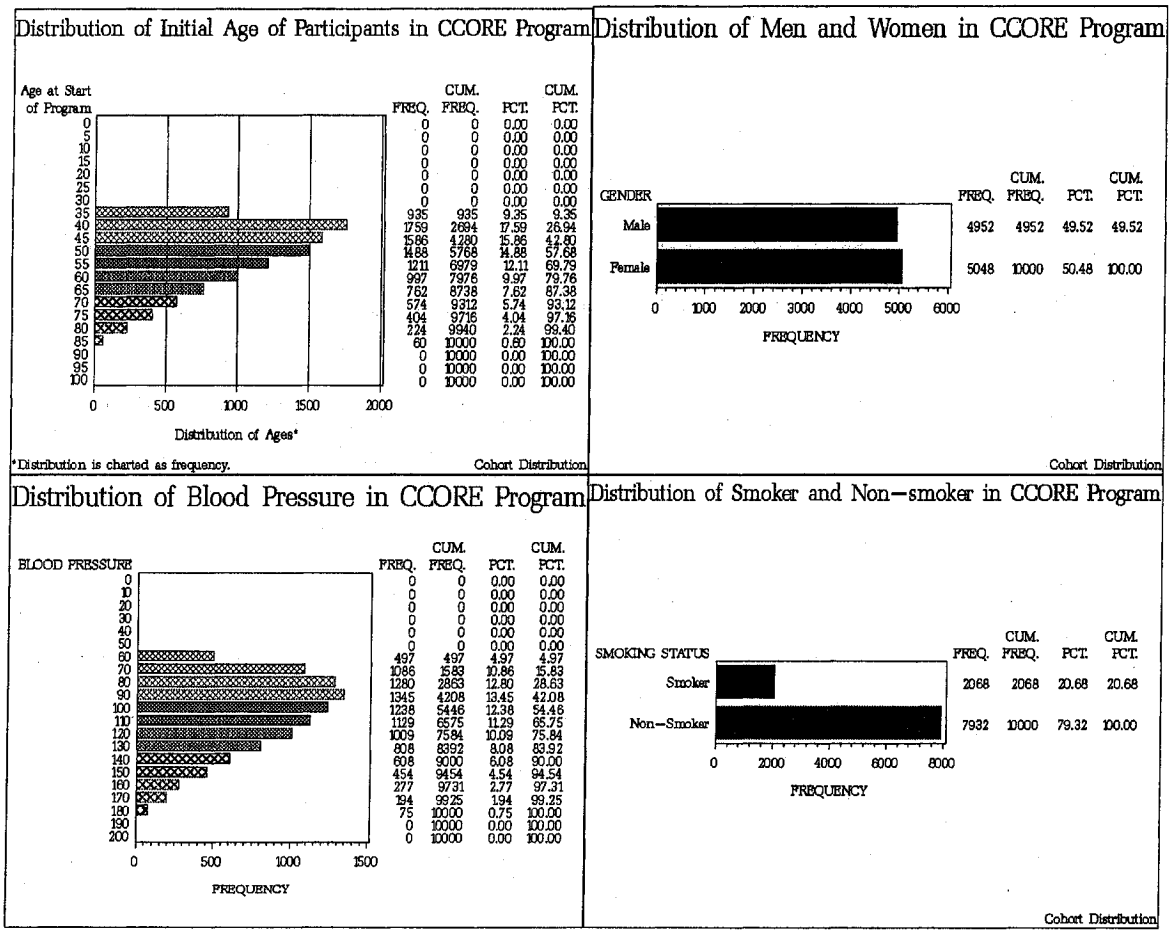

Figure 11 Distributions of Age, Gender, Smoking Status, and Blood Pressure of the target population after simulation. It shows that the percentage of male and female are almost equal; 20.68% populations are smokers; the distributions of age, and blood pressure are closed to normal distribution. The values are close to those used to generate the cohort.

The target population can be divided into subgroups based on the values of the risk factors so that decision makers can make decision examine policies or interventions at specific groups. For illustration purpose, in this thesis, the cohort was partitioned, based on age, into three subgroups: 35-50, 50-65, and 66-84; and further divided by gender, smoking status, and blood pressure.

4.3.3 Cost Effectiveness Analysis on Average Costs, QALYs, and ICERs

The mean values and distributions of ***Costs***, ***QALYs,*** and ***ICERs*** on different policies were depicted in the Figure 12-14.

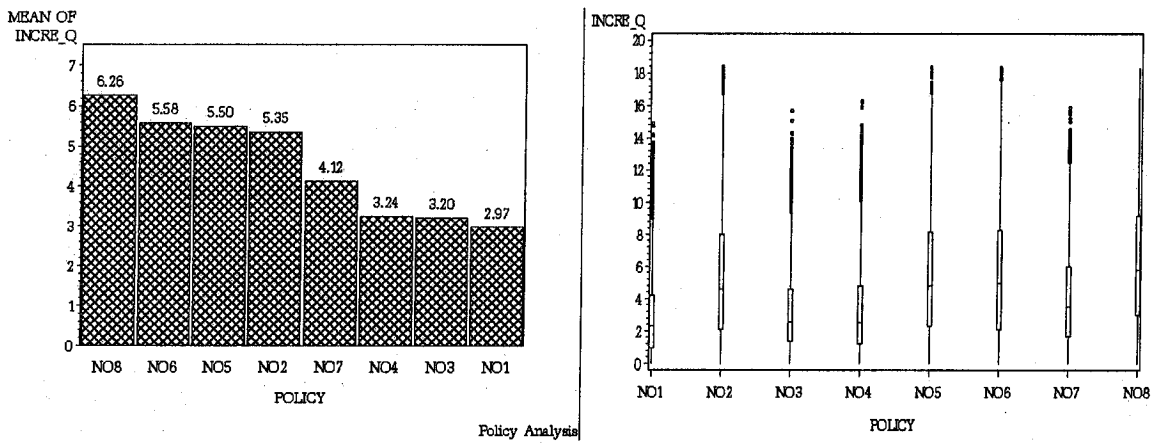

Figure 12 The Distributions and box-plots of ***QALYs*** gained on 8 policies.

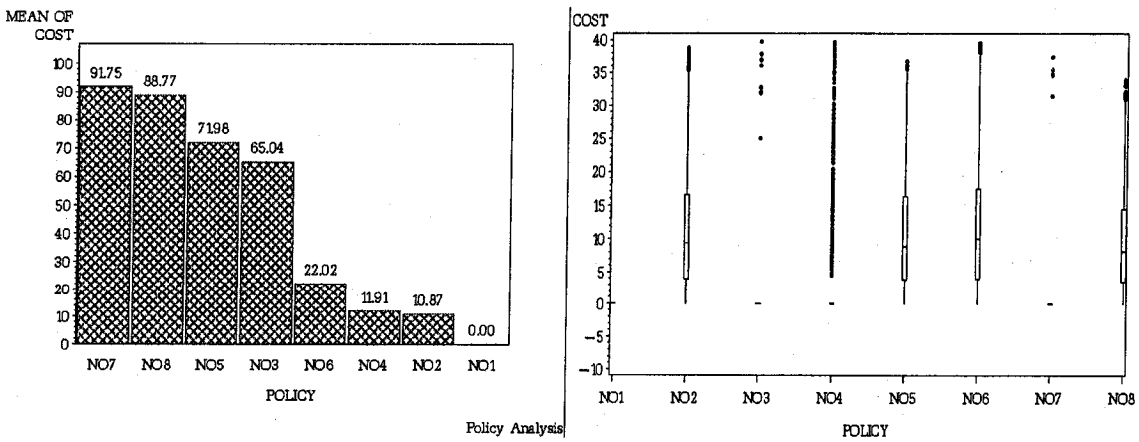

Figure 13 The Distributions and box-plots of ***Cost*** on 8 policies.

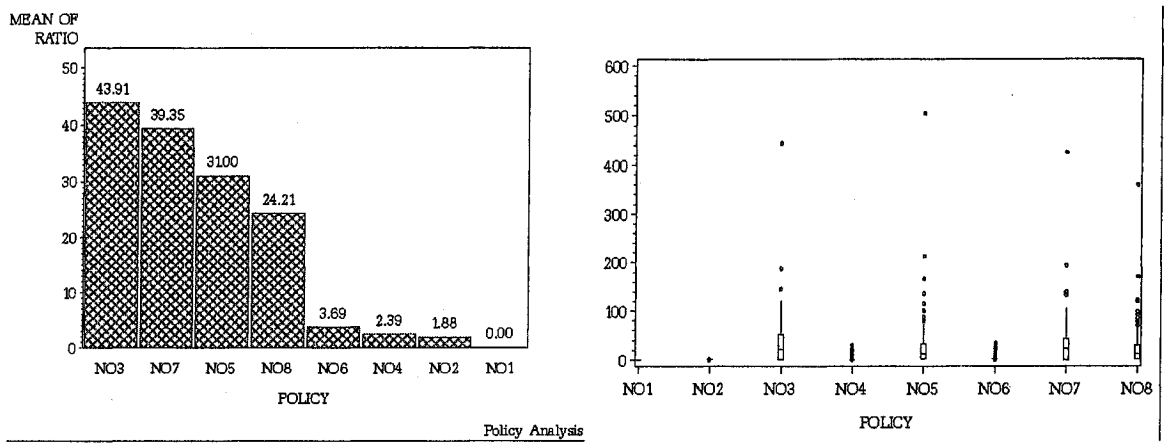

Figure 14 The Distributions and box-plots of the Incremental **Ratio** on 8 policies. The mean of ratio here is calculated from the ratio of the ***COST*** divided by the ***QALYs*** gained under the same policy for each individual.

The results of Figure 12-14 are summarized in the Table 11.

Number of Policy	Mean of QALYs	Std. Of QALYs	Mean of COST	Std. Of COST	Mean of ICERs	Std. Of ICERs	Rank of ICERs
Policy_1	2.97	0.0	0.0	0.0	0.0	0.0	1
Policy_2	5.35	3.96	10.87	8.46	1.88	0.47	2
Policy_3	3.20	2.50	65.04	44.59	43.90	72.60	8
Policy_4	3.23	2.75	11.91	39.44	2.39	6.43	3
Policy_5	5.50	3.92	71.98	45.53	31.00	61.29	6
Policy_6	5.57	4.00	22.01	39.15	3.69	5.43	4
Policy_7	4.12	3.07	91.45	78.29	39.34	70.80	7
Policy_8	6.26	4.03	88.77	79.50	24.21	45.13	5

Table 11 shows the mean and standard deviation values of ***QALYs*** gained, ***COST***, and ***ICERs*** for each policy, and the rank of ***ICERs*** for policies from the lowest to the highest.

Based on *the Basic Cost-Effectiveness Model* in section 4.3.1, with a given limited resource to get maximum aggregated ***QALYs*** gained, the optimal allocation of a given

resource is to adopt the policy in the order of 2, 4, 6, 8, 5, 7, and 3. It indicates society will be better off at the aggregate level if resources are spent on preventive treatment for ***NON_CVD*** or/and ***POST_CVD*** individuals than if spent on acute intervention for ***INI_CVD*** people. The emphasis here is not on the conclusion, as it was a superficial result based on hypothetical cost and utility functions, but on how to use the *Basic Cost-Effectiveness Model*.

4.3.4 Cost Effectiveness Analyses on Joint Distributions

Frequently decision-makers need to know under what condition a new program can replace the current program. In this sample case, ***SSFCEA*** generated 28 different pairs of policies (8 x 7/2 = 28) distributions on incremental ***Cost*** and ***QALYs***. For illustration and simplicity, here we only demonstrate the comparison analysis between policy_3—with acute treatment on ***INI_CVD***—and Policy_2—with preventive treatment on ***NON_CVD***, and the latter used as comparator. From the last section, we already know that for a given budget policy_2 can produce a larger aggregate number of ***QALYs*** gained than policy_3. The purpose of the comparison here is to find out under what conditions the acute interventions on ***INI_CVD*** will be preferred to preventive interventions on ***NON_CVD.***

We treat the life-paths generated from a common starting individual as paired data, and compute a per-individual increment in performance. The estimated cost and ***QALYs*** gained of each individual under policy_2 and under policy_3 are denoted as C_2^i, E_2^i, C_3^i, and E_3^i respectively, where i represents the ID number of individual in the target population. Defining $\Delta C^i = C_3^i - C_2^i$, $\Delta E^i = E_3^i - E_2^i$, and $ICERs^i = \frac{\Delta C^i}{\Delta E^i}$, the following situations can arise, which are shown in Figure 15.

- $\Delta C^i>0$, $\Delta E^i>0$, $ICERs^i>0$: new treatment is more costly but more effective for those individuals locating in **Quadrant I**;
- $\Delta C^i>0$, $\Delta E^i<0$, $ICERs^i<0$: comparator is dominant for those individuals locating in **Quadrant II**;
- $\Delta C^i<0$, $\Delta E^i>0$, $ICERs^i<0$: new treatment is dominant for those individuals locating in **Quadrant III**;
- $\Delta C^i<0$, $\Delta E^i<0$, $ICERs^i>0$: new treatment is less costly but less effective for those individuals locating in **Quadrant IV**;

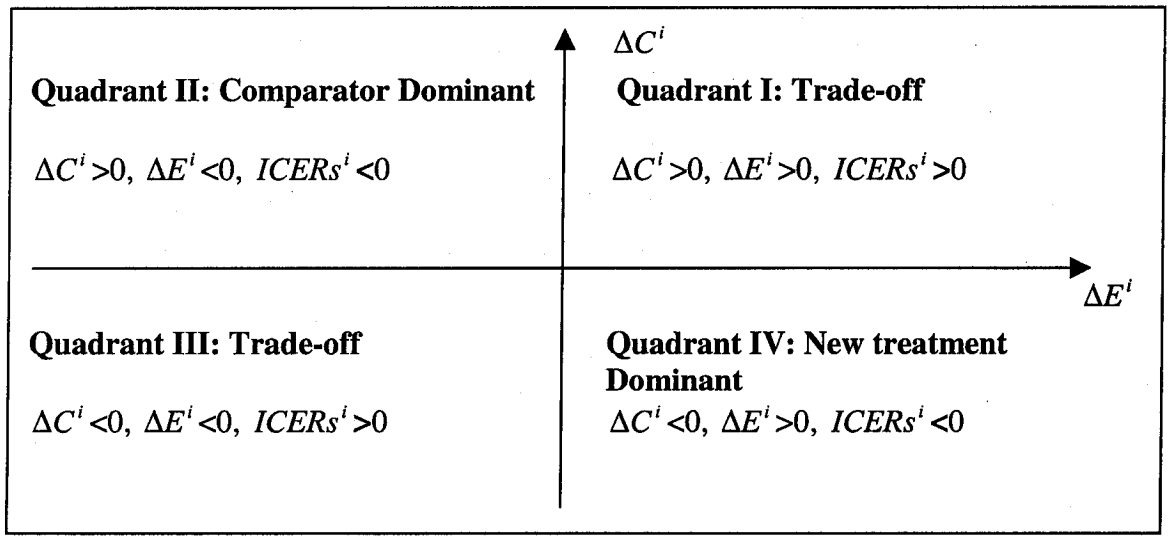

Figure 15 shows the schematic representation of the situations of the incremental ***Cost*** and ***QALYs*** gained for each individual between two policies on a cost-effectiveness plane.

Figure 16 shows the joint distributions of ΔC^i and ΔE^i between policy_3 and policy_2 from the estimation results. The horizontal and vertical axes are the difference in *QALYs* (ΔE^i=INCR_Q32) and the difference in the cost (ΔC^i=INCR_C32), respectively. Each spot represents an individual's incremental ***Cost*** and ***QALYs*** gained when policy_2 is replaced by policy_3, which formed two separate groups at the cost-effectiveness plane.

About 50% of the individuals of the upper group with $\Delta C^i > 0$ and with $\Delta E^i < 0$ locating in **Quadrant II**, where policy_2 is dominant. Only about 10% individuals are found in **Quadrant IV** with $\Delta C^i < 0$ and $\Delta E^i > 0$, where policy_3 is dominant. When neither policy_3 nor policy_2 is dominant, i.e., **Quadrant I** and **III,** the convention is to examine the incremental cost-effectiveness ratio (*ICERs*), see 4.3.5.

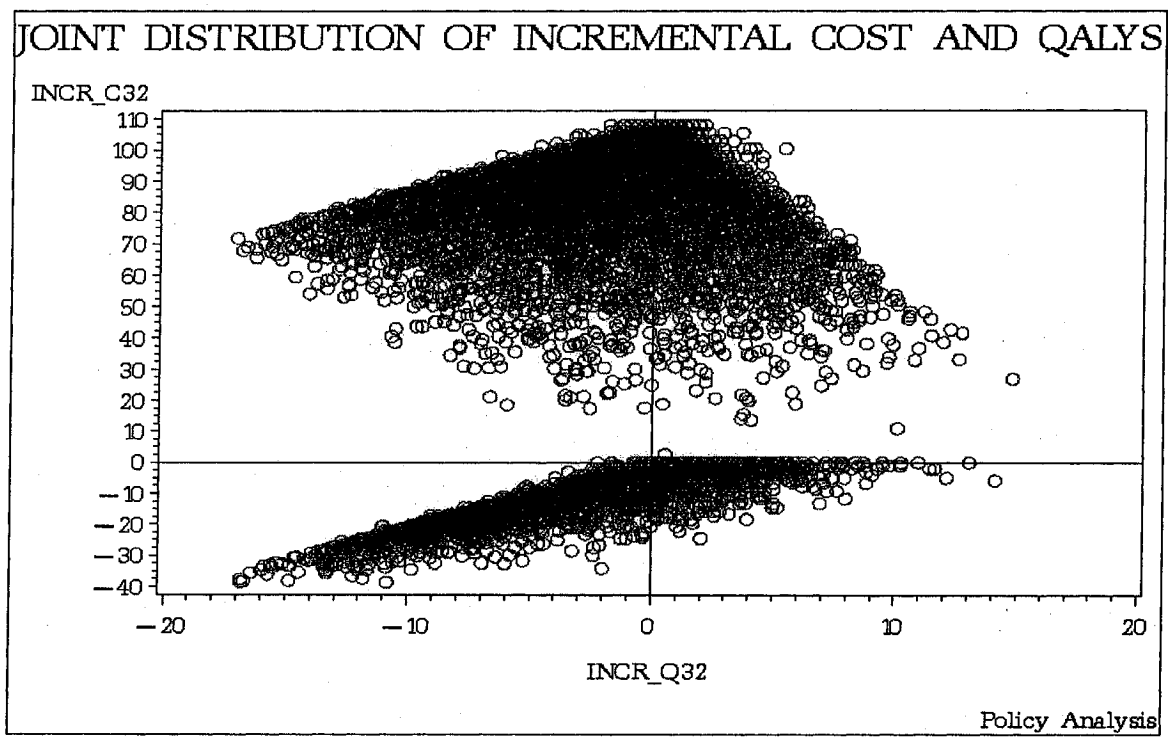

Figure 16 Illustration of joint distributions of 10,000 individuals' incremental ***Cost*** and ***QALYs*** gained when policy_2 is replaced by policy_3.

4.3.5 Analyses on the incremental cost-effectiveness ratio (ICERs)

When $ICERs^i > 0$, there is a trade-off between costs and effects for those individuals, and decision makers must choose their maximum threshold, Willingness To Pay (***WTP***), for an additional unit of ***QALYs*** in order to define the boundary of what is 'cost-effective'. ***CCORE SAS-IML*** created accumulative ***ICERs*** curves for all possible policy comparisons (28). In this thesis, the accumulative ***ICERs*** curves is defined as the sorted ***ICERs*** versus the

accumulative percentage of ***ICERs*** for individuals with $\Delta E^i > 0$ or ***ICERs***>0. Individuals with $\Delta E^i < 0$ and ***ICERs*** <0 are not accounted in the accumulative curve as they are located in **Quadrant II** where the comparator is dominant.

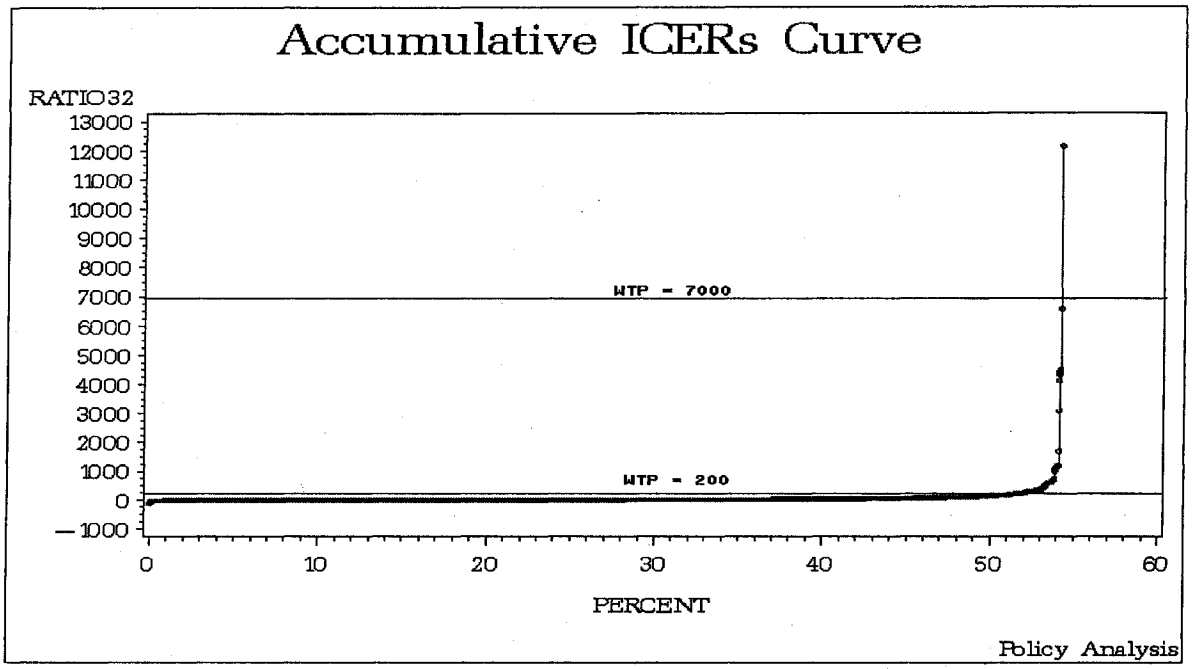

Figure 17 The accumulative ***ICERs*** curve for policy comparison between policy_3 and policy_2 with $\Delta E^i > 0$ or ***ICERs***>0.

For example, from Figure 17 we can see that the accumulative percentage is only about 55% with $\Delta E^i > 0$ or ***ICERs***>0, which means that about 45% of individuals have $\Delta E^i < 0$ and ***ICERs***<0, i.e., located in **Quadrant II** . This result is consistent with the comparator dominance found above that about 50% individuals locate in Policy_2 dominant Quadrant II. If we suppose the maximum ***WTP*** is 200 units per ***QALYs*** gained, there will be 51% of individuals accept the tradeoff between 200 unit costs and 1 unit ***QALYs*** gained. If the maximum ***WTP*** increases to 12000 units per ***QALYs*** gained, there will be only 4% more individuals accept the tradeoff between the cost and the ***QALYs*** gained. It indicates the poor are more likely to reject replacing policy_2 by policy_3; but the rich will more likely accept this change. Overall, about 45% of individuals will absolutely reject replacing policy_2 by

policy_3; the percentage of individuals who may accept this replacement will be conditional upon the value of ***WTP.***

4.3.6 Cost Effectiveness Analyses on Subgroups

So far, all the analyses have been conducted at aggregate level, considering the target population as a whole. The target population can be divided into a number of subgroups based on the similarities in initial risk factors. Different subgroups may have different distributions on COST, ***QALYs*** gained, ***ICERs*** under the same policy. In other words, different subgroups may have different policy preferences.

The ***SAS CCORE framework*** created a number of tables to illustrate the distributions on ***COST***, ***QALYs*** gained, ***ICERs*** of different policies in each sub-group. If the sub-groups were divided to the point where all members of the subgroup have almost the same values on all risk factors, decision-makers would have the information on which policy is the best for a given homogeneous group. Here, as an example, Table 10 shows the distributions on ***COST***, ***QALYs*** gained, ***ICERs*** in one sub-group, see *4.3.2 Target Population Structure Analyses* with risk factors' value as age 35 to 50, female, nonsmokers, and extra high blood pressure. Table 12 shows the differences on outcomes between the subgroups and the whole cohort.

AGE	GENDER_1	S_STATUS	BLOOD	POLICY	N Obs	Variable	N	Mean	Std Dev
35-50	FEMALE	N_SMO	EXT_HI	NO1	195	QALYS	195	45.596	4.953
						INCRE_Q	195	3.319	2.602
						COST	195	0.000	0.000
						RATIO	190	0.000	0.000
				NO2	195	QALYS	195	48.238	6.301
						INCRE_Q	195	5.961	4.483
						COST	195	12.044	9.598
						RATIO	190	1.831	0.529
				NO3	195	QALYS	195	45.717	5.177
						INCRE_Q	195	3.440	2.589
						COST	195	67.868	42.988
						RATIO	187	38.010	53.153
				NO4	195	QALYS	195	45.943	5.295
						INCRE_Q	195	3.666	3.064
						COST	195	13.966	44.918
						RATIO	186	2.651	6.771
				NO5	195	QALYS	195	48.414	6.697
						INCRE_Q	195	6.137	4.275
						COST	195	74.529	42.665
						RATIO	189	29.219	61.749
				NO6	195	QALYS	195	49.116	6.198
						INCRE_Q	195	6.839	4.266
						COST	195	31.987	59.680
						RATIO	194	4.247	6.187
				NO7	195	QALYS	195	47.352	6.016
						INCRE_Q	195	5.075	3.574
						COST	195	107.711	90.758
						RATIO	192	35.505	70.008
				NO8	195	QALYS	195	49.471	6.697
						INCRE_Q	195	6.973	4.355
						COST	195	99.898	88.663
						RATIO	191	27.070	58.009

Table 12 The mean and standard deviation values of ***Cost***, ***QALYs*** gained and ***Ratio*** under different policies for the given subgroup.

Number of Policy	Cohort QALYs	Subgroup QALYs	Cohort COST	Subgroup COST	Cohort ICERs	Subgroup ICERs	Rank of ICERs
Policy_1	2.97	3.31	0.0	0.0	0.0	0.0	1
Policy_2	5.35	5.96	10.87	12.04	1.88	1.83	2
Policy_3	3.20	3.44	65.04	67.87	43.90	38.01	8
Policy_4	3.23	3.67	11.91	13.97	2.39	2.65	3
Policy_5	5.50	6.13	71.98	74.53	31.00	29.22	6
Policy_6	5.57	6.84	22.01	31.99	3.69	4.25	4
Policy_7	4.12	5.08	91.45	107.71	39.34	35.51	7
Policy_8	6.26	6.97	88.77	99.90	24.21	27.07	5

Table 13 Comparisons on the mean values of ***Cost***, ***QALYs*** gained and ***Ratio*** between the cohort and the subgroup.

Table 13 indicates that the mean of Cost and ***QALYs*** in the subgroup increased, but for some policies the ICERs increased and for others it decreased. In particular, ***ICERs*** of policy_3 and policy_7 dropped significantly, which means that the acute intervention policies have more ***QALYs*** gained in this subgroup than for the whole target population. Further analysis on subgroups can be conducted using the same methods and this will provide more information on how to implement different policies for distinct subgroups or even distinct individuals.

4.4 Sensitivity Analysis

Sensitivity analysis (Sox et al., 1988; Pauker and Kassirer, 1987) is a technique used to discover which factors are the most important in a given decision. The Multiprocessor SAS framework provides the means to do sensitivity analysis on uncertain factors, such as the distributions of risk factors, the values of $S_0(t)$, β, cost, utility weight, and interest rate at different level.

4.4.1 Sensitivity Analysis on Distributions of Risk Factors

The Change of distributions of risk factors will change individuals' characters: ***X***, i.e., the target population will be changed and all the following simulation and estimation algorithms will be followed. Figure 18 shows the flow chart of sensitivity analysis of distributions of risk factors.

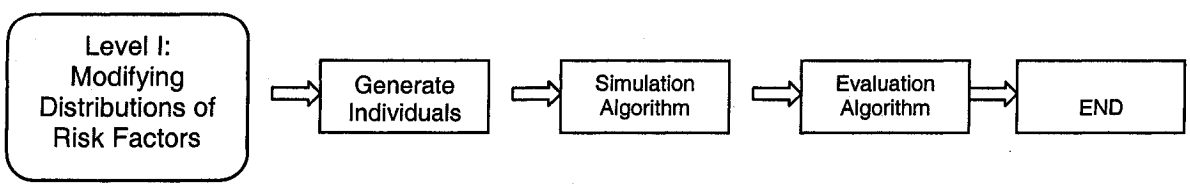

Figure 18 Flow chart of sensitivity analysis of distributions of risk factors

As we assume the distributions of risk factors are independent of each other, one-way sensitivity analysis can be conducted to see which factor has significant impact on the policy preference. As an example, sensitivity analysis on the distribution of age, the default distribution is normal; the compared distribution is even. We run the ***SAS CCORE framework*** two times to obtain the economic evaluation results of all policies for those two age distributions with all other parameters unchanged. The results were listed on Table 14.

Number of Policy	**Normal Distribution Of Age**			**Even Distribution Of Age**		
	Mean of Cost	Mean of QALYs	Mean of Ci/Ei	Mean of Cost	Mean of QALYs	Mean of Ci/Ei
Policy_1	0	3.27	0	0	3.02	0
Policy_2	23.64	11.28	**2.05**	20.85	9.95	2.06
Policy_3	64.60	3.43	39.41	62.03	3.28	41.69
Policy_4	10.37	3.63	2.16	9.00	3.20	**2.00**
Policy_5	48.73	11.60	8.99	43.79	10.09	9.45
Policy_6	26.89	11.42	2.52	24.00	10.09	2.46
Policy_7	87.43	4.19	38.25	83.44	3.96	37.60
Policy_8	53.26	11.74	8.55	44.36	10.14	8.16

Table 14 Sensitivity Analysis on distributions of age

Table 14 shows that when the distribution of age is changed from Normal to Even—more aging population—both cost and QALYs decrease, but the changes of Ci/Ei are mixed. For instance, Ci/Ei of policy_3 increases from 39.41 to 41.69, i.e., it will cost more money to obtain one unit QALYs. However, policy_4 became more efficiency than policy_2.

4.4.2 Sensitivity Analysis on $S_0(t)$ and β

The changes of $S_0(t)$ or β may result in the changes of the transition probabilities, and as a consequent individuals' life paths may be changed; but individuals' characters X, i.e., the target population, are not changed. Figure 19 shows the flow chart of sensitivity analysis of parameters of survivor function.

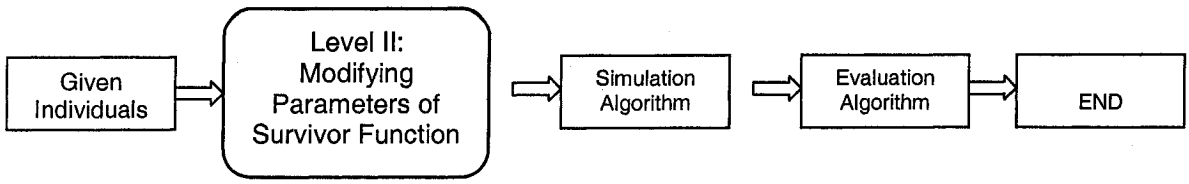

Figure 19 Flow chart of sensitivity analysis of parameters of survivor function

If we assume that $S_0(t)$, β, and their elements are independent of each other, we can do one-way simple sensitivity analysis on $S_0(t)$ or β with one element at one time. Otherwise, we need do multiple-way simple sensitivity analysis. For sensitivity analysis on $S_{11}(t)$ (the $S_0(t)$ on NON_CVD state), on the basis of the current value of $S_{11}(t)$ under Intervention option on NON_CVD state we modified the value of $S_{11}(t)$ two times: one with 10% reduction and another with 10% increment, and kept all other parameters unchanged. By running the simulation and evaluation algorithms of the framework we can estimate the mean and standard deviation of COST, QALYs and Ci/Ei for different values of $S_{11}(t)$. The results were listed on Table 15.

Number of Policy	$S_{11}(t)=0.985$			$S_{11}(t)=0.99$			$S_{11}(t)=0.995$		
	Mean of Cost	Mean of QALYs	Mean of Ci/Ei	Mean of Cost	Mean of QALYs	Mean of Ci/Ei	Mean of Cost	Mean of QALYs	Mean of Ci/Ei
Policy_1	0	3.28	0	0	3.27	0	0	3.28	0
Policy_2	21.53	10.31	2.03	23.64	11.28	2.05	29.60	14.08	2.08
Policy_3	62.91	3.45	40.90	64.60	3.43	39.41	63.96	3.65	38.68
Policy_4	11.20	3.60	2.28	10.37	3.63	2.16	10.52	3.50	2.21
Policy_5	54.34	10.26	12.87	48.73	11.60	8.99	45.29	14.20	6.61
Policy_6	25.68	10.17	2.75	26.89	11.42	2.52	31.35	14.16	2.33
Policy_7	88.85	4.28	36.83	87.43	4.19	38.25	89.71	4.43	34.66
Policy_8	59.72	10.52	10.60	53.26	11.74	8.55	46.39	14.34	5.33

Table 15 Sensitivity Analysis on $S_{11}(t)$ with intervention on NON_CVD state

Table 15 shows that the change of $S_{11}(t)$ will result in significant changes on COST, QALYs and Ci/Ei of policies containing intervention on NON_CVD state. The higher the value of $S_{11}(t)$ the more preferable the policies that contain intervention on NON_CVD state.

4.4.3 Sensitivity Analysis on cost, utility weight, and interest rate

The change of cost, or utility weight, or interest rate will have impact on economic evaluation results of life paths, i.e., COST, QALYs and ICERs, but have no impact on life paths themselves. Figure 20 shows the flow chart of sensitivity analysis of parameters of survivor function.

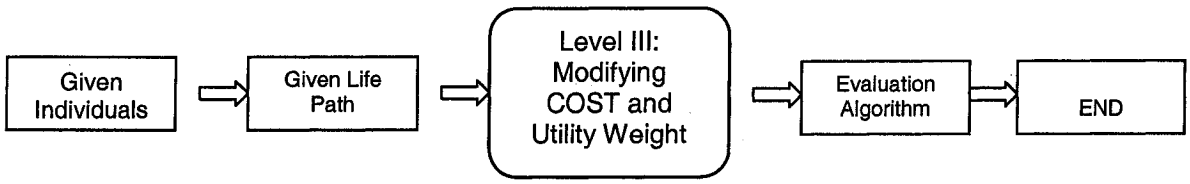

Figure 20 Flow chart of sensitivity analysis of COST and Utility Weight

Sensitivity analysis on these uncertain factors must be conducted basing on the same individuals' life paths. As an example, we conducted sensitivity analysis on interest rate in the range from 4% to 6% with interval 1%. By modifying the interest rate through User's Interface (keeping cost and utility weight unchanged) and running the evaluation algorithm of the framework we can estimate the mean and standard deviation of COST, QALYs and Ci/Ei for different interest rates. The results were listed on Table 16.

Number of Policy	Interest Rate 4%			**Interest Rate 5%**			Interest Rate 6%		
	Mean of Cost	Mean of QALYs	Mean of Ci/Ei	Mean of Cost	Mean of QALYs	Mean of Ci/Ei	Mean of Cost	Mean of QALYs	Mean of Ci/Ei
Policy_1	0	3.38	0	0	3.27	0	0	3.16	0
Policy_2	26.19	12.50	2.05	23.64	11.28	2.05	21.52	10.27	2.05
Policy_3	66.86	3.55	39.58	64.60	3.43	39.41	62.49	3.32	39.24
Policy_4	11.14	3.78	2.20	10.37	3.63	2.16	9.67	3.50	2.14
Policy_5	54.23	12.87	9.14	48.73	11.60	8.99	44.15	10.55	8.85
Policy_6	29.88	12.67	2.53	26.89	11.42	2.52	24.39	10.38	2.50
Policy_7	91.35	4.37	38.37	87.43	4.19	38.25	83.84	4.02	38.12
Policy_8	59.50	13.03	8.70	53.26	11.74	8.55	48.04	10.67	8.40

Table 16 Sensitivity Analysis on Interest Rate

From Table 16, we can see that with the increment of interest rate the present value of the mean of COST, QALYs, and Ci/Ei decrease, but the rank of Ci/Ei does not change. Those results indicate that the change of interest rate may affect the economic evaluation result of policies, but may not change the preference of policies. The same procedure can be applied to sensitivity analysis on cost and utility weight, in which only one factor: cost or weight on one state will be changed at one time.

4.5 Performance Analysis on Different Platforms

4.5.1 Sequential Programming of the SAS CCORE framework on PC

Initially, this framework was written sequentially following the computing algorithm above and was implemented on a PC with one 1.2 GHZ CPU, RAM=512 MB, and 55 GB hard drive windows platform. The simulation was conducted for different cohort sizes (from 10,000 to 100,000) with 8 policies, and different cycle lengths (1, 6). Each simulation was repeated for three times and the average running time for each simulation was listed on the Table 17.

Cohort Size	One Month Cycle		Six Month Cycle	
	2 Policies	8 Policies	2 Policies	8 Policies
10,000	0: 06: 10. 72	0: 30: 29. 54	0: 2: 25.60	0: 12: 14. 56
50,000	0: 34: 40. 17	2: 10. 57. 85	0: 8: 40. 63	0: 37: 47. 12
100,000	1: 35: 45. 51	6: 14: 16. 63	0: 23: 32. 95	1: 32: 46. 28

Table 17 The performance results of sequential program implemented for different cohort size, number of policies

4.5.2 Parallel programming of the SAS CCORE framework on HPCVL

As all the simulation processes are based on the status of individuals' risk factors, and it is reasonable to assume that the status of one individual's risk factors is independent from other ones. Furthermore, an individual's lifetime path or evolution of health states over time depends on his/her status of risk factors and intervention programs, but is independent from other individuals. We can divide the target cohort of 100,000 individuals into a number of completely independent sub-cohorts that can be simulated simultaneously. Each process has its own data and there is no communication among them until the whole simulation and all estimation processes of lifetime paths, costs and utilities were completed. Figure 21 shows the parallel algorithm.

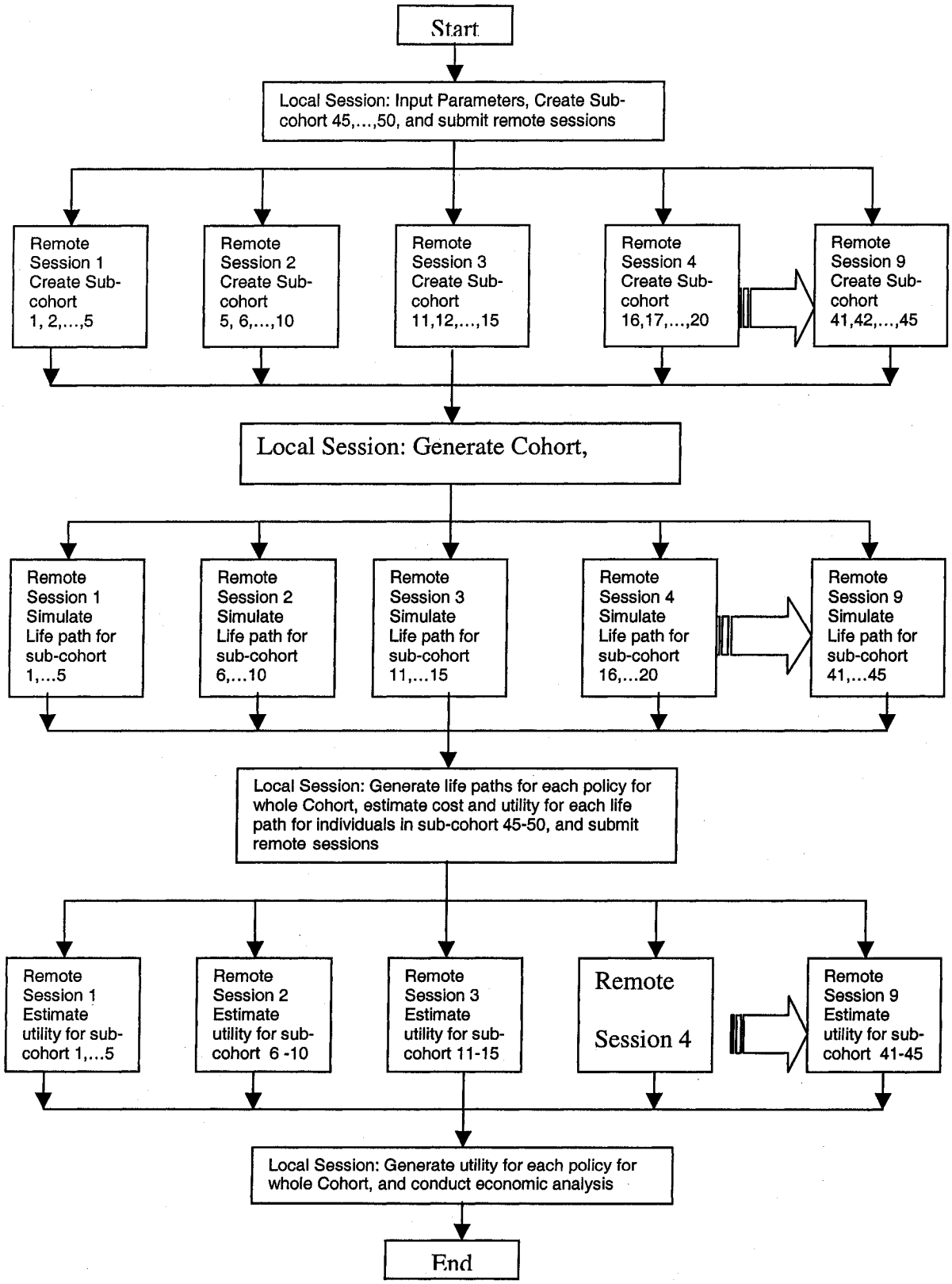

Figure 21 Parallel Algorithm of the ***SAS CCORE framework***

To increase computational speed the ***SAS CCORE framework*** was implemented on the HPCVL at University of Ottawa on ten processors with each processor containing 5 sub-cohorts, which has 20 CPUs with speed at 900 MHZ, RAM=522 MB, and 20 GB hard drive. The simulation was conducted for different cohort sizes (from 10,000 to 100,000) with different number of policies (2, 8), and different cycle lengths (1, 6). Each simulation was repeated for three times and the average running time for each simulation was listed on the Table 18.

Target Population	One Month per Cycle		Six Months per Cycle	
	2 Policies Compared	8 Policies Compared	2 Policies Compared	8 Policies Compared
10,000	0: 08: 49. 02	0: 28: 04. 73	0: 02: 06: 31	0: 10: 08. 78
50,000	0: 27. 59. 92	1: 07: 15. 36	0: 06: 30. 35	0: 14: 16. 04
100,000	0: 45: 32. 18	2: 18: 35. 78	0: 12: 09. 41	0: 20: 42: 75

Table 18 The performance results for different cohort size, number of policies, and the cycle length

Table 18 shows that the running time has dropped significantly on HPCVL both for one-month cycle and six-month cycle. Table 17-18 shows that the running times are proportionate to the size of cohort, number of policies, and the length of cycle. Among these three components, the length of cycle has the greatest impact on the running time as it determines how many simulation iterations to be made for each life path, and the number of column in the life path matrices. When the cycle length is 6 months, the maximum number of cycles in one lifetime is 98; but if the cycle length changed to 1 month, the maximum number of cycles in one lifetime will be 588. The second influential factor is the number of policies, which determines how many life paths to be simulated and evaluated for each individual. If two policies simulated, each individual will have two possible life paths; if

eight policies simulated, the same individual will have eight possible life paths. The last factor is the cohort size it determines how many individuals will be simulated.

For a given platform, to obtain simulation results within a reasonable time, users may need to make the balance among the size of cohort, the number of policies, and the length of cycles. For example, to simulate a large number of policies, user may need to compromise the length of cycles or the number of populations. Nevertheless, for the sample case in this thesis, the testing results show that the running times of the ***SAS CCORE framework*** both on PC and HPCVL are acceptable; in particular, the testing results show that HPCVL has great potential to the running time even when the ***SAS CCORE framework*** incorporates more states and more policies.

Chapter 5 Conclusions and Implications

5.1 Conclusions about research questions

The ***SAS CCORE framework*** has the following features:

- It can be used to simulate life paths at individual level for a large number of, i.e., 100,000, individuals under different intervention policies over 50-year period.
- It can be used to estimate the total present value of cost and utility for each life path and automatically make comparisons among intervention policies by generating graphs and tables.
- By modifying parameters through the User's Interface, a user can use the ***SAS CCORE framework*** to do sensitivity analysis on uncertain factors, such as the distributions of risk factors, the values of $S_0(t)$, β, cost, utility weight, and interest rate.
- The ***SAS CCORE framework*** can be easily implemented both on a powerful PC (with one processor) and on ***HPCVL*** (with multi-processors) and will generate results more rapidly on ***HPCVL*** than on PC.

5.2 Implications for Case Study

Although the sample case is hypothetical, we still can draw some implications from its analysis results in Chapter 4 to validate the ***SAS CCORE framework***.

- For a given budget, prevention policies are more efficient than acute intervention policies in generating aggregate ***QALYs,*** which is consistent with the observation that medical care has been accountable for only about 10% to 15% of the decline in

premature deaths that have occurred in the twentieth century—the reminder attributable to factors that have helped prevent illness and injury from occurring.

- Individuals with higher willingness to pay for a treatment are more likely to accept new, costly and effectively intervention policies than individuals with lower willingness to pay for the same treatment, which coincides with the fact that people living in poorer neighborhoods tend to have less access to some of these services and are more likely to die following a stroke than those living in wealthier neighborhoods.
- For the same life paths, the change of interest rate will change the present value of cost and ***QALYs***, but will not change the rank of ***ICERs*** for different policies, i.e., may not affect the preference of policies.
- For the same target population, the change of the estimated value of the baseline survival function $S_0(t)$ will change the present value of cost, QALYs, and the rank of ***ICERs*** for different policies, i.e., may affect the selection of policies.
- The change of distributions of risk factors will result in the change of preference of interventions or policies.

5.3 Limitations and areas for further research

The following limitations of the ***SAS CCORE framework*** may affect the simulation of individuals' life paths or the economic evaluations of an intervention or a policy, which would draw attention for further research.

First of all, the ***SAS CCORE framework*** has a constant length of transition cycle over individuals' life paths for all possible intervention and policies, and the effect of an intervention or a policy was captured as the direct impact on transition probabilities from a

state in the current cycle to a state in the next cycle. In this approach, the ***SAS CCORE framework*** could not reflect the delay effect of an intervention or a policy, which may not appear right after an event but show up after several cycles. For example, an acute intervention may reduce the mortality of the initial ***CVD,*** but it may result in morbidity after certain time. One way to handle the problem may be to extend the length of transition cycle so that the impact of such an intervention or a policy would be fully considered in transitions or in transition probabilities.

Second, the ***SAS CCORE framework*** assumes that the risk factors are independent from each other in the target population. In reality, some risk factors may be correlated to each other, for example, diastolic blood pressure may be correlated to cholesterol level, which means for a given population in the real world the distribution of risk factors could not have the same distributions of risk factors as in the simulated target population. To deal with the problem of correlations among risk factors, age and gender, first we have to quantify the relationship among these factors; then, we would incorporate the quantitative relations into generation of the target population in the program so that the distributions of risk factors are conditional on age, gender or other risk factors.

Finally, the ***SAS CCORE framework*** uses a constant interest rate over a long time period to discount the future cost and the future ***QALYs***. As the ***SAS CCORE framework*** is designed to simulate life paths and evaluate cost and ***QALYs*** up to 50 years, it is unrealistic to assume the discount rate to be constant over such long period. One way to make the discount rate used more realistic is to use different discount rates for different periods instead of a constant rate over 50 years. In either way, the discount rate remains unknown; we can only make projections of cost and ***QALYs*** at different imaginary discount rates.

References

1. Allan S. Detsky, Gary Naglie, etc (1997). Primer on Medical Decision Analysis: Part 2—Building a Tree. Med Decis Making; 17: 126-135.
2. Andrew R. W. and Bernie J. O. (1999) Sample size and Power Issues in Estimating Incremental Cost-Effectiveness Ratios from Clinical Trials Data. Health Econ. 8:203-211.
3. Anonymous. (1994). Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994; 343: 311-22.
4. Anonymous. (1999a). SAS/IML User's Guide, Version 8. SAS Institute Inc., Cary, NC, US.
5. Anonymous. (1999b) 1999 Fupdate: ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction: Executive Summary and Recommendations. Circulation 100:1016-1030.
6. Anonymous. (2000). Guideline 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. International consensus on Science. Circulation 2000;102 (8 Sppl I):1-291.
7. Anonymous. (2002a). Health Care in Canada 2002.
8. Anonymous. (2002b). Multiprocessing with SAS Software Course Notes. SAS Institute Inc., Cary, NC 27513, USA.
9. Arrow, K.J. (1963). Uncertainty and the welfare economics of medical care. America Economic Review 53:941-73.
10. Babad H, Sanderson C, Naidoo B, White I, and Wang D. (2002).The Development of a Simulation Model of Primary Prevention Strategies for Coronary Heart Disease. Health Care Management Science 5, 269-274.
11. Bellman, Richard E. Dynamic Programming. Princeton: Princeton Univ. Press, 1957.
12. Benslay DC, Watson PS and Morrison GW. (1995). Pathways of coronary care – a computer-simulation model of the potential for health gain, IMA Journal of Mathematics Applied in Medicine and Biology 12 (1995) 315-328.
13. Briggs A, Sculpher M, Buxton N. (1994).Uncertainty in the Economic Evaluation of Health Care Technologies: The Role of Sensitivity Analysis. Health Economics, VOL. 3: 95-104.
14. Briggs A. Sculpher M. (1998). An Introduction to Markov Modeling for Economic Evaluation. Pharmoco-economics Apr: 13(4): 397-409.
15. Briggs A, Fenn P. (1998). Confidence intervals or surfaces? Uncertainty on the cost-effectiveness plane. Health Econ 1998; 7(8): 723-40.
16. Briggs AH, O'Brien BJ. (2000). The death of cost-minimization analysis? Health Econ Lett 2000; 4(4): 3-10.
17. Cairns J.A. (1992). Health, wealth and time preference. Project Appraisal (March):31-40.
18. Canadian Coordinating Office for Health Technology Assessment. (1997). Guidelines for Economic Evaluation of Pharmaceuticals: Canada. 2nd ed. Ottawa, Canada.
19. Cappeleri JC, Ioannidis JPA, Schmid CH, de Ferranti SD, Aubert M, Chalmers TC, et al. (1996). Large trials vs. Meta-analysis of smaller Trials. How Do Their Results Compare? JAMA 276:1332-1338.

20. Collett D. (1994). Modeling Survival Data in Medical Research. Chapman & Hall.
21. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, et al. (2000). Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. Eur Heart J 21(24):2071-2078.
22. Cooper K et al. (2002).The Development of a Simulation Model of the Treatment of Coronary Heart Disease. Health Care Management Science 5, 259-267.
23. Critchfield GC, Willard KE. (1986). Probabilistic analysis of decision trees using Monte Carlo simulation. Med Decis Making 6: 86-92.
24. Delta Report. (2000). The Delta Report Summary of Findings. (DELTA: Drug Expenditure Longitudinal Analysis). Ottawa: Glaxo Wellcome Inc. and Brogan Inc.; 2000.
25. Davis R. (1994). Simulation for planning services for patients with coronary artery disease. European Journal of Operational Research 71: 323-332.
26. Dickersin K, Scherer R, Lefebvre C. (1994). Identifying Relevant Studies for systematic Reviews. BJM 309:1286-91.
27. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. (1985). Probabilistic sensitivity analysis using Monte Carlo simulation. Med Decis Making; 5(2): 157-177.
28. Drummond, M. F. (1987). Methods for the economic evaluation of health care programmers. Oxford [Oxfordshire]; New York: Oxford University Press.
29. Dubi, A. (2000). Monte Carlo Applications in Systems Engineering. Chichester; New York: John Wiley & Sons.
30. Eddy, D.M. (1989). Screening for breast cancer. Ann Intern Med 111: 389-99.
31. Edleson JT, Weinstein MC, Tosteson AN, Williams L, Lee TH, Goldman L. (1990). Long-term cost-effectiveness of various initial mono-therapies for mild to moderate hypertension. JAMA; 263(3): 407-13.
32. Feeny D, Furlong W, Boyle M, Torrance GW. (1995). Multi-attribute Health Status Classification Systems: Health Utilities Index. PharmacoEconomics, 6:490-502.
33. Efron B, Tibshirani RJ. (1993). An Introduction to the Bootstrap. New York: Chapman and Hall.
34. Frank A. S. (1995). Valuing Health Care: Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies. Duke University, Cambridge University Press.
35. Garber, A.M., and Phelps, C.E. (1995). Economic Foundations of cost-effectiveness analysis. National Bureau of Economic Research.
36. Garner C. (2001). Multiprocessing with Version 8 of the SAS System. Cary, N.C: SAS Inc.;
37. Gold MR, Siegel JE, Russell LB, Weinstein MC. (1996). Cost-effectiveness in Health and Medicine. New York: Oxford University Press.
38. Goldman L, Coxson P, Hunink MG, Doldman PA, Tosteson AN, Mittleman M, et al. (1999). The relative influence of secondary versus primary prevention using the National Cholesterol Education Program Adult Treatment Panel II guidelines. J Am Coll Cardiol 1999; 34(3): 768-76.
39. Goldman L, Weinstein MC, Williams LW. (1989). Relative impact of targeted versus population wide cholesterol interventions on the incidence of coronary heart disease. Projections of the Coronary Heart Disease Policy Model. Circulation 1989; 80(2): 254-60.

40. Gregory C. C, Keith. W, (1986). Probabilistic Analysis of Decision Trees Using Monte Carlo Simulation. Med Desci Making 6:85-92,
41. Grover S. A., Coupal L., Paquet S., and Zowall H..(1999). Estimating the Benefits of Modifying Risk Factors of Cardiovascular Disease: A Comparison of Primary vs. Secondary Prevention. Archives of Internal Medicine, March 22, 1999; 159(6): 593 - 600.
42. Grover SA, Paquet S, Levinton C, Coupal L, Zowall H. (1998). Estimating the benefits of modifying risk factors of cardiovascular disease: a comparison of primary vs. secondary prevention [published erratum appears in Arch Intern Med 1998 Jun 8; 158(11):1228]. Arch Intern Med; 158(6): 655-62.
43. Heart and Stroke Foundation of Canada, (1999). The Changing Face of Heart Disease and Stroke in Canada 2000, Heart and Stroke Foundation of Canada: On-line at: http://www.hc-sc.gc.ca/hpb/lcdc/bcrdd/hdsc2000.
44. Hunink MG, Goldman L, Tosteson AN, Mittleman MA, Williams LW,,et al. (1997). The recent decline in mortality form coronary heart disease, 1980-1990. The effect of secular trends in risk factors and treatment. Jama; 277(7):535-42.
45. Hutubessy RC, Baltussen RM, Evans DB, Barebdregt JJ, Murray CJ. (2001). Stochastic leaguer tables: communicating cost-effectiveness results to decision-makers. Health Econ 2001;10(5): 473-7.
46. Ioannidis JPA, Cappelleri JC, Lau J. (1998). Issues in Comparisons Between Meta-analysis and Large Trials. JAMA 1998; 279:1089-93.
47. Johannesson, M., J.S. Pliskin, and M.C. Weinstein. (1994). A note on QALYs, time tradeoff, and discounting. Med Decis Making 14:188-93; 1994.
48. John M. Jeff R. Peter S. Helga K. (1998).The Allocation of Health Care Resources: An Ethical Evaluation of the 'QALY' Approach, Ashgate, Dartmouth, April 1998.
49. Jolliffe JA, Rees K, Taylor RS, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease (Cochrane Review). (2001). In: The cochrane Library. Oxford: Update Software Inc.
50. Kalbfleisch, J.D. and Prentice, R.L. (1980). Statistical analysis of Failure Time Data. John Wiley and Sons, New York; 1980.
51. Kaplan, R.M. and J.P.Anderson. (1988). A general health policy model: Update and applications. Health Serv Res 23:203-35; 1988.
52. Karhan et al. (1994). Screening for prostate cancer. A decision analytic view. JAMA 272: 773-80. 1994.
53. Krahn, M.., and A. Gafni. (1993). Discounting of in economic evaluation of health care interventions. Med Care 31:403-18; 1993.
54. Larosa JC, He J, Vupputuri S. (1999). Effects of statins on risk of coronary disease: meta-analysis of randomized controlled trials. Jama 1999; 282(24):2340-6.
55. Lau J, Schmid CH, Chalmers TC. (1995). Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. J Clin Epidemiol 1995; 48(1): 45-57.
56. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. (1997). Discrepancies Between Meta-analyses and Subsequebt Large Randomized Controlled Trials. N Enfl J Med 1997(337):536-42.
57. Lieu, T.A. et al. (1994). Cost-effectiveness of a routine varicella vaccination program for US children. JAMA 271:375-81.
58. Lothgren M, Zethraeus N. (2000). Definition, Interpretation and Calculation of Cost-Effectiveness Acceptability Curves. Health Econ 2000; 9: 623-630.

59. Mandelblatt et al. (1992). Breast cancer screening for elderly women with and without co-morbid conditions: A decision model. Ann Intern Med 328: 1365-71.
60. Maria G. M. et al. (1998). Uncertainty in Decision Models Analyzing Cost-Effectiveness: The joint Distribution of Incremental Costs and Effectiveness Evaluated with a Nonparametric Bootstrap Method. Med Decis Making; 18:337-346.
61. McDonald D. (1995). Elements of Applied Probability for Engineering, Mathematics and Systems Sciences. Printed in Canada.
62. Mui S. (1999). Projecting Coronary Heart Disease Incidence and Cost in Australia: Results from the incidence module of the cardiovascular disease policy model. Australia and New Zealand Journal of Public Health 23 (1999) 11-19.
63. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. (1997). Primer on Medical Decision Analysis: Part 5—Working With Markov Processes. Med Decis Making; 17: 152-159.
64. Nichol G, Stiell IG, Laupacis A, Pham B, De Maio V, Wells GA. (1999). A Cumulative Meta-analysis Of The Effectiveness of Defibrillator-Capable Emergency Medical Services For Victims Of Out-Of-Hospital Cardiac Arrest. Annals of Emergency Medicine 1999; 34(4): 517-525.
65. Nichol, G. et al. (2002). Cardiovascular Outcomes Related to Economics (CORE) Group.
66. O'Brien B, Drummond M, Labelle R, and Willan A. (1994). In Search of Power and Significance: Issue in the design and Analysis of Stochastic Cost-Effectiveness Studies in Health Care. Medical Care Vol. 32, Number 2: 150-163.
67. O'Brien B, Sculpher M. (2000). Building Uncertainty into Cost-Effectiveness Rankings: Portfolio Risk-Return Trade-offs and Implications for Decision Rules. Med Care. 2000; 38: 460-468.
68. Pauker, S.G. and Kassirer, J.P. (1980). The threshold approach to clinical decision-making. New England Journal of Medicine. 1980; 302:1109-1117.
69. Pauker, S.G. and Kassirer, J.P. (1987). "*Decision analysis.*" N Eng J Med, 316: 250-58.
70. Personal communication, Alison Edwards, August 15, 2001.
71. Philips KA, Shlipak MG, Coxson P, Heidenreich PA, Hunink MG, Goldman PA, et al. (2000). Health and economic benefits of increased beta-blocker use following myocardial infarction. Jama 2000; 284(21): 2748-54.
72. Picard, A. (2003). "Lives being lost because few know CPR, doctor says". The Globe and Mail. October 7, 2003.
73. Pliskin, J.S., D.S. Shepard, and M.C. Weinstein. (1980). Utility function for life years and health status. Management Science 28:206-24.
74. Prosser LA, Weinstein MC, Williams LW, Hunink MG, Goldman L, et al. (2000). Cost-effectiveness of cholesterol-lowing therapies according to selected patient characteristics. Ann Intern Med 2000; 132(10): 769-79.
75. Raiffa, H. (1968). Decision analysis: Introductory lectures on choices under uncertainty. Reading, MA: Addison-Wesley Publishing Company.
76. Sox HC, Jr., Blatt MA, Higgins MC, Marton KI. (1988). Medical Decision Making. Toronto: Butterworth.
77. Sonnenberg FA, Beck JR. (1993). Markov models in medical decision-making: a practical guide. Medical Decision Making; 13: 322-338.
78. Statistic Canada. (2003). Age Distribution of the Population of Canada July 1, 2003.
79. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. (1997). A Comparison of Antiarrhythmic Drug Therapy with Implantable Defibrillators in Patients

Resuscitated from Near-Fatal Ventricular Arrhythmias. N Engl Med 1997; 33:1576-1583.
80. Tice JA, Ross E, Coxson PG, Rosenberg I, Weinstein MC, Hunink MG, et al. (2001). Cost-effectiveness of vitamin therapy to lower plasma homocysteine levels for the preventio of coronary heart disease: effect of grain fortification and beyond. Jama 2001; 286 (8): 936-43.
81. Torrance GW, Furlong W, Feeny D, Boyle M. (1995). Multi-attribute preference functions: Health Utilities Index. PharmacoEconomics, 6:503-520.
82. Tosteson AN, Weinstein MC, Williams LW, Goldman L. (1990). Long-term impact of smoking cessation on the incidence of coronary heart disease. Am J Public Health 1990; 80(12): 1481-6.
83. Tosteson AN, Weinstein MC, Hunink MG, Mittleman MA, Williams LW, Goldman PA et al. (1997). Cost-effectiveness of population wide educational approaches to reduce serum cholesterol levels. Circulation 1997; 95(1): 24-30.
84. Tsevat J, Weinstein MC, Williams LW, Tosteson ANA and Goldman PA. (1991). Expected gains in life expectancy from various coronary heart disease risk factor modifications, Circulation 83: 1194-1201.
85. Van Hout BA, al Maiwenn I, Gordon GS, Rutten FFH. (1994). Costs, effects and C/E ratios alongside a clinical trial. Health Economics 1994; 3: 309-19.
86. Weinstein, Milton C., and Richard J. Zeckhauster. (1972). Critical Ratios and Efficient Allocation. Journal of Public Economics 2(2): 147-57
87. Weinstein, M.C.,H.V. Fineberg, A.S. Frazier, D. Neuhauser, R.R. Neutra, and B.J. McNeil. (1980). Clinical decision analysis. Philadelphia: W.B. Saunders.
88. Weinstein MC, Coxson PG, Williams LW, Pass TM, Stason WB and Goldman L. (1987). Forecasting coronary heart disease incidence mortality and cost: The Coronary Heart Disease Policy Model. America Journal of Public Health 77: 1417-1426.
89. Weinstein, Milton C. 1990. Principles of Cost-Effectiveness Resource Allocation in Health Care Organizations. International Journal of Technology Assessment in Health Care 6(1): 93—103.
90. Wilkins, R., Adams, O. and Brancker, A. (1989). "Changes in Mortality by Income in Urban Canada from 1971 to 1986," Health Reports, Vol. 1 (2) pp. 137-174; Statistics Canada (2001), Estimates of Premature Deaths (Prior to Age 75) Due to Cardiovascular Disease Among Canadians, Special Tabulation Of Mortality by Neighborhood Income Data for Urban Canada: Ottawa, Canada.
91. Wilkinson, B. and Allen, M. (1999). Parallel Programming. Prentice Hall, Upper Saddle River, New Jersey 07458.
92. Wolfson MC. (1992). POHEM—A new approach to the estimation of health status adjusted life expectancy: Canadian Institute for Advanced Research; April 1992. Report No.: population Health Working Paper No. 11.
93. Wolfson MC. (1994). POHEM – a framework for understanding and modeling the health of human population. WHO Statistics Quarterly 47 (1994) 157-175.
94. www.HPCVL.org.