Effect of Time Horizon on Incremental Cost-Effectiveness Ratios

by

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ABSTRACT

Background: Estimation of cost-effectiveness of a therapy as compared with another, in healthcare, is often based on a single perspective and a single time horizon. In this thesis, I explored methods of extrapolating the survival effect of different interventions and the effect of time horizon on incremental cost-effectiveness ratios when comparing two strategies.
Methods: Two strategies for a patient are compared: new or usual treatment. A hypothetical model based on US life tables (for a 64-year old) assumed that the new and usual treatment strategies resulted in patient survivals identical to a person who is 5 and 10 years older, respectively, than the patient's chronologic age. The hazard rates over time were calculated and transformed to linear equations for least-squares linear regression to fit exponential, linear exponential, Weibull and Gompertz distributions. The survival model yielding the maximal likelihood estimate was extrapolated over different time horizons: 5, 10 and 15-year in addition to lifetime. In addition, I extracted survival data from a published trial evaluating thrombolysis in patients with myocardial infarction and applied this methodology over different time horizons. Finally, I developed a matrix of incremental cost-effectiveness ratios over different time horizons, based on an overview model, examining alternative assumptions when the cumulative difference in cost and effectiveness of the two strategies: 1) decrease 2) remain constant or 3) increase. I used a statistical programming language "R" for evaluation and analysis.
Results: When considering a US life-table based hypothetical model, Gompertz curve was the best-fitting model. A linear-exponential model had the best fit when considering a survival model of thrombolysis patients. A matrix of incremental cost-effectiveness ratios with decreasing, constant and increasing cumulative difference in cost and effectiveness showed considerable change in incremental cost-effectiveness ratios over different time horizons. The magnitude of effect of time horizon was flattened with increasing discount rate for future cumulative differences in cost and effectiveness. With the exception of similarly behaving and proportionate cumulative difference in cost and effectiveness leading to unchanged incremental cost-effectiveness ratios, incremental cost-effectiveness ratios decreased when cumulative difference in effectiveness increased and increased when cumulative difference in effectiveness decreased, irrespective of behavior of cumulative difference in costs.
Conclusions: When conducting cost-effectiveness analysis of two competing strategies, choice of time horizon has a substantial effect. Incremental cost-effectiveness ratio changes considerably with changes in duration of time horizon. Discounting flattens the effect of time horizon in cost-effectiveness analysis. Care must be taken in choosing the time horizon in a cost-effectiveness analysis and alternative time horizons must be evaluated in all cost-effectiveness analyses.

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1. INTRODUCTION

1.1 Significance

With advances in technology and healthcare, new interventions are constantly being evaluated and compared with existing interventions. The evaluation of health interventions is usually based on a single perspective or a single time horizon e.g. societal perspective [1, 2] or a patient's lifetime [3, 4] is often used. However, evaluations based on different time horizons and different perspectives may provide a better understanding of costs and health outcomes for the different stakeholders involved. In addition, clinical trials are being conducted to study the effectiveness of different interventions. As the costs of conducting these trials are increasing, study investigators have an increased interest in the role of the time interval of trials, the duration of intervention and the duration of effectiveness from the intervention in such health economic evaluations.

Cost-effectiveness analysis (CEA) is a methodology used to evaluate interventions in healthcare on the basis of outcomes and costs of individual interventions. cost-effectiveness analysis involves estimating net or incremental costs and effectiveness of an intervention and comparing it with an alternative intervention. The comparison may be between two different interventions or use and no use of an intervention or two different intensities of intervention. The cost-effectiveness ratio comparing the two alternatives is calculated as the difference in costs between the alternatives divided by the difference in health outcomes. Commonly, cost-effectiveness analyses are done on the entire lifetime based on yearly subunits. However, evaluating cost-effectiveness based on different time horizons may give different results.

The time horizon of the cost-effectiveness analysis should extend far enough into the future to capture the economic costs and major health outcomes including intended effects and unintended side effects. As a result, many cost-effectiveness analyses are done over the duration of patients' life. However, some

interventions may have a smaller duration of effectiveness or due to budgetary constraints, one is interested in cost-effectiveness of an intervention over a shorter interval of time. As the appropriate time horizon of cost-effectiveness analysis may extend beyond the availability of primary data, extrapolated or modeled data are frequently used. In fact, Gold et al. [5] recommends analyzing data using several time horizons. A short-term horizon can be used for primary data while a long-term horizon can also include extrapolated data. For example, Mark et al. [2] evaluated thrombolytic interventions during myocardial infarction over 1-year trial duration as well as a long-term horizon by modeling additional 14-year survival based on Duke Cardiovascular Disease Database and further extrapolated it to a lifetime horizon using a fitted Gompertz function. In addition, modeling should be used to estimate gains in life expectancy due to differential survival. Therefore, extrapolation of analysis should be done far enough to capture important life saving effects. For example, cholesterol-lowering program conducted for 5 years captures only 10% of the benefit and the effectiveness should be extrapolated to achieve a realistic cost-effectiveness [6].

1.2 Objectives

The objective of this study is to

1. Explore methods of extrapolating the survival effect of different interventions
2. Evaluate the effect of time horizon on incremental cost effectiveness ratios

2. BACKGROUND

2.1 Approaches to economic evaluation of healthcare

There are two major approaches used in economic evaluation of health care [7]. The first approach of economic evaluation involves measuring economic costs and health outcomes in a randomized controlled trial as end points. This approach relies on the strengths of randomized trials that include prospective, complete data collection; a rigorous protocol; and the use of random assignments to different interventions. This helps to eliminate selection bias and to balance patient characteristics affecting outcomes. The advantages of this approach are the use of consistent and direct data. The clinical outcomes data are obtained from the same patient populations in a clinical trial rather than different trials or data sources. Additionally, the economic and clinical outcomes are measured directly, with few assumptions and minimal modeling. However, the simplicity of this approach leads to a few distinct disadvantages. Trial-based economic analyses do not include the results of the other pertinent trials and lack the totality of evidence about a given treatment. Studies with small sample sizes may give unreliable estimates of economic and clinical outcomes. Protocol-driven care in trials may mandate deviation from usual clinical practice and distort resource utilization and render economic analyses unsuitable. Finally, patients enrolled in trials may be highly selected and not representative of patients in routine clinical practice, making the cost-effectiveness calculation a best-case scenario.

The second major approach involves using a model to project the costs and clinical outcomes of alternative strategies. The models based on this approach are usually sophisticated and base projections on the best available evidence from a variety of sources. Therefore, the models using costs and health outcomes based on meta-analyses of randomized clinical trials or on large, representative patient cohorts are considered more credible. The advantages of this approach include the flexibility to examine cost-effectiveness under different assumptions about risk, benefit, and cost, and to consider the implication of a strategy in different

groups of patients. The disadvantages of these models include the need to synthesize information from disparate sources with inconsistent or biased data. Furthermore, the complexity and sophistication of these models may make them less transparent, limiting peer review and independent verification of the findings. In addition, these models may have been extrapolated beyond the empirical data without explicit recognition that this has occurred.

In practice, these alternative approaches to economic evaluation are not mutually exclusive. Increasingly, economic models are developed based on a particular trial data extrapolated with appropriate data from a longer duration clinical trial database [2]. This hybrid approach allows the investigator to project results of various alternatives not tested in the trial or to highlight strategies not evaluated directly.

2.2 Methods of economic analysis in healthcare

Cost-identification analysis (cost analysis): It is a type of economic analysis that only accounts for the relevant resources and associated costs incurred by a given disease, treatment, healthcare technology or strategy. The analysis does not assess health benefits for alternative strategies. It is implicitly assumed that the outcomes are the same for the strategies in consideration and the optimal strategy can be identified by choosing the cheapest strategy. Cost-identification, thus, measures the economic burden of a treatment or strategy and the results apply to a specified cohort or population in a particular context.

Cost-benefit analysis (CBA): It is a form of economic-efficiency analysis in which both the costs and outcomes (health benefits) are expressed in the same unit, as a single attribute, typically in monetary terms. A monetary value of human life is calculated usually by the human capital method based on lost earnings or willingness to pay method based on willingness to pay to decrease risk for death or disease. The optimal strategy is the one with highest net benefit (benefit minus cost). This is more commonly used in the business

world. However, the disadvantage of willingness to pay methodology is that it is heavily influenced by ability to pay, on the conundrum of assigning an economic value to human life or life years.

Cost-effectiveness analysis (CEA): This form of economic-efficiency analysis involves valuing costs in the same unit, e.g., dollars or monetary terms and valuing health benefits in the same unit, e.g., years or natural units. However, it differs from cost-benefit analysis as it uses another single attribute - the unit for measurement of cost is different from the unit for measurement of health benefits. An incremental cost-effectiveness ratio compares differences in cost and effectiveness of some treatment strategy or new healthcare technology of interest with a relevant alternative. However, besides comparing the strategies, it allows one to choose a strategy for funding that falls beneath a cutoff expenditure per life year gained. This analysis is more widely used in medicine.

$$\text{Incremental Cost-Effectiveness Ratio (ICER)} = \frac{(\text{Cost}_{\text{New treatment}} - \text{Cost}_{\text{Usual treatment}})}{(\text{Effectiveness}_{\text{New treatment}} - \text{Effectiveness}_{\text{Usual treatment}})}$$

Table 1: Cost-effectiveness comparison of strategies N and U [8]

	Health Outcome		
Cost	**N > U**	**N = U**	**N < U**
N > U	Calculate incremental CER	U less expensive: choose U	U dominates N: choose U
N = U	N better outcome: choose N	Makes no difference	U better outcome: choose U
N < U	N dominates U: choose N	N less expensive: choose N	Calculate incremental CER

CER = cost-effectiveness ratio, N = new treatment, U = usual treatment

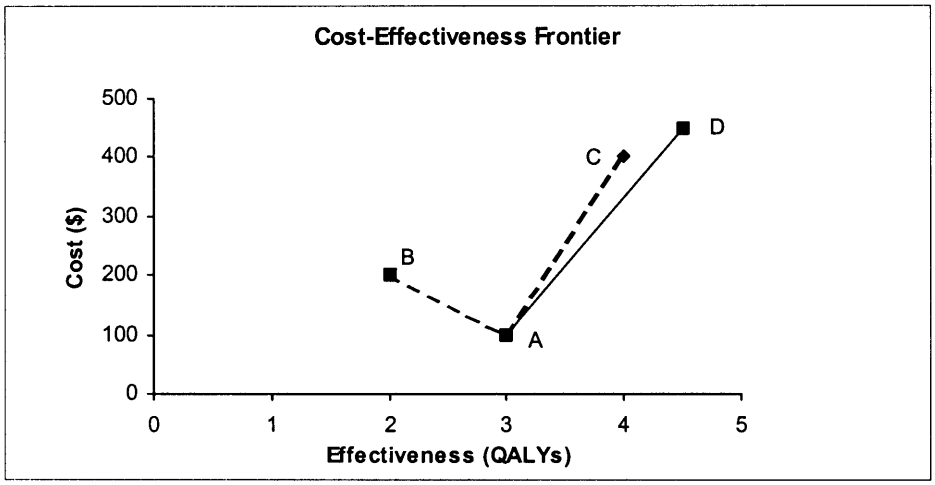
As displayed in Table 1, cost-effectiveness analysis is useful when the new treatment strategy costs more and is more effective than usual treatment strategy or when the new treatment strategy costs less and is less effective than usual treatment strategy. A negative cost-effectiveness ratio, however, does not distinguish between a more expensive and less effective or a less expensive and more effective strategy. Similarly, a positive cost-effectiveness ratio does not distinguish between a less costly and less effective or a more expensive and more effective strategy.

In its most common form, a new strategy is compared with current practice (the "low-cost alternative") in the calculation of the cost-effectiveness ratio. The result might be considered as the "cost" of the additional outcome purchased by switching from current practice to the new strategy (e.g., $8,000 per life year gained). If the price is low enough, the new strategy is considered "cost-effective." Cost-effective interventions either improve a health outcome and save money in the process or provide a health benefit at an "acceptable" cost. "Acceptable" means what the decision-maker is comfortable paying for an improvement in outcome. Given this definition, the following common misunderstandings are clarified. Cost-effectiveness is not equivalent to effectiveness, which only involves health benefits. Cost-effectiveness does not mean cost saving, because the lowest cost option is not necessarily the most cost-effective when both the relative benefit and cost are considered. Naturally, if an intervention is more effective and costs less than an alternative strategy, then the intervention should be pursued and is considered to be dominant.

Cost-utility analysis (CUA): It is a variant of cost-effectiveness analysis in which the health benefits include quality of life adjustments. The health benefits are expressed in a scale that incorporates both longevity and patient preferences (utilities) for the health states produced. Dollars per quality adjusted life year (QALY) added is the most common form of cost-utility ratio in the medical literature.

When choosing between multiple mutually exclusive treatment options, it is common to construct a cost-effectiveness frontier on the cost-effectiveness plane that represents efficient points from among the treatment choices. Dominance of an alternative strategy exists when other strategies are cheaper and more effective and are on the cost-effective frontier. Similarly, extended dominance of an alternative strategy exists when other strategies are more expensive and have lower incremental cost-effectiveness ratios and are on the cost-effectiveness frontier. Cost-effectiveness frontier can be estimated, when considering multiple alternatives, either graphically or in a tabular form.

Figure 1: Cost-effectiveness frontier



Graphical Method: Costs are plotted on the y-axis while effectiveness of different strategies are plotted on the x-axis. A cost-effectiveness frontier can be obtained by graphing a series of line segments connecting every two non-dominated alternatives. The frontier slope becomes steeper as one moves from less expensive to more expensive non-dominated alternatives. As shown in Figure 1, all alternatives not on the cost-effectiveness frontier "lose" to alternatives on this frontier e.g. B and C fall above and to the left of the frontier. These treatment options are considered inefficient and are excluded either by dominance, e.g. B, (line BA connecting to the frontier has a negative slope) or by appealing to the principle of extended dominance, e.g. C, (line AC has a greater positive slope while emanating from A on the cost-effectiveness frontier). This representation of costs on the y-axis and effectiveness on the x-axis helps in easy visualization of a cost-effectiveness analysis along with concepts of dominance and extended dominance as the slope of the line represents incremental cost-effectiveness ratio for the competing strategies.

Tabular Method: Arrange alternatives from least expensive to most expensive in a table as in Table 2a. If any of the alternatives is out of increasing order for total effect, it is dominated and should be removed. Therefore, alternative B is eliminated by dominance. Then, calculate incremental costs for all alternatives other than the least expensive. Doing nothing with no cost and no effect is not assumed to be an option.

Table 2a: Calculating incremental cost-effectiveness ratios

Alternative	Total cost	Total effect	Incr. cost	Incr. effect	ICER
A	100	3			
B	200	2	100	-1	-100
C	400	4	200	2	100
D	450	4.5	50	0.5	100
Remove B due to dominance (of A)					

Incr.= Incremental, ICER = Incremental cost-effectiveness ratio

Then, incremental effectiveness for all alternatives other than the least expensive and all incremental cost-effectiveness ratios are calculated. Starting from the least expensive, one eliminates any alternative that is in the middle of three, if the incremental cost-effectiveness ratio comparing first (A) and second (C) alternatives is larger than the incremental cost-effectiveness ratio comparing the second (C) and third (D) alternatives in Table 2b. Alternative C is thus eliminated by extended dominance. Continue the process moving down the table. One moves from least to most expensive, least to most effective, and lowest to highest incremental cost-effectiveness ratio. Only two alternatives remain in this example.

Table 2b: Calculating incremental cost-effectiveness ratios and cost-effectiveness frontier

Alternative	Total cost	Total effect	Incr. cost	Incr. effect	ICER
A	100	3			
C	400	4	300	1	300
D	450	4.5	50	0.5	100
Remove C due to extended dominance (of D)					
Alternative	Total cost	Total effect	Incr. cost	Incr. effect	ICER
A	100	3			
D	450	4.5	350	1.5	233

Incr.= Incremental, ICER = Incremental cost-effectiveness ratio

Accounting for Uncertainty: Cost-effectiveness analysis is subject to uncertainty. However, when uncertainty is considered, options excluded under the baseline analysis may form part of the cost-effectiveness frontier. Three categories of uncertainty as described by Briggs et al. [9] relate to observed data inputs, extrapolation and the analytic methods used. Cost-effectiveness acceptability curves [10] are

used to represent the uncertainty concerning the cost-effectiveness of a health care intervention in the context of decisions involving two interventions, as an alternative to confidence intervals around incremental cost-effectiveness ratios. These curves provide a graphical representation of the probability that a particular intervention is optimal over a range of values.

The economic evaluation should be subjected to sensitivity analysis. Probabilistic sensitivity analysis [11] is preferred to the more limited one-way sensitivity analysis. For example, probabilistic sensitivity analysis, using a large number of Monte Carlo simulations can be used to examine the effects on the results of an economic evaluation when the underlying variables are allowed to simultaneously vary across a plausible range of predefined distributions. By adopting a Bayesian approach, where distributions for model parameters are specified, uncertainty in the decision concerning which treatment option should be implemented is addressed directly. Such distributional models are preferred to pure deterministic models as they facilitate the use of cost effectiveness acceptability curves to demonstrate cost-effectiveness.

2.3 Time horizon

Time horizon is the length of time into the future considered in the analysis over which costs and effectiveness are projected. Depending on the perspective and clinical situation, the patient outcomes and the costs involved may be relevant over different time horizons. For an employer, the costs incurred and clinical outcomes obtained are relevant over the duration of employment while for a patient the outcomes are relevant over an individual's lifetime. Similarly, the time horizon in a clinical setting may depend on the duration of ER visit from an emergency department perspective or the duration of hospitalization from a hospital's perspective. Society and third-party payers may have very different time horizons. The Panel on Cost-Effectiveness in Health and Medicine recommends performing analyses from the societal perspective [12]. In contrast, from the payer's perspective, the only relevant costs are those that occur during the time in

which the payer is responsible for the patient. Even third-party time horizons may be different for different parties. For example, Sonnenberg et al [13] evaluated strategies for prevention and treatment of colorectal cancer and inferred that colonoscopy has low incremental cost-effectiveness ratio compared with other screening tests. Lewis [14] observed that, although, their analysis was from the perspective of third-party payers, yet their time horizon was the lifetime of the patient. For third-party payers, including Medicare, the strategy of screening colonoscopy every 10 years incurs large up-front costs in exchange for reduced future costs of care for colorectal cancer. Further, Lewis noticed that from the perspective of third-party payers other than Medicare, the time horizon may be too long. However, even Medicare has odd "scoring systems" that reflect budgetary and cash flow constraints and effectively conducts economic evaluation over short time horizons and high effective discount rates.

Costs and patient outcomes should be measured over the same time horizon. In addition, regardless of the perspective taken, the time horizon of cost-effectiveness analysis should be of sufficient length to capture all positive and negative patient outcomes affected by the interventions. For example, in chronic diseases such as HIV, the benefits of the intervention may be realized over a lifetime for the recipients of the intervention. Data obtained from a trial should be carefully extrapolated to estimate cost and effectiveness over a long time horizon. In a study of early zidovidine therapy for patients with HIV [15], data showing benefit of the therapy observed over one year was extrapolated for cost-effectiveness analysis. However, after 3 years, there was no difference in life expectancy noticed irrespective of the intervention received by patients. The extrapolated cost-effectiveness of the therapy turned out to be erroneous.

Time horizon plays an important role in some of the published cost-effectiveness analyses. In a study for the treatment of clinically localized prostrate cancer, the addition of androgen suppression therapy to radiation therapy was found to be "cost effective" but the magnitude of the cost-effectiveness was highly dependent upon time horizon [16]. Another study done to assess the cost-effectiveness of bicalutamide (Casodex) as adjuvant treatment in early prostate cancer used a time horizon of 15 years, and obtained an incremental

cost-effectiveness of 27,059 euros/QALY. The main factors influencing conclusions included the time horizon and the duration of bicalutamide treatment, which was set at a maximum (5 years) in the base case [17]. In another study, assessing the efficacy and cost-effectiveness of standard chemotherapy and high-dose chemotherapy with autologous bone marrow transplantation (ABMT) in metastatic breast cancer, it was found that ABMT was the preferred approach under almost all assumptions, but the size of the benefit varied greatly. ABMT had a survival benefit of 6.0 months at 5 years at an incremental cost of $115,800 per year of life saved. If patients who were free of disease after 5 years had normal survival, the benefit was 18.1 months at an incremental cost of $28,600 per year [18].

In many situations, modeling may be required to examine the relationship between costs and benefits over time to assess extended time horizons. The cost-effectiveness observed within the trial may be substantially different from what would have been observed with continued follow-up. Therefore, modeling is used to estimate costs and projected outcomes in chronic diseases such as diabetes, coronary artery disease or hyperlipidemia. Modeling may be done not only to extrapolate the progression of clinical outcomes beyond that observed in a trial, but also to translate intermediate outcomes into final outcomes. In addition, it is done to use the evidence from additional trials, systemic reviews and meta-analyses to reflect what might happen in a certain clinical setting or population. When the trial period is long enough, or when a subset of patients are observed for a longer time, direct modeling of long term costs and outcomes is feasible. Parametric survival models estimated on trial data are recommended for such projections. In cases where such direct modeling is not feasible, it may be possible to "merge" trial data to long-term observational data in a model, e.g., when evaluating thrombolysis in acute myocardial infarction patients as done by Mark et al [2]. However, the main requirements are that the modeling should be explicit and clear, as well as stating which variables or parameters have been modeled rather than directly observed in a particular sample, and the uncertainties noted.

In addition, there may be need for discounting. Weinstein et al. [5] suggested that the reference case should include discounting of future costs and health outcomes occurring during different time periods to their present value, and stated that they should be discounted at the same rate. There are techniques and formulas for discounting, and one simple approach is to multiply the cost incurred or the survival experienced in a given future year by using the following formula: $(1 + r)^{-t}$, where "r" is the discount rate, and "t" is the number of years from the current year. Weinstein et al. claimed that direct evidence on time preference for health outcomes is consistent with a discount rate of 3%. Additionally, empirical evidence of the rate of return on riskless, long-term securities, such as government bonds, is in the vicinity of 3% per annum. While a 3% discount rate is the preferred rate for the reference case, it is also recommended to use 5% due to the large number of previous studies that have used this rate, as well as 0% and 7% in sensitivity analysis. The BMJ guidelines [19], on the other hand, suggest the analyst use an appropriate discount rate but leave the choice more flexible e.g. the government recommended rate, and conduct a sensitivity analysis using other rates. The use of a zero discount rate for health benefits in the sensitivity analysis is also suggested, so as not to penalize preventive programs. In addition, the discounting of health effects significantly alters cost-effectiveness ratios. Many of these influences are inherently associated with any cost-effectiveness analysis related to treatment of early, slowly progressing malignancies because such an analysis requires a sufficient time horizon to include not only the treatment costs but its benefits as well.

Cost-effectiveness ratios should be calculated at various time horizons (e.g., 2, 5, 10 yrs, or as appropriate for the disease), both to accommodate the needs of decision makers and to provide a "trajectory" of summary measures over time. The effects of long-term health care costs not directly related to treatment should be taken into account and assumptions used must be described and justified.

2.4 Regression analysis

In order to extrapolate beyond trial horizon, several logical methods can be used. One method is to fit a function to the available data, e.g., regression analysis while another method could be fitting known survival curves observed in different populations. Regression analysis is a statistical method used to predict the value of one characteristic from the knowledge of another. This method is also called linear regression, simple linear regression, or least squares regression. The term linear regression refers to the fact that correlation and regression measure only a straight line or linear relationship between two variables. The term simple regression means only one explanatory independent variable and not multiple is used to predict outcome. The least square method describes the mathematical method for obtaining the regression equation. It is a way to determine the equation of the line that provides a good fit to the points when visualized in a scatter plot graph. Besides, regression of non-linear functions is often by transforming them into functions that exhibit linear relationships.

Regression is a method of obtaining a mathematical relationship between an outcome variable (y) and an explanatory variable (x). Assuming a linear relationship, the equation can be represented as a straight line. If the point where the line crosses, or intercepts, the y-axis is denoted by a and the slope of line by b, then the equation of the regression line is

$$y = a + bx$$

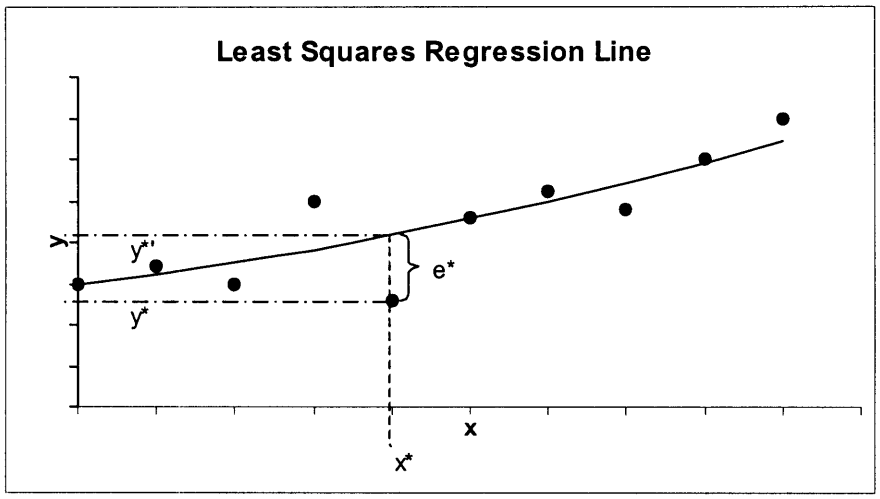
The slope of the line measures the amount of change y changes each time x changes by a unit. If the slope is positive, y increases as x increases. If the slope is negative, y decreases as x increases. In the regression model, the slope of the population is generally represented by β_1, called the regression coefficient and β_0 represents the intercept of regression line. β_1 and β_0 are population parameters in regression. However, most of the time, the points do not fall along the straight line. The regression model therefore contains an error term, ϵ, which is the distance the actual values of y depart from the regression line. In summary, the regression equation is given by

$$y = \beta_0 + \beta_1 x + \epsilon$$

The regression equation used to describe the relationship in a sample of the population is commonly written as

$$\hat{y} = \beta_0 + \beta_1 x$$

Figure 2: Regression and least squares method



solid dots = data points, solid line = regression line

For a given value of x, say x*, the predicted value y* is found by extending a horizontal line from the regression line to the y-axis as in Figure. The difference between the actual value for y* and the predicted value, e*=y*-y*', can be used to judge how well the line fits the data points. The distances e, calculated for all points, is a measure of the failure of the line to fit the actual data points. The least squares method determines the line that minimizes the sum of the squared vertical differences between the actual and predicted values of the y variable; i.e., β_0 and β_1 can be obtained so that $\Sigma(y-y')^2$ is minimized. The formulas for β_0 and β_1 are found using differential calculus and in terms of the sample estimates these formulas are

$$\beta_1 = \Sigma(x-xbar)\,(y-ybar)/\Sigma(x-xbar)^2$$

$$\beta_0 = ybar - \beta_1 xbar$$

The least squares regression line satisfies two conditions:

1. $\Sigma e = 0$, that is, there is a degree of symmetry of points about the line

2. Σe^2 is as small as possible, that is, the sum of squares of the deviations about the line (hence, least squares) is minimized.

There is only one straight line that will fulfill all the conditions described above and this has a slope or 'regression coefficient' b given by the equation.

The regression equation includes assumptions of homogeneity or homoscadasticity and linearity. For each value of x variable, the y variable is assumed to have a normal distribution, and the mean of the distribution is assumed to be the predicted value, y'. In addition, no matter the value of the x variable, the standard deviation of y is assumed to be the same. Thus one can imagine a large number of individual normal distributions of the y variable, all of equal sizes, one for each value of x. The assumption of this equal variation in the y's across the entire range of the x's is called homogeneity. The straight line or linear assumption requires that the mean values of y corresponding to various values of x fall in a straight line. The values of y are assumed to be independent of one another.

Since the regression equation computed for one sample of observations is just one estimate of the true population regression equation, choosing other samples from the population will lead to regression equations that vary from one sample to another with respect to both their slopes and their intercepts. An estimate of this variation is symbolized Sy.x and is called the standard error of regression or the standard error of the estimate. It is based on squared deviations of the predicted y's from the actual ys and is found as follows:

$$Sy.x=\sqrt{\Sigma(y-y')^2/(n-2)}$$

Correlation is a method of describing relationship between two variables. For the purpose of correlation, both variables are dependant. Statistician Karl Pearson, in 1902, proposed the 'product moment correlation coefficient' (given the symbol r) (Table 2). The denominator of r contains the sums of squares of the x and y values, that is, it is the square root of the product of the variations in x and y measured separately. The numerator of r is the 'sums of products', that is, the sum of the deviations of the products of the x and y

values from their mean. Hence, r is the ratio of the joint variation of the two variables to the product of their individual variation. There is a considerable similarity between the equation for the slope b and that for Pearson's r. The numerator is the sums of products as before but the denominator is the sums of squares of the x values alone. Hence, the slope of the line b is the ratio of the mutual variation of x and y to that of variation of the x values.

The correlation coefficient varies from a perfect positive correlation (+1) to a perfect negative correlation (-1). When r = +1, all the data points will lie on a straight line of positive slope and when r = -1, all the data points will lie on a straight line of negative slope. By contrast, when r = 0 no linearity is present and the data points are scattered more or less randomly. Intermediate values of r result from data points scattered around a fitted line; less scatter when r is close to 1 or -1 and a greater degree of scatter when r is close to zero. If there is a significant relationship between x and y that is non-linear, then the value of 'r' will be smaller and some curvilinear relationships, especially if they deviate significantly from a straight line, could result in a non-significant r.

Having calculated r from the data, its absolute value, ignoring the sign, is compared to the distribution of the correlation coefficient to test the degree of significance and to obtain a p-value. Pearson's correlation coefficient has n - 2 degrees of freedom because the means of both the x and y values have to be calculated from the data and therefore, there are two restrictions in the calculation of r. It is important to test the 'goodness-of-fit' or 'validity' of the line, that is, to determine how well the line fits the data points. The square of the correlation coefficient r^2, also known as the 'coefficient of determination', measures the proportion of the variance associated with the y values that can be accounted for or 'explained' by the linear relationship of y on x.

2.5 Survival analysis using actuarial method

Analysis of survival times can be done by actuarial or life table analysis (also called Cutler-Edere method). Astronomer Edmund Haley (of Haley's Comet fame) first used life tables in the 17th century to describe survival times of residents of a town. The actuarial method is computationally easier than the Kaplan -Meier product limit method. When analysis of survival is done while some patients in the study are still living, the observations on these patients are called censored observations. In my thesis, I have not used censored observations.

Table 3: Life table for the total population: United States, 2001

Time interval ages x to x+1	Probability of dying between ages x and x+1	Number surviving to age x	Number dying between ages x to x+1	Person-years lived between ages x to x+1	Total number of person-years lived above age x	Expectation of life at age x
Age	qx	lx	dx	Lx	Tx	ex
0–1..	0.006842	100,000	684	99,404	7,716,990	77.2
1–2..	0.000518	99,316	52	99,290	7,617,586	76.7
2–3..	0.000342	99,264	34	99,247	7,518,296	75.7

Survival analysis using life table of a population [20] is shown in Table 3 and is explained below:

1. Time interval ages x to x+1 (Age): The first column (Table 3) shows the age interval is the period between the exact two ages stated. For example, 1-2 means the one-year span between 1st and 2nd birthday.

2. Probability of dying during age interval (qx): For age interval 1–2 years, the probability of dying is 0.000518. The ''probability of dying'' column forms the basis of the life table; all subsequent columns are derived from it.

3. Number living at beginning of age interval (lx): I use lx to indicate the number of persons, starting with the original cohort 100,000 live births, who survive to the exact age marking the beginning of each interval. Each lx value is computed by subtracting the number dying during the interval for the previous age interval from the lx for the interval

4. Number dying during age interval (dx): The number of persons of the original 100,000 who die during each successive age interval denoted by dx.

5. Person-Years Lived in interval (Lx): The symbol Lx designates the totality of years lived by the survivors of the original 100,000 between the ages x and x+n.

6. Total number of Person-Years (Tx): The symbol Tx denotes the total number of person-years lived by lx survivors from year x to death. It is obtained by cumulating the person-years lived in the intervals.

7. Expectation of Life (ex): It is the most valuable feature of a life-table. It denotes life expectation, the average number of years of life remaining to those who survive to the beginning of the age interval. It is calculated by dividing the number of person-years lived after a given age, by the number who reached the same age.

2.6 Regression of survival data

Fitting complex forms of survival data by regression is often difficult and usually entails considerable computation. Fortunately, after some manipulation of the data, it is possible to apply a more familiar linear regression analysis. For example, the relationship $y=ac^{bx}$ will upon taking logarithms, give log y = log a + bx(log c). Defining new values as follows y' = log y, a' = log a, b' = b(log c) gives the linear relationship y'=a' + b'x to which linear regression techniques can be applied. In other words, one fits a linear regression of log y on x.

When data are arranged in a life table analysis, a regression method for survival distribution fitting can be used as suggested by Gehan and Siddiqui [21]. They suggested considering four theoretical distributions for such regression: exponential, Weibull, Gompertz and linear exponential. The hazard functions are estimated by a non-parametric method for each interval and parameters of distribution are then estimated by the method of weighted least squares. The best fit among the four distributions is selected by comparing the

likelihood values of the observed data under the four distributions. The distribution that gives the largest likelihood value provides the best fit.

2.7 Hazard function

It is also called the conditional failure rate, instantaneous mortality rate, force of mortality, condition mortality rate or age specific failure rate or the incidence density function. The hazard function, $\hat{h}(t)$, is the probability of the occurrence of an event in a small time interval, per unit time, on the condition that the event has not occurred before the interval. When considering the event of death, it is conditional on the patient being alive at the beginning of the interval.

$$\hat{h}(t) = \frac{\text{number of patients dying in the time interval starting at time t}}{\text{(number of patients surviving at t) (interval width)}}$$

$$\hat{h}(t) = \frac{\text{number of patients dying per unit time in the interval}}{\text{(number of patients surviving at t)}}$$

$$\hat{h}(t) = \frac{\text{number of patients dying per unit time in the interval}}{\text{(number of patients surviving at t) -1/2 (number of deaths in the interval)}}$$

In terms of failure, it is the probability of failure during a very small time interval assuming that the individual has survived to the beginning of the interval. From the definition, it follows that the hazard function is the probability density function divided by the survival function. Therefore, $h(t)=f(t)/1-F(t)=f(t)/S(t)$ where $F(t)$ is the cumulative failure function and $S(t)$ is the cumulative survival function.

The hazard functions of these four distributions are as following:

1. Exponential: $h(t) = \lambda$, $\lambda>0$
2. Weibull: $h(t) = \lambda'\gamma t^{\gamma-1}$, λ', $\gamma>0$, $\lambda' = \lambda^{\gamma}$

3. Gompertz: $h(t) = \exp(\lambda + \gamma t)$, $h(t) > 0$
4. Linear Exponential: $h(t) = \lambda + \gamma t$, $h(t) > 0$

Transforming hazard functions: Interestingly, these four distributions share a common property regarding the hazard function. The hazard function h(t) or its logarithmic transform $\log_e h(t)$ is a linear function of t or $\log_e t$. Considering this property, these four models can be rewritten as

1. $h(t) = \lambda$
2. $\log_e h(t) = \log_e h(\gamma\lambda') + (\gamma - 1)\log_e(t)$
3. $\log_e h(t) = \lambda + \gamma t$
4. $h(t) = \lambda + \gamma t$

To simplify, let y= h(t) or $\log_e h(t)$, then the models can be written in the general form:

$y = b0 + b1x$

For exponential model

$y = h(t)$ $b0 = \lambda$ $b1 = 0$

For Weibull model

$y = \log_e h(t)$ $b0 = \log_e h(\gamma\lambda')$ $b1 = \gamma - 1$ $x = \log_e(t)$

For Gompertz model

$y = \log_e h(t)$ $b0 = \lambda$ $b1 = \gamma$ $x = t$

For linear exponential model

$y = h(t)$ $b0 = \lambda$ $b1 = \gamma$ $x = t$

Therefore, if x and y are known, the coefficients b0 and b1 can be easily estimated. The advantage of the data arrangement in life table fashion is that the hazard function can be estimated and t can be taken as the midpoint of the interval. Thus, for the nth interval, $y_n = b0 + b1x_n$ where y_n is the estimated hazard function or its logarithm and x_n is the midpoint of the interval or its logarithm. Having y_n and x_n for each interval, I can estimate b0 and b1.

Similarly, the survivorship functions for the four models are as following:

For exponential model

1. $S(t)= \exp(-\lambda t)$

For Weibull model

2. $S(t)= \exp[-(\lambda t)^{\gamma}]$

For Gompertz model

3. $S(t)= \exp\{-\exp(\lambda)/\gamma[\exp(\gamma t)-1]\}$

For linear exponential model

4. $S(t)= \exp[-(\lambda t+1/2\gamma t^2)]$

Substituting the least-square estimates of λ and γ, I can obtain estimated values of $\log_e L$ for each model.

The best fit among the four distributions is selected by comparing the likelihood values of observed data under the four distributions. The idea is to maximize the likelihood or log-likelihood function or to minimize the negative log-likelihood function while choosing a model. For a given prediction of survival and life table as in Table 3, the likelihood function is defined as:

$$L = (qx)^{dx} (px)^{lx-dx}$$

That is, one may calculate the likelihood by multiplying the chance of dying raised to the number of deaths and the chance of living raised to the number of survivors for each interval. Given the respective model, the larger the likelihood of the model, the larger is the probability of the dependent variable values to occur in the sample. Therefore, the greater the likelihood, the better is the fit of the model to the data.

Having chosen the best fitting model among the four, a 'goodness-of-fit' test can be performed. This is done by considering twice the difference between the log-likelihood under the best fitting model and the sample data. It follows approximately the chi square distribution with n-1-k degrees of freedom, where n is the number of intervals and k is the number of parameters estimated in the model (k=1 for exponential and k=2 for Weibull, Gompertz and linear exponential models).

2.8 Survival curves and the calculation of life expectancy

A survival curve graphs the fraction of patients in a cohort who are alive at different times. The survival function, S(t), is also referred to as survivorship function or cumulative survival rate and can be expressed as the probability (p) that an individual survives a time T longer than an arbitrary time t. By definition, the initial survival at time zero is one and that at time infinity is zero.

$S(t)$ = P(an individual lives longer than t)

$= P(T>t)$

$= 1$ for $t = 0$

$= 0$ for $t = \infty$

$$\hat{S}(t) = \frac{\text{number of patients surviving longer than t}}{\text{total number of patients}}$$

Figure 2b. Survival curve for 65-year old based on US life tables

For example, Figure (2b) shows a survival curve based on survival at age 65 from US life tables. The area under the curve equals the average life expectancy for any member of the cohort. Thus, the integral of a survival function equals life expectancy.

$$\text{Life Expectancy} = \int_0^\infty S(t)dt$$

Life expectancy can be approximated by summing the areas of consecutive rectangles as shown in Figure 2b. Unfortunately, although survival functions such as Gompertz provide a good fit to actual survival curves, there is no simple closed form solution to the integral of Gompertz and other models of survival. Thus, making estimates of life expectancy using these models is difficult. Markov modeling is, therefore, used for estimating life expectancies.

2.9 Markov model

Markov models are built to model events over long time horizons e.g. lifetime of a patient. A Markov process describes a state-transition model to project prognosis over time [22]. Markov models are especially useful for modeling prognosis when the risk recurs repetitively over a long period of time, when the likelihood of an event changes over time or when the utility of the associated outcome depends on when the event occurs. A Markov model consists of a small set of clinical states to describe the possible health states of a patient. A cohort of identical patients begins the process assigned in one or sometimes several states at the start of the simulation (time zero). A clock runs at a fixed rate, and with each tick of the clock, patients move from one state to another state based on "transition probabilities," that summarize a base of knowledge or assumptions about prognosis. Since only a single effective transition occurs in a given clock cycle of a Markov model, it is important to have a sufficiently short cycle time to maintain fidelity. Transition

probabilities based on annual event rates will be converted to monthly rates and from those rates to monthly transitional probabilities.

With each clock tick, the membership of each state is recorded, providing a "trace" or curve of each state's membership over time. A basic assumption of such a model is that only a single state-transition can occur when moving from one cycle to another. The basic property of a Markov model is that it has no memory of previous states, which is termed the Markovian assumption. All patients in the same health state have the same prognosis regardless of their history. The model also estimates that costs associated with being a member of each health state. By multiplying the state's membership by its estimated costs, the annual and cumulative cost of healthcare, over time, for the entire cohort can be calculated. Simulations will be run until the entire initial cohort has transitioned to the absorbing state, such as the "Dead" state. An "absorbing state" means the probability of transition to another state is 0.

In a model consisting of only two states, "Alive" and "Dead," the trace of the "Alive" state over time would describe the cohort's survival curve. The characteristic S-shaped curve of a healthy population was described over a century ago by Gompertz and can be produced using a function of the form $(A*\exp^{(B*age)})$ to describe the instantaneous (as opposed to the average) mortality rate at each attained age of the cohort. Given a projected survival curve, one can calculate life expectancy (or a cohort's average survival) by calculating the area beneath the survival curve. In performing such calculations of life expectancy, the so-called "half-cycle" correction is included, to compensate for the fact that observations are made at the beginning or end of each cycle, and not continuously. If the cycle length is sufficiently short, the need for a half cycle correction disappears.

2.10 Overview of programming languages and R

Interpreted versus compiled languages: Like Java and Basic, R is an interpreted language, in which individual language expressions are read and then immediately executed [23]. The R interpreter carries out

the actions specified by the R expressions. It is always interposed between R functions and the machine those functions are running on.

Fortran and C, by contrast, are compiled languages, in which complete programs in the language are translated by a compiler into the appropriate machine language. Once a program is compiled, it runs independently of the compiler.

The great advantage of an interpreted language such as R is that it allows incremental development and, therefore, is an excellent prototyping tool. Programmers can write a function, run it, write another function, run that, and then write a third function that calls the previous two. They can create an empty shell of a function, add features as desired, and relatively quickly create a working version of virtually any application.

The disadvantage of an interpreted language is related to the requirement of an interpreter and the overhead associated with it. Compiled code runs faster by optimizing the machine code to perform the required steps in the most efficient manner and requires less memory than interpreted code.

Object-oriented programming: Traditional computer programming deals with programs, which are sequences of instructions that tell the computer what to do. In the sense that a computer language is a language, programs are verbs. Object-oriented programming, by contrast, deals largely with nouns, namely, the data objects that traditional programs manipulate. In object-oriented programming, a programmer thinks about a type of object and tries to imagine all the actions that can be performed on objects of that type. The programmer, then, defines the actions specifically for that type of object.

R is an object-oriented programming language, and takes full advantage of the powerful concepts of classes and methods. The advantages of object-oriented programming are not evident when writing a single function

for a particular purpose. Instead, the advantages arise when designing a large system that will do similar, but not identical, things to a variety of data objects.

Object-oriented programming uses the data being acted upon to determine what actions take place. Thus, a common synonym for object-oriented is data-driven. Because the actual actions are determined by the data, the commands or function calls are, in effect, simply requests from the user to the data: "print yourself", "summarize yourself". These requests are generally expressed as calls to generic functions. A generic function, such as print or plot, takes an arbitrary object as its argument. The nature of the object then determines how the action specified by the generic function is carried out. The actual actions are performed by defined methods which implement the action called for, by the generic function for a particular type of data. Most generic functions have default methods which are used if no more specific method can be found. For example, if you type the expression print(myobject) with myobject a factor, R will print myobject using the method print.factor. If myobject is a vector, the printing is performed by print.default.

Methods are named using the convention action.class, where action is the name of the generic function, and class is the class to which the method is specific. Thus plot.factor is the plot method for factors, and is.na.data.frame is the missing value test method for data frames. R determines which method to use for a given object by looking at the class attribute of the object, if it exists. If the class attribute is missing, the default class is assumed. For example, factors are identified by class "factor", while vectors have no class attribute, so are of class default.

A class attribute is just a character vector, and it can be of any length. The first element in the class attribute is the most specific class of the object. Thus, for example, an ordered factor has class attribute c("ordered", "factor"), and is said to have class ordered. Subsequent elements in the class attribute specify classes from which the specific class inherits.

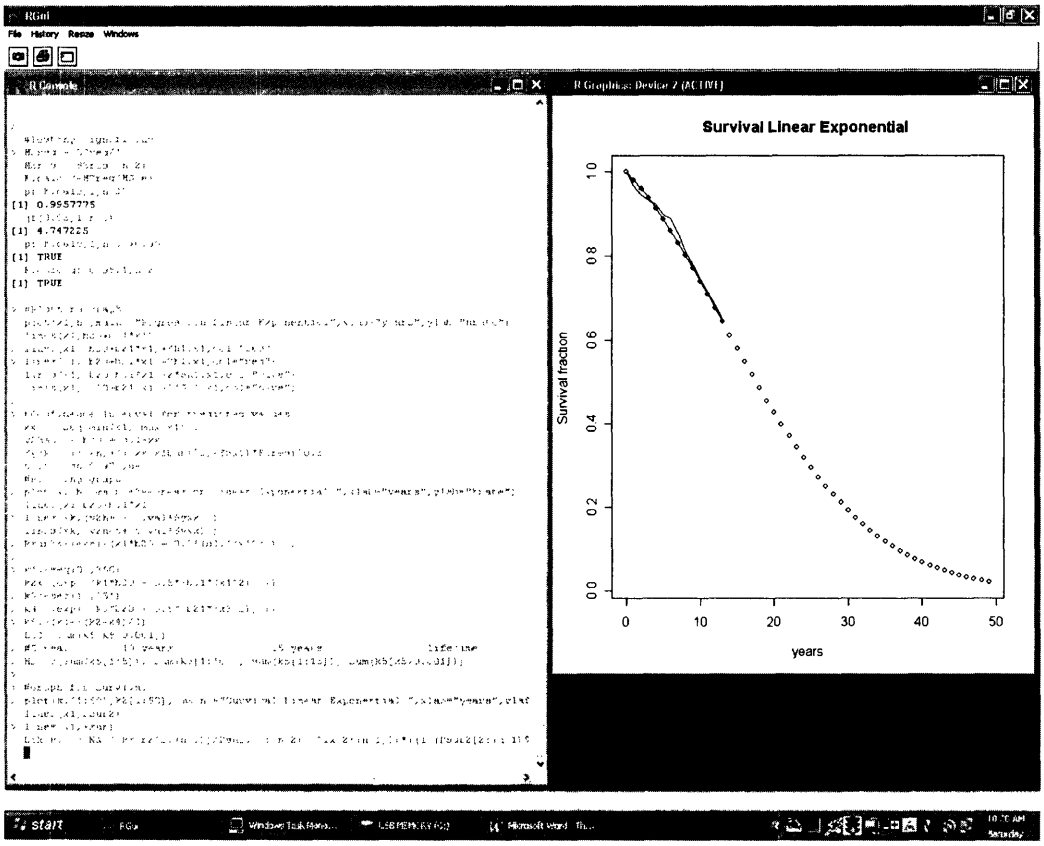
Inheritance is a powerful concept in object-oriented programming, because it lets a user define a new class with only the features needed to distinguish it from classes from which it inherits. Thus, ordered factors are simply factors for which the levels have a specific ordering

History and uses of R: It is a language and environment for statistical computing and graphics. R is a different implementation of S, which was developed at Bell Laboratories by John Chambers and colleagues. R is an integrated suite of software facilities for data manipulation, calculation and graphical display. It includes an effective data handling and storage facility and a suite of operators for calculations on arrays especially matrices. It provides a large, coherent, integrated collection of intermediate tools for data analysis. R has graphical facilities for data analysis and can display either on-screen or on hardcopy. One of R's strengths is the ease with which well-designed publication-quality plots can be produced, including mathematical symbols and formulae where needed. It can be regarded as a well-developed, simple and effective programming language that includes conditionals, loops, user-defined recursive functions and input and output facilities. R is an environment within which statistical techniques are implemented. R can be extended via packages. For computationally-intensive tasks, C, C++ and Fortran code can be linked and called at run time. Advanced users can write C code to manipulate R objects directly. It compiles and runs on a wide variety of UNIX platforms, Windows and MacOS.

Programming tools in R: There are two main tools for developing R programs: the Commands window and Script windows. The > prompt in the Commands window indicates R is ready for your input. You can now type expressions for R to interpret. The Commands window button on the Standard toolbar window, simply use the close window tool on the top right of the window. The command > q() will close down R altogether. Script windows, on the other hand, do not execute each statement as it is typed in, nor is there a prompt character. They are for developing longer R programs, and for building programs from a variety of sources, such as the history log.

The R graphical user interface: R's graphical user interface is an object-oriented system. Graph elements, menus, and dialog components are all objects which may be manipulated. The two most common actions to perform on an object are creating the object and modifying the object. Objects may also be copied, moved, and removed. Documents such as graph sheets and scripts may be created, opened, viewed, saved, and removed. Graphical user interface objects persist in memory for the duration of an R session. Interface elements such as menus and dialogs are automatically saved to disk at the end of a session. The user is

FIGURE 3. Graphical user interface for R



prompted as to whether graph objects are to be saved as the end of a session. R graphical user interface is available for windows. A Java based graphic user interface is also available.

3. MATERIALS AND METHODS

3.1 Data sources

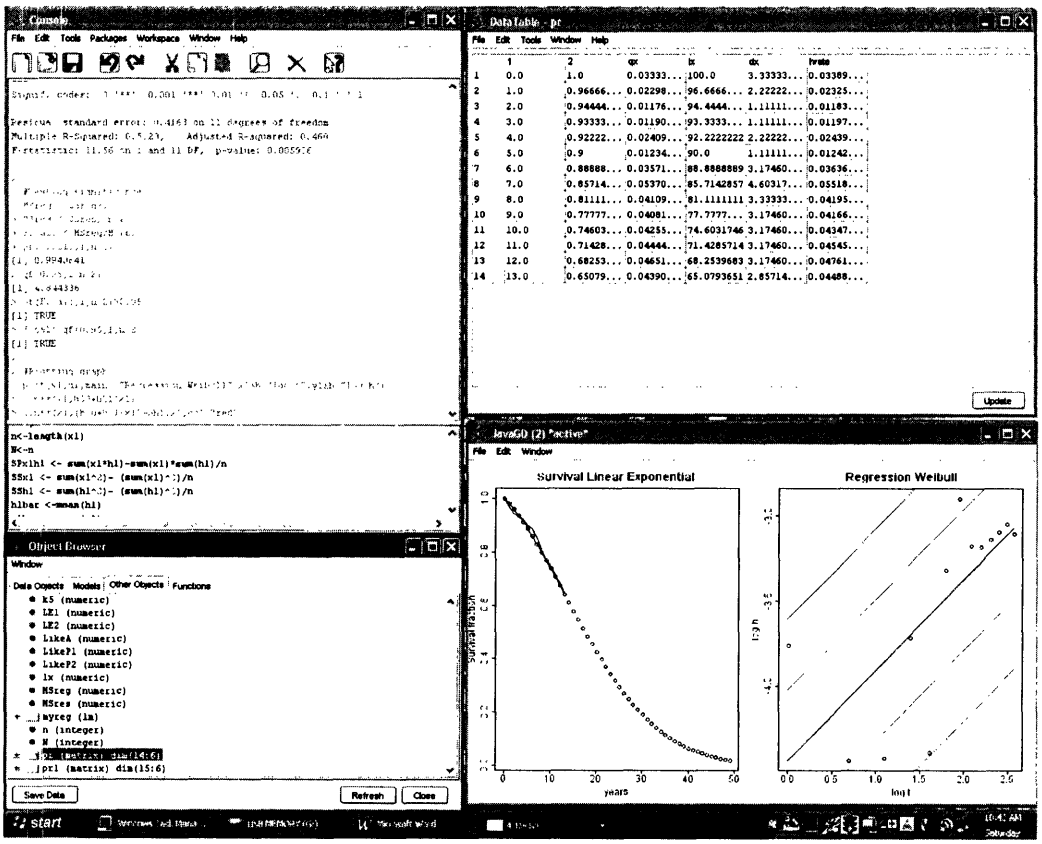
First, survival data were extracted from US life tables[20] to derive survival function for two competing strategies of a hypothetical model. Assuming that the new and usual treatment strategies resulted in a survival identical to persons 5 and 10 years older (than age 64) respectively; the survival data starting at age 69 years and 74 years were obtained for this hypothetical model for the duration of 10 years (Appendix 1). In addition, for the real data model, 15-year survival data were obtained from a published trial evaluating the strategies of thrombolysis in patients with myocardial infarction [2]. This study included 14-year data on survivors of myocardial infarction in the Duke Cardiovascular Disease Database. Finally, for the theoretical overview model, cumulative differences in cost and effectiveness of the two strategies were assumed to: 1) decrease, 2) remain constant or 3) increase over time and incremental cost-effectiveness ratios were obtained over varying time horizons.

3.2 Data analysis software and environment

Data analysis was done using R (Computing Version 2.1.1 (2005-06-20)). R is an integrated suite of software facilities for data manipulation, calculation and graphical display. It includes an effective data handling and storage facility and a suite of operators for calculations on arrays especially matrices. It provides a large, coherent, integrated collection of intermediate tools for data analysis. It can be regarded as a well-developed, simple and effective programming language that includes conditionals, loops, user-defined recursive functions and input and output facilities. R is an environment within which statistical techniques are implemented.

I used R scripts for regression analysis and fitting of survival curves (Appendix 4). First, an object table was created by reading in a .csv file. This table was then manipulated to get the hazard rate. A linear regression model was developed by using linear model (lm) function and regression of hazard rate and time or their logarithm were performed as appropriate for the chosen model by applying user-defined functions e.g. Gompertz or Weibull (Appendix 3). Statistics for significance of regression and R^2 were obtained by implicit R functions. By using R's graphical interface, a fitted survival curve was plotted. User-defined functions for likelihood estimation, its logarithm and maximal likelihood estimation were used for model selection. Goodness of fit was also obtained by user-defined functions. A hierarchal, object–oriented environment in R leads to a graphical interface (Figure 4) displaying use of functions, models and objects including graphs and tables.

FIGURE 4. Graphical user interface showing object-oriented elements of R



3.3 Estimation of effectiveness and costs

3.3.1 Hypothetical model

I compared two strategies for patients: undergoing the new therapy or usual therapy. As stated above, I extracted survival data from US life tables for 10 years starting at age 69 for the new treatment strategy and age 74 for the usual treatment strategy. I created a hypothetical model of a trial with survival data in a life table format as previously shown (Table 3).

In addition, I used simple linear regression of the interval start time and hazard rate or their logarithm based on the model chosen. The statistical formulae as shown in Table 4 were encoded in R for calculations and plotting graphs. Other relevant statistics were available as functions in R.

Table 4. Regression and correlation - statistical tests and formulae

Statistic	Symbol	Formula	Purpose
Pearson's correlation	r	$\Sigma xy/\sqrt{\Sigma x^2 \Sigma y^2}$	Linear relationship between x and y
Regression coefficient	b	$\Sigma xy/\Sigma x^2$	Measure change in y per unit of x
Standard error of b	sb	$sy.x/\Sigma x^2$	Enables 't test of b (t = b/ sb)
Prediction of y*	SEy*	$sy.x \sqrt{(1/n + x^2/\Sigma x^2)}$	CI for mean y at specific x
Prediction of y	SEy	$sy.x \sqrt{(1 + 1/n + x^2/\Sigma x^2)}$	CI for individual y at specific x

CI = confidence interval, n = number of pairs of observations, Σx^2 = sums of squares of x, Σy^2 = sums of squares of y, Σxy = sums of products of x and y, sy.x = mean square deviation from regression

Using R scripts, I calculated the hazard functions over 10 years and transformed them to linear equations in terms of time t or log t, as needed, for exponential, linear exponential, Weibull and Gompertz distributions

and fit hazard functions to the data using the least-squares linear regression method. Then, the likelihood of different survival models was estimated, and the model yielding the maximal likelihood estimate was selected as the best fitting model. The goodness-of-fit of the model was then estimated by taking twice the difference between the log-likelihood under the best fitting model and the sample data. The initial and the extrapolated data were compared over different time horizons: 5-, 10- and 15-year in addition to lifetime.

I fit four commonly used hazard functions as following:

Exponential Regression: In this model, the hazard function h(t) is a constant, $h(t) = \lambda$. I calculated the mean of the hazard function to obtain λ.

Linear Exponential Regression: The hazard function h(t) in this model is a linear function of time t, $h(t) = \lambda + \gamma t$. I performed linear regression to determine the slope γ and intercept λ.

Gompertz Regression: Characteristically, in the Gompertz model, the hazard function h(t) is a function of time t, of the form $h(t) = \exp^{(\lambda + \gamma t)}$, $h(t) > 0$. This can be transformed to a linear relation by taking the logarithm of h(t): $\log_e h(t) = \lambda + \gamma t$. I performed linear regression to determine the slope γ and intercept λ.

Weibull Regression: In the Weibull model, the hazard function h(t) is a function of time t, of the form $h(t) = \lambda' \gamma t^{\gamma-1}$, $\lambda', \gamma > 0$, $\lambda' = \lambda^{\gamma}$. This can be transformed to a linear relation by taking the logarithms of h(t) and t: $\log_e h(t) = ((\gamma-1)\log_e(\lambda) + \log_e(\gamma\lambda)) + (\gamma-1)\log_e(t)$. I performed linear regression to determine the slope $(\gamma-1)$ and intercept $(\gamma-1)\log_e(\lambda) + \log_e(\gamma\lambda)$.

For a given prediction of survival and life table, the likelihood function is given by

$$L = \Pi\, [1-(S(t_{i+1})/S(t_i))]^{d_i}[S(t_{i+1})/S(t_i)]^{n_i-d_i}$$

That is, one may calculate the likelihood by multiplying the chance of dying $[1-(S(t_{i+1})/S(t_i))]$ raised to the number of deaths (d_i) and the chance of living raised $[S(t_{i+1})/S(t_i)]$ to the number of survivors (n_i-d_i) for each interval (i). Then, the survival model yielding the highest likelihood may be selected as the best fitting model for the data. It is mathematically equivalent to the maximal likelihood function.

3.3.2 Model with real data

I extracted 15-year survival data published in a model used for cost-effectiveness study of thrombolytics in patients with myocardial infarction [2] to show applicability to real data. For further exploration, I excluded the first-year acute hazard rate in order to model chronic disease rather than acute mortality.

I created a hypothetical model of a trial with survival data in a life table format as shown below:

Table 5: Modified life table method for a trial

Interval Start Time	Number Surviving to Age x	Number dying between ages x to x+1	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End
	lx	dx	qx	px	sx
			dx/(lx-(dx/2))	1-qx	(px*p(x-1))
0	100.000	2.266	0.0229197	0.97708	0.9770803
1	97.734	2.411	0.0249811	0.975019	0.9526718

However, when using the life table method to calculate life expectancy from a given survival curve in the real data model, one has to modify the above method as shown in Table 5. This is because the probability of dying between ages x and x+1 is not explicit when deriving data from a survival curve. Assuming there is no withdrawal of patients, the first column shows the start of the interval. The second column (lx) shows the number of patients at the start of an interval, the third column (dx) shows the number of patients dying during the interval. The column (qx) gives the proportion terminating. The actuarial method assumes that the patients die randomly through the interval; therefore on an average, they die half way during the time represented by the interval. This method gives patients, who die during the interval, credit for being alive for half of the period. This assumption is of less consequence when short intervals are analyzed. However, considerable bias can be introduced if the intervals are large. The proportion surviving is then calculated in column (px). In the end, cumulative proportion surviving (sx) is calculated by multiplying the proportion surviving in the interval x to x+1 and the proportion surviving in all previous intervals. Life expectancy can be calculated based on this method.

3.3.3 Overview model

I explored estimation of incremental cost-effectiveness ratios for the two strategies A and B over different time horizons: 1-, 5- and 10-years. A theoretical model was developed for costs and effectiveness of the two strategies. Assuming that the cumulative differences in cost and effectiveness of the two strategies: 1) decrease 2) remain constant or 3) increase, I obtained incremental cost effectiveness ratios for the different time horizons for the two interventions. Thus, I developed a matrix of incremental cost-effectiveness ratios for different time horizons based on the model.

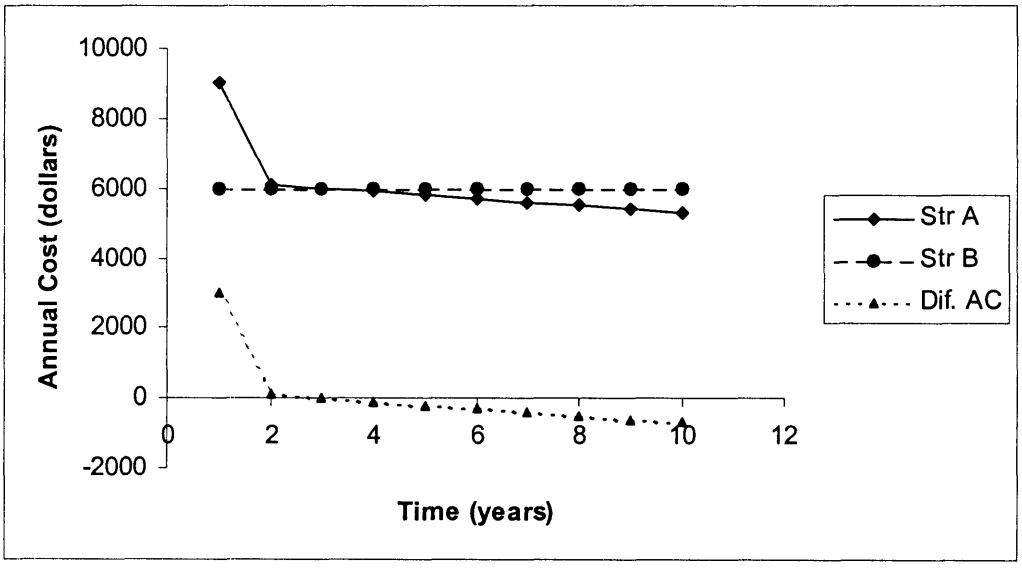
3.3.4 Annual versus cumulative difference in costs and survival

Annual cost of strategy A refers to the mean cost over a year for the strategy. The difference between the annual cost of strategy A and B is the difference in cost of the strategy A as compared with B for a given year. Cumulative cost is the sum of costs over a given time horizon for a strategy. Cumulative difference in cost at a given time horizon is the sum of the differences of cost of strategy A as compared with strategy B in the preceding time. Surviving fraction of patients is the fraction of cohort surviving at a given time as compared with the cohort at the start time t=0 and therefore the survival function S at time t= 0 is depicted as S(0)=1. As time approaches infinity, surviving fraction tends to 0. In other words, as time increases, surviving fraction decreases and becomes 0 over a "long enough" time duration. The surviving fraction when plotted over time depicts the survival curve. Life expectancy can be obtained as the cumulative survival over time, or graphically as the area under the survival curve for a strategy. The cumulative difference in surviving fraction of two competing strategies A and B, i.e. the difference in areas under the survival curves, is the cumulative difference in effectiveness or life expectancy of strategy A compared with strategy B.

3.3.5 Distributions of cost

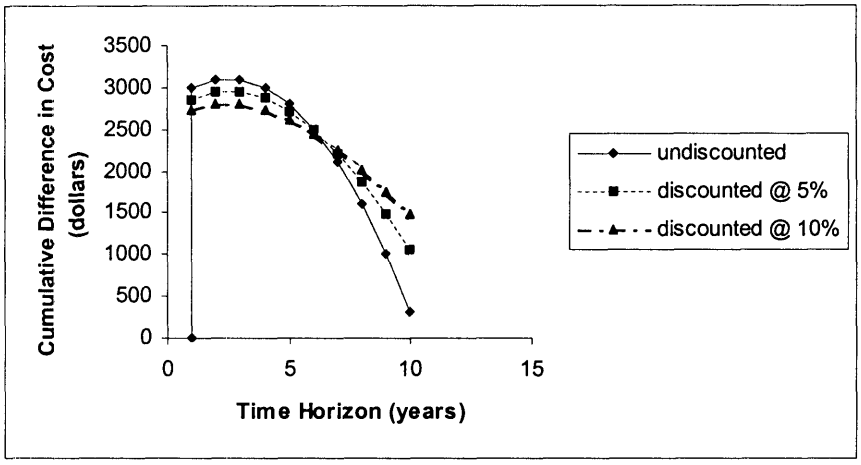
Decreasing cumulative difference in cost: Let us follow costs of two strategies A and B over 10 years. The annual cost for each year of a hypothetical trial is shown in Figure 5a. With increasing time, the annual cost of strategy A, which is initially higher than strategy B, falls below the annual cost of strategy B. Thus, the difference in incurred cost of strategy A over Strategy B decreases each year and becomes negative, i.e., strategy B has a higher annual cost than strategy A as time in the trial progresses. This leads to a decreasing cumulative difference in cost over increasing time horizon. In addition, cumulative difference in cost discounted at 5% is shown in Figure 5b. Discounting tends to flatten the cumulative difference in cost over different time horizons. The cumulative difference curve becomes increasingly deep at later time horizon as the discounting decreases to values near zero. The cumulative difference curve initially slopes up due to the data chosen for this hypothetical model.

Figure 5a. Annual incurred cost showing decreasing difference in cost (not the absolute difference)



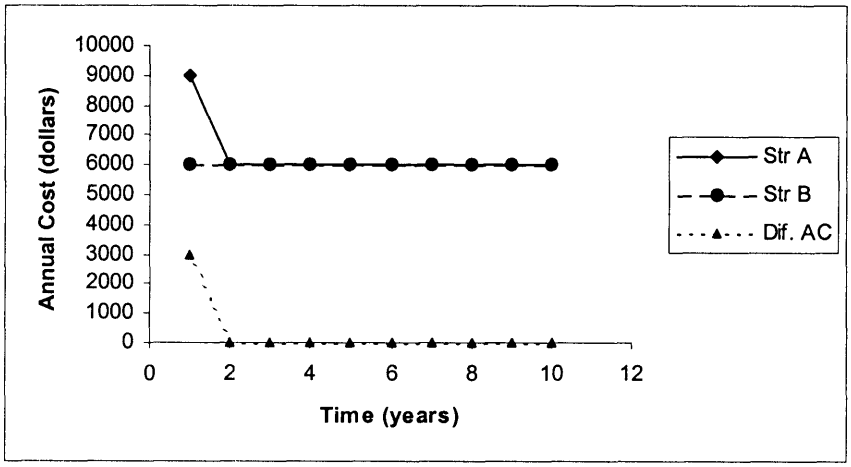
Str A = Strategy A annual incurred cost, Str B = Strategy B annual incurred cost, Incr. AC = Difference in annual cost

Figure 5b. Cumulative difference in cost (when annual difference in cost is decreasing)



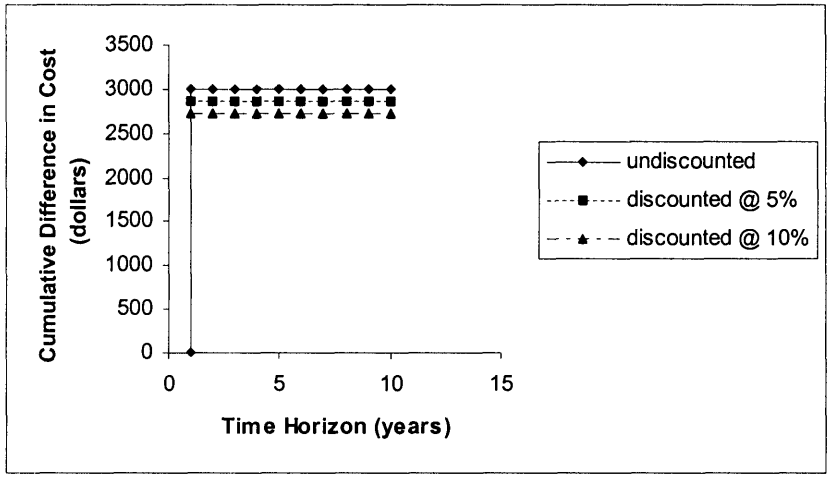
Constant cumulative difference in cost: Similarly, if I follow the costs of two strategies A and B over 10 years, the annual cost of this hypothetical trial is shown in Figure 5c. With increasing time, the annual cost of strategy A, which was higher than strategy B in the beginning, falls to the annual cost of strategy B. Therefore, the difference in incurred cost of strategy A over Strategy B decreases over time and becomes zero, i.e., strategy B costs the same as strategy A. This leads to a constant cumulative difference in cost over increasing time horizon (Figure 5d).

Figure 5c. Annual incurred cost showing cost of strategy A=cost of strategy B and constant cumulative difference in cost



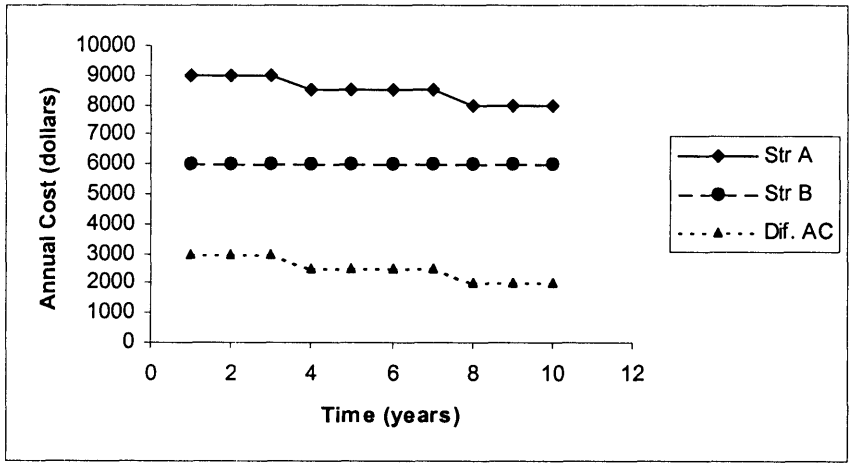
Str A = Strategy A annual incurred cost, Str B = Strategy incurred B annual cost, Dif. AC = Difference in annual cost

Figure 5d. Cumulative difference in cost (when annual difference in cost = 0)



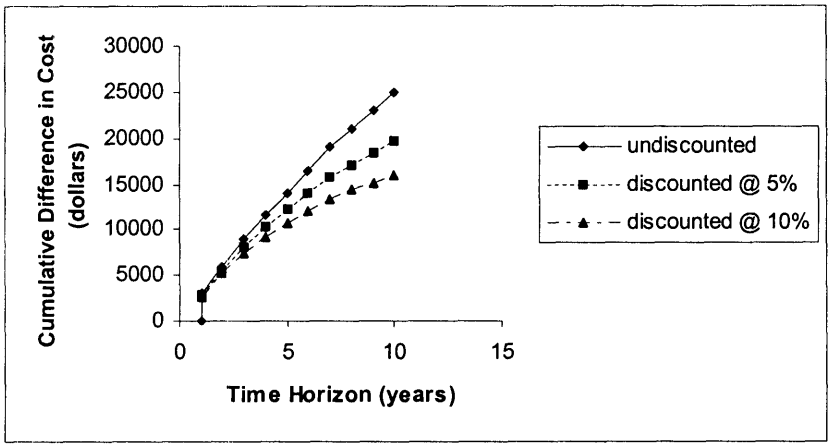
Increasing cumulative difference in cost: Figure 5e. displays the annual cost of a hypothetical trial over 10 years. With increasing time, as long as the annual cost of strategy A, remains higher than the annual cost of strategy B, the difference in incurred cost of strategy A over Strategy B will remain positive. This leads to an increasing cumulative difference in cost over increasing time horizon (Figure 5f).

Figure 5e. Annual incurred cost when difference in cost is positive



Str A=Strategy A annual incurred cost, Str B=Strategy B annual incurred cost, Incr. AC= Difference in annual cost

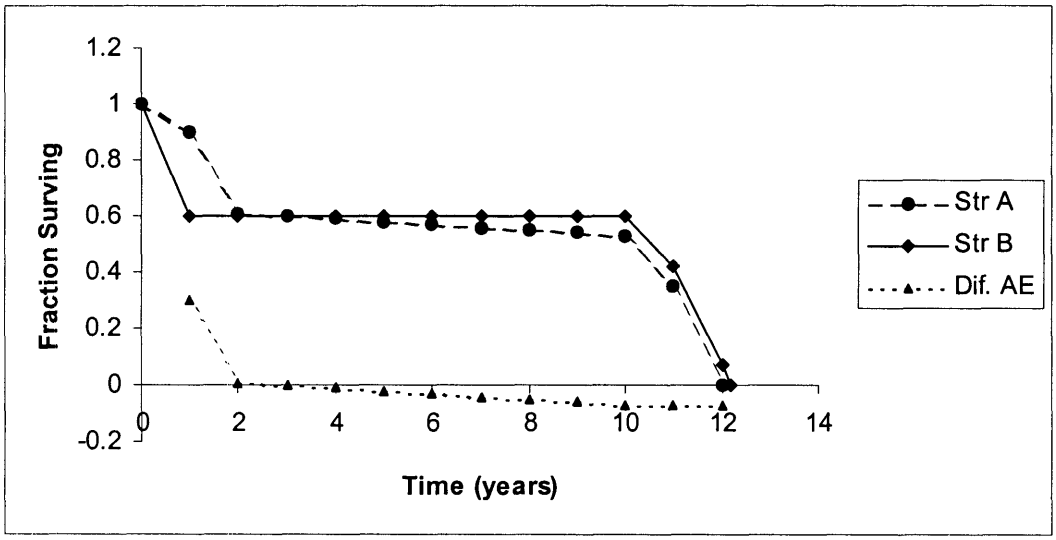
Figure 5f. Cumulative difference in cost (based on positive annual difference in cost)



3.3.6 Distributions of effectiveness

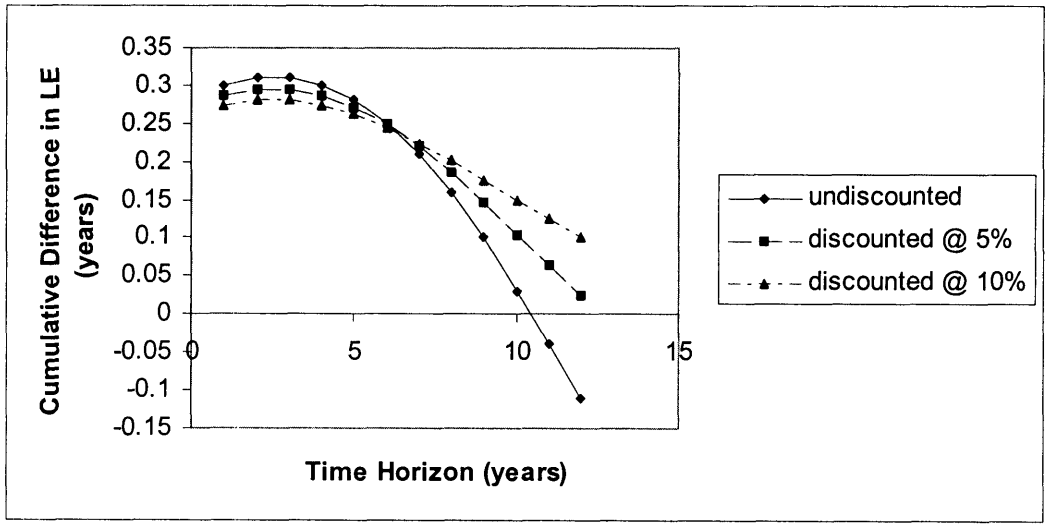
Decreasing cumulative difference in effectiveness: Let us follow the fraction of patients surviving when comparing two strategies A and B over 12 years. Survival must decrease as time increases and becomes zero as time increases to infinity (or approximately 12 years in this case). Figure 6a. gives the fraction of patients surviving each year of the trial as compared to survival at time t=0 to 12 years. With increasing time, the fractional survival of patients of strategy A, which was higher than strategy B in the beginning, falls below the fractional survival of strategy B and the difference in effectiveness of patients treated with strategy A over Strategy B decreases each year and becomes negative i.e. strategy B has a higher fractional survival than strategy A. This leads to a decreasing cumulative difference in effectiveness or survival over increasing time horizon. In addition, I have shown cumulative difference in survival discounted at 5% (Figure 6b). Notice that the cost curve "flattens".

Figure 6a. Annual effectiveness showing decreasing difference in effectiveness (not the absolute difference)



Str A = Strategy A effectiveness, Str B = Strategy B effectiveness, Dif. AE = Difference in annual effectiveness

Figure 6b. Cumulative difference in effectiveness (based on decreasing difference in effectiveness)

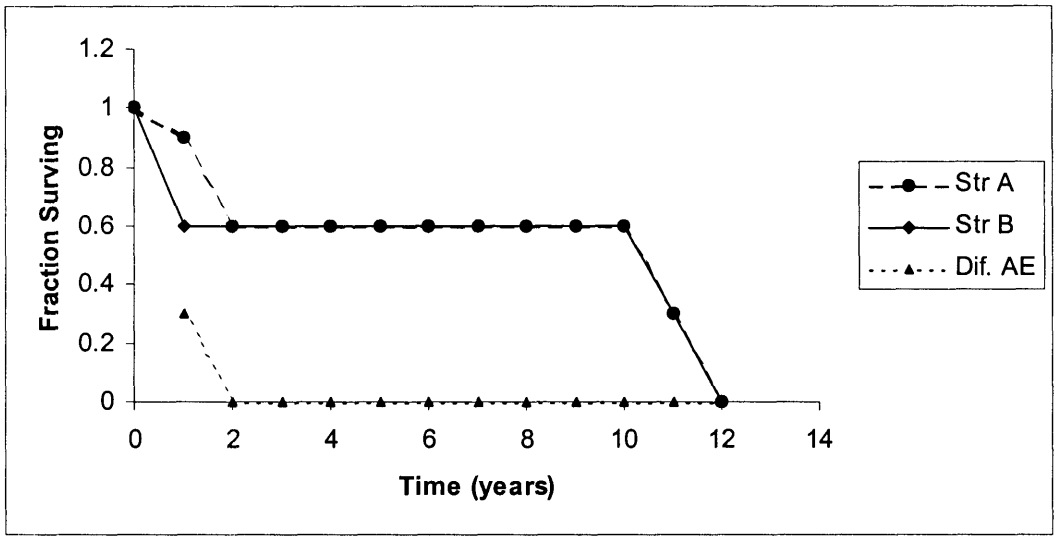


LE = Life expectancy

Constant cumulative difference in effectiveness: Similarly, the fraction of patients surviving with strategies A and B can be followed over 12 years (Figure 6c). With increasing time, the initially higher fractional

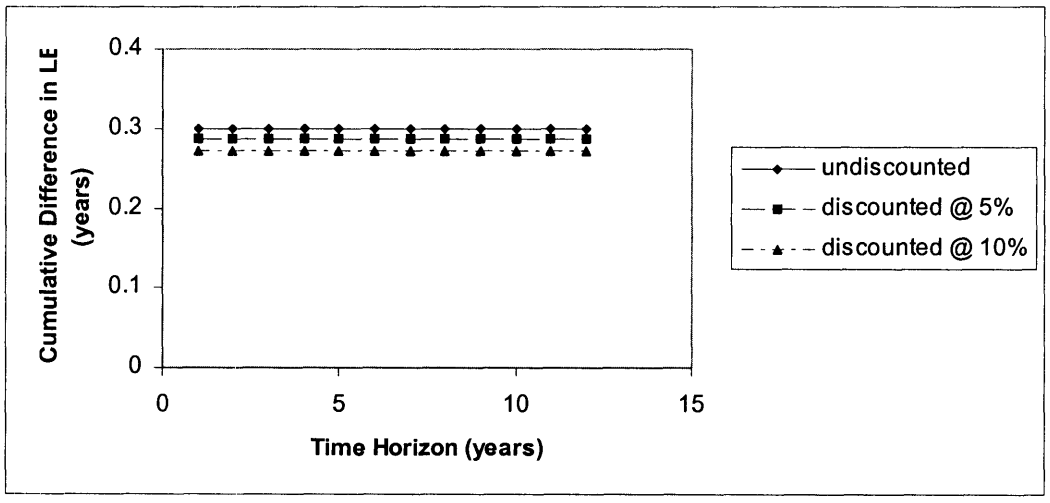
survival of strategy A falls to the level of fractional survival of strategy B and, therefore, the difference in survival of strategy A over strategy B decreases and becomes zero i.e. survival for strategy B is the same as strategy A. This leads to a constant cumulative difference in survival over longer time horizon (Figure 6d).

Figure 6c. Annual effectiveness when difference in effectiveness = 0 (year 2- 10)



Str A = Strategy A effectiveness, Str B = Strategy B effectiveness, Dif. AE = Difference in annual effectiveness

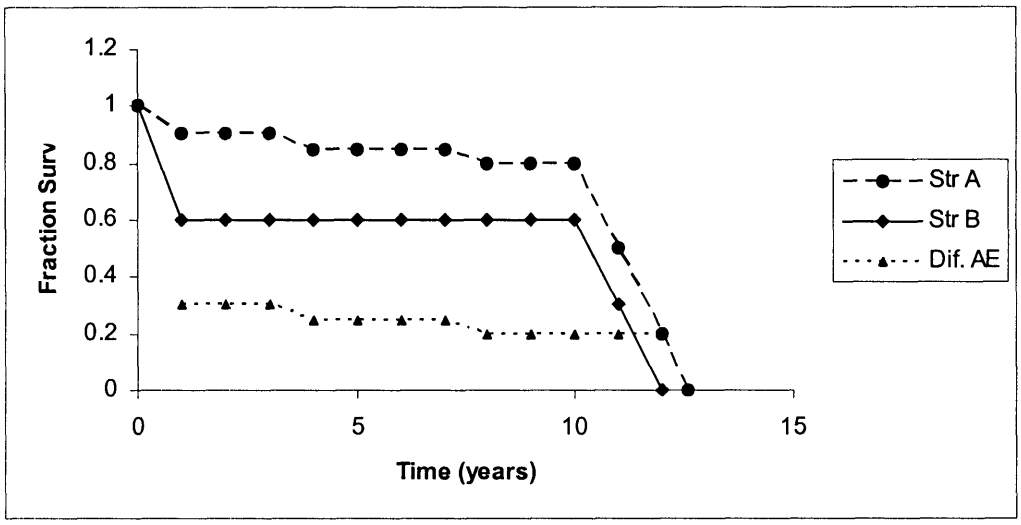
Figure 6d. Cumulative difference in effectiveness (when difference in effectiveness = 0)



LE = Life expectancy

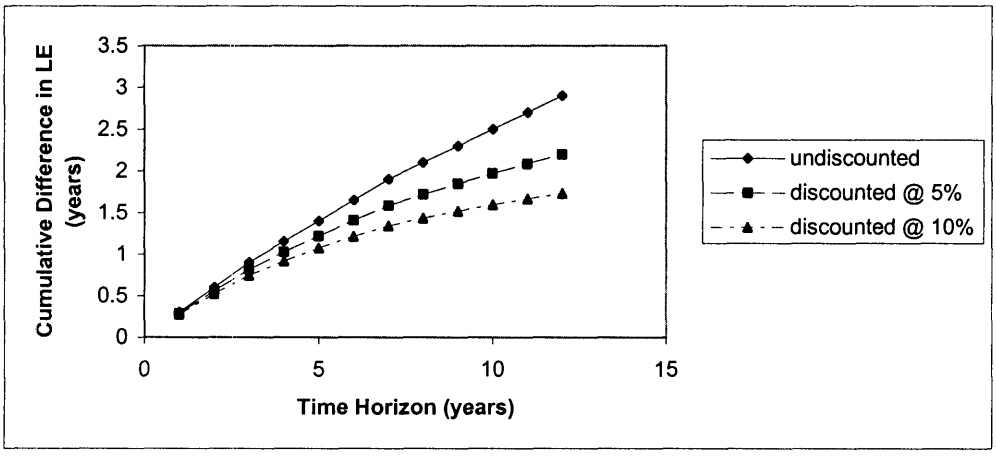
Increasing cumulative difference in effectiveness: Figure 6e. displays the fraction of surviving patients each year with strategy A and strategy B. At time=0, fraction surviving for each strategy is 1. With increasing time, the fractional survival of strategy A remains higher than the fractional survival of strategy B; therefore, the difference in survival of strategy A over B is positive each year. This leads to an increasing cumulative difference in survival or life expectancy over increasing time horizon (Figure 6f). However, since the survival over extended time horizon falls to 0, the curves must eventually asymptote.

Figure 6e. Annual effectiveness showing positive difference in effectiveness



Str A = Strategy A effectiveness, Str B = Strategy B effectiveness, Dif. AE = Difference in annual effectiveness

Figure 6f. Cumulative difference in effectiveness (when positive difference in effectiveness)



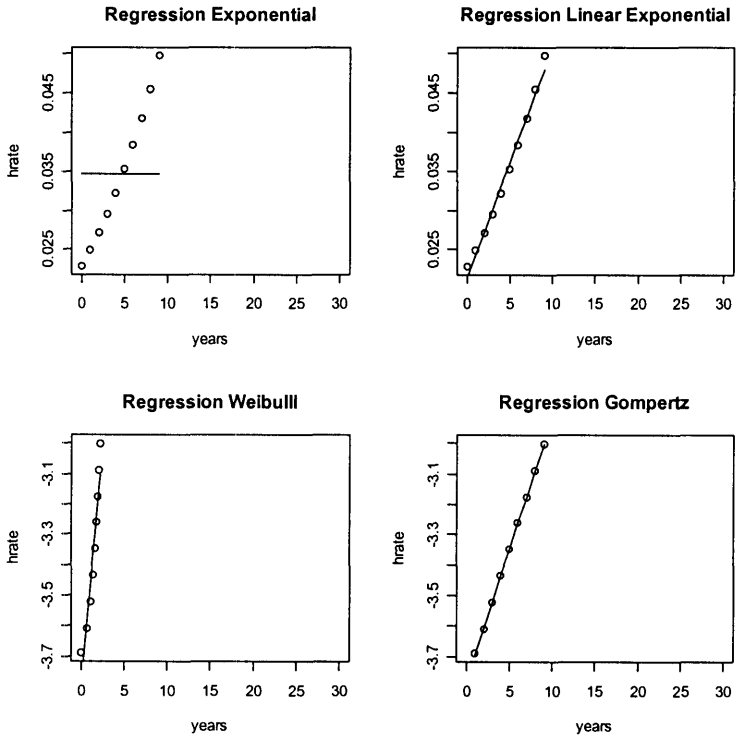
LE = Life expectancy

4. RESULTS

4.1 Hypothetical model

Based on the hypothetical model derived from US life tables, survival data for the two interventions were obtained for 10 years and the hazard functions for the two interventions were derived using R scripts. The hazard function for the new treatment arm was regressed successfully using four distributions - exponential, linear exponential, Weibull and Gompertz distributions (Figure 7). The r^2 for simple linear regression was between 0.89 to 0.99, and test statistic for regression was significant for all four distributions. Using lifetime time horizon, the life expectancy (in years) based on exponential model was 18.1, linear exponential model was 12.6, Weibull model was 14.1 and Gompertz model was 12.1. Gompertz model had the highest value of likelihood estimation and is the model of choice.

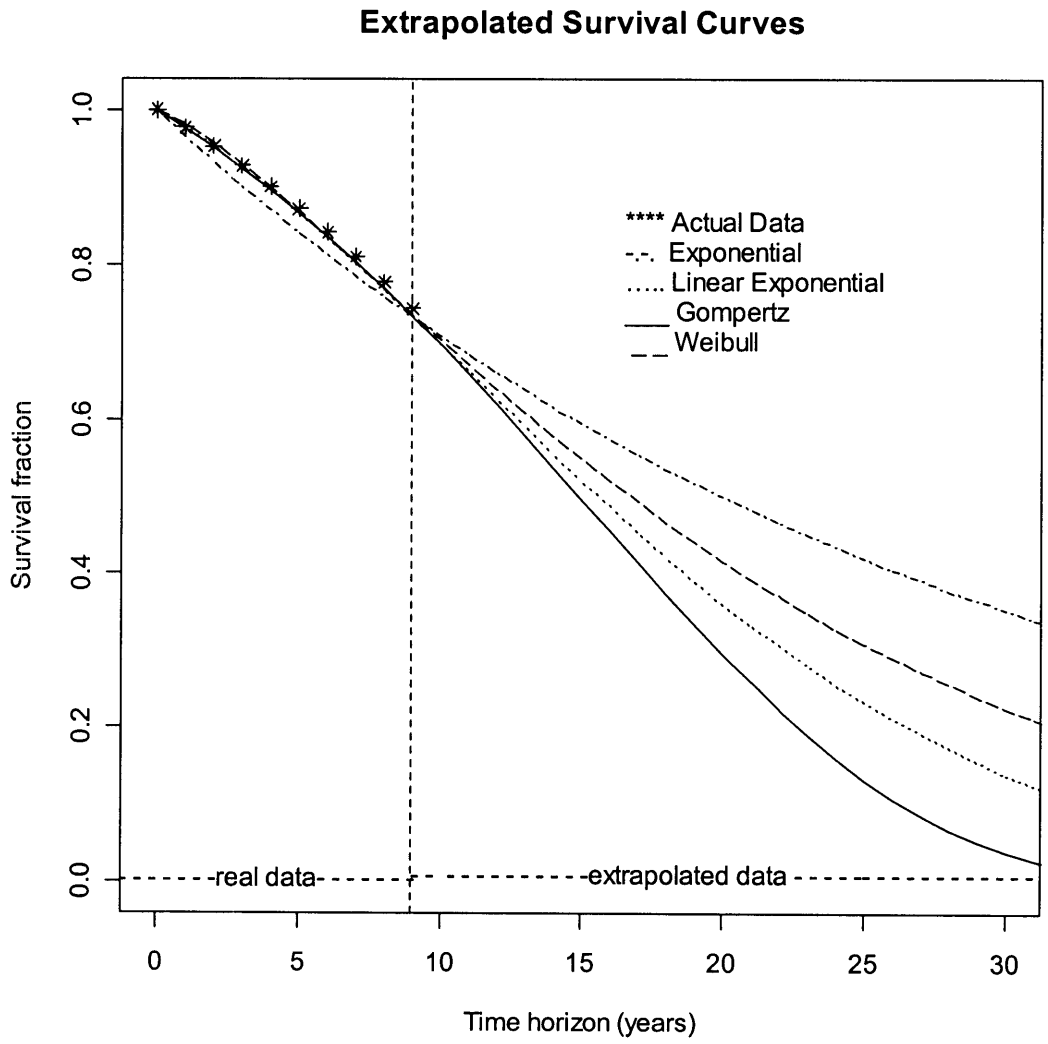
Figure 7a. Regression of hazard function of the new treatment arm in the hypothetical model



Open circles = real data points, solid line = regression line

Similarly for the usual treatment arm, the hazard function was successfully regressed to obtain the above four distributions. The coefficient of determination (r^2) for simple linear regression was between 0.89 and 0.99, and the test statistic for regression was significant for all four distributions. Using lifetime time horizon, the life expectancy (in years) based on exponential model was 18.1, linear exponential model was 12.6, Weibull model was 14.1 and Gompertz model was 12.1. Similar to the treatment branch, Gompertz model had the maximal likelihood estimation and is the model of choice.

Figure 7b. Survival curves based on the new treatment arm in the hypothetical model



Using a constant cost function of $100,000 for new treatment and $50,000 for usual treatment in the hypothetical model over different time horizons, incremental cost-effectiveness ratios were successfully obtained as shown in Table 6.

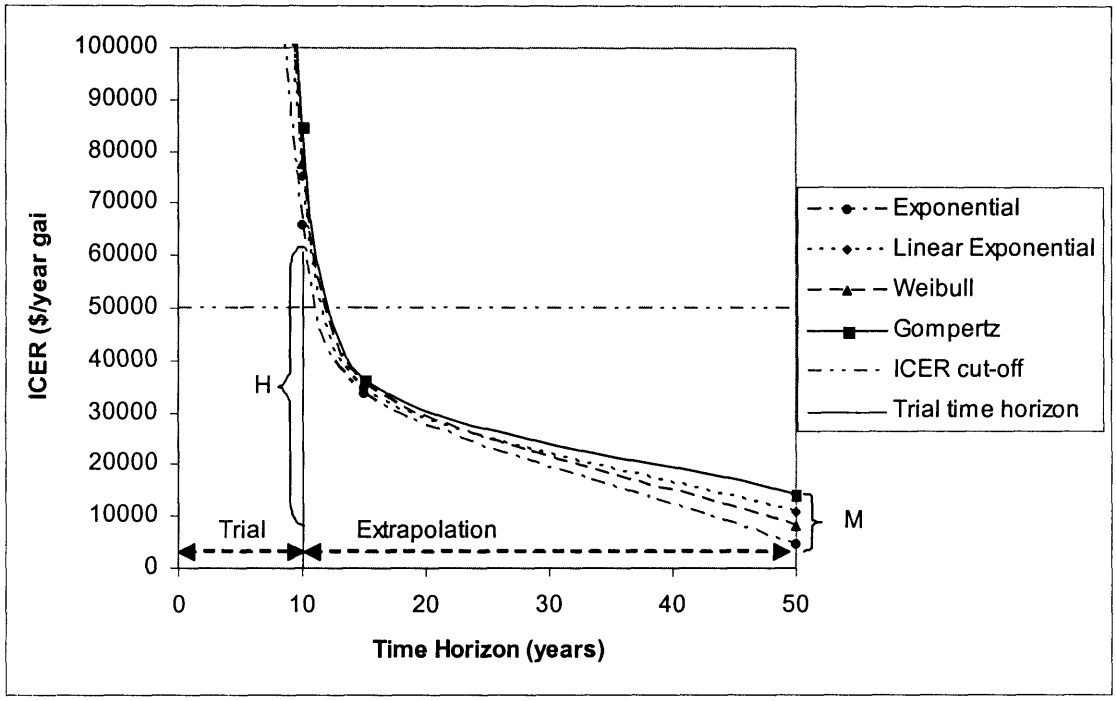
Table 6: Cost-effectiveness analysis over different time horizons

Horizon (years)	New Rx LE (years)	Usual Rx LE (years)	Delta LE (years)	Delta Cost (dollars)	Incremental CER (dollars/years gained)
5	4.75	4.63	0.12	50,000	405,236
10	8.76	8.17	0.59	50,000	84,984
15	11.84	10.47	1.37	50,000	36,401
50	15.61	12.07	3.53	50,000	14,150

Rx = treatment, LE = life expectancy, CER = cost-effectiveness ratio, delta = cumulative difference

As the time horizon in consideration encompasses increased difference in the total effectiveness of two arms, for a constant cost difference, the incremental cost-effectiveness ratios decreased as shown in Figure 8. In addition, it is interesting to note that the maximal change of incremental cost-effectiveness ratio with time horizon when using extrapolation is considerably greater than maximal change of incremental cost-effectiveness ratio based on different fitted models. In this case the time horizon plays a greater role on incremental cost-effectiveness ratio than choice of the fitted model.

Figure 8: Time horizon and incremental cost-effectiveness ratios for the hypothetical model

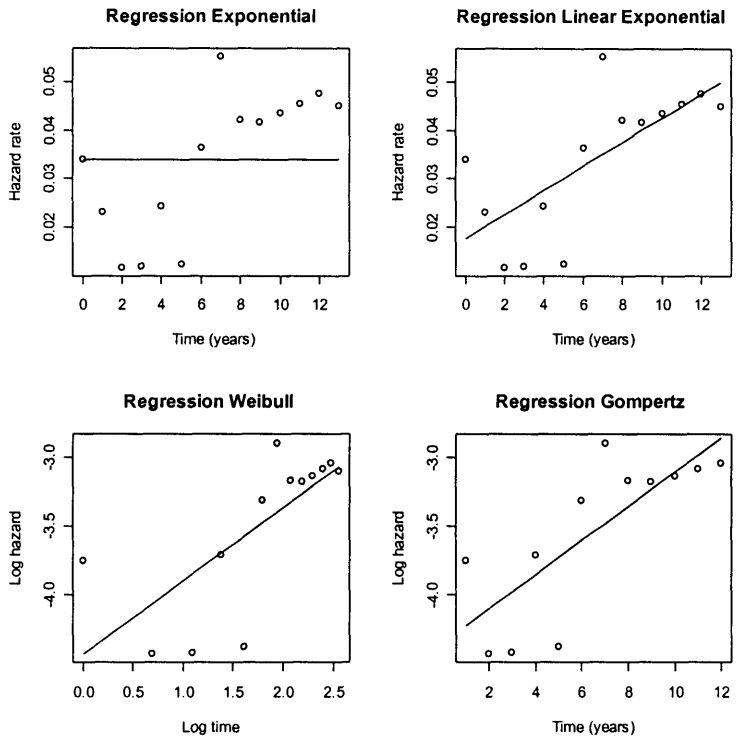


ICER = incremental cost-effectiveness ratio, H = maximal change over time horizon, M = maximal change over models

4.2 Model based on real data

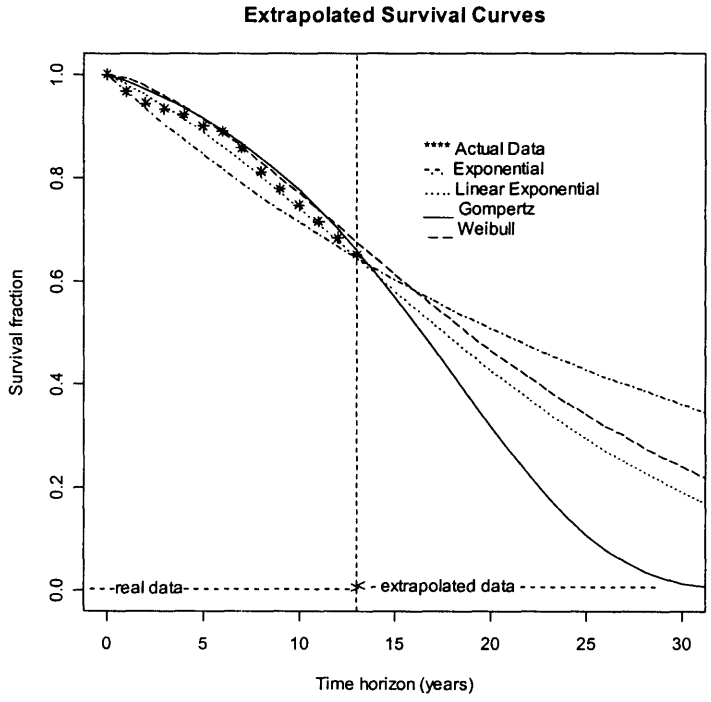
Data from survival of cohort of patients was extracted from the article. Based on the article data, survival function was created over 15 years for patients treated with t-PA and the hazard function was derived. Using least squared method, the hazard function or its logarithm was successfully regressed over the four distributions (Figure 9a) and test statistic for regression was significant. However, the r^2 for regression ranged from 0.5 to 0.6. Using lifetime time horizon, the life expectancy (in years) from survival curves (Figure 9b) based on exponential model exponential model was 29.5, linear exponential model was 19.3, Weibull model was 21.5 and Gompertz model was 16.5. Using the maximal likelihood estimation, at the 15-year data level, linear exponential model had the highest value and the model of choice.

Figure 9a: Regression of hazard function in a model based on published data



Open circles = real data points, solid line = regression line

Figure 9b: Survival curves based on hazard function regression in the model of published data



4.3 Overview model of effect of time horizon on incremental cost-effectiveness ratios

Cumulative differences in cost and effectiveness of the two strategies were assumed to: 1) decrease 2) remain constant or 3) increase over different time horizons: 1, 5 and 10 years. Incremental cost-effectiveness ratios were calculated as the ratio of cumulative difference in costs and cumulative difference in life expectancies for the two strategies for a given time horizon. Thus, I developed a matrix of incremental cost-effectiveness ratios for different time horizons based on this theoretical model as shown in a fixed-axis range format in Figure (10a) below. The distribution of incremental cost-effectiveness ratios over different time horizons in a bigger graph format can be visualized in Figure (10 b). Looking diagonally at the matrix from top to bottom, incremental cost-effectiveness ratios remained constant over different time horizons when the cumulative difference in cost and cumulative difference in effectiveness were in constant proportion and behaved identically i.e. both were increasing, decreasing or remaining constant. When one looks at the matrix horizontally, incremental cost-effectiveness ratios increased over longer time horizon when the cumulative difference in effectiveness was decreasing as long as cumulative difference in cost was also not decreasing at a rate greater than that of cumulative difference in effectiveness. Similarly, in the last row of the matrix, incremental cost-effectiveness ratios decreased over longer time horizon when the cumulative difference in effectiveness was increasing as long as cumulative difference in cost was also not increasing at the same rate or higher i.e. cumulative difference in cost was decreasing, remaining constant or increasing albeit at a lower rate than that of cumulative difference in effectiveness. However, when cumulative difference in effectiveness was constant over different time horizons, incremental cost-effectiveness ratio behaved similar to the behavior of cumulative difference in costs (as the cost component is in the numerator of the incremental cost-effectiveness ratio formulation). When the cumulative difference in cost was constant, the behavior of the incremental cost-effectiveness ratio was inverse to the behavior of the cumulative differences in effectiveness.

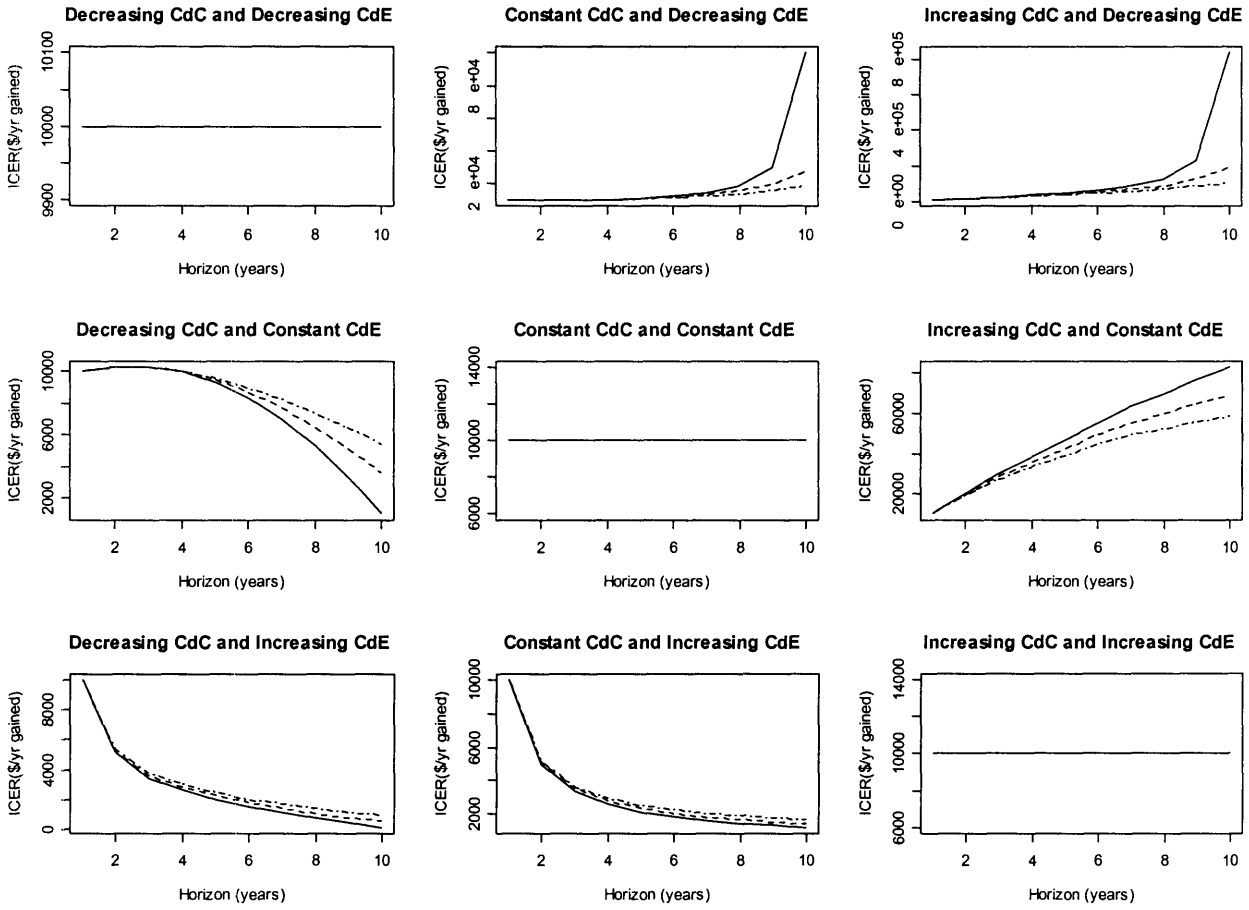
Figure 10a: Effect of time horizon on incremental cost-effectiveness ratios with and without discounting (using a fixed axis-range format shown in page 55)

ΣdCost= cumulative difference in cost, ΣdEffect= cumulative difference in effectiveness, solid line (column 1 and row 1)=strategy A and strategy B, dashed line (column1 and row 1)=annual difference in strategy A and strategy B, solid line (except column 1 and row 1)= undiscounted, dashed line (except column 1 and row 1) =discounted, ICER=incremental cost-effectiveness ratio, ($/yr gained)=additional dollars spent for each additional year of life expectancy gained

Note: Increasing incremental cost-effectiveness ratios eventually asymptote due to finite survival and cost disappearing when survival at a given time becomes zero.

COST
Annual
Cumulative Difference
EFFECTIVENESS
Annual
Cumulative Difference
Annual Cost
Cost (dollars)
Time Horizon (years)
∑dCost
∑dCost(dollars)
Annual Effect
S(t)
∑dEffect
∑dLE(years)
ICER D
ICER
ICER ($/yr gained)
ICER I
0 2 4 6 8 10

Figure 10b: Effect of time horizon on incremental cost-effectiveness ratios with and without discounting



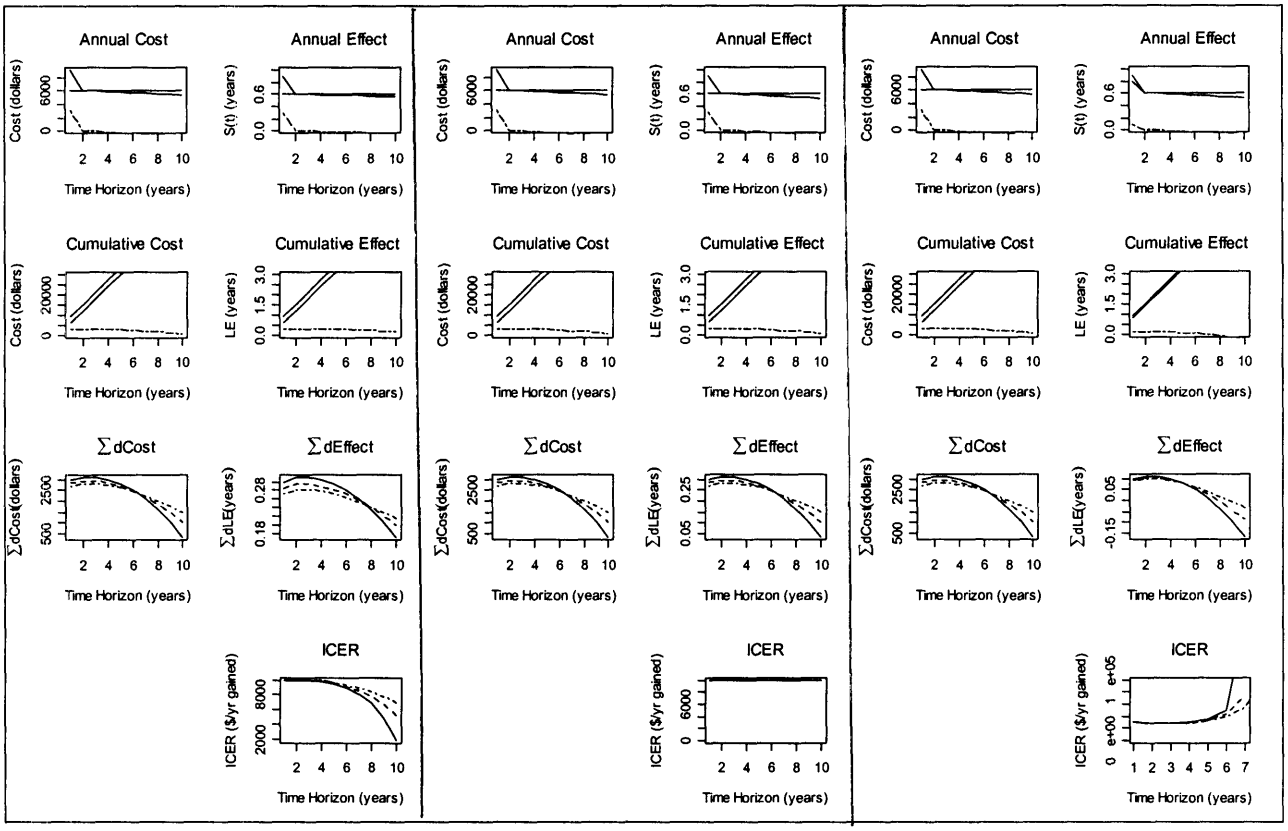
CdC = cumulative difference in cost, CdE = cumulative difference in effectiveness, solid line = undiscounted, dashed line = discounted, ICER = incremental cost-effectiveness ratio,--- discount rate = 5% and -.-.- discount rate = 10% for both cost and effectiveness, ($/yr gained) = additional dollars spent for each additional year of life expectancy gained

Further the cumulative differences in cost and effectiveness above were explored with discounting for cost and effectiveness over time. The discount rate for both cost and effectiveness was taken as 5% per year. The distributions were plotted graphically and the effects on incremental cost-effectiveness ratios were

visualized as shown by the dashed line in Figure (10 a and b). As compared with no discounting, there is no change in overall behavior of incremental cost-effectiveness ratios when considering cumulative differences in cost and effectiveness with discounting; although there is flattening of incremental cost-effectiveness ratio noticed with discounting over increasing time horizons.

To further explore changes in incremental cost-effectiveness ratio when cumulative difference in cost and effectiveness behave similarly i.e. both are decreasing or increasing, but are not constantly proportionate over time, the incremental cost-effectiveness ratios, shown in the matrix in Figure 10a as ICER D and ICER I were further explored as shown in Figure 11 a and b. incremental cost-effectiveness ratios over longer time

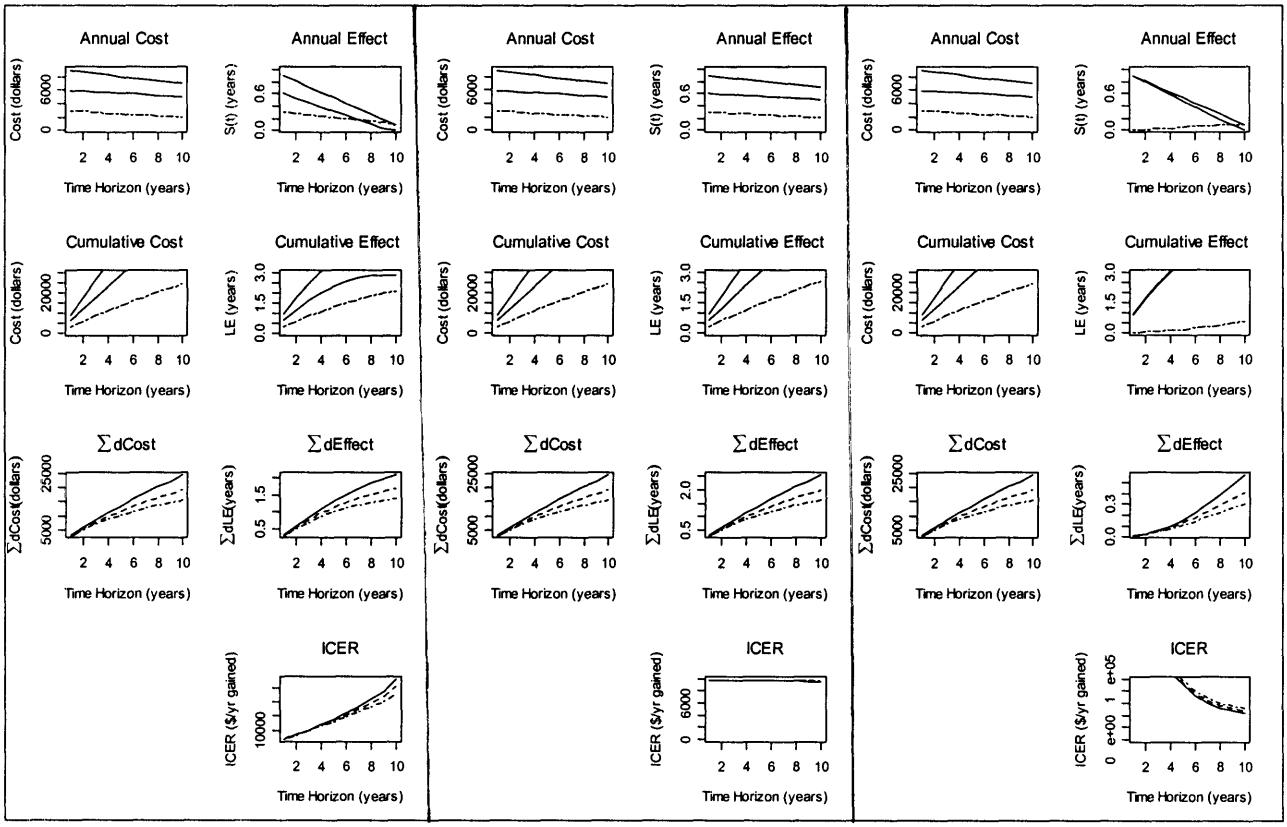
Figure 11a. ICER when cumulative differences in cost as well as effectiveness are decreasing



ΣdCost = cumulative difference in cost, ΣdEffect = cumulative difference in effectiveness, solid line (row 1) = strategy A and strategy B, dashed line (row 1) = annual difference in strategy A and strategy B, solid line (except row 1) = undiscounted, dashed line (except row 1) = discounted, ICER = incremental cost-effectiveness ratio, ($/yr gained) = additional dollars spent for each additional year of life expectancy gained, S(t) = survival at time t, LE = life expectancy

horizon decreased if the proportion of decrease in cumulative difference in effectiveness was greater than the decrease in cumulative difference of costs and vice versa as shown in Figure 11a. Similarly, incremental cost-effectiveness ratios over longer time horizon increased if the proportion of increase in cumulative difference in effectiveness was less than the increase in cumulative difference of costs and vice versa as shown in Figure 11b. However, increasing incremental cost-effectiveness ratios eventually asymptote due to finite survival and cost disappearing when survival at a given time becomes zero.

Figure 11b. ICER when cumulative differences in cost as well as effectiveness are increasing



ΣdCost = cumulative difference in cost, ΣdEffect = cumulative difference in effectiveness, solid line (row 1)=strategy A and strategy B, dashed line (row 1) = annual difference in strategy A and strategy B, solid line (except row 1) = undiscounted, dashed line (except row 1) = discounted, ICER = incremental cost-effectiveness ratio, ($/yr gained) = additional dollars spent for each additional year of life expectancy gained, S(t) = survival at time t, LE = life expectancy

5. DISCUSSION

This project explores the effect on incremental cost-effectiveness ratios when evaluating two competing strategies over different time horizons by using a statistical language and environment "R" for the methodologies of least square regression and uncensored survival analysis based on four distributions. At the intersection of medical informatics and healthcare and technology research, this thesis tries to bring together different methods and tools to explore the topic. The ultimate goal is to improve both health care decision making and health care outcomes by integrating information from a variety of sources into work processes by providing better user interfaces, extending powerful integration and navigation and developing flexible ways to represent, acquire, structure, and use knowledge of various sorts in computer systems for task-oriented applications. These methodologies must bridge specific applications so that the representations and the knowledge they encode can be widely shared and reused.

In the recent past, evidence-based medicine has gained importance. The practice of evidence-based medicine requires the integration of individual clinician's expertise with the best available external clinical evidence from systematic research and the patient's unique values and circumstances. Evidence-based health care further extends the application of the principles of evidence-based medicine to all professions associated with health care, including purchasing and management. Therefore, there is a focus towards data and trials to ascertain objectively if a therapy is effective and for what costs and how much of the effectiveness can be quantified in general and specific populations. However, most trials have finite time horizon. This is to capitalize on the trends of effectiveness and costs observed over smaller time horizons and then applying it to routine clinical medicine rather than waiting for generations to prove the cost-effectiveness over a longer time horizon. Therefore, modeling is required for evaluations of cost-effectiveness especially in the context of limited resources and lifetime horizon or full life expectancy is now used in many analyses. However, recently some evidence-based medicine proponents have become worried about lifetime analyses that necessarily extrapolate beyond the durations of all trials and have begun to report cost-effectiveness using

"hard data" available from the trial-only time-horizon. In this thesis, I hypothesized that such right-censored analyses might affect the cost-effectiveness analysis, i.e. their incremental cost-effectiveness ratios. I used modeling techniques to explore how extrapolation beyond a trials horizon of data might affect the incremental cost-effectiveness ratio.

For cost-effectiveness analysis, the evaluator focuses on the costs and effectiveness of competing strategies for analysis. In general, for a given strategy survival over time decreases while cumulative cost over time may increase or remain constant. Since the survival follows a more predictable i.e. decreasing pattern over time, I have focused on survival modeling and extrapolation. On the other hand, for a surgical treatment, often costs may be upfront and then have a smaller on going follow-up cost and for a medical treatment costs may increase, decrease or remain constant generally in a linear fashion over time. When comparing two strategies, the cumulation or sum of the difference in cost and effectiveness over a time horizon is considered in a cost-effectiveness analysis. This cumulative difference in cost and effectiveness may increase, decrease or remain constant over a time horizon.

In this thesis, first I used a hypothetical model based on US life tables to lay down the basic tools and techniques to be used. Gehan and Siddiqui have previously described the methodologies of integrating regression and survival analysis [17] for the purpose of selection of a model that can be used for extrapolation of survival. The idea is to use survival data in a life table format to derive the hazard function or it transformation and use it for regression. Based on this regression, fitted survival functions in different distributions are obtained. Then, the best-fitting model for extrapolation over different time horizons is chosen. In the hypothetical model, the hazard function was successfully regressed and survival functions were derived based on exponential, Weibull, Gompertz and linear exponential models. Then, maximum-likelihood estimates were used to choose the best fitting model from among alternative survival functions rather than making an arbitrary choice. This methodology may lead to a more accurate extrapolation of

survival data within decision-analytic models. Since survival of general population closely fits a Gompertz function, the hypothetical model fitted the Gompertz curve the best.

In the second model, I used published data, to apply the methodology developed and used previously in the hypothetical model. Again, least-square regression was performed on the hazard function or its transformation and then using four survival distributions, the best-fitting model was selected using the maximal likelihood method. The survival data was then extrapolated in different time horizons beyond the trial time. Real survival data from patients undergoing competing interventions may fit any distribution. In this model based on published data from Duke Cardiovascular Database, the distribution best fitting survival distribution was linear-exponential. However, since the publication did not explicitly display the survival curve of the competing strategy the incremental effectiveness over different time horizons could not be obtained.

To further generalize my observations, I developed an overview model. A graphical matrix was developed to visualize the interplay of cumulative differences in costs and effectiveness and to develop an intuition of how incremental cost-effectiveness ratios behaved over different time horizons and what role discounting plays in modifying this behavior. In the overview model, a matrix of incremental cost-effectiveness ratios over different time horizons, based on decreasing, constant and increasing cumulative differences in cost and effectiveness was obtained. To show the effect of difference in the scale used, the graphs are presented it in two different formats.

With the exception of similar behaving cumulative differences in cost and effectiveness in constant proportion leading to unchanged incremental cost-effectiveness ratios, incremental cost-effectiveness ratios decreased when cumulative difference in costs was decreasing and increased when cumulative difference in costs was increasing. When the cumulative difference in cost was constant, the behavior of the incremental cost-effectiveness ratio was opposite to the behavior of the cumulative differences in effectiveness. Even

with discounting, the incremental cost-effectiveness ratios showed behavior similar to that obtained from cumulative differences in cost and effectiveness without discounting. Thus, exploring the effect of time horizon on incremental cost-effectiveness ratios can give us an explicit understanding when analyzing the cost-effectiveness of two competing strategies.

From the models developed in the thesis, there are quite a few insights that can be gained. Firstly, time horizon makes a difference in incremental cost-effectiveness ratios. In literature review of cost-effectiveness analysis, it is common to come across analyses where the time horizon used is barely mentioned or is defaulted to lifetime time horizon. However, as explored in this thesis, cost-effectiveness ratios may differ considerably depending on the time horizon chosen. For example, as long as the cumulative difference in costs is decreasing (higher than the proportion of cumulative difference in effectiveness) or the cumulative difference in effectiveness is increasing (higher than the proportion of cumulative difference in cost), cost-effectiveness ratios decrease over longer time horizon. Therefore, in cost-effectiveness analysis based on competing projects over shorter time horizon and having cumulative difference in cost and effectiveness as previously described, a project may not be selected as the incremental cost-effectiveness ratio of the project may be high and above the arbitrary project selection threshold. Thus, the project will lose to other projects whose incremental cost-effectiveness ratios are under the cut-off or have a lower incremental cost-effectiveness ratio at a shorter time horizon. In such situations, a "surgical" strategy with high up-front costs and modest up-front effectiveness may lose to a "medical" strategy with lower cumulative difference in cost and effectiveness. Similarly, as long as the cumulative difference in costs is increasing or the cumulative difference in effectiveness is decreasing, cost-effectiveness ratios increase. In such studies, cost-effectiveness analysis based on shorter time horizon may be below the arbitrary project selecting cut-off and makes the cut. Thus, edging out other projects that have high initial cost-effectiveness ratios and are under the cut-off at a longer time horizon. Additionally, increase or decrease in cumulative difference of costs and effectiveness affects incremental cost-effectiveness ratio. Even when, the differences in cost and effectiveness are behaving similarly, incremental cost-effectiveness ratio may change over different time

horizons. In addition, as seen over time, when the cumulative difference in cost increases more than the cumulative difference in effectiveness, the incremental cost-effectiveness ratio increases over extended time horizons. Similarly, over time, when the cumulative difference in cost decreases less than the cumulative difference in effectiveness, the incremental cost-effectiveness ratio decreases over extended time horizons. Discounting of cost and effectiveness dampens the magnitude of relative increase or decrease of cost and effectiveness.

Secondly, modeling makes a difference in incremental cost-effectiveness ratios. Cost-effectiveness analysis based on trial-only time horizon may not capture all the effectiveness or all of the costs of the project. In case of an overall beneficial strategy that shows greater effectiveness over a long time horizon with minimal increase in cost, (and may show minimal improvement in effectiveness in a trial-only time horizon), a trial-only cost-effectiveness analysis will underestimate the effectiveness and, therefore, overstate the cost-effectiveness ratio, making the therapy less "cost-effective" as it may be over an arbitrary cut-off. However, a cost-effectiveness analysis based on trial as well as extrapolated time horizon may capture all of the difference in effectiveness and the costs of the competing strategies, making the incremental cost-effectiveness ratio lower than the cut-off and therefore making the strategy "cost-effective". Over a long time horizon, an overall "ineffective" strategy may show a considerable increase in cost but minimal improvement in effectiveness e.g. an experimental chemotherapy when compared with radiation therapy may initially improve survival at a lower cost at 5-year time horizon, but may induce leukemia and excess mortality over a 15-year time horizon. In such a case, a long-term time horizon will capture the entire cumulative difference in effectiveness and costs and, therefore, resulting in a high cost-effectiveness ratio, making the therapy less "cost-effective" over a long time horizon as it may be over an arbitrary cut-off. However, modeling involves various assumptions and can be complicated. In many real trials, the regression models may not fit the data well and, therefore, may not be useful in extrapolating costs and effectiveness in a meaningful fashion. A recent article has shown that conclusion from cost-effectiveness analyses are sensitive to choice of distribution of costs and how well a distribution fits the data is an insensitive guide to

model choice and therefore sensitivity analysis is recommended to address uncertainty about choice of distribution [24].

Another interesting insight in this thesis is the interaction between discounting and time horizon. In general, discounting can be seen to mitigate the effect of time horizon on incremental cost-effectiveness ratios. Intuitionally, with increasing discount rate, the changes in the distant future become less substantial. As seen in Figure 10a, discounting decreases the magnitude of increase of incremental cost-effectiveness ratios that were increasing over longer time horizon and the magnitude of decrease in incremental cost-effectiveness ratios that were decreasing over longer time horizons. In addition, as the discount rate increases, the decrease in the magnitude of increase in incremental cost-effectiveness ratios that were increasing over longer time horizon is greater. In other words the decrease or increase in cumulative difference in cost and effectiveness is less steep and therefore discounting has a "flattening" effect on incremental cost-effectiveness ratios. However, when the incremental cost-effectiveness ratio over extended time horizon is constant, it remains constant with discounting as both the numerator and denominator (cumulative difference in costs and effectiveness) are based on discounting (the costs and effectiveness) equally. However, since the accepted discount rate is around 5%, from the figures, it is evident that time horizon plays a greater role than discounting on incremental cost-effectiveness ratios in realistic cost-effectiveness analysis. Discounting also has a dampening effect on cumulative difference in costs and effectiveness when considered over long time horizons.

In addition, from this thesis, it reaffirms the advice to use several time horizons including lifetime while extrapolating cumulative difference in costs and effectiveness. Different stakeholders evaluate cost-effectiveness of competing strategies with different perspectives and over different time horizons. Since, time horizon affects cost-effectiveness ratios considerably; it is advisable to conduct a detailed cost-effectiveness analysis from different viewpoints. Therefore, one must evaluate cost-effectiveness ratios over different time horizons and not just over trial-only or lifetime.

5.2 Limitations of study

There are several potential limitations to this analysis. The study evaluates retrospective data and has not been tested on comparative prospective data. Not all survival distributions may reliably fit into these four distributions and each may, in fact, be a combination of distributions. Since human survival is finite, the models used in extrapolating survival should be explored with realistic constraints in mind. In addition, trial data often requires censoring. In this thesis, I have not dealt with censored data nor have extended analyses to using Cox proportional hazard model or survival estimation by Kaplan-Meier product limit method. As implemented in "R", regression of survival and cost-effectiveness analyses requires significant knowledge of the programming language

5.3 Future directions

I can use this methodology as an additional tool for evaluating the cost-effectiveness of prospective trials. It can be a means to provide sensitivity analysis while the trial is being conducted. This study can be easily applied to censored data. R has a "survival analysis package" with functions for survival analysis including Kaplan-Meier product limit and Cox proportional hazard methods. In addition, by using C or java, I can make a user-friendly interface, for direct data entry into the program, display of analysis and printing of reports. This could also be done on a web-based interface.

5.4 Conclusion

When conducting cost-effectiveness analysis of two competing strategies, choice of time horizon can have a substantial effect. Incremental cost-effectiveness ratio changes substantially with changes in duration of time horizon considered. Discounting of cost and effectiveness dampens the effect of increasing time horizon. Care must be taken in choosing the time horizon in a cost-effectiveness analysis and alternative time horizons must be evaluated in all cost-effectiveness analyses.

APPENDICES

Appendix A: Hypothetical model derived from US life tables

New Strategy

S	Age	qx	lx	dx	hrate
0	69–70	0.02266	100.00000	2.26630	0.02292
1	70–71	0.02467	97.73370	2.41138	0.02498
2	71–72	0.02674	95.32232	2.54901	0.02710
3	72–73	0.02904	92.77330	2.69432	0.02947
4	73–74	0.03166	90.07898	2.85217	0.03217
5	74–75	0.03459	87.22681	3.01700	0.03520
6	75–76	0.03768	84.20981	3.17260	0.03840
7	76–77	0.04089	81.03720	3.31329	0.04174
8	77–78	0.04444	77.72392	3.45382	0.04545
9	78–79	0.04853	74.27010	3.60433	0.04974

Usual Strategy

S	Age	qx	lx	dx	hrate
0	74–75	0.03459	100.00000	3.45880	0.03520
1	75–76	0.03768	96.54120	3.63719	0.03840
2	76–77	0.04089	92.90401	3.79847	0.04174
3	77–78	0.04444	89.10554	3.95958	0.04545
4	78–79	0.04853	85.14595	4.13213	0.04974
5	79–80	0.05331	81.01382	4.31909	0.05477
6	80–81	0.05884	76.69473	4.51279	0.06062
7	81–82	0.06509	72.18194	4.69854	0.06728
8	82–83	0.07214	67.48340	4.86825	0.07484
9	83–84	0.07985	62.61515	4.99982	0.08317

Appendix B: Model based on published data

SN	pS (A)
0	1.00000
1	0.96667
2	0.94444
3	0.93333
4	0.92222
5	0.90000
6	0.88889
7	0.85714
8	0.81111
9	0.77778
10	0.74603
11	0.71429
12	0.68254
13	0.65079
14	0.62222

Appendix C: Programming user-defined functions in R

```
##Weibull -user defined function/class -function weib

weib<- function(y1, y2){

 # rudimentary sanity checks...
          if(length(y1) != length(y2))
          stop("different lengths of input vectors")
          if(length(y1) == 0)
          stop("empty input")

#transformation of hazard rates
          x1  <- log(y1); h1  <- log(y2)

#least squared regression
          myreg<-lm(h1~x1)
          myreg

}




# Gompertz-user defined function/class -function gomp

gomp<- function(y1, y2) {

          n1  <- length(y1); n2  <- length(y2)

# rudimentary sanity checks...
          if(n1 != n2)
          stop("different lengths of input vectors")
          if(n1 == 0)
          stop("empty input")

# transformation of hazard rate
          x1  <- y1; h1  <- log(y2)

#least squared regression
          myreg<-lm(h1~x1)
          myreg
}
```

Appendix D: R program for regression and survival extrapolation of the model based on published data

```
#Script for Thrombolytics shortest
#Shows all steps explicitly

# Read data table
dr<-read.table(file="thr1.csv",sep=",",header=T)
 n<-length(dr[,2])

lx<-dr[1:n,2]*100
dx<-(dr[1:n,2]-dr[2:(n+1),2])*100
hrate<- dx/(lx-(dx*0.5))
# prob of dying
qx<-dx/lx
pr1<-cbind(dr[1:n,1],dr[1:n,2],  qx, lx,dx,hrate)
pr<-pr1[1:(n-1),]
x1<-pr[,1]
h1<-pr[,6]
c(mean(h1),   sd(h1),   var(h1))

#Regression using mean
y1<-rep(mean(h1),c(length(h1)))

 # Graph for regression
par(mfrow=c(4,2))
plot(x1,h1,main ="Regression Exponential",xlab="years",ylab="hrate")
lines(x1,y1)
#lines(x1,h1)
Psur1<-(exp(-y1*x1))
Asur<-(pr[,4])/100
k1<-seq(0 ,350)
k2<-(exp(-k1*mean(h1)))
k3<-seq(1 ,351)
k4<-(exp(-k3*mean(h1)))
k5<-(k2-((k2-k4)/2))
LE1<-sum(k5[k5>0.001])
#5 year      10 years          15 years          lifetime
H1<-c(sum(k5[1:5]), sum(k5[1:10]), sum(k5[1:15]), sum(k5[k5>0.001]))

#Graph for survival
plot(k1[1:50],k2[1:50],main =" Survival Exponential",xlab="years",ylab="Survival fraction")
lines(x1,Psur1)
lines(x1,Asur)
LikeA<-c(NA,((Asur[2:(n-1)]/Asur[1:(n-2)])^lx[2:(n-1)])*((1-(Asur[2:(n-1)]/Asur[1:(n-2)]))^dx[2:(n-1)]))
LikeP1<-c(NA,((Psur1[2:(n-1)]/Psur1[1:(n-2)])^lx[2:(n-1)])*((1-(Psur1[2:(n-1)]/Psur1[1:(n-2)]))^dx[2:(n-1)]))

#2nd Model - Regression for linear exp model
n<-length(x1)
N<-n
SPx1h1 <- sum(x1*h1)-sum(x1)*sum(h1)/n
SSx1 <- sum(x1^2)- (sum(x1)^2)/n
```

```
SSh1 <- sum(h1^2)- (sum(h1)^2)/n
h1bar <-mean(h1)
x1bar <-mean(x1)
b21<-SPx1h1 /SSx1
b20<- mean(h1)-b21*mean(x1)
b21
b20
SSreg <-b21*SPx1h1
SSres <- SSh1 -SSreg
Sh1.x1<-(SSres/(n-2))^0.5
r2 <-SSreg/SSh1
Sh1.x1
r2

#regression
lm(h1~x1)
myreg<-lm(h1~x1)
summary(myreg)

#Testing significance
MSreg<- SSreg/1
MSres <-SSres/(n-2)
F.calc <-MSreg/MSres
pf(F.calc,1,n-2)
qf(0.95,1,n-2)
pf(F.calc,1,n-2)>0.95
F.calc>qf(0.95,1,n-2)

#Plotting graph
plot(x1,h1,main ="Regression Linear Exponential",xlab="years",ylab="hrate")
lines(x1,b20+b21*x1)

#Confidence Interval for predicted values
xk <- seq(min(x1),max(x1),1)
y2hat <- b20 + b21*xk
Syxk <-((1/n)+(((xk-x1bar)^2)/SSx1)*MSres)^0.5
t.val<-qt(0.975,n-2)
Psur2<-(exp(-(x1*b20 + 0.5*(b21*(x1^2)))))

k1<-seq(0 ,350)
k2<-(exp(-(k1*b20 + 0.5*(b21*(k1^2)))))
k3<-seq(1 ,351)
k4<-(exp(-(k3*b20 + 0.5*(b21*(k3^2)))))
k5<-(k2-((k2-k4)/2))
LE2<-sum(k5[k5>0.001])
#5 year      10 years          15 years          lifetime
H2<-c(sum(k5[1:5]), sum(k5[1:10]), sum(k5[1:15]), sum(k5[k5>0.001]))

#Graph for survival
plot(k1[1:50],k2[1:50], main ="Survival Linear Exponential ",xlab="years",ylab="Survival fraction")
lines(x1,Psur2)
lines(x1,Asur)
LikeP2<-c(NA,((Psur2[2:(n-1)]/Psur2[1:(n-2)])^lx[2:(n-1)])*((1-(Psur2[2:(n-1)]/Psur2[1:(n-2)]))^dx[2:(n-1)]))

#Model 3 Weibull Model
x1<-log(pr[2:N,1])
```

```
h1<-log(pr[2:N,6])

#regression for Weibull model
n<-length(x1)
N<-n
SPx1h1 <- sum(x1*h1)-sum(x1)*sum(h1)/n
SSx1 <- sum(x1^2)- (sum(x1)^2)/n
SSh1 <- sum(h1^2)- (sum(h1)^2)/n
h1bar <-mean(h1)
x1bar <-mean(x1)
b31<-SPx1h1 /SSx1
b30<- mean(h1)-b31*mean(x1)
b31
b30
SSreg <-b31*SPx1h1
SSres <- SSh1 -SSreg
Sh1.x1<-(SSres/(n-2))^0.5
r2 <-SSreg/SSh1
Sh1.x1
r2

#regression
lm(h1~x1)
myreg<-lm(h1~x1)
summary(myreg)

#Testing significance
MSreg<- SSreg/1
MSres <-SSres/(n-2)
F.calc <-MSreg/MSres
pf(F.calc,1,n-2)
qf(0.95,1,n-2)
pf(F.calc,1,n-2)>0.95
F.calc>qf(0.95,1,n-2)

#Plotting graph
plot(x1,h1,main ="Regression Weibull",xlab="log t",ylab="log h")
lines(x1,b30+b31*x1)


gamma<-1+b31
lambda<-exp((b30-log(gamma))/gamma)
Psur3<-exp(-(lambda*pr[,1])^gamma)

# Calculating life expectamcy
k1<-seq(0 ,350)
k2<- exp(-(lambda*k1)^gamma)
k3<-seq(1 ,351)
k4<-exp(-(lambda*k3)^gamma)
k5<-(k2-((k2-k4)/2))
LE3<-sum(k5[k5>0.001])
#5 year      10 years          15 years          lifetime
H3<-c(sum(k5[1:5]), sum(k5[1:10]), sum(k5[1:15]), sum(k5[k5>0.001]))


#Graph for survival
```

```
plot(k1[1:50],k2[1:50],main ="Survival Weibull ",xlab="years",ylab="Survival fraction")
lines(pr[,1],Psur3)
lines(pr[,1],Asur)
#LikeP3<-c(NA,((Psur3[2:(n-1)]/Psur3[1:(n-2)])^lx[2:(n-1)])*((1-(Psur3[2:(n-1)]/Psur3[1:(n-2)]))^dx[2:(n-#1)]))
LikeP3<-c(NA,((Psur3[2:(n)]/Psur3[1:(n-1)])^lx[2:(n)])*((1-(Psur3[2:(n)]/Psur3[1:(n-1)]))^dx[2:(n)]))

#Model 4 Gompertz Model

x1<-pr[2:n,1]
h1<-log(pr[2:n,6])
#regression for g model
n<-length(x1)
SPx1h1 <- sum(x1*h1)-sum(x1)*sum(h1)/n
SSx1 <- sum(x1^2)- (sum(x1)^2)/n
SSh1 <- sum(h1^2)- (sum(h1)^2)/n
h1bar <-mean(h1)
x1bar <-mean(x1)
b41<-SPx1h1 /SSx1
b40<- mean(h1)-b41*mean(x1)
b41
b40
SSreg <-b41*SPx1h1
SSres <- SSh1 -SSreg
Sh1.x1<-(SSres/(n-2))^0.5
r2 <-SSreg/SSh1
Sh1.x1
r2

#regression
lm(h1~x1)
myreg<-lm(h1~x1)
summary(myreg)

#Testing significance
MSreg<- SSreg/1
MSres <-SSres/(n-2)
F.calc <-MSreg/MSres
pf(F.calc,1,n-2)
qf(0.95,1,n-2)
pf(F.calc,1,n-2)>0.95
F.calc>qf(0.95,1,n-2)

#Plotting graph
plot(x1,h1,main ="Regression Gompertz ",xlab="years",ylab="log h")
lines(x1,b40+b41*x1)

#Confidence Interval for predicted values
xk <- seq(min(x1),max(x1),((max(x1)-min(x1))/n))
y4hat <- b40 + b41*xk
Syxk <-((1/n)+(((xk-x1bar)^2)/SSx1)*MSres)^0.5
t.val<-qt(0.975,n-2)

gamma<-b41
lambda<-b40
Psur4<- exp((-exp(b40)/b41)*(exp(b41*pr[,1])-1))
```

```
# Calculating life expectamcy
k1<-seq(0 ,350)
k2<- exp((-exp(b40)/b41)*(exp(b41*k1)-1))
k3<-seq(1 ,351)
k4<- exp((-exp(b40)/b41)*(exp(b41*k1)-1))
k5<-(k2-((k2-k4)/2))
LE4<-sum(k5[k5>0.001])
#5 year      10 years          15 years          lifetime
H4<-c(sum(k5[1:5]), sum(k5[1:10]), sum(k5[1:15]), sum(k5[k5>0.001]))

#Graph for survival
plot(k1[1:50],k2[1:50], main ="Survival Gompertz ",xlab="years",ylab="Survival fraction")
lines(pr[,1],Psur4)
lines(pr[,1],Asur)

LikeP4<-c(NA,((Psur4[2:(n+1)]/Psur4[1:(n)])^lx[2:(n+1)])*((1-(Psur4[2:(n+1)]/Psur4[1:(n)]))^dx[2:(n+1)]))
A<-c(LE1, LE2,LE3,LE4)
A
G<-cbind(sum(log(LikeP1[2:N]))-sum(log(LikeA[2:N])),sum(log(LikeP2[2:N]))-
sum(log(LikeA[2:N])),sum(log(LikeP3[2:N]))-sum(log(LikeA[2:N])),sum(log(LikeP4[2:N]))-sum(log(LikeA[2:N])))
G
exp(G)
```

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