Medical Decision Making: Modelling Multiple Treatments

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Signed Statement

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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Abstract

Every day, practicing physicians make life changing decisions for patients, based on data gathered from clinical trials. Treatment benefit data is primarily based on results from trials conducted on patients in a specific controlled setting; they usually have limited health issues other than the disease for which treatment is intended. Realistically, patients for whom treatment is intended, particularly older patients, will have multiple conditions, called comorbidities, which could affect the actual benefit of treatment. In this thesis, we create a model that can predict the lifetime benefit of treatment for a patient with multiple comorbidities.

Currently, there are very few articles in the literature that focus on calculating treatment benefit in the presence of comorbidities, and no known satisfying solutions to this problem. One approach involves using Markov models to track the progression of a singular disease over time, and using a 'comorbidity index' to account for the effect of multiple conditions on the calculated benefit. An advantage of this method is the simplicity in which it captures comorbidity in the calculation. However, it could be difficult to quantify the level of comorbidity in a patient using this scale, still leading to an inaccurate predicted benefit. Furthermore, using this method, the specific comorbidities are not modelled; instead, the index is used only to increase the rate of death for these patients.

Another approach in the literature considers each patient individually, taking note of all of their comorbidities and the 'snapshot' benefit values assigned to each one. Under the assumption of independence between conditions, these values are analysed to find a more accurate benefit value for treating one of more of the diseases

at once. However, this only allows us to calculate the benefit at a single point in time, rather than a lifetime benefit that Markov model approaches allow. Since benefits can change over time, a lifetime measure allows us to find a better approximation of the true benefit of treatment. Both of these methods demonstrate that when multiple comorbidities are taken into account, the reported benefit of treatment decreases.

We consider a combination of both of these approaches to calculate a more accurate benefit of individual treatment in the presence of multiple comorbidities, and also the benefit of multiple treatments simultaneously. In this method, we use Markov chains to model the progression of individual episodic diseases over time. We then combine the individual models to create a Markov model that can track multiple comorbidities simultaneously.

For two specific treatments (carotid endarterectomy for carotid artery stenosis, and coronary artery bypass graft surgery for coronary artery disease), we use this model to demonstrate that the benefit of treatment measured in the presence of another disease is less than the benefit measured in isolation.

We also prove theoretically that for sensible treatments, the sum of the individual benefits measured in isolation is always greater than the benefits measured in the presence of comorbidities. We show that the same is true for the risk of treatment, where the risk is defined as the iatrogenic loss of treatment and is measured in the same units as benefit. This result is due to the effect of comorbidity on the benefit of multiple treatments. We are also able to show that, even accounting for the effect of comorbidity on the individual treatments, the sum of the individual benefits in the presence of other treatments (the withdrawal benefits) is greater than the combined benefit of treating all diseases at once. This implies that there is also an interaction between the treatments, as well as the comorbidities.

However, there are still some drawbacks with this model. For simplicity, we assume that both treatments occur simultaneously at the beginning of the chain. For surgical treatments though, this is unrealistic, since surgery can take a toll

on the patient. Thus, there is room for further refinement of the current model, and opportunity to allow for various other types of diseases to be modelled as well. Further research into the trade-off between model complexity and computation time could also be conducted in the future.

Chapter 1

Introduction

1.1 Motivation

Practicing physicians make decisions on treatments based on clinical trial data. These data (on risks and benefits) are based on trials primarily conducted on healthy volunteers, or volunteers with few other health issues than the one for which the trial is concerned (see Section 2.2). In reality, patients often have existing conditions, called comorbidities, that affect the risks and benefits associated with receiving these treatments. Due to these comorbidities, the benefits (and risks) of any treatment may become overestimated, such that the cost vs. benefit could mean that the treatment may not be "worth" receiving [19].

Treatments also need to be approved based on a cost-effectiveness analysis, meaning that the benefit must justify the cost of the treatment [10]. The (monetary) cost of multiple independent treatments is usually just the sum of the individual costs; however, multiple comorbidities, and thus treatment benefits, do not interact in the same way. For example, assume that a patient has two diseases, and receives treatment for both. Assume one treatment is expected to extend the patient's life by four years, and the other by five years from the same point, so that the sum of the individual benefits is that the treatments extend the patient's life by nine years.

However, after four years, the patient will die from the first disease, and so the total benefit is clearly not the sum of the individual benefits. Thus, when comparing multiple comorbidities, care must be taken to analyse how the conditions, and hence the benefits, interact with each other. In this thesis, however, we do not consider the cost-effectiveness analysis of treatment, and focus only on how the benefit of multiple treatments can be better estimated by taking into account the interactions of the comorbidities.

1.2 Background

Benefits are commonly measured in quality adjusted life years (QALYs), which are calculated using utilities. Quality adjusted life years are the number of years that a patient gains, adjusted to account for the quality (utility) of that patient's life. The utilities used to calculate the QALYs are an indication of the value of a health state a patient may be in. These utility values range from 0 to 1, where a measurement of 0 indicates death, and a measurement of 1 indicates perfect health. Calculating these values can prove to be difficult as there are many factors that need to be considered when measuring a patient's quality of life. There are the obvious physical and medical factors, as well as psychological factors, the ability to continue with work and home life, and the effect on the patient's social wellbeing [3].

There is limited literature regarding the calculation of benefit values accounting for comorbidities, and there are no known satisfying solutions to this problem. There are two main approaches in which this has been tackled, both with certain trade-offs. Several articles have used Markov models to simulate the progression of the disease (with and without treatment), and included a 'comorbidity index' [7, 11]. This index looks at levels of comorbidity and can be used on general groups of patients, with patients being assigned a level based on the severity of their comorbidities. In this approach, the specific comorbidities are not modelled; instead, the index is used only to increase the rate of death for these patients. Another approach is

to consider each patient individually, taking note of all of their comorbidities and the utilities assigned to each one. Under the assumption of independence between conditions, these values can then be analysed to show a truer benefit value for treating one or more of the diseases [4, 17]. This method, however, only focuses on the benefit at a single point in time, rather than a lifetime benefit that Markov model approaches allow. Since benefits can vary over time, a lifetime measure will give a better approximation of the true benefit of treatment. In this thesis, we combine the two methods described above to be able to calculate the benefit of treating multiple specific conditions over time. Using this method, we achieve a more accurate measure of the benefit of treatments in the presence of multiple comorbidities. Both of the methods mentioned demonstrate that when comorbid states are taken into account, the reported benefit of treatment decreases.

The paper by Fitzgerald and Bean [4] also considers treating all diseases at once, rather than just calculating the benefit of a single treatment in the presence of comorbidities. Again, the benefit is found to be overestimated when comorbidities are not taken into account; the combined benefits of treating all diseases simultaneously is always less than the sum of the individual treatment benefits. These results are not restricted to conventional comorbidities; in their analysis, age is considered to be a comorbidity as well, in the sense that as a patient ages, the benefit of receiving treatment is likely to decrease. This makes logical sense, as receiving a treatment at a younger age should result in more years gained, or more quality years gained, than at an older age.

A parallel consideration to that of measuring benefit, is to consider how the risk of receiving treatment would change depending on the number, or severity, of comorbidities in a patient. In one article [11], risk is considered briefly in the sensitivity analysis. Here, risk is not measured in the same way as benefit, but is considered only as the probability of a bad outcome during surgery. As the risk of treatment increased, the benefit of the treatment, in QALYs, decreased. However, this analysis included only the effect of increased risk on treatment benefit, and not

the effect of comorbidity on risk. In our analysis, we want to be able to quantify risk in the same way as benefit, and also consider the effects of multiple conditions on this risk quantity.

We show that including multiple comorbidities into the lifetime benefit and risk calculations reduces the estimated benefit of treatment. Furthermore, we show that the lifetime benefit of treating all comorbidities at once is less than the sum of the individual lifetime benefits of treating each disease in isolation, due to the interaction between these comorbidities. The lifetime benefits and risks are also affected by the interaction between different treatments. We show that, due to the interaction of treatment effects, the combined benefit of treating all diseases at once is also less than the sum of the individual benefits, measured in the presence of the other treatments. We also show that these same relationships hold for the risk of treatment; that is, risk behaves in the same way as benefit.

1.3 Summary

When first considering multiple comorbidities, we look at work by Fitzgerald and Bean [4]. In this paper, they have defined a model that accurately calculates the benefit of treatment in the presence of multiple conditions, at a specific point in time: the snapshot benefit. To do this, they first define the benefit of a treatment as the reduction in probability of a negative outcome for the target disease. From here they prove theoretically, that the combined benefit of treating all of the diseases a patient is suffering from is less than the sum of the individual treatment benefits, when the diseases are considered in isolation. We extend upon these results to also include a measure for risk, which we define as the 'iatrogenic loss', or the probability of a negative outcome due to the treatment, rather than the disease. This also naturally extends to the idea of a 'perfect' treatment, which would result in an 'ideal benefit'; that is, the benefit of treating a disease, given the treatment has no negative effects.

Fitzgerald and Bean also briefly consider the benefit of treatment using an ex-

pected quality of outcome measure, rather than just the reduction in probability of a negative outcome. Since in this thesis we use also use an expected quality measure for the lifetime benefit of treatment, we define the same benefit and loss measures as we did in the probability environment, in this expected quality of outcome environment, so that we can later make comparisons. We also make some assumptions about the expected quality of outcome to ensure that we are only considering sensible treatments. We can then prove that the same results from the probability environment hold in the expected quality of outcome environment. That is, in expected quality of outcome, the benefits and risks are overestimated when calculated without considering comorbidities. This is the focus of Chapter 3.

However, since benefits are not always constant over time (such as in the case of surgery), we consider a model that can track the progression of a disease, and hence the benefit of treatment, over a patient's lifetime. In the existing literature, this is usually achieved by using Markov chains to model both the treatment and control options, and comparing the outcomes. In this thesis, we utilise an already established Markov model and attempt to recreate the published results of benefit in quality adjusted life years (QALYS), before assessing its validity [11]. In this paper, the benefit of carotid endarterectomy (CEA) surgery to treat carotid artery stenosis, for both symptomatic and asymptomatic patients, is analysed. Carotid artery stenosis is a disease that can cause strokes in its sufferers. Hence, it is what we call an episodic disease, where a stroke is the episode or 'event' caused by the disease. We then improve upon this model of CEA surgery by correcting some simple modelling flaws.

This model is generalised so that it can be used to track the progression of other episodic diseases. Using this general model, we track the progression of a different disease and the accompanying treatment. We choose to find the lifetime benefit of coronary artery bypass graft surgery (CABG), which is the treatment for coronary artery disease. To do this, we first source the necessary data to use as the parameters in our model, and then use the same method of calculating the expected QALYs

for both the treatment and control chains, and hence the benefit, as in the previous model. This is presented in Chapter 4.

Since the main aim of this thesis is to be able to calculate the realistic lifetime benefit of treatment in the presence of multiple comorbidities, in Chapter 5 we use our general model for an individual disease and modify it to accommodate for multiple diseases. This allows us to track the progression of all diseases and their treatments simultaneously, and hence calculate a combined benefit, and also the individual benefits in the presence of the other diseases. Using our models of CEA and CABG, we demonstrate that for this particular case, the lifetime benefits have the same relationship as the snapshot benefits considered in Chapter 3.

By showing that the lifetime benefits in expected QALYs can be written as the sum of the relevant snapshot benefits in expected QALYs, we then also prove, under certain conditions, that the same theoretical results hold for the lifetime benefits as they did for the snapshot benefits in Chapter 3. We also theorise, but are not able to prove, that these results will hold for the lifetime measures of all sensible treatments. That is, when considering multiple comorbidities, the lifetime benefit of treatment is overstated when not calculated with the other comorbidities in mind, and that the same holds true for the risk, or iatrogenic loss of treatment. More specifically, the effect of comorbidity on benefit means that the combined benefit of treating all diseases simultaneously, is less than the sum of the individual benefits of treating each disease in isolation. The effect of interacting treatment benefits on the total benefit, means that the combined benefit is also less than the sum of the withdrawal benefits of treating each disease in the presence of other treatments.

Chapter 2

Background

2.1 Discrete-Time Markov Chains

In this section, we consider a collection of random variables, X, called a stochastic process, describing the progression of some system over time. This process, $X = \{X_t | t \in \mathbb{N}\}$, where t represents discrete time steps, takes values in the set S, called the state space, such that if $X_t = i$, the process is in state i at time t [14]. In this thesis, we consider only finite state spaces, S.

In particular, we consider discrete-time Markov chains (DTMCs), where a stochastic process as described above is considered a Markov chain if it satisfies the Markov property. That is, if the probability of being in any state at the next time step depends only on the current state, and not on any previous states. More specifically:

Definition 1. The process $X = \{X_t | t \in \mathbb{N}\}$ is a **discrete-time Markov chain (DTMC)** on a state space S if:

- $X_t \in S, \forall t \in \mathbb{N}$,
- $P(X_{t+1} = i_{t+1} | X_t = i_t, \ldots, X_0 = i_0) = P(X_{t+1} = i_{t+1} | X_t = i_t), \forall t \in \mathbb{N}$, and $\forall i_0, \ldots, i_t, i_{t+1} \in S$ (Markov Property).

In most of the available literature, we see results focussing around the time-

homogeneous DTMC. In a time-homogeneous DTMC, the probability of transitioning from one state to another in a single time step does not change with time.

Definition 2. The DTMC X on a state space S is **time homogeneous** if for all $t, k \in \mathbb{N}$ and $i, j \in S$,

$$P(X_{t+k} = j | X_k = i) = P(X_t = j | X_0 = i).$$

These one-step probabilities of transitioning between states can be represented in a matrix, commonly called the transition matrix.

Definition 3. The **transition probability matrix** $\mathbb{P}$ of the Markov chain X, is the matrix whose $(i, j)^{th}$ entry corresponds to the probability that the process is in state j at the next time step, given that it was in state i, for $i, j \in S$. That is,

$$\mathbb{P}_{i,j} = P(X_{t+1} = j | X_t = i), \quad \forall i, j \in S.$$

Then $\mathbb{P}$ is a stochastic matrix since, by definition, it satisfies the properties

- $\mathbb{P}_{i,j} \geq 0$,
- $\sum_{i \in S} \mathbb{P}_{i,j} = 1$,

for all $i, j \in S$ [14].

This matrix allows us to quickly find the probability of residing in any state numerous time steps after beginning in a particular state. Let the $(i, j)^{th}$ entry of the t-step transition matrix, $\mathbb{P}^{(t)}_{i,j}$, be the probability that the process starting in state i will be in state j after t discrete time steps. Mathematically,

$$\mathbb{P}^{(t)}_{i,j} = P(X_t = j | X_0 = i),$$

for $t \in \mathbb{N}$ and $i, j \in S$. To calculate these t-step transition probabilities, we use the Chapman-Kolmogorov equations.

Theorem 1. *Let X be a time-homogeneous DTMC on the state space S. Then,*

$$\mathbb{P}_{i,j}^{(t+k)} = P(X_{t+k} = j | X_0 = i) = \sum_{n \in S} P(X_{t+k} = j | X_t = n) P(X_t = n | X_0 = i),$$

or,

$$\mathbb{P}^{(t+k)} = \mathbb{P}^{(t)} \times \mathbb{P}^{(k)}.$$

Proof. Proof of this theorem can be found in [14]. □

This theorem can be extended to show that for a time-homogeneous DTMC, the t-step transition matrix is simply the one-step transition matrix multiplied by itself t times.

Corollary 1. *Let X be a time-homogeneous DTMC on the state space S. Then, for all $t \in \mathbb{N}$,*

$$\mathbb{P}^{(t)} = \mathbb{P}^t.$$

Proof. This is a consequence of the Chapman-Kolmogorov equations (inductive proof) [14]. □

2.1.1 Time-Inhomogeneous DTMCs

Despite more commonly seeing the simpler time-homogeneous DTMC as described above, not all real life situations have transition probabilities that remain constant over time. In this thesis, we model disease progression over a patient's lifetime, and the transition probabilities will depend on the time since a patient's treatment or diagnosis. Therefore, in this thesis we consider Markov chains that do not satisfy the time-homogeneous property. That is, we consider time-*in*homogeneous DTMCs. In this case, the transition matrix $\mathbb{P}$ will depend on the discrete time step $t \in \mathbb{N}$, so that

$$\mathbb{P}(t)_{i,j} = P(X_{t+1} = j | X_t = i) \neq P(X_1 = j | X_0 = i), \quad \forall i, j \in S.$$

Using the equivalent of the Chapman-Kolmogorov equations for time-inhomogeneous DTMCs, we can still write the t-step transition matrix as a product of individual one-step transition matrices.

Theorem 2. *For a time-inhomogeneous DTMC, X, on the state space S:*

$$P(X_t = j | X_0 = i) = \mathbb{P}_{i,j}^{(t)} = (\mathbb{P}(0) \times \mathbb{P}(1) \times \ldots \times \mathbb{P}(t-1))_{i,j},$$

for $t \in \mathbb{N}$.

Proof. The proof of this follows the same reasoning as the proof of the time-homogeneous case, making the necessary changes to account for time-inhomogeneity. □

Both time-homogeneous and time-inhomogeneous DTMCs are useful for modelling the outcomes of real life situations, and can be extended further to allow us to include decision making throughout the process. This is useful when the process can be altered depending on decisions made at the discrete steps of the DTMC, and we wish to find the set of decisions to find the optimal outcome. These types of processes are called Markov decision processes.

2.1.2 Discrete-Time Markov Decision Processes

In this thesis, we utilise a simplification of a finite horizon, discrete-time Markov decision process, to calculate the expected reward, or outcome, of a process. Markov decision processes (MDPs) are essentially an extension of DTMCs, such that at each discrete time step, t, a decision is made to take a certain action, a_t. At each time point, called a decision epoch, we can also calculate a reward value, $R_t(a_t, S_t)$, determined by the action taken, and the current state of the process, S_t. Typically, there is some sort of discounting γ on future reward values [2]. More formally:

Definition 4. [2] A Markov decision process (MDP) is a quintuple $(S, A, \mathbb{P}_\bullet, R, \gamma)$, such that:

- S is the finite state space (or set of states);
- A is the finite set of actions;
- $(\mathbb{P}_a^{(t)})_{i,j} = P(X_{t+1} = j | X_t = i, a_t = a)$ is the probability of the process being in state j at time $t+1$, given action a_t was chosen in state i at time t;

- $R_t(X_t = i, a_t = a)$ is the expected reward of taking action a from state i at time t;
- $\gamma \in [0, 1]$ is the discounting factor, which places more importance on present rewards than future rewards.

MDPs are used to find an optimal policy. A policy is a function, $\pi : S \to A$, which determines the action to be taken in each state, at each time. The optimal policy, π^*, is the policy that maximises the total expected reward. To determine this optimal policy, over a finite horizon T, we want to solve:

$$V^* = \max_\pi \mathbb{E}\left[\sum_{t=0}^{T-1} \gamma^t R_t(X_t, a_t) + \gamma^T R_T(X_T)\right],$$

where π^* is the policy that produces the optimal action at each time step, and V^* is the maximum expected discounted reward, up to our finite horizon T [2, 12].

Finite horizon problems can be solved by utilising value iteration, also known as the backward induction algorithm. Since we assume we know the expected reward of every state $i \in S$ at the finite horizon, T, we can then calculate the total expected reward over the whole lifetime using a recursive algorithm.

Let the expected value of taking action a from state i at time t be

$$V_t(i, a) = R_t(i, a) + \gamma \sum_{j \in S} P(X_{t+1} = j | X_t = i, a_t = a) V_{t+1}(j), \qquad \text{for } 0 \leq t < T,$$

and let

$$V_T^*(i) = R_T(i)$$

be the known expected reward of state i at the final discrete time T.

1. Begin with $V_T^*(i) = R_T(i)$,
2. then for $t = T - 1, \ldots, 0$, and for each state $i \in S$ calculate the optimal value:

$$V_t^*(i) = \max_a V_t(i, a)$$

where $\pi^*(i) = \text{argmax}_a V_t(i, a)$.

3. Then $V^* = V_0^*(s_0)$, where s_0 is the initial state [12].

In our simplification of this process, only one decision is made at the beginning of the process. This is equivalent to comparing multiple chains, each using its own action throughout. Therefore, the total expected reward, or value, must be calculated for each chain, before an optimal action can be determined. Let $\mathbb{P}_a$ be the transition probability matrix corresponding to choosing action a at the beginning (and hence at every decision epoch) of the process. The modified algorithm we utilise to calculate the total expected rewards for a discrete-time MDP over a finite horizon, T, is:

1. For action a, begin with $V_T(i) = R_T(i)$.

2. For $t = T-1, \ldots, 0$, and for each state $i \in S$ calculate the expected reward:

$$V_t(i) = R(i) + \gamma \sum_{j \in S} P_a(X_{t+1} = j | X_t = i) V_{t+1}(j).$$

3. Then the total expected value is $V = V_0(s_0)$, where s_0 is the initial state.

Utilising the expected reward calculations in this way enables us to be able to measure the difference in outcome values of different actions, rather than only choosing the optimal action to take. This is useful in our analysis of treatment benefit measures later in this thesis.

2.2 Clinical Trials

To understand the importance of this research, first we must understand how benefit data is determined. An important part of this process are clinical trials. A clinical trial is the part of the treatment development process that involves testing on human subjects. Clinical trials are often used to test the safety and effectiveness of a new treatment on its own, or over another pre-existing treatment. They are also used to assess whether a dosage change in already approved treatments is effective,

or whether one of these treatments has alternative uses. Clinical trials have four different phases: three before the treatment is approved and one after [6].

Phase I is to determine the safety and dosage limits of the treatment, and is usually performed on healthy individuals. Phase II involves testing of patients suffering from the target disease. This phase is used to assess whether there are significant short term effects and whether to continue testing. Testing moves on to a third phase if the effects from the second are significant enough, and if adverse effects are not too severe [6].

Phase III of a clinical trial is what could be considered the 'main' phase, and it is from here that it is decided whether a treatment should be approved for distribution. This phase consists of large studies to demonstrate the usefulness of the treatment in a 'specific disease setting'; usually patients with only the disease in question. These studies contain different testing groups; usually a group of patients receiving the treatment, and a control group. In these studies, the distribution of patients into either the treatment or the control group is randomised to reduce bias in the results [6].

Phase IV is conducted on large groups of patients after the treatment has already been approved, and is to look for side effects not seen in previous phases of the trial. This phase is also used to assess how a treatment is performing in a particular population, or in a more practical setting. The findings from this phase may cause the removal of the drug (this is uncommon), a change of dosage, or even a change from the original intended application of the treatment [6].

The most common type of phase III trial read about in the literature are randomised controlled trials (RCTs). These are currently accepted as the most unbiased method for testing the effectiveness of new treatments. However, due to the strict selection criteria (called inclusion and exclusion criteria) designed to uphold the validity of the trial, often patients for whom the treatment is intended are excluded from the trial. For example, patients with multiple comorbidities are often excluded as this can produce unreliable data, and possibly have harmful side effects. This

exclusion can lead to physicians not having enough information about the effectiveness and/or possible side effects on these types of patients after the approval of the treatment [19].

2.2.1 Randomised Controlled Trials

Randomised controlled trials are studies in which subjects are randomly allocated to one of two groups receiving different interventions. One is the group receiving the intervention of interest, currently being investigated in the trial. The other group is generally a 'control' group, used as a comparison to the intervention being tested. A control intervention can be a placebo (an intervention with no clinical effect), or the currently accepted form of treatment.

The randomisation is in the allocation of subjects to a group to avoid bias in the selection of patients from physicians or investigators. It is also to promote similarities in the demographics of each group, which decreases the chance of any differences in the outcomes being from anything other than the treatment received.

Randomised controlled trials should ideally have one primary outcome or endpoint and should answer a clinical need. The disease that the RCT is targetting should be serious enough that an intervention will impact upon a significant proportion of the population and it should be clear from phases I and II that there is promise of efficacy. If another treatment is already in practice, for an RCT to go ahead, there needs to be genuine question as to whether there would be an improvement over the established practice.

Even though RCTs are useful for producing bias-free data for treatment of individual diseases, they are often not reflective of general usage and sometimes cannot be generalised to be useful to particular patients. This can be due to strict exclusion and inclusion criteria, and a number of other reasons such as selection bias, practitioner preferences, and limited number of willing participants. This means that patients with multiple comborbidities are generally excluded from RCTs as it

can be difficult to predict the effect the intervention will have on the other illnesses. However, without these strict criteria, trials may be unsafe for the participant or may produce unreliable data.

When controlled trials are not possible, there are also uncontrolled studies. Controlled trials may not be possible for a number of reasons, such as not being able to recruit enough patients, or financial restrictions. Uncontrolled trials are essentially observational only, as there is no control group for comparisons to be made; over time, the intervention and its effect are observed to see the result. Uncontrolled trials are useful for surgical trials, where patient recruitment numbers are an issue, and also in long term trials on chronic sufferers. Uncontrolled trials have fewer restriction criteria so can recruit larger numbers of patients, and unlike RCTs, can better reflect everyday practice.

2.3 Quality of Life

The problem of how to determine the benefit of a treatment for patients with comorbidities also brings up the issue of how to measure benefit in the first place. There are various ways to consider how a treatment may be benefiting a patient, other than the obvious medical benefits. For example, the treatment, although possibly not necessary to prolong a patient's lifespan, may vastly improve their wellbeing, or quality of life. There are many factors that influence a person's quality of life, and measuring quality of life can be subjective. The following discussion is based heavily on a paper by de Haan *et al.* [3]. They state that there are at least four dimensions that should be included in a quality of life assessment: physical, functional, psychological and social wellbeing.

Physical wellbeing refers to the obvious disease and treatment related symptoms; functional wellbeing relates to self-care ability and the capacity to carry out family or work roles; psychological wellbeing is about the patient's cognitive functioning, emotional status, and their general happiness; and social wellbeing measures the

qualitative and quantitative aspects of the patient's social contacts and interactions. There are obvious issues with being able to accurately measure some of these aspects of quality of life, and different diseases will often need to concentrate more on one aspect over another.

There are also differing methods of measuring quality of life, including generic scales, disease specific scales, and a battery of varying scales. While generic scales are good for comparing cross-domain and cross-population quality of life measurements, they are not always specific enough to the disease, treatment or population. On the other hand, disease specific measures do not allow for cross-disease comparisons, even though the measurements are more accurate. A battery of scales for measuring quality of life of different aspects of health is good for a more in depth assessment of each aspect, but then may not be comparable for cross-study purposes.

In using these measures, often patient interviews and questionnaires are needed to determine quality of life. However, this is not always possible to do; for example, in stroke patients with cognitive disorders. In these instances, other methods can be employed, such as a physician, or significant other, providing the rating. In either case there are drawbacks: physicians will commonly focus solely on the medical aspect of quality of life, and complaints are often underrated by significant others.

Most commonly, utility measures are used for quality of life measurements, where a utility is the value attached to a specific level of health. Utility scales work by classifying various health states and then assigning numerical values between 0 (indicating death or the worst possible outcome) and 1 (indicating perfect health or the best possible outcome). These values are obtained through previous assessments of patient samples or a panel of experts. It is these scores that are then used as 'evaluative end points' in clinical trials, and through these single scores results across studies can be compared.

These individual utility scores can then be combined to represent joint comorbid states. A paper by Strong and Oakley [17] used three different approaches with which to calculate a combined utility value. They assume that treatment is perfect;

if a patient receives treatment for one disease, then that disease is completely cured and can be removed from consideration.

The first approach is a multiplicative one, in which the utility weight of a joint state is the product of the individual utilities for each condition that makes up the state. The second approach is to use the minimum utility value of the single diseases that make up the state, as the utility of the joint state (that is, assuming the worst outcome). The third is an additive model, in which the sum of the 'impairments', or utility decrements, is calculated. The impairment for each condition is considered to be the reduction in utility between the well state (having no diseases) and the disease state [17].

The multiplicative approach considers that the utility weight of each individual condition is a proportion of a patient's "wellness". For example, if a patient begins in a health state with a utility value of 0.5, then suffers an illness with a utility value of 0.4, the patient is now at 40% of their original health state value; that is, the combined utility value is 40% of 0.5, which is $0.4 \times 0.5 = 0.2$. This approach, however, assumes that the health states are independent of each other, which is likely to be a simplification of the complex interactions between diseases. However, it does guarantee that the combined utility scores remain between 0 and 1, as required.

Consider the same example for the minimum utility approach; a patient suffers from two conditions, one with a utility value of 0.5, and the other with a utility value of 0.4. Since suffering from two conditions is at least as bad as suffering from only one, then the utility value must be at least as bad as the worst disease from which they are suffering. Therefore, taking the minimum utility value of 0.4 ensures that having only one condition cannot be better than having both. However, if we consider only the minimum utility value of the single diseases, then we are only considering the best possible case. Having multiple conditions would likely be worse than (rather than just as bad as) having only one condition, and again we are ignoring the possible interactions between diseases.

Instead of considering utility values (the "worth" of a health state), the additive

approach considers impairments. Assume a patient is in perfect health, and therefore has a utility value of 1, then suffers an illness with a utility of 0.4; the impairment of that disease is 0.6 (the reduction in utility value). Using the same example as above, consider a patient that has two diseases: one with an impairment of 0.6, and the other with an impairment of 0.5. Under the additive model, the total impairment of the both diseases is 1.1, meaning that the combined utility value is -0.1. This is impossible, since utility values must remain between 0 and 1, by convention. More generally, considering the sum of impairments can lead to a situation in which this sum exceeds a value of 1, as demonstrated.

We believe that the most appropriate method of combining utility values is the multiplicative approach, since there is at least some consideration of disease interaction, and this method ensures that the utility values remain between 0 and 1, as is required. This is also the preferred method used to combine utility values in the American Medical Association Guides to the Evaluation of Permanent Impairment [1].

Despite the unreasonable initial assumption of treatment being perfect, and the questionable validity of the latter two approaches of combining utility values, Strong and Oakley [17] still demonstrate an overestimation of treatment benefits when ignoring comorbidities.

Utility scores can also be used to obtain quality adjusted life years (QALYs), which can be defined as the 'gained years of life resulting from intervention corrected by utility of that life' [3]. QALYs are often used to determine how detrimental a disease is (in terms of QALYs lost), or how effective a treatment may be (QALYs gained). Both QALYs and the utility measures for quality of life are used in the literature to demonstrate the benefits and/or risks of a treatment. They can also be used to calculate the risks and benefits of a treatment in patients with comorbidities. Later in this thesis, we use utility values to calculate the expected outcomes of different treatment options in terms of QALYs.

2.4 The Effect of Comorbidity on Treatment Benefits

Throughout the literature there have been many attempts to account for ageing and comorbidities in calculating the benefits of certain treatments. These include the use of Markov models with death from causes other than the target disease as a possible state, a rate of death function modified with a comorbidity index included as a factor of the function, and various other methods. However, many of the previously used methods incorporate comorbidity calculations in a less than satisfactory manner, and leave gaps and questions unanswered.

In an article comparing the benefits of 'watchful waiting' and radical prostatectomy as treatments for prostate cancer, Kattan *et al.* [7] use a Markov model to model the progression of the disease. The model included various possible states in which a patient could be, including different stages of prostate cancer and death from prostate cancer. Given that many more people with prostate cancer die of causes other than the cancer itself, Kattan *et al.* incorporate comorbidity into their model by including a non-cancer death state. The transition rates in the model were collected from previous studies and pooled analyses, and are considered constant over time. The death risk from comorbidity was obtained from a large study of prostate cancer patients over several years, in which it was found that more comorbidities means greater death risk.

However, more than just risk of death needs to be considered when comparing these two treatments. For example, radical prostatectomy has potential non-life threatening complications such as impotence and incontinence, and health states such as these need to be modelled as well. For this purpose, Kattan *et al.* use utilities to put a value on each health state, with the conventional values 0 for death and 1 for perfect health. These utilities were obtained from interviewing 31 men without prostate cancer between the ages of 55 and 75.

The preferred health state, in this analysis, is the state in which a patient has

been treated with a radical prostatectomy, with no adverse effects from treatment and no sign of disease progression. Even though this is the 'best outcome', it does not have a utility of 1 as it is still not necessarily 'perfect health'. Instead, it is assigned a value of 0.84 - the mean utility value for men between the ages of 64 and 75 from a large study of health states [5].

In the sensitivity analysis of this model, comorbidity is included through the use of the Index of Coexistent Disease. This comorbidity index has four levels, ranging from 0, the lowest level of comorbidity, to 3, the highest level. The results from this analysis indicate that the preferred treatment for prostate cancer is radical prostatectomy in most cases. As the comorbidity index is raised, however, it becomes less preferred, and at the highest level of comorbidity in older men, watchful waiting of the prostate cancer becomes the preferred treatment course.

Similarly, in an article analysing the benefit of carotid endarterectomy (CEA) for carotid artery stenosis, Nagaki *et al.* [11] use a Markov model to show the progression of the disease. In the model, patients have either asymptomatic or symptomatic stenosis. To begin with, patients are well with stenosis. From this state, a patient could end up, at the end of each year, in one of three states:

- well with stenosis (no change in their health state);
- post stroke (they become disabled as a result of a stroke);
- or dead (either they have suffered a stroke and died as a result, or died of causes other than a stroke).

Through surgery (CEA) a patient may move from well with stenosis to well without stenosis. This transition does not necessarily happen at the end of a yearly cycle, however we only observe a patient's health state at the end of each year. In other words, during the year a patient may have surgery and be in the well without stenosis state, but at the end of the year could end up in either well without stenosis, post-stroke or dead (as before). Other states are also obtainable through the surgery

as there are obviously risks involved. If a patient does encounter risks in surgery, they may become disabled and end up in the post stroke state (for simplicity, these are considered equivalent), or die.

From the post stroke state, patients will either remain in this state or be dead at the end of the next year, and patients who are dead at the beginning of a yearly cycle obviously remain dead at the end.

To approximate the death rate of patients with carotid artery stenosis, Nagaki *et al.* [11] use a modified version of the hazard function (the annual death rate of the general population at age x) by multiplying it by a comorbidity index, c:

$$p(x) = c \times e^{-10.58+0.095x}.$$

For normal life expectancy $c = 1$, for reduced life expectancy of normal-risk carotid stenosis patients $c = 2$, and for high-risk patients $c = 3$. The analysis with $c = 2$ corresponded well with reported results of a population based survival study of CEA patients. This shows that even this imprecise method of including comorbidity into analysis may better approximate the real benefits and/or risks of a treatment.

In their analysis, Nagaki *et al.* defined the expected benefit of the treatment to be the QALY gain; that is, the difference between the expected QALYs with immediate CEA, and expected QALYs without CEA. Since the value of treatment is worth more to the patient in the present than it is later, a discount rate of 3% per year was used to make the QALYs time sensitive.

The results suggest that in asymptomatic patients the benefit is very small or sometimes negative. In older patients there seems to be no benefit of treatment, and in other patients, the already small benefits decrease significantly as the number of comorbidities increases. In symptomatic patients, a baseline analysis shows large gains in QALYs after surgery. At the different levels of comorbidity and in older patients, the QALY gain of CEA still remains greater for symptomatic patients than for asymptomatic patients.

These articles demonstrate that even with a very basic inclusion of comorbidity

into benefit analyses, the reported benefit of treatments can be significantly affected. In the first case, when considering age and the level of comorbidity, the benefit of radical prostatectomy is significantly less for older patients with more comorbidities [7]. In the second case, the benefit of CEA on patients with symptomatic carotid artery stenosis decreases as the comorbidity index rises, but is still shown to be more beneficial than not undergoing the surgery [11]. Although both of these analyses use only an imprecise method of incorporating comorbidity into benefit calculations, they do consider the benefits over time, rather than only at a single moment.

On the other hand, Fitzgerald and Bean [4] consider individual comorbidities in their benefit calculations and are hence able to also consider the benefits for multiple treatments simultaneously. In their analysis the benefits are considered as 'the reduction in the probability of harm from disease'. Before doing any calculations, assumptions about treatments and comorbidities need to be made:

- the benefits of a certain treatment only affect the target condition;
- a patient's response to different treatments are independent of each other;
- and increasing age is considered a comorbidity.

They consider a patient with a set of N diseases, labeled $i = 1, 2, ..., n$, with the probability of a patient suffering negative consequences from disease i being $1 - p_i$, assuming no treatment is received for this disease. Since the benefit of treating a disease, b_i, is the reduction in probability of negative consequences from a disease, the probability of the patient suffering negative consequences with treatment is $1 - p_i - b_i$. The ideal outcome in this situation is that the set of diseases from which the patient is suffering negative consequences, $S \subseteq N$ is empty; that is, $S = \varnothing$.

The probability that a patient suffers negative consequences from the set of conditions $S \subseteq N$, assuming none of $i \in N$ have been treated, is given by:

$$P(S, N) = \prod_{i \in S} (1 - p_i) \prod_{j \in N \setminus S} p_j, \quad \text{for all } S \subseteq N.$$

Now assume that a patient has been treated for all conditions $i \in M$, for some $M \subseteq N$. Then the probability that they suffer negative consequences from conditions $S \subseteq N$ is:

$$P_M(S,N) = \prod_{i \in M \cap S} (1 - p_i - b_i) \prod_{j \in M \cap (N \setminus S)} (p_j + b_j) \prod_{i \in (N \setminus M) \cap S} (1 - p_i) \prod_{j \in (N \setminus M) \cap (N \setminus S)} p_j,$$

for all $M, S \subseteq N$.

Let the combined benefit of treating all N diseases be defined as the difference between the probability of having no negative consequences given that those diseases are treated, and the probability of no negative consequences given no treatment. That is:

$$B^C = P_N(\varnothing, N) - P(\varnothing, N).$$

In Theorem 1, Fitzgerald and Bean [4] show that

$$B^C < \sum_{i \in N} b_i.$$

That is, the combined benefit of treating all N diseases is less than the sum of the individual treatment benefits. They also consider different ways of measuring individual benefit in the presence of comorbidities. More specifically they define what we call the withdrawal benefit, and the added benefit. The withdrawal benefit of treating disease i is the benefit considering that all other conditions are being treated, and the added benefit of treating disease i is the benefit when none of the other conditions are being treated. We assume that the withdrawal benefit is the best method of measuring the benefit of a single treatment in the presence of multiple comorbidities. They then prove that for both of these definitions of benefit, the result is less than the reported individual benefit of treating disease i.

In the next chapter, we explore and extend upon these initial results by Fitzgerald and Bean, considering a measure for the risk of treatment and a measure for the benefit of 'perfect' treatment. We also consider the effect of concurrent treatments on the benefit, as opposed to the effect of multiple comorbidities on the benefit.

Chapter 3

An Extension of the Snapshot Model

In Chapter 2 we saw that Fitzgerald and Bean [4] defined a model for multiple diseases using probabilities of positive or negative outcomes. The benefit defined in this model is measured at a specific period of time after treatment is given, hence we refer to it as the "snapshot" benefit. In this model, they show that the perceived benefit is always greater than the actual benefit of treating multiple diseases, as well as some other important results when considering the benefit in the presence of multiple conditions.

In this chapter, we extend upon their existing results, and introduce new measures of benefit, including the idea of an "ideal" benefit. We also investigate how the treatment risks behave by defining them as the iatrogenic losses of treatment.

Fitzgerald and Bean [4] also briefly touch on the benefit measured as the expected quality of outcome at a specific period of time after treatment. We extend all of the results for the snapshot benefit measured in probabilities, to the snapshot benefit measured in expected quality of outcome.

3.1 Defining Benefit and Loss

Fitzgerald and Bean [4] consider the "snapshot" benefit of treatment at a specific point in time, where the benefit is measured as the reduction in probability of harm from the disease. More specifically, they assume that if a person has a set $N = \{1, 2, ..., n\}$ of diseases, the probability that they suffer negative consequences from a single disease i is $1 - p_i$ if no treatment is given, and $1 - p_i - b_i$ assuming treatment *is* given [4]. Since this measure of benefit encompasses the risk of treatment, we can think of it as the "net benefit" of treating an individual disease.

Another measure we could consider is the ideal benefit of treatment; that is, the benefit if there were no risks associated with treatment. We can consider p_i to be the proportion of patients that do not suffer negative consequences from disease i assuming no treatment is given, and $p_i + b_i$ to be the proportion of patients that do not suffer negative consequences from disease i if treatment *is* given. Let s_i be the proportion of patients with disease i that suffer negative consequences attributable to the treatment, not the disease. Then the proportion of patients that suffer negative consequences from treatment i, that would *not* have suffered negative consequences from the disease if treatment was risk-free, is

$$s_i \times \frac{(p_i + b_i)}{(1 - s_i)},$$

where $\dfrac{(p_i + b_i)}{(1 - s_i)}$ is the proportion of all patients who did not suffer negative consequences from treatment, who also suffered no negative consequences from the disease (with treatment).

Since the individual ideal benefit, b_i^I, is the reduction in probability of harm from disease i given risk-free treatment, we have that

$$b_i^I = b_i + s_i \times \frac{(p_i + b_i)}{(1 - s_i)}.$$

Therefore, the risk associated with treatment i is

$$s_i \times \frac{(p_i + b_i)}{(1 - s_i)}.$$

We regard this as the iatrogenic loss of treatment i, ℓ_i, where the term 'iatrogenic' refers to effects 'induced inadvertently by a physician or surgeon or by a medical treatment or diagnostic procedures' [9].

Assumption 1. *We assume that individual treatment in isolation is always beneficial, otherwise would not be considered. We also assume that every treatment has a risk with which it is associated, and that in the risk-free environment, it is possible for treatment to be perfect. That is, we assume*

$$0 \leq p_i < p_i + b_i < p_i + b_i + \ell_i \leq 1.$$

3.2 Existing Results

In their snapshot model, Fitzgerald and Bean [4] prove some important results about the net benefit of treatments considering a patient with multiple diseases. To do so, they first define the probability of a patient suffering negative consequences from multiple conditions, with and without treatment.

Definition 5 (Definition 1 from Fitzgerald and Bean [4])**.**
Let $P(S, N)$ be the probability that a person suffers negative consequences precisely from the set of diseases $S \subseteq N$, assuming that the person has not been treated for any of the diseases $i \in N$. Then,

$$P(S, N) = \prod_{i \in S}(1 - p_i) \prod_{j \in N \setminus S} p_j,$$

for all $S \subseteq N$.

Definition 6 (Definition 2 [4])**.**
Let $P_M(S, N)$ be the probability that a person suffers negative consequences from precisely the set of diseases $S \subseteq N$, assuming the person has been treated for those diseases $i \in M$. Then,

$$P_M(S, N) = \prod_{i \in M \cap S} (1 - p_i - b_i) \prod_{j \in M \cap S^c} (p_j + b_j) \prod_{i \in M^c \cap S} (1 - p_i) \prod_{j \in M^c \cap S^c} p_j,$$

for all $M, S \subseteq N$, where we recall that A^c is the complement of any set A and is given by $A^c = N \setminus A$.

Theorem 3 (Theorem 1 [4])**.**
Let the benefit of treating all diseases in a set N be the difference in the probability of the person having no negative consequences assuming that they have treatment for all the diseases versus treatments for none of the diseases. The benefit is always strictly less than the sum of the individual benefits. Put mathematically,

$$P_N(\varnothing, N) - P(\varnothing, N) < \sum_{i \in N} b_i.$$

In Theorem 3, we call $P_N(\varnothing, N) - P(\varnothing, N)$ the combined benefit of treating all diseases simultaneously, and in future denote it by

$$B^C = P_N(\varnothing, N) - P(\varnothing, N).$$

Therefore, Fitzgerald and Bean have shown that in their snapshot model, the combined benefit of treatment is less than the sum of the individual benefits:

$$B^C < \sum_{i \in N} b_i.$$

Theorem 4 (Theorem 2 [4])**.**
If we define the benefit of the individual treatment i as $\overline{B_i} = P_N(\varnothing, N) - P_{N \setminus \{i\}}(\varnothing, N)$ *then the sum of the benefits of the individual treatments is greater than the overall benefit of treatment. Mathematically,*

$$\sum_{i \in N} \overline{B_i} > P_N(\varnothing, N) - P(\varnothing, N).$$

Instead, if we define the benefit of the individual treatment i as $\underline{B_i} = P_{\{i\}}(\varnothing, N) - P(\varnothing, N)$ *then the sum of the benefits of the individual treatments is less than the overall benefit of treatment. Mathematically,*

$$\sum_{i \in N} \underline{B_i} < P_N(\varnothing, N) - P(\varnothing, N).$$

Here, we call $\overline{B_i}$ the withdrawal benefit of treating disease i, and $\underline{B_i}$ the added benefit of treating disease i. Thus, Fitzgerald and Bean [4] have shown that the sum of the withdrawal benefits is greater than the combined benefit, and that the sum of the added benefits is less than the combined benefit. Mathematically,

$$\sum_{i \in N} \underline{B_i} < B^C < \sum_{i \in N} \overline{B_i}.$$

We accept the withdrawal benefit of an individual disease as the most logical method of measuring the benefit of treatment in the presence of other diseases. Thus, this result demonstrates that there is an interaction between the treatment benefits that affects the true benefit of treating multiple comorbidities. Even when considering the effect of other treatments on the benefit of treating a single condition, the benefit is still greater than when considering all treatments simultaneously. While the added benefit does not have the same significance as the withdrawal benefit, we include it in our analyses throughout this thesis for mathematical completeness.

3.2.1 Extension of Existing Results

This result can be strengthened by also showing that the sum of the withdrawal benefits is less than the sum of the individual benefits in isolation.

Corollary 2.

$$\sum_{i \in N} \underline{B_i} < B^C < \sum_{i \in N} \overline{B_i} < \sum_{i \in N} b_i.$$

Proof. We only need to prove $\sum_{i \in N} \overline{B_i} < \sum_{i \in N} b_i$:

$$\begin{aligned}
\overline{B_i} &= P_N(\varnothing, N) - P_{N \setminus \{i\}}(\varnothing, N) \\
&= \prod_{j \in N} (p_j + b_j) - p_i \prod_{j \in N \setminus \{i\}} (p_j + b_j) \\
&= (p_i + b_i - p_i) \prod_{j \in N \setminus \{i\}} (p_j + b_j) \\
&= b_i \prod_{j \in N \setminus \{i\}} (p_j + b_j).
\end{aligned}$$

$$< b_i, \quad \forall i \in N,$$

since $0 < p_j + b_j < 1$ for all $j \in N$. It then follows that

$$\sum_{i \in N} \overline{B_i} < \sum_{i \in N} b_i.$$

Therefore, from the result of Theorem 4,

$$\sum_{i \in N} \underline{B_i} < B^C < \sum_{i \in N} \overline{B_i} < \sum_{i \in N} b_i.$$

□

3.3 Ideal Benefit and Iatrogenic Loss Results

Recall that the ideal benefit, b_i^I, of treating disease i is the reduction in probability of harm with risk-free treatment; that is $b_i^I = b_i + \ell_i$. So, if risk-free treatment is given, the probability of suffering negative consequences from disease i is $1 - p_i - b_i - \ell_i$.

By replacing b_i with the ideal benefit b_i^I in the definitions of combined, withdrawal and added benefits, all of the results follow for the ideal benefit.

Definition 7. Let $P_M^I(S, N)$ be the probability that a person suffers negative consequences from precisely the set of diseases $S \subseteq N$, assuming the person has been given risk-free treatment for those diseases $i \in M$. Then,

$$\begin{aligned} P_M^I(S, N) &= \prod_{i \in M \cap S} (1 - p_i - b_i^I) \prod_{j \in M \cap S^c} (p_j + b_j^I) \prod_{i \in M^c \cap S} (1 - p_i) \prod_{j \in M^c \cap S^c} p_j \\ &= \prod_{i \in M \cap S} (1 - p_i - b_i - \ell_i) \prod_{j \in M \cap S^c} (p_j + b_i + \ell_i) \prod_{i \in M^c \cap S} (1 - p_i) \prod_{j \in M^c \cap S^c} p_j, \end{aligned}$$

for all $M, S \subseteq N$.

Definition 8. Let $P_{L,M}(S, N)$ be the probability that a person suffers negative consequences from precisely the set of diseases $S \subseteq N$, assuming the person has

been given normal risk treatments for those diseases $i \in L$, risk-free treatment for those diseases $j \in M$, and no treatment for those diseases $k \in N \setminus (L \cup M)$. Then,

$$P_{L,M}(S,N) = \prod_{i \in L \cap S} (1 - p_i - b_i) \prod_{j \in M \cap S} (1 - p_j - b_j - \ell_j) \prod_{i \in L \setminus S} (p_i + b_i) \times \prod_{j \in M \setminus S} (p_j + b_j + \ell_j) \prod_{i \in S \setminus (M \cup L)} (1 - p_i) \prod_{j \in S^c \setminus (M \cup L)} p_j,$$

for all $M, L, S \subseteq N$, with $M \cap L \varnothing$.

Definition 9. Let $B^{I,C}$ be the **combined ideal benefit** of treating all diseases in a set N. That is,

$$B^{I,C} = P^I_N(\varnothing, N) - P(\varnothing, N).$$

Let $\overline{B^I_i}$ be the **withdrawal ideal benefit** of treating disease i, and $\underline{B^I_i}$ be the **added ideal benefit** of treating disease i. That is,

$$\overline{B^I_i} = P^I_N(\varnothing, N) - P^I_{N \setminus \{i\}}(\varnothing, N),$$

and

$$\underline{B^I_i} = P^I_{\{i\}}(\varnothing, N) - P(\varnothing, N).$$

Theorem 5.

$$\sum_{i \in N} \underline{B^I_i} < B^{I,C} < \sum_{i \in N} \overline{B^I_i} < \sum_{i \in N} b^I_i.$$

Proof. We have that

$$B^{I,C} = \prod_{j \in N} (p_j + b_j + \ell_j) - \prod_{j \in N} p_j,$$

$$\overline{B^I_i} = \prod_{j \in N} (p_j + b_j + \ell_j) - p_i \prod_{j \in N \setminus \{i\}} (p_j + b_j + \ell_j) \qquad \text{and,}$$

$$\underline{B^I_i} = (p_i + b_i + \ell_i) \prod_{\jmath \in N \setminus \{i\}} p_j - \prod_{j \in N} p_j.$$

Since $0 < b_j < b_j + \ell_j \leq p_j + b_j + \ell_j \leq 1$ for all $j \in N$, we can replace b_j with $b_j + \ell_j$ in the proofs of Theorems 3 and 4, and Corollary 2, and the results follow. □

However, we are also interested in how the risks, or iatrogenic losses due to treatment, combine when considering multiple conditions. We now show that the snapshot combined iatrogenic loss of treatment, defined in terms of the probability of suffering negative consequences, behaves in a similar way to the benefit.

Definition 10. Let the **combined iatrogenic loss**, or the iatrogenic loss of treating all diseases in the set N, be the difference between the probability of suffering no negative consequences given that we treat all N diseases with risk-free treatment, and that we treat all N diseases with normal risk treatment. That is,

$$\ell^C = P^I_N(\varnothing, N) - P_N(\varnothing, N).$$

Let the **added iatrogenic loss** of treatment i be the difference between the probability of suffering no negative consequences given that we treat disease i with risk-free treatment, and that we treat disease i with normal risk treatment, while treating no other diseases. That is,

$$\underline{\ell_i} = P^I_{\{i\}}(\varnothing, N) - P_{\{i\}}(\varnothing, N).$$

Let the **withdrawal iatrogenic loss** of treatment i be the difference between suffering no negative consequences with risk-free treatment of all diseases $j \in N$, and with normal risk treatment of disease i while having risk-free treatment for all diseases $j \in N \setminus \{i\}$. That is,

$$\overline{\ell_i} = P^I_N(\varnothing, N) - P_{\{i\},N\setminus\{i\}}(\varnothing, N).$$

Lemma 1.

$$\ell^C = \sum_{i\in N} \ell_i \prod_{\substack{j\in N;\\ j<i}} (p_j + b_j) \prod_{\substack{k\in N;\\ k>i}} (p_k + b_k + \ell_k),$$

$$\underline{\ell_i} = \ell_i \prod_{j\in N\setminus\{i\}} p_j,$$

and,

$$\overline{\ell_i} = \ell_i \prod_{j\in N\setminus\{i\}} (p_j + b_j + \ell_j).$$

Proof. The combined iatrogenic loss is:

$$\begin{aligned}\ell^C &= P_N^I(\varnothing, N) - P_N(\varnothing, N)\\ &= \prod_{j\in N}(p_j + b_j + \ell_j) - \prod_{j\in N}(p_j + b_j).\end{aligned}$$

Expanding the term $\prod_{j\in N}(p_j + b_j + \ell_j)$ gives,

$$\begin{aligned}\ell^C &= \prod_{j\in N}(p_j + b_j) + \sum_{i\in N}\left[\left\{\prod_{\substack{j\in N;\\ j<i}}(p_j + b_j)\right\}\ell_i\left\{\prod_{\substack{k\in N;\\ k>i}}(p_k + b_k + \ell_k)\right\}\right] - \prod_{j\in N}(p_j + b_j)\\ &= \sum_{i\in N}\ell_i \prod_{\substack{j\in N;\\ j<i}}(p_j + b_j)\prod_{\substack{k\in N;\\ k>i}}(p_k + b_k + \ell_k).\end{aligned}$$

The added iatrogenic loss is:

$$\begin{aligned}\underline{\ell_i} &= P_{\{i\}}^I(\varnothing, N) - P_{\{i\}}(\varnothing, N)\\ &= (p_i + b_i + \ell_i)\prod_{j\in N\setminus\{i\}} p_j - (p_i + b_i)\prod_{j\in N\setminus\{i\}} p_j\\ &= \ell_i \prod_{j\in N\setminus\{i\}} p_j.\end{aligned}$$

Lastly, the withdrawal iatrogenic loss is:

$$\begin{aligned}\overline{\ell_i} &= P_N^I(\varnothing, N) - P_{\{i\},N\setminus\{i\}}(\varnothing, N)\\ &= \prod_{j\in N}(p_j + b_j + \ell_j) - (p_i + b_i)\prod_{j\in N}(p_j + b_j + \ell_j)\\ &= [p_i + b_i + \ell_i - (p_i + b_i)]\prod_{j\in N\setminus\{i\}}(p_j + b_j + \ell_j)\\ &= \ell_i \prod_{j\in N\setminus\{i\}}(p_j + b_j + \ell_j).\end{aligned}$$

□

We can then show that similar inequalities to those for the benefits, hold for the iatrogenic losses.

Theorem 6.

$$\sum_{i\in N} \underline{\ell_i} < \ell^C \leq \sum_{i\in N} \overline{\ell_i} \leq \sum_{i\in N} \ell_i.$$

Proof.

$$\underline{\ell_i} = \ell_i \prod_{j\in N\setminus\{i\}} p_j,$$

therefore,

$$\begin{aligned}\sum_{i\in N} \underline{\ell_i} &= \sum_{i\in N} \ell_i \prod_{j\in N\setminus\{i\}} p_j \\ &< \sum_{i\in N} \ell_i \prod_{\substack{j\in N;\\ j<i}} (p_j + b_j) \prod_{\substack{k\in N;\\ k>i}} (p_k + b_k + \ell_k) \\ &= \ell^C,\end{aligned}$$

since $0 < b_j < b_j + \ell_j$ for all $j \in N$.

$$\overline{\ell_i} = \ell_i \prod_{j\in N\setminus\{i\}} (p_j + b_j + \ell_j),$$

therefore,

$$\begin{aligned}\sum_{i\in N} \overline{\ell_i} &= \sum_{i\in N} \ell_i \prod_{j\in N\setminus\{i\}} (p_j + b_j + \ell_j) \\ &> \sum_{i\in N} \ell_i \prod_{\substack{j\in N;\\ j<i}} (p_j + b_j) \prod_{\substack{k\in N;\\ k>i}} (p_k + b_k + \ell_k) \\ &= \ell^C,\end{aligned}$$

since

$$\prod_{\substack{j\in N;\\ j<i}} (p_j + b_j + \ell_j) \geq \prod_{\substack{j\in N;\\ j<i}} (p_j + b_j)$$

for all $i \in N$. This is because $\ell_j > 0$ for all $j \in N$.

Also,

$$\begin{aligned}\sum_{i\in N}\overline{\ell_i} &= \sum_{i\in N}\ell_i \prod_{j\in N\setminus\{i\}}(p_j+b_j+\ell_j)\\ &\leq \sum_{i\in N}\ell_i,\end{aligned}$$

since,

$$0 < p_j + b_j + \ell_j \leq 1 \quad \forall j \in N.$$

□

In any reasonable situation, for at least one $j \in N$ ideal treatment is not perfect, so the inequality is strict. That is,

$$\sum_{i\in N}\underline{\ell_i} < \ell^C < \sum_{i\in N}\overline{\ell_i} < \sum_{i\in N}\ell_i.$$

Thus, we can see that the iatrogenic loss of treatment behaves similarly to the benefit.

3.4 Expected Quality of Outcome

In the same paper, Fitzgerald and Bean [4] explore the idea of measuring the benefit of treatment in terms of the difference in the expected quality of outcome between different treatment paths, rather than the reduction in probability of suffering a negative outcome.

Definition 11 (Definition 3 from Fitzgerald and Bean [4])**.**
For all $S \subseteq N$, where S is a set of diseases from which a patient suffers negative consequences, let $q(S)$ denote the **quality of outcome** of S. We assume throughout that $q(\varnothing) = 1$ (thus, $0 \leq q(S) \leq 1$), and that $q(S) \leq q(T)$ if $T \subseteq S$. This means that any outcome, S, which consists of at least the set of negative consequences, T, must have a quality that is no greater than the quality of outcome T.

Definition 12 (Definition 4 [4])**.**
The **expected quality of outcome** associated with a set N of diseases, assuming that no treatment is given, is defined by

$$E(N) = \sum_{S \subseteq N} P(S, N)q(S),$$

and the **expected quality of outcome** associated with a set N of diseases, assuming that treatments are given for all comorbidities in $M \subset N$, is defined by

$$E_M(N) = \sum_{S \subseteq N} P_M(S, N)q(S).$$

Theorem 7 (Theorem 4 [4])**.** *For any quality of outcome function $q(\cdot)$ obeying Definition 11,*

$$E_N(N) - E(N) < \sum_{i \in N} b_i.$$

That is, Fitzgerald and Bean [4] showed that the combined benefit of treating all of a set of N diseases, measured in terms of the expected quality of outcome, is less than the sum of the individual benefits (measured in the decrease in the probability of negative consequences). However, in order to compare the combined and individual benefits with the same form of measurement, we now show that the combined benefit in expected quality of outcome is less than the sum of the individual benefits in expected quality of outcome.

Using the above definitions, the expected quality of outcome of a single disease, i, given no treatment is

$$\begin{aligned} E(i) &= P(\varnothing, i)q(\varnothing) + P(i, i)q(i) \\ &= p_i + (1 - p_i)q(i). \end{aligned}$$

The expected quality of outcome of a single disease, i, given it *is* treated is

$$\begin{aligned} E_i(i) &= P_i(\varnothing, i)q(\varnothing) + P_i(i, i)q(i) \\ &= (p_i + b_i) + (1 - p_i - b_i)q(i). \end{aligned}$$

Therefore, the benefit, $\mathfrak{b}_i$, of an individual treatment, i, in isolation, is

$$\begin{aligned}\mathfrak{b}_i &= E_i(i) - E(i)\\ &= p_i + b_i + (1 - p_i - b_i)q(i) - p_i - (1 - p_i)q(i)\\ &= b_i - b_i q(i)\\ &= b_i(1 - q(i)).\end{aligned}$$

We also assume that the quality of outcome of suffering negative consequences from a set of diseases, S, is the product of the quality of outcomes of the individual diseases in S. We assume the multiplicative approach to combining the quality of outcome, as it is equivalent to the utility of a particular health state. Other methods of combining utility values have been shown to be mathematically flawed in Chapter 2, and the multiplicative method ensures that the values remain between 0 and 1. Furthermore, this is in agreement with the method of combining utilities, or quality of outcomes, recommended by the American Medical Association Guides to the Evaluation of Permanent Impairments [1]. That is, we assume

$$q(S) = \prod_{j \in S} q(j).$$

We can also introduce measures for expected quality of outcome, taking into account risk-free treatments, and a combination of both risk-free and normal risk treatments.

Definition 13. Let

$$E^I_M(N) = \sum_{S \subseteq N} P^I_M(S, N)q(S)$$

be the expected quality of outcome associated with a set of N diseases, assuming risk-free treatments are given to $M \subseteq N$ diseases.

Let

$$E_{L,M}(N) = \sum_{S \subseteq N} P_{L,M}(S, N)q(S)$$

be the expected quality of outcome associated with a set of diseases, N, assuming that normal-risk treatments are given for all diseases $L \subseteq N$ and that risk-free treatments are given for all diseases $M \subseteq N$, such that $M \cap L = \varnothing$.

Assumption 2. *We assume that for a set of diseases N, with $M \subset N$, the expected quality of outcome of treating any set of diseases M must be at least as good as treating none of the diseases, and that treating one more disease $i \in N$ must be at least as good as treating only those diseases in M. We also assume that treating those diseases in M ideally is at least as good as treating them normally, and that treating one more disease $i \in N$ ideally is at least as good again. That is,*

$$0 \leq E(N) \leq E_M(N) \leq E_{M\cup\{i\}}(N) \leq E(N),$$

and

$$E_M(N) \leq E^I_M(N) \leq E^I_{M\cup\{i\}}(N) \leq E^I(N).$$

Lastly, we assume that treating all of the diseases in N with normal risk treatment must be strictly better than treating none of them, and that treating all of the diseases with risk-free treatment is strictly better than treating them normally. That is,

$$E(N) < E_N(N) < E^I_N(N).$$

Using the above definitions and assumptions, we can extend our definitions of combined, added and withdrawal benefit to be measured in terms of difference in the quality of outcome between certain treatment and non-treatment options.

Definition 14. Consider that a patient is suffering from a set of diseases, N. The **combined benefit** of treating all diseases is the difference in expected quality of outcome between treating all diseases, and treating none. Mathematically,

$$\mathfrak{B}^C = E_N(N) - E(N).$$

The **added benefit** of treating disease i is the difference in expected quality of outcome between treating that one disease, and treating none. Mathematically,

$$\mathfrak{B}^A_i = E_i(N) - E(N).$$

The **withdrawal benefit** of treating disease i is the difference in expected quality of outcome between treating all diseases, and all except disease i. Mathematically,

$$\mathfrak{B}_i^W = E_N(N) - E_{N\setminus\{i\}}(N).$$

We can then further simplify these definitions into more meaningful expressions, as follows.

Lemma 2.

$$\mathfrak{B}^C = \sum_{i\in N} b_i(1-q(i))E_{\{j\in N|j>i\}}(N\setminus\{i\}),$$
$$\mathfrak{B}_i^A = b_i(1-q(i))E(N\setminus\{i\}),$$

and,

$$\mathfrak{B}_i^W = b_i(1-q(i))E_{N\setminus\{i\}}(N\setminus\{i\}).$$

Proof. The combined benefit is:

$$\begin{aligned}
\mathfrak{B}^C &= E_N(N) - E(N) \\
&= \sum_{S\subseteq N} P_N(S,N)q(S) - \sum_{S\subseteq N} P(S,N)q(S) \\
&= \sum_{S\subseteq N} \left[P_N(S,N) - P(S,N)\right] q(S) \\
&= \sum_{S\subseteq N} \left[\prod_{j\in S}(1-p_j-b_j) \prod_{j\in N\setminus S}(p_j+b_j) - \prod_{j\in S}(1-p_j)\prod_{j\in N\setminus S} p_j\right] q(S) \\
&= \sum_{i\in N} b_i \left[\sum_{S\subseteq N} \prod_{\substack{j\in S;\\ j<i}}(1-p_j) \prod_{\substack{j\in N\setminus S;\\ j<i}} p_j \prod_{\substack{j\in S;\\ j>i}}(1-p_j-b_j)\right. \\
&\qquad\qquad \left. \times \prod_{\substack{j\in N\setminus S;\\ j>i}} (p_j+b_j)(-1)^{I(i\in S)} q(S)\right].
\end{aligned}$$

All sets $S \subseteq N$ can be be broken up into those sets that contain disease i and those that do not, and there is a one to one relation between the elements of these two

collections of sets. Consider the sets $T \subseteq N \setminus \{i\}$; that is, the sets that do not contain disease i. Since the products within the sum above do not contain i, we can rewrite the sum as a sum over $T \subseteq N \setminus \{i\}$, and so

$$\begin{aligned}
\mathfrak{B}^C &= \sum_{i \in N} b_i \Bigg[\sum_{T \subseteq N \setminus \{i\}} \prod_{\substack{j \in T; \\ j<i}} (1-p_j) \prod_{\substack{j \in N \setminus T; \\ j<i}} p_j \prod_{\substack{j \in T; \\ j>i}} (1-p_j-b_j) \\
&\qquad \times \prod_{\substack{j \in N \setminus T; \\ j>i}} (p_j+b_j)(q(T)-q(T \cup \{i\})) \Bigg] \\
&= \sum_{i \in N} b_i \Bigg[\sum_{T \subseteq N \setminus \{i\}} \prod_{\substack{j \in T; \\ j<i}} (1-p_j) \prod_{\substack{j \in N \setminus T; \\ j<i}} p_j \prod_{\substack{j \in T; \\ j>i}} (1-p_j-b_j) \\
&\qquad \times \prod_{\substack{j \in N \setminus T; \\ j>i}} (p_j+b_j) \left(q(T)-q(T)q(i)\right) \Bigg] \\
&= \sum_{i \in N} b_i (1-q(i)) \Bigg[\sum_{T \subseteq N \setminus \{i\}} q(T) \prod_{\substack{j \in T; \\ j<i}} (1-p_j) \prod_{\substack{j \in N \setminus T; \\ j<i}} p_j \\
&\qquad \times \prod_{\substack{j \in T; \\ j>i}} (1-p_j-b_j) \prod_{\substack{j \in N \setminus T; \\ j>i}} (p_j+b_j) \Bigg], \\
&= \sum_{i \in N} b_i (1-q(i)) E_{\{j \in N | j>i\}}(N \setminus \{i\}).
\end{aligned}$$

Note that in future use of the expected quality of outcome, we use the simpler notation $E_{\{\text{conditions on } j\}}(N)$, where it is assumed that $j \in N$, instead of the more complete $E_{\{j \in N | \text{conditions on } j\}}(N)$.

The added benefit is:

$$
\begin{aligned}
\mathfrak{B}_i^A &= E_i(N) - E(N) \\
&= \sum_{S\subseteq N} P_{\{i\}}(S,N)q(S) - \sum_{S\subseteq N} P(S,N)q(S) \\
&= \sum_{S\subseteq N} [P_{\{i\}}(S,N) - P(S,N)]q(S)] \\
&= \sum_{S\subseteq N} \left[(1-p_i-b_i)^{I(i\in S)}(p_i+b_i)^{I(i\in N\setminus S)} \prod_{j\in S\setminus\{i\}} (1-p_j) \prod_{j\in N\setminus S\setminus\{i\}} p_j - \prod_{j\in S}(1-p_j) \prod_{j\in N\setminus S} p_j \right] q(S) \\
&= \sum_{T\subseteq N\setminus\{i\}} \left\{ \left[(p_i+b_i)\prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j - p_i \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j \right] q(T) \right. \\
&\qquad\qquad \left. + \left[(1-p_i-b_i)\prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j - (1-p_i)\prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j \right] q(T\cup\{i\}) \right\} \\
&= \sum_{T\subseteq N\setminus\{i\}} \left\{ [(p_i+b_i-p_i)q(T) + (1-p_i-b_i-(1-p_i))q(T)\times q(i)] \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j \right\}.
\end{aligned}
$$

Therefore,
$$
\begin{aligned}
\mathfrak{B}_i^A &= b_i(1-q(i)) \sum_{T\subseteq N\setminus\{i\}} q(T) \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j \\
&= b_i(1-q(i))E(N\setminus\{i\}).
\end{aligned}
$$

The withdrawal benefit is:

$$
\begin{aligned}
\mathfrak{B}_i^W &= E_N(N) - E_{N\setminus\{i\}}(N) \\
&= \sum_{S\subseteq N} P_N(S,N)q(S) - \sum_{S\subseteq N} P_{N\setminus\{i\}}(S,N)q(S) \\
&= \sum_{S\subseteq N} \left[P_N(S,N) - P_{N\setminus\{i\}}(S,N)\right] q(S) \\
&= \sum_{S\subseteq N} \left[\prod_{j\in S}(1-p_j-b_j) \prod_{j\in N\setminus S}(p_j+b_j) - (1-p_i)^{I(i\in S)} p_i^{I(i\in N\setminus S)} \prod_{j\in S\setminus\{i\}}(1-p_j-b_j) \prod_{j\in N\setminus S\setminus\{i\}}(p_j+b_j)\right] q(S) \\
&= \sum_{T\subseteq N\setminus\{i\}} \left[\left((p_i+b_i)\prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j) - p_i\prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j)\right) q(T)\right. \\
&\qquad \left. + \left((1-p_i-b_i)\prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j) - (1-p_i)\prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j)\right) q(T\cup\{i\})\right] \\
&= \sum_{T\subseteq N\setminus\{i\}} \left\{[(p_i+b_i-p_i)q(T) + (1-p_i-b_i-(1-p_i))q(T)q(i)] \prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j)\right\} \\
&= b_i(1-q(i)) \sum_{T\subseteq N\setminus\{i\}} q(T) \prod_{j\in T}(1-p_j-b_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j).
\end{aligned}
$$

Therefore, $\mathfrak{B}_i^W = b_i(1-q(i))E_{N\setminus\{i\}}(N\setminus\{i\})$.

□

Using these expressions, it is then simple to show that the snapshot benefits in expected quality of outcome have the same relationship as the benefits measured in probability of negative outcome. However, due to the weaker assumptions regarding the expected quality of outcome, the inequalities are not strict, as before.

Theorem 8.

$$\sum_{i\in N}\mathfrak{B}_i^A \le \mathfrak{B}^C \le \sum_{i\in N}\mathfrak{B}_i^W \le \sum_{i\in N}\mathfrak{b}_i.$$

Proof.

$$\mathfrak{B}_i^A = b_i(1-q(i))E(N\setminus\{i\}),$$

therefore,

$$\begin{aligned}\sum_{i\in N}\mathfrak{B}_i^A &= \sum_{i\in N} b_i(1-q(i))E(N\setminus\{i\}) \\ &\le \sum_{i\in N} b_i(1-q(i))E_{\{j>i\}}(N\setminus\{i\}),\end{aligned}$$

since

$$E(N\setminus\{i\}) \le E_{\{j>i\}}(N\setminus\{i\}), \quad \forall i\in N,$$

because treating some of a set of diseases can be no worse than treating none of them, by Assumption 2. That is,

$$\sum_{i\in N}\mathfrak{B}_i^A \le \sum_{i\in N} b_i(1-q(i))E_{\{j>i\}}(N\setminus\{i\}) = \mathfrak{B}^C.$$

Now,

$$\begin{aligned}\mathfrak{B}^C &= \sum_{i\in N} b_i(1-q(i))E_{\{j>i\}}(N\setminus\{i\}) \\ &\le \sum_{i\in N} b_i(1-q(i))E_{N\setminus\{i\}}(N\setminus\{i\}),\end{aligned}$$

as

$$E_{\{j>i\}}(N\setminus\{i\}) \le E_{N\setminus\{i\}}(N\setminus\{i\}) \quad \forall i\in N,$$

since treating all of a set of diseases must be no worse than treating only some of them. That is,

$$\mathfrak{B}^C \leq \sum_{i \in N} b_i(1 - q(i))E_{N\setminus\{i\}}(N \setminus \{i\}) = \sum_{i \in N} \mathfrak{B}_i^W.$$

Lastly,

$$\begin{aligned}\sum_{i \in N} \mathfrak{B}_i^W &= \sum_{i \in N} b_i(1 - q(i))E_{N\setminus\{i\}}(N \setminus \{i\}) \\ &\leq \sum_{i \in N} b_i(1 - q(i)),\end{aligned}$$

since

$$0 \leq E_{N\setminus\{i\}}(N \setminus \{i\}) \leq 1 \quad \forall i \in N.$$

That is,

$$\sum_{i \in N} \mathfrak{B}_i^W \leq \sum_{i \in N} b_i(1 - q(i)) = \sum_{i \in N} \mathfrak{b}_i.$$

It therefore follows that,

$$\sum_{i \in N} \mathfrak{B}_i^A \leq \mathfrak{B}^C \leq \sum_{i \in N} \mathfrak{B}_i^W \leq \sum_{i \in N} \mathfrak{b}_i.$$

□

Ideal Benefit and Iatrogenic Loss

We can also define the ideal benefit and iatrogenic loss in terms of expected quality of outcome. Recall, the ideal benefit in terms of the decrease in probability of negative outcomes of treating disease i is $b_i^I = b_i + \ell_i$. Therefore the ideal benefit of an individual treatment i in expected quality of outcome is:

$$\begin{aligned}\mathfrak{b}_i^I &= E_i^I(i) - E(i) \\ &= p_i + b_i + \ell_i - (1 - p_i - b_i - \ell_i)q(i) - p_i - (1 - p_i)q(i) \\ &= (b_i + \ell_i)(1 - q(i)) \\ &= b_i^I(1 - q(i)).\end{aligned}$$

Definition 15. Consider that a patient is suffering from a set of diseases, N. The **combined ideal benefit** of treating all diseases in expected quality of outcome is

$$\mathfrak{B}^{I,C} = E^I_N(N) - E(N).$$

The **added ideal benefit** of treating disease i in expected quality of outcome is

$$\mathfrak{B}^{I,A}_i = E^I_i(N) - E(N).$$

The **withdrawal ideal benefit** of treating disease i in expected quality of outcome is

$$\mathfrak{B}^{I,W}_i = E^I_N(N) - E^I_{N\setminus\{i\}}(N).$$

Lemma 3.

$$\mathfrak{B}^{I,C} = \sum_{i\in N} b^I_i(1-q(i))E^I_{\{j>i\}}(N\setminus\{i\}),$$

$$\mathfrak{B}^{I,A}_i = b^I_i(1-q(i))E(N\setminus\{i\}),$$

and,

$$\mathfrak{B}^{I,W}_i = b^I_i(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}).$$

Proof. We know

$$\mathfrak{b}^I_i = (b_i+\ell_i)(1-q(i)),$$

and

$$\mathfrak{b}_i = b_i(1-q(i)).$$

Since $0 \le \ell_i \le 1-b_i$, for all $i \in N$, we replace b_i with $b_i+\ell_i$ in the proof of Lemma 2, and the results hold. □

Theorem 9.

$$\sum_{i\in N}\mathfrak{B}^{I,A}_i \le \mathfrak{B}^{I,C} \le \sum_{i\in N}\mathfrak{B}^{I,W}_i \le \sum_{i\in N}\mathfrak{b}^I_i.$$

Proof. Firstly,

$$\mathfrak{B}^{I,A}_i = b^I_i(1-q(i))E(N\setminus\{i\}),$$

Therefore,

$$\begin{aligned}\sum_{i\in N}\mathfrak{B}_i^{I,A} &= \sum_{i\in N} b_i^I(1-q(i))E(N\setminus\{i\}) \\ &\leq \sum_{i\in N} b_i^I(1-q(i))E^I_{\{j>i\}}(N\setminus\{i\}),\end{aligned}$$

since treating some diseases ideally must be at least as beneficial, in terms of expected quality of outcome, as treating no diseases. That is,

$$\sum_{i\in N}\mathfrak{B}_i^{I,A} \leq \sum_{i\in N} b_i^I(1-q(i))E^I_{\{j>i\}}(N\setminus\{i\}) = \mathfrak{B}^{I,C}.$$

Now,

$$\begin{aligned}\mathfrak{B}^{I,C} &= \sum_{i\in N} b_i^I(1-q(i))E^I_{\{j>i\}}(N\setminus\{i\}) \\ &\leq \sum_{i\in N} b_i^I(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}),\end{aligned}$$

since treating all of a set of diseases ideally must be no worse than treating only some of them, even if ideally (Assumption 2). That is,

$$\mathfrak{B}^{I,C} \leq \sum_{i\in N} b_i^I(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}) = \sum_{i\in N}\mathfrak{B}_i^{I,W}.$$

Lastly,

$$\begin{aligned}\sum_{i\in N}\mathfrak{B}_i^{I,W} &= \sum_{i\in N} b_i^I(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}) \\ &\leq \sum_{i\in N} b_i^I(1-q(i)),\end{aligned}$$

since,

$$0 \leq E^I_{N\setminus\{i\}}(N\setminus\{i\}) \leq 1.$$

That is,

$$\sum_{i\in N}\mathfrak{B}_i^{I,W} \leq \sum_{i\in N} b_i^I(1-q(i)) = \sum_{i\in N}\mathfrak{b}_i^I.$$

It then follows that,

$$\sum_{i\in N}\mathfrak{B}_i^{I,A} \leq \mathfrak{B}^{I,C} \leq \sum_{i\in N}\mathfrak{B}_i^{I,W} \leq \sum_{i\in N}\mathfrak{b}_i^I.$$

□

We can also show that the same inequalities hold for the iatrogenic losses in terms of the expected quality of outcome.

Definition 16. The **combined iatrogenic loss** in expected quality of outcome is

$$\mathfrak{L}^C = E_N^I(N) - E_N(N),$$

the **added iatrogenic loss** of treating disease i in expected quality of outcome is

$$\mathfrak{L}_i^A = E_i^I(N) - E_i(N),$$

and the **withdrawal iatrogenic loss** of treating disease i in expected quality of outcome is

$$\mathfrak{L}_i^W = E_N^I(N) - E_{\{i\},N\setminus\{i\}}(N).$$

Lemma 4.

$$\mathfrak{L}^C = \sum_{i\in N} \ell_i(1-q(i))E_{\{j<i\},\{j>i\}}(N\setminus\{i\}),$$
$$\mathfrak{L}_i^A = \ell_i(1-q(i))E(N\setminus\{i\}),$$

and,

$$\mathfrak{L}_i^W = \ell_i(1-q(i))E_{N\setminus\{i\}}^I(N\setminus\{i\}).$$

Proof.

$$\begin{aligned}
\mathfrak{L}^C &= E_N^I(N) - E_N(N) \\
&= \sum_{S\subseteq N} \left[P_N^I(S,N) - P_N(S,N)\right] q(S) \\
&= \sum_{S\subseteq N} \left[\prod_{j\in S}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus S}(p_j+b_j+\ell_j) - \prod_{j\in S}(1-p_j-b_j) \prod_{j\in N\setminus S}(p_j+b_j)\right] q(S) \\
&= \sum_{S\subseteq N}\sum_{i\in N} \ell_i \prod_{\substack{j\in S;\\ j<i}}(1-p_j-b_j) \prod_{\substack{j\in N\setminus S;\\ j<i}}(p_j+b_j) \prod_{\substack{j\in S;\\ j>i}}(1-p_j-b_j-\ell_j) \\
&\qquad\qquad \times \prod_{\substack{j\in N\setminus S;\\ j>i}}(p_j+b_j+\ell_j)(-1)^{I(i\in S)} q(S)
\end{aligned}$$

$$= \sum_{T\subseteq N\setminus\{i\}} \sum_{i\in N} \ell_i \prod_{\substack{j\in T;\\ j<i}} (1-p_j-b_j) \prod_{\substack{j\in N\setminus T;\\ j<i}} (p_j+b_j)$$
$$\times \prod_{\substack{j\in T;\\ j>i}} (1-p_j-b_j-\ell_j) \prod_{\substack{j\in N\setminus T;\\ j>i}} (p_j+b_j+\ell_j)[q(T)-q(T\cup\{i\})]$$
$$= \sum_{i\in N} \ell_i(1-q(i)) \sum_{T\subseteq N\setminus\{i\}} q(T) \prod_{\substack{j\in T;\\ j<i}} (1-p_j-b_j) \prod_{\substack{j\in N\setminus T;\\ j<i}} (p_j+b_j)$$
$$\times \prod_{\substack{j\in T;\\ j>i}} (1-p_j-b_j-\ell_j) \prod_{\substack{j\in N\setminus T;\\ j>i}} (p_j+b_j+\ell_j)$$
$$= \sum_{i\in N} \ell_i(1-q(i)) E_{\{j<i\},\{j>i\}}(N\setminus\{i\}).$$

$$\mathfrak{L}_i^A = E_i^I(N) - E_i(N)$$
$$= \sum_{S\subseteq N} [P_{\{i\}}^I(S,N) - P_{\{i\}}(S,N)]q(S)$$
$$= \sum_{S\subseteq N} \Bigg[(p_i+b_i+\ell_i)^{I(i\notin S)}(1-p_i-b_i-\ell_i)^{I(i\in S)} \prod_{j\in N\setminus\{i\}\setminus S} p_j \prod_{j\in S\setminus\{i\}} (1-p_j)$$
$$-(p_i+b_i)^{I(i\notin S)}(1-p_i-b_i)^{I(i\in S)} \prod_{j\in N\setminus\{i\}\setminus S} p_j \prod_{j\in S\setminus\{i\}} (1-p_j) \Bigg] q(S)$$
$$= \sum_{S\subseteq N} \big[(p_i+b_i+\ell_i)^{I(i\notin S)}(1-p_i-b_i-\ell_i)^{I(i\in S)}$$
$$-(p_i+b_i)^{I(i\notin S)}(1-p_i-b_i)^{I(i\in S)}\big] \prod_{j\in N\setminus\{i\}\setminus S} p_j \prod_{j\in S\setminus\{i\}} (1-p_j) q(S)$$
$$= \sum_{T\subseteq N\setminus\{i\}} [q(T)((p_i+b_i+\ell_i)-(p_i+b_i))$$
$$-q(T\cup\{i\})((1-p_i-b_i-\ell_i)-(1-p_i-b_i))] \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j$$
$$= \sum_{T\subseteq N\setminus\{i\}} [\ell_i q(T) - \ell_i q(T)q(i)] \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j$$
$$= \ell_i(1-q(i)) \sum_{T\subseteq N\setminus\{i\}} q(T) \prod_{j\in T}(1-p_j) \prod_{j\in N\setminus\{i\}\setminus T} p_j$$
$$= \ell_i(1-q(i))E(N\setminus\{i\}).$$

$$
\begin{aligned}
\mathfrak{L}_i^W &= E_N^I(N) - E_{\{i\},N\setminus\{i\}}(N) \\
&= \sum_{S\subseteq N} P_N^I(S,N)q(S) - \sum_{S\subseteq N} P_{\{i\},N\setminus\{i\}}(S,N)q(S) \\
&= \sum_{S\subseteq N} \left[P_N^I(S,N) - P_{\{i\},N\setminus\{i\}}(S,N)\right] q(S) \\
&= \sum_{S\subseteq N} \Bigg[\prod_{j\in S}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus S}(p_j+b_j+\ell_j) - (1-p_i-b_i)^{I(i\in S)}(p_i+b_i)^{I(i\notin S)} \\
&\qquad\qquad \times \prod_{j\in S\setminus\{i\}}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus S\setminus\{i\}}(p_j+b_j+\ell_j)\Bigg] q(S) \\
&= \sum_{S\subseteq N} \left[(1-p_i-b_i-\ell_i)^{I(i\in S)}(p_i+b_i+\ell_i)^{I(i\notin S)} - (1-p_i-b_i)^{I(i\in S)}(p_i+b_i)^{I(i\notin S)}\right] \\
&\qquad\qquad \times \prod_{j\in S\setminus\{i\}}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus S\setminus\{i\}}(p_j+b_j+\ell_j) q(S) \\
&= \sum_{T\subseteq N\setminus\{i\}} \prod_{j\in T}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j+\ell_j) \\
&\quad \times \left[((p_i+b_i+\ell_i)-(p_i+b_i))q(T) - ((1-p_j-b_j-\ell_j)-(1-p_j-b_j))q(T\cup\{i\})\right] \\
&= \sum_{T\subseteq N\setminus\{i\}} \left[\ell_i q(T) - \ell_i q(T)q(i)\right] \prod_{j\in T}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j+\ell_j) \\
&= \ell_i(1-q(i)) \sum_{T\subseteq N\setminus\{i\}} q(T) \prod_{j\in T}(1-p_j-b_j-\ell_j) \prod_{j\in N\setminus\{i\}\setminus T}(p_j+b_j+\ell_j) \\
&= \ell_i(1-q(i))E_{N\setminus\{i\}}^I(N\setminus\{i\}).
\end{aligned}
$$

□

Theorem 10.

$$\sum_{i\in N}\mathfrak{L}_i^A < \mathfrak{L}^C \le \sum_{i\in N}\mathfrak{L}_i^W \le \sum_{i\in N}\mathfrak{l}_i.$$

Proof. Firstly,

$$\mathfrak{L}_i^A = \ell_i(1-q(i))E(N\setminus\{i\}),$$

therefore,

$$\begin{aligned}\sum_{i\in N}\mathfrak{L}_i^A &= \sum_{i\in N}\ell_i(1-q(i))E(N\setminus\{i\})\\ &< \sum_{i\in N}\ell_i(1-q(i))E_{\{j<i\},\{j>i\}}(N\setminus\{i\}),\end{aligned}$$

since treating all of a set of diseases must be strictly better than treating none of them. That is,

$$\sum_{i\in N}\mathfrak{L}_i^A < \sum_{i\in N}\ell_i(1-q(i))E_{\{j<i\},\{j>i\}}(N\setminus\{i\}) = \mathfrak{L}^C.$$

Now,

$$\begin{aligned}\mathfrak{L}^C &= \sum_{i\in N}\ell_i(1-q(i))E_{\{j<i\},\{j>i\}}(N\setminus\{i\})\\ &\leq \sum_{i\in N}\ell_i(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}),\end{aligned}$$

since treating those diseases $j < i$ ideally must be no worse than treating them normally. That is,

$$\mathfrak{L}^C \leq \sum_{i\in N}\ell_i(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\}) = \sum_{i\in N}\mathfrak{L}_i^W.$$

Lastly,

$$\begin{aligned}\sum_{i\in N}\mathfrak{L}_i^W &= \sum_{i\in N}\ell_i(1-q(i))E^I_{N\setminus\{i\}}(N\setminus\{i\})\\ &\leq \sum_{i\in N}\ell_i(1-q(i)),\end{aligned}$$

since

$$0 \leq E^I_{N\setminus\{i\}}(N\setminus\{i\}) \leq 1.$$

That is,

$$\sum_{i\in N}\mathfrak{L}_i^W \leq \sum_{i\in N}\ell_i(1-q(i)) = \sum_{i\in N}\mathfrak{l}_i.$$

It then follows that,

$$\sum_{i\in N}\mathfrak{L}_i^A < \mathfrak{L}^C \leq \sum_{i\in N}\mathfrak{L}_i^W \leq \sum_{i\in N}\mathfrak{l}_i.$$

□

However, all of these results only consider the snapshot benefits; that is, the benefit at a single point in time rather than over a patient's lifetime, as we would like. In the following chapter we first create a model to measure the benefit of treating an individual disease over time, to later create a combined model to calculate the benefit of treating *multiple* diseases over time. Eventually, we show that the results we have proved in this chapter can be applied to the benefits and losses over a patient's lifetime.

Chapter 4

Markov Models for Individual Treatments

Ultimately, our aim is to be able to calculate the true benefit of combined treatments over time, rather than simply adding individual benefits. Therefore we would like to create a Markov model for each individual disease, and its respective treatment, that is transferable to other diseases. We later would like to use these to create a combined model to calculate the true benefit of multiple treatments over time.

We deliberately choose a simple individual model, so that overlaying multiple single disease models is feasible later on. We consider states that could be easily transferred to various diseases, and transition probabilities for which there is data easily available.

4.1 An Existing Model of CEA

We use a previously defined Markov model of carotid endarterectomy (CEA) on patients with carotid artery stenosis (CAS) as the basis for our model [11]. As mentioned previously, carotid endarterectomy, or CEA, is surgical treatment for carotid artery stenosis (CAS). That is, it is surgery to remove a blockage in the carotid artery. We know that this blockage can cause strokes in patients who are

suffering from CAS, and the probability of stroke varies depending on the extent of the blockage or occlusion. Since surgery is generally a risky treatment option, we only consider patients with severe symptomatic stenosis, as it has been shown that under general circumstances, CEA on asymptomatic patients shows little benefit [15]. Nagaki *et al.* [11] defined patients with symptomatic stenosis to have had a 'transient ischemic attack or nondisabling stroke within the previous 6 months', and we consider 'severe' stenosis to be 70-99% occlusion of the carotid artery.

We choose this article as it has the only fully defined model in the literature, including all states, transitions and parameters, that we have been able to find. In this article, Nagaki *et al.* define four health states, "well with stenosis", "well without stenosis", "post stroke", and "dead", that are exhaustive and mutually exclusive. The states are defined as follows: A patient in the "well with stenosis" state (state 1) has 'severe, symptomatic stenosis' but is still functional; that is, not disabled as a result of the stenosis. A patient in "well without stenosis" (state 2) is non-disabled and no longer suffering from stenosis, after surgery. In "post stroke" (state 3), a patient has had a sufficiently severe stroke that has disabled them in some capacity, be it physically or neurologically. Finally, a patient in the "dead" state (state 4) has died, either from a stroke or other causes. These states are general enough to be easily adaptable to other diseases by carefully redefining them.

Building upon this model, Nagaki *et al.* also make some assumptions about the transitions between the states:

- the only way to transition from "well with stenosis" to "well without stenosis" is via the surgery (CEA);
- once a patient reaches "well without stenosis" they cannot return to "well with stenosis". That is, once the disease is treated successfully, it does not return;
- from the "post stroke" state, a patient cannot recover back to the "well-" states;

- in the "post stroke" state there is only one level of 'disabled'. Further, no second strokes are considered, therefore once a patient reaches "post stroke" they can only either die, or remain at the same level of disablement;

- once a patient reaches the "dead" state they clearly cannot return to any other state.

This method of classifying the states works well for episodic diseases. That is, for diseases that cause an event, such as a stroke, from which a patient can die or become disabled. However, if we were to consider diseases that are degenerative in nature, *e.g.* dementia, congestive heart failure, *etc.*, meaning that they do not cause an impairing event, but instead cause a patient to become gradually more impaired over time, we would need to create a different model. In this thesis, however, we consider only episodic diseases.

In this particular case, a discrete-time Markov model is used to track the progress of the disease over time. Even though the transitions can happen at any point in time, meaning that continuous time may be more accurate, we are only interested in the outcomes at the end of each year after surgery. Discrete time models are also simpler to evaluate, and most of the clinical trial data available is presented with, or easily converted to, annual probabilities. The time intervals we use are one year in length, with the exception of the first two intervals of the chain, the reason for which we will see later in this chapter.

We can use this model as a basis to create our single disease models. To find the benefit of a single treatment we need to use two different Markov chains: one without the treatment that we are analysing (the control), and one with the treatment. For example, in the case of this CEA model, one chain with medical treatment only, and one with surgical treatment (CEA) as well as continued medical treatment. In this case, our control chain is the medical treatment only, as surgical clinical trials often consider surgical treatment in addition to medical treatment.

4.1.1 Medical Chain

First, let us consider the control chain of the CEA model, where the control group receives only medical treatment. As described above, the state space is:

$$S = \{1 \text{ (well with stenosis)}, 2 \text{ (well without stenosis)}, 3 \text{ (post stroke)}, 4 \text{ (dead)}\}.$$

We assume that all patients start in state 1, "well with stenosis", otherwise they would not be considering the surgery. Since we also assume that the only way to become "well without stenosis" is to undergo CEA, a patient in the medical chain will not reach the "well without stenosis" state. That is,

$$\begin{aligned} p_{i,2} &= 0 \quad \forall i \in S, \\ \text{and} \quad p_{2,i} &= 0 \quad \forall i \in S. \end{aligned}$$

If a patient is in "well with stenosis", they can either have a stroke and transition to "post stroke", die, or remain in "well with stenosis" at the end of an interval. The probability that they go from "well with stenosis" to "post stroke" is the probability that they have a stroke and do not die. That is,

$$\begin{aligned} p_{1,3} &= P(\text{have stroke} \cap \text{don't die}) \\ &= P(\text{have stroke})P(\text{don't die}|\text{have stroke}), \end{aligned}$$

where $P(\text{have stroke})$ is the annual probability (as our time intervals are one year) of a stroke occurring in patients with severe symptomatic stenosis who have not had surgery, as taken from clinical trial data. Also,

$$P(\text{don't die}|\text{have stroke}) = 1 - P(\text{die}|\text{have stroke}),$$

where

$$P(\text{die}|\text{have stroke}) = d$$

is the probability of death from a stroke in patients with stenosis, as taken from the literature.

For a patient to reach "dead" from "well with stenosis", they could either die from a stroke or die from other causes. That is,

$$\begin{aligned} p_{1,4} &= P(\text{have stroke} \cap \text{die}) + P(\text{die other causes}) \\ &= P(\text{have stroke})P(\text{die}|\text{have stroke}) + P(\text{die other causes}) \\ &= P(\text{have stroke}) \times d + P(\text{die other causes}), \end{aligned}$$

where $P(\text{have stroke})$ and d are as defined previously.

In the original CEA model [11], $P(\text{die other causes})$ is taken to be the difference between the age related probability of death in the general population and the probability of dying from stroke, where the age related probability of death is $p(x)$, with x the patient's age in years. That is,

$$P(\text{die other causes}) = p(x) - P(\text{have stroke} \cap \text{die}),$$

so that,

$$p_{1,4} = p(x).$$

Therefore, using the original model, the probability of remaining "well with stenosis" is:

$$\begin{aligned} p_{1,1} &= 1 - p_{1,3} - p_{1,4} \\ &= 1 - P(\text{have stroke} \cap \text{don't die}) - p(x). \end{aligned}$$

If a patient has had a non-fatal event and they are in the "post stroke" state, then at the end of the next cycle they could either stay in "post stroke" or transition to the "dead" state. Since we assume that once a patient has had a stroke, they do not have another, then:

$$p_{3,4} = p(x).$$

That is, the probability of transitioning to the "dead" state is just the age related probability of death of the general population. Therefore, the probability of remaining in the "post stroke" state is the same as the probability of not dying. That

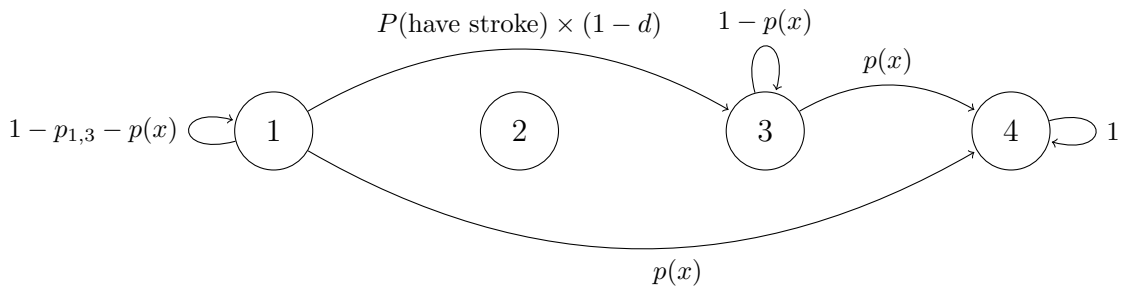


Figure 4.1: State diagram showing the transitions in the medical chain, for the original CEA model.

is,

$$p_{3,3} = 1 - p(x).$$

Clearly, once a patient reaches the "dead" state, they are unable to leave, and hence "dead" is an absorbing state. That is,

$$p_{4,4} = 1.$$

The transitions in the non-surgical chain are depicted in Figure 4.1.

4.1.2 Surgical Chain

We now establish the transition probabilities of the treatment (CEA) Markov chain, similarly to the control chain. This will allow us to compare and hence calculate the benefit of CEA.

In the treatment chain, or in this case, surgical chain, we assume all patients are ungerdoing the surgery, and that the surgery occurs at the beginning of the chain. Since all patients are having the surgery, they can now transition to the "well without stenosis" state, by having successful surgery.

Since the patient does have the surgery, the probability of going from "well with stenosis" to "well without stenosis" is the probability that they do not suffer a stroke caused by the treatment. Here, we are considering a surgical treatment, where the

surgery only happens once, rather than an ongoing treatment. We use,

$$p_{1,2} = 1 - s,$$

where $s =$ surgical risk, is the probability of suffering from a stroke or dying within 30 days of the surgery [11].

Similarly, a patient can go from "well with stenosis" to "post stroke" due to the surgery; this transition probability is the probability of suffering from surgical risk and not dying. That is,

$$\begin{aligned} p_{1,3} &= P(\text{have stroke from treatment} \cap \text{don't die}) \\ &= P(\text{have stroke from treatment})P(\text{don't die}|\text{have stroke}) \\ &= s \times (1 - P(\text{die}|\text{have stroke})) \\ &= s \times (1 - d). \end{aligned}$$

Then the probability of going from "well with stenosis" to "dead" is just the probability of dying from the treatment. That is,

$$\begin{aligned} p_{1,4} &= P(\text{have stroke from treatment} \cap \text{die}) \\ &= P(\text{have stroke from treatment})P(\text{die}|\text{have stroke}) \\ &= s \times d. \end{aligned}$$

Therefore, it makes sense that a patient cannot stay in the "well with stenosis" state, as they must have the surgery, which could either be successful and have them in the "well without stenosis" state, or not and have them in the "post stroke" or "dead" states. That is, we assume that the surgery cannot be ineffective in the sense that a patient cannot be in the same state after undergoing the surgery, and so

$$p_{1,1} = 0.$$

From the "well without stenosis" state, a patient could still suffer from a stroke and transition to the "post stroke" state, but with a different, presumably lower,

probability than before surgery. This transition probability is just:

$$\begin{aligned} p_{2,3} &= P(\text{have stroke after CEA} \cap \text{don't die}) \\ &= P(\text{have stroke after CEA})P(\text{don't die}|\text{have stroke}) \\ &= P(\text{have stroke after CEA})(1-d), \end{aligned}$$

as before.

From the "well without stenosis" state, a patient could still also die from either a stroke or other causes. This is similar to the transition probability from "well with stenosis" to "dead" in the control chain. That is,

$$p_{2,4} = p(x).$$

Since we assume that if a patient is in the "well without stenosis" state after successful CEA, they cannot then return to having the disease, that is, cannot return to the "well with stenosis" state, we have that

$$p_{2,1} = 0.$$

Therefore, the probability of remaining in "well without stenosis" is the same as the probability of not having a stroke or dying. That is,

$$p_{2,2} = 1 - P(\text{have stroke after CEA})(1-d) - p(x).$$

As in the medical chain, the only way to transition from "post stroke" is to die. That is,

$$\begin{aligned} & p_{3,4} = p(x) \\ \text{and} \quad & p_{3,3} = 1 - p(x), \end{aligned}$$

and, again, clearly

$$p_{4,4} = 1.$$

The transitions for the surgical chain are depicted in Figure 4.2.

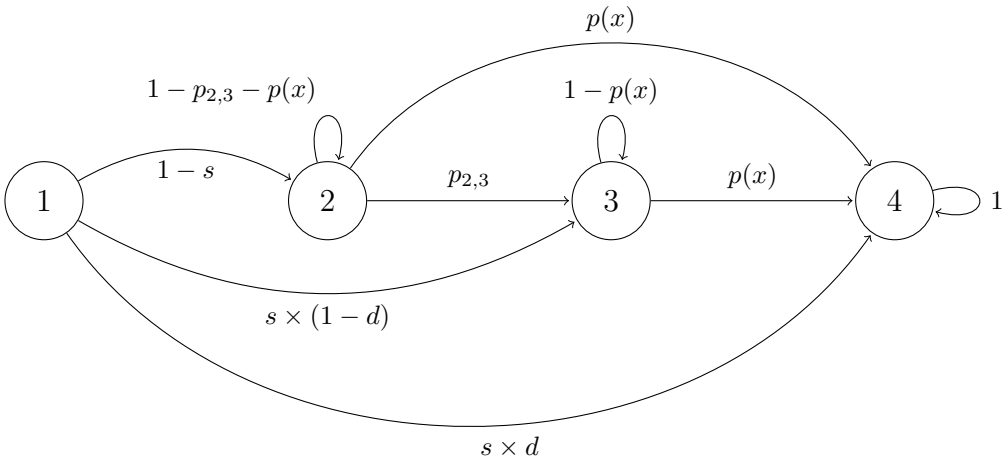


Figure 4.2: State diagram showing the transitions in the surgical chain, for the original CEA model.

4.1.3 Recreating Established Parameters for a CEA Model

To verify the validity of this model, we can obtain the parameters that are required by utilising the same source that Nagaki *et al.* [11] use in the original model [15]. The aim is to be able to reproduce and understand where the numbers in the model come from, and to be able to gain the necessary knowledge and practise to be able to source parameters for Markov models of other diseases and treatments. In this section, we are able to source and recreate most of the probabilities used in Nagaki *et al.*'s model, with some exceptions and disagreements.

Nagaki *et al.* used discrete time steps of one year, therefore, we also use time steps of one year in our model. However, to account for the surgical risk period, we break the first year into two different time periods: a 30 day period for surgical risk, and the remaining 335 days of the year.

As mentioned previously, the state space we are considering, for both the surgical and non-surgical chains, is:

$$S = \{1 \text{ (well with CAS)}, 2 \text{ (well without CAS)}, 3 \text{ (post stroke)}, 4 \text{ (dead)}\}.$$

We now have two discrete-time Markov chains with a clearly defined state space,

and we only need to specify the transition probabilities.

Medical Chain

As mentioned before, first we create the control chain. In this particular case, the control group is the group that had only medical treatment, thus we call it the medical chain. Using the established base model, the positive transition probabilities for the medical chain are:

$$\begin{aligned} p_{1,1} &= 1 - P(\text{have stroke}) \times (1-d) - p(x) \\ p_{1,3} &= P(\text{have stroke}) \times (1-d) \\ p_{1,4} &= p(x) \\ p_{3,3} &= 1 - p(x) \\ p_{3,4} &= p(x) \\ p_{4,4} &= 1. \end{aligned}$$

In the original model, Nagaki *et al.* use the annual probability of death of the population at age x:

$$p(x) = e^{-10.58+0.095x}$$

which was obtained by regression analysis of death rates from Japanese Life Statistics data [11].

Let $P(\text{have stroke}) = e$, where e is the annual risk of stroke in patients with severe symptomatic stenosis. Nagaki *et al.* use a value for the probability of stroke that changes depending on the number of years it has been since the beginning of the chain. In the medical patients, it is originally stated as:

$$e = \begin{cases} 0.16 & \text{for 0-1 year} \\ 0.08 & \text{for 1-2 years} \\ 0.05 & \text{for 2-3 years} \\ 0.017 & \text{for 3 years onwards} \end{cases}$$

based on a pooled analysis of clinical trial data [11].

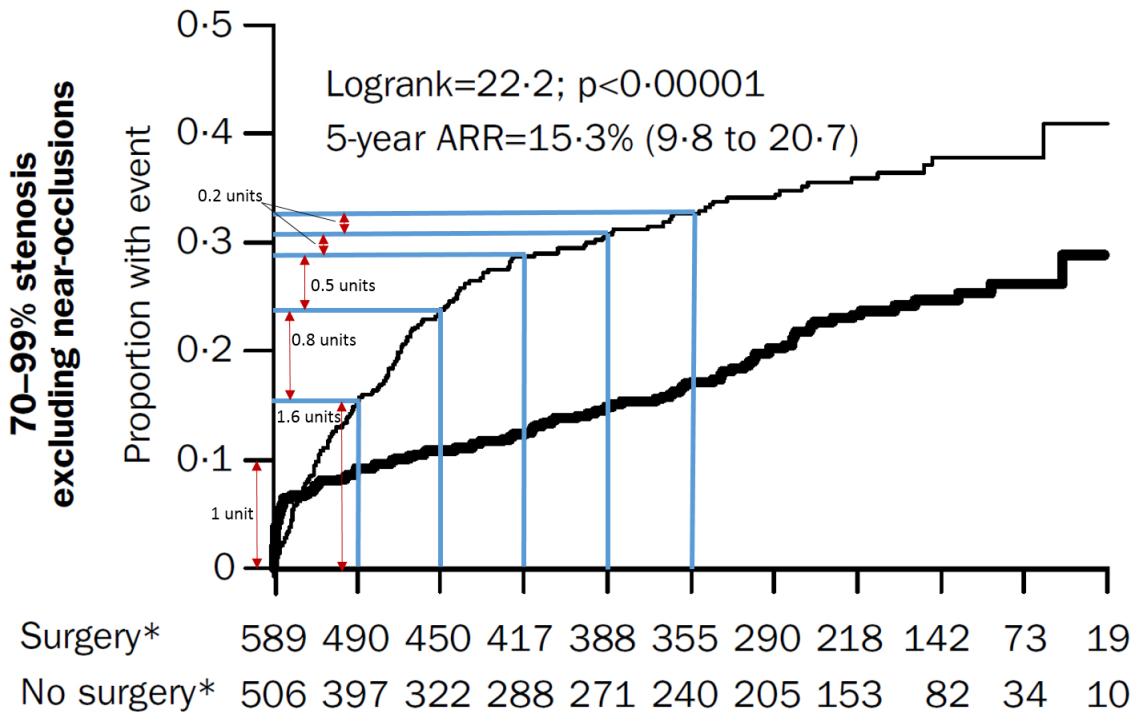


Figure 4.3: Kaplain-Meier curve of any stroke or operative death [15]. The thin line represents the medical group of patients, the thick line represents the surgical group, and each step along the x axis is one year.

To recreate these numbers, we source the pooled analysis [15] and analyse the data available. We focus only on the patients with 70-99% occlusion, as this group of patients are defined to have 'severe symptomatic stenosis', as in the model. We are given, after 5 years, that the absolute reduction in risk of stroke or operative death is 15.6%, and the relative reduction in risk is 0.52%. Assuming that the cumulative proportion of patients who suffered a stroke or operative death each year is roughly linear, we could use this data to find e, the annual probability of stroke in the medical chain. However, we can see from the Kaplan-Meier curve of any stroke or operative death, Figure 4.3, provided in the pooled analysis, that the proportions in the medical group are not linear. Therefore, since we are not provided with the data for individual years, we use the crude method of ruling straight lines on the figure to approximate the values for e at each year.

First we draw straight, vertical lines at years one to five, that meet the 'No surgery' curve, then a horizontal line from this point to the y-axis. At this intersection, we find the approximate proportion of medical patients that have suffered a stroke up until that time point. Then by carefully measuring the height corresponding to a proportion of 0.1, and the height of the difference in proportion each year, we obtain estimates of the annual risk of stroke (Figure 4.3). After three years, the medical curve is approximately linear, so we assume that the probability of stroke after three years does not change.

As can be seen in Figure 4.3, we let a proportion of 0.1 on the graph be 1 unit. This makes calculating the annual probabilities relatively simple. We have that the height of the difference at year 1 is 1.6 units, between year 1 and 2 is 0.8 units, between year 2 and 3 is 0.5 units, and between year 3 and 4 is 0.2 units.

Therefore, the probability of stroke or death, e, is:

$$e = \begin{cases} \text{0-1 year is} \approx 1.6 \times \frac{1}{10} = 0.16 \\ \text{1-2 years is} \approx 0.8 \times \frac{1}{10} = 0.08 \\ \text{2-3 years is} \approx 0.5 \times \frac{1}{10} = 0.05 \\ \text{3-4 years is} \approx 0.2 \times \frac{1}{10} = 0.02. \end{cases}$$

These obtained values match almost exactly to the values provided in Nagaki *et al.*'s model, the exception being e at 3-4 years. We assume that Nagaki *et al.* were able to obtain more precise data, and in order to recreate their final results, we use the values of e from their paper.

The only remaining value to be sourced is $P(\text{die}|\text{have stroke}) = d$. Nagaki *et al.* state that transient ischemic attacks or minor strokes without disability are not included in their analysis. Without reference, they estimate 'that the mortality rate after stroke would be 20%, and that the survivors (80%) would sustain disability' [11]. That is,

$$d = 0.2.$$

Since no references are provided, we cannot verify these values. However, for now we

only wish to find if the model structure is sensible, so we use them in this instance, and alter them in future models.

Since there are probabilities that depend on the years since the beginning of the chain, the Markov chain is time inhomogeneous. Therefore, for the medical chain, we now have transition probability matrix:

$$ {}_m\mathbb{P}(y) = \begin{pmatrix} 1 - e(y) \times (1-d) - p(a+y) & 0 & e(y) \times (1-d) & p(a+y) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 - p(a+y) & p(a+y) \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

where a is the starting age of the patient,

$$ e(y) = \begin{cases} 0.16 & \text{for } y = 0 \\ 0.08 & \text{for } y = 1 \\ 0.05 & \text{for } y = 2 \\ 0.017 & \text{for } y = 3, 4, ..., \end{cases} $$

and y is the number of years since the beginning of the chain. We also have that $d = 0.2$ and $p(x) = e^{-10.58+0.095x}$.

Even though the majority of our discrete time steps in the model have a length of one year, at the beginning of the chain we must account for the 30 day surgical period, as the transitions happen differently in this time period. At the beginning of the chain, all patients start in the "well with stenosis" state. In the surgical chain, they undergo CEA and after 30 days are either in "well without stenosis" if they have had successful surgery, "post stroke" if they have suffered a non-fatal stroke as a result of the surgery, or "dead" if they have suffered fatal complications from the surgery. After this first 30 day surgical risk period, the patients in the surgical chain can then transition between these states according to the annual transition probabilities.

In the medical chain, again, all patients begin "well with stenosis". During the initial 30 day period, these patients are still able to transition between the states

according to annual probability matrix, ${}_m\mathbb{P}(0)$, since we are still within the first year. However, we would not observe the changes until the end of the year. For computational reasons, we also need to observe the outcome of the transitions in the medical chain after the first 30 days. Therefore, we introduce two different matrices in the first year of the chain; the first matrix corresponding to the initial 30 day period, and the second corresponding to the remaining 335 days of the first year. Since the length of these two periods is not one year, we alter the appropriate annual probabilities to account for this.

In our transition matrix, the probability of stroke in the first year, $e(0)$, becomes $\frac{30}{365}e(0)$ for the first 30 days, and $\frac{335}{365}e(0)$ for the remainder of the first year. The age related probability of death, $p(a)$ becomes $\frac{30}{365}p(a)$ for the first 30 days, and $\frac{335}{365}p(a)$ for the remaining 335 days. More accurately, instead of multiplying the probabilities by these fractions, we should take them to the power of these fractions; for example $e(0)$, should become $e(0)^{\frac{30}{365}}$ for the first 30 days. However, this becomes computationally expensive, and since this occurs for only the first year, we use the more simple method of multiplication.

The transition matrix for the first 30 day period is then:

$${}_m\mathbb{P}(0)_{30} = \begin{pmatrix} 1 - \frac{30}{365}e(0) \times (1-d) - \frac{30}{365}p(a) & 0 & \frac{30}{365}e(0) \times (1-d) & \frac{30}{365}p(a) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 - \frac{30}{365}p(a) & \frac{30}{365}p(a) \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

For the remaining 335 days of the first year, the matrix is:

$${}_m\mathbb{P}(0)_{335} = \begin{pmatrix} 1 - \frac{335}{365}e(0) \times (1-d) - \frac{335}{365}p(a) & 0 & \frac{335}{365}e(0) \times (1-d) & \frac{335}{365}p(a) \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1 - \frac{335}{365}p(a) & \frac{335}{365}p(a) \\ 0 & 0 & 0 & 1 \end{pmatrix},$$

where a is the starting age of the patient.

After the first year of the chain, we use the regular one year time steps and the corresponding annual transition matrices, ${}_m\mathbb{P}(y)$, as above.

Surgical Chain

We now create the treatment chain, to compare to the control chain and calculate the lifetime benefit. Here, the treatment is CEA, which is surgery. Using the established model as before, the positive transition probabilities for the surgical chain are:

$$
\begin{aligned}
p_{1,2} &= 1 - s \\
p_{1,3} &= s \times (1 - d) \\
p_{1,4} &= s \times d \\
p_{2,2} &= 1 - P(\text{have stroke after treatment})(1 - d) - p(x) \\
p_{2,3} &= P(\text{have stroke after treatment})(1 - d) \\
p_{2,4} &= p(x) \\
p_{3,3} &= 1 - p(x) \\
p_{3,4} &= p(x) \\
p_{4,4} &= 1.
\end{aligned}
$$

From the medical chain, we established that the mortality rate after stroke was estimated to be 20%, so again, $d = 0.2$.

Using the same pooled analysis [15], we find the surgical risk to be $s = 0.062$, for patients with severe symptomatic stenosis (70-99% stenosis), where the surgical risk is defined to be stroke or death within 30 days of the surgery. However, this does not match up to the surgical risk used in the paper, which is 3%. Therefore, we assume that Nagaki *et al.* did not use surgical risk from the pooled analysis, but rather from other 'known' surgical risks. That is, a value that physicians or surgeons would normally tell their patients. To keep the model as close to the original as possible to begin with, we use their value of $s = 0.03$.

Now the only remaining value to find is $P(\text{have stroke after treatment})$. The probability that a patient has a stroke in the surgical chain is different than in the medical chain, as we expect that the risk of stroke is lower after having surgery. In Figure 4.3 we can see that after the surgical risk (the large 'jump' in the curve at the

beginning), the proportion of patients having a stroke after surgery is approximately linear. Therefore, using other given data in the pooled analysis we are able to approximate the annual probability of stroke after surgery [15].

As mentioned in the medical chain, we are given that for patients with 70-99% stenosis, after 5 years, the absolute reduction in risk is 15.6%, and the relative reduction in risk is 0.52% [15]. From Figure 4.3, we see that after the initial surgical period, the cumulative proportion of patients who suffer a stroke each year is roughly linear. Therefore, we are able to use this 5 year data to calculate the annual proportions of patients who suffer a stroke in the surgical group. If we let r_{s5} be the proportion of surgical patients that have a stroke after 5 years, and r_{m5} be the proportion of medical patients that have a stroke after 5 years, we know that

$$r_{s5} - r_{m5} = 0.156 \qquad \text{and} \qquad \frac{r_{s5}}{r_{m5}} = 0.52.$$

This implies that $r_{s5} = 0.169$ and $r_{m5} = 0.325$.

Comparing r_{m5} to Figure 4.3, we can see that this number agrees with the proportion of medical patients who suffer a stroke or death at the five-year mark on the Kaplan-Meier curve.

In this calculation, r_{s5} is inclusive of the proportion of patients who suffer a stroke or death within 30 days of surgery, which is given to be 0.062 from the analysis. Since we are already including this risk separately, we do not need to include it in the 5-year proportion. Therefore, the 5-year proportion is actually $(r_{s5} - s)$. Now the annual probability of stroke after surgery, r_s, can be calculated because $1 - (r_{s5} - s)$ is the probability of not having a stroke in the first 5 years after successful surgery. This is the probability of not having a stroke in the first year, and not having a stroke in the second year, and not in the third year, etc. So we have:

$$\begin{aligned}(1 - r_s)^5 &= 1 - (r_{s5} - s) \\ &= 1 - 0.169 + 0.062 \\ &= 0.893.\end{aligned}$$

$$\text{Therefore,} \quad r_s = 1 - 0.893^{1/5}$$
$$\approx 0.0224,$$

where r_s is the probability of having a stroke in a single year after successful surgery. That is,

$$P(\text{have stroke after treatment}) = 0.022.$$

The value of this parameter used in Nagaki *et al.* is 0.023, which is very close to ours. Since we assume that Nagaki *et al.* had access to more data than we do, and we are satisfied that we have obtained a similar value, we use their value of 0.023 [11].

Therefore, the transition probability matrix for the surgical chain is now:

$${}_s\mathbb{P}(y) = \begin{pmatrix} 0 & 1-s & s\times(1-d) & s\times d \\ 0 & 1-0.023\times(1-d)-p(a+y) & 0.023\times(1-d) & p(a+y) \\ 0 & 0 & 1-p(a+y) & p(a+y) \\ 0 & 0 & 0 & 1 \end{pmatrix}$$

where a is the starting age of the patient, y is the number of years since surgery, $s = 0.03$, $d = 0.2$ and $p(x)$ is the age related probability of death of the general population.

As in the medical chain, we divide the first year of the process into two time periods of differing lengths. The first time period is the 30 days at the beginning of the chain corresponding to the surgical risk period, the second is the remaining 335 days of the first year. Since all patients begin "well with stenosis" and must have the surgery when the chain commences, the only transition probabilities that correspond to the first 30 day period are the surgical transition probabilities, $p_{1,2}$, $p_{1,3}$, and $p_{1,4}$. Since these probabilities are not annual probabilities and are only to do with the surgery, there is no need to alter the matrix, ${}_s\mathbb{P}(0)$ for the first 30 day period.

However, for the remaining 335 days of the first year, patients cannot be in the "well with stenosis" state, and will transition according to the next three rows of the

probability matrix. Since this period is not a full year, we do alter the appropriate probabilities as we did in the medical chain. The transition matrix for this period is then:

$$ {}_s\mathbb{P}(0)_{335} = \begin{pmatrix} 0 & 1-s & s\times(1-d) & s\times d \\ 0 & 1-\frac{335}{365}0.023\times(1-d)-\frac{335}{365}p(a) & \frac{335}{365}0.023\times(1-d) & p(a) \\ 0 & 0 & 1-\frac{335}{365}p(a) & \frac{335}{365}p(a) \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

where a is the starting age of the patient. Again, for the remainder of the chain the discrete time steps are one year, therefore we use the regular annual transition matrix, ${}_s\mathbb{P}(y)$, above.

4.1.4 Calculating the Benefit

After carefully defining both the treatment (surgical) and control (medical) Markov chains for the treatment in question, carotid endarterectomy, we can now use these to calculate the expected benefit of CEA over a patient's lifetime. Nagaki *et al.* define the benefit of carotid artery endarterectomy as the expected quality adjusted life years (QALYs) gained over that lifetime [11]:

$$\text{CEA Benefit} = \mathbb{E}[\text{QALYs with CEA}] - \mathbb{E}[\text{QALYs without CEA}].$$

In general, the expected number of QALYs over a lifetime is:

$$\sum_{i\in S} u_i \mathbb{E}(\text{years in state } i),$$

where $0 \leq u_i \leq 1$ is a utility value assigned to health state i. Using this definition and the Markov chains we have defined, we can then find the expected number of QALYs over a patient's lifetime for both the surgical and medical chains, taking the difference as the benefit of surgery.

In the article [11], death is assigned a utility value of 0 as per convention, the post stroke state is assigned a utility of 0.6, and the states well with or without

stenosis are both assigned a utility of 1, so that:

$$\mathbf{u} = (u_1, u_2, u_3, u_4)^T = (1, 1, 0.6, 0)^T.$$

Let R be the random variable denoting the total reward earned, and let u_i be the reward for one year in state i. Then we can find the expected total reward given that we start in state i at time 0:

$$\mathbb{E}[R|X_0 = i].$$

Since our transition probabilities depend on the number of years after the decision to have, or not have, surgery, the Markov chains are time inhomogeneous. Let us use the notation $\mathbb{P}(t)$ to denote the transition probability matrix at the beginning of the t^{th} time period after surgery. Let R_t be the reward earned by the end of the t^{th} period. Therefore, we can write the expected total reward given that we start in state i as:

$$\mathbb{E}[R|X_0 = i] = \mathbb{E}[R_0|X_0 = i] + \sum_{j \in S} P_{i,j}(0)\mathbb{E}[R|X_1 = j].$$

Let

$$\mathbf{w}_i(t) = \mathbb{E}[R|X_t = i].$$

That is, $\mathbf{w}_i(t)$ denotes the expected reward from the t^{th} time period onwards, given that we are in state i at the beginning of this period.

The first time period we consider is the first 30 days after the beginning of the chain (the decision to have surgery, or not). The next is the remaining 335 days of the first year. For these time periods, we use the adjusted transition matrices defined in the models. We also need to scale the reward for those time periods, so that:

$$\begin{aligned} \mathbf{w}(0) &= \frac{30}{365}\mathbf{R}_0 + \mathbb{P}(0)\mathbf{w}(1), \quad \text{and} \\ \mathbf{w}(1) &= \frac{335}{365}\mathbf{R}_1 + \mathbb{P}(1)\mathbf{w}(2), \end{aligned}$$

where, $\mathbb{P}(0)$ is the transition matrix corresponding to the first time period, which is the first 30 days after surgery, and $\mathbb{P}(1)$ corresponds to the second time period, the remaining 335 days of the first year.

However, since we only observe the state the patient is in at the end of the time period (we do not know exactly when they transition in that time period), and we assume there is a constant rate of them transitioning throughout, the expected time that a patient transitions is halfway through that time period.

Therefore, we expect to receive half of the reward from the state the patient is in at the beginning of the period, and half from the state after they transition. If a patient is in state i at the beginning of a time period t and state j at the end, the expected reward for that time period only is:

$$\left(\frac{u_i}{2} + \sum_{j \in S} \mathbb{P}_{i,j}(t)\frac{u_j}{2}\right) \times (\text{length of time period})$$

as a patient could transition to any state $j \in S$ according to $\mathbb{P}(t)$.

In vector form, we have that:

$$\begin{aligned}\mathbf{w}(0) &= \frac{30}{365}\left(\frac{\mathbf{u}}{2} + \mathbb{P}(0)\frac{\mathbf{u}}{2}\right) + \mathbb{P}(0)\mathbf{w}(1) \quad \text{and} \\ \mathbf{w}(1) &= \frac{335}{365}\left(\frac{\mathbf{u}}{2} + \mathbb{P}(1)\frac{\mathbf{u}}{2}\right) + \mathbb{P}(1)\mathbf{w}(2).\end{aligned}$$

After the first time period, the length of the time periods are a full year, so we also have:

$$\mathbf{w}(t) = \frac{1}{2}(\mathbf{u} + \mathbb{P}(t)\mathbf{u}) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t \geq 2.$$

Therefore, our reward equations are:

$$\begin{aligned}\mathbf{w}(0) &= \frac{30}{365} \times \frac{1}{2}(\mathbf{u} + \mathbb{P}(0)\mathbf{u}) + \mathbb{P}(0)\mathbf{w}(1), \\ \mathbf{w}(1) &= \frac{335}{365} \times \frac{1}{2}(\mathbf{u} + \mathbb{P}(1)\mathbf{u}) + \mathbb{P}(1)\mathbf{w}(2) \quad \text{and} \\ \mathbf{w}(t) &= \frac{1}{2}(\mathbf{u} + \mathbb{P}(t)\mathbf{u}) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t \geq 2,\end{aligned}$$

where the i^{th} entry of $\mathbf{w}(0)$, $\mathbf{w}_i(0)$, is the expected total reward given that a patient started in health state i at time 0. Since for our model, we assume that everyone

starts in state 1, "well with stenosis", the entry that corresponds to the expected lifetime QALY is $\mathbf{w}_1(0)$.

We also need to consider discounting the utilities each year, by some discounting factor, f. This is due to the idea that the value, or utility, of the treatment is worth more to the patient in the present, than it is in a few years time. This is similar to the idea of net present value in finance, which says that money now is more valuable than money later on. In the original article [11], Nagaki *et al.* use a discounting of 3% each year, so in our QALY calculations, each year after the beginning of the chain, the utility is discounted by 3% as well. This gives us:

$$\begin{aligned}
&\mathbf{u}(0) = \mathbf{u}(1) = \mathbf{u}, \qquad \text{(since these two periods are in the first year)}\\
&\mathbf{u}(2) = (1-f) \times \mathbf{u}(1) = (1-f) \times \mathbf{u},\\
&\mathbf{u}(3) = (1-f) \times \mathbf{u}(2) = (1-f)^2 \times \mathbf{u},\\
&\quad \vdots
\end{aligned}$$

and so on. That is,

$$\mathbf{u}(t) = (1-f)^{(t-1)} \times \mathbf{u},$$

where $\mathbf{u}(t)$ is the utility at time period t, and $f = 0.03$.

Therefore, the expected reward can be given by:

$$\begin{aligned}
\mathbf{w}(0) &= \frac{30}{365} \times \frac{1}{2}(\mathbf{u}(0) + \mathbb{P}(0)\mathbf{u}(0)) + \mathbb{P}(0)\mathbf{w}(1),\\
\mathbf{w}(1) &= \frac{335}{365} \times \frac{1}{2}\left(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)\right) + \mathbb{P}(1)\mathbf{w}(2) \quad \text{and}\\
\mathbf{w}(t) &= \frac{1}{2}(\mathbf{u}(t) + \mathbb{P}(t)\mathbf{u}(t)) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t \geq 2.
\end{aligned}$$

Since the equation for each $\mathbf{w}(k)$ includes $\mathbf{w}(k+1)$, we can calculate $\mathbf{w}(0)$ using backwards recursion. However, to use backwards recursion, a problem needs to have a finite horizon, T, and a known value for $\mathbf{w}(T)$. In this case, the horizon is simply the death of the patient, as eventually everyone must die.

According to our death function $p(x)$ [11], the longest a person can live is 112 years, since $p(112) > 1$. Therefore, we truncate our calculations here, and make the

horizon for our problem:

$$T = 112 - a,$$

where a is the age of the patient at the time of their decision to have surgical treatment, or not.

We know that the patient is dead at the end of the year, however since we assume transitions happen halfway through the year, the expected reward $\mathbf{w}(T) = \frac{1}{2}\mathbf{u}(T)$, and for all years after T, the expected reward is 0. Knowing this value, we can recursively calculate $\mathbf{w}(T)$ to eventually get $\mathbf{w}(0)$, the expected lifetime QALYs for both the surgical and medical chains. Hence the lifetime benefit, $\mathbf{b}$, of treatment is:

$$\mathbf{b} = ({}_s\mathbf{w})_1(0) - ({}_m\mathbf{w})_1(0),$$

where ${}_s\mathbf{w}$ is the reward associated with the surgical chain, and ${}_m\mathbf{w}$ is the reward from the medical chain, and since we assume that all patients begin well with stenosis (in state 1), we use the first entry of each of the reward vectors. Here, we sometimes use the term 'net benefit', which refers to benefit in the presence of iatrogenic loss, as defined in Chapter 3.

4.1.5 Validation of the Model

We use the above method for calculating the expected lifetime quality adjusted life years and net benefit, and compare our results to those in the original paper. Figure 4.4 depicts the number of lifetime expected QALYs that patients aged 40 to 110 would expect to have if they choose to have the surgery at that age (the blue line), or choose not to (the green line). The benefit of treatment, CEA in this case, is the difference between these expected QALYs. That is, it is the expected number of QALYs gained from the treatment.

Figure 4.5 shows this difference for the various ages. In other words, it depicts the lifetime benefit of CEA in expected QALY gain. As we expect, the figure mostly exhibits that the expected lifetime benefit for older patients having surgery is less

than for younger patients. However, between the ages of 40 and approximately 50, there is a plateau, and in fact a slight increase, in lifetime benefit. The benefit of surgery for a 40-year-old is 0.5007 QALYs, whereas for a 50-year-old it is 0.5021 QALYs. This is due to the probability of having a stroke eventually becoming less in the medical chain that it is in the surgical chain. In the medical chain, $e(y) = 0.017$ for $y = 3, 4, ...$, whereas in the surgical chain $e = 0.023$ every year after the surgical period. Since younger patients are expected to live for a longer period of time, over their lifetimes they accumulate more of the negative effects of this issue on their benefit, until eventually it outweighs the positive effect of surgery, causing the slight 'dip' in benefit from a 50-year-old to a 40-year-old.

Figure 4.5 also shows that even for a 40-year-old patient, the benefit of surgery seems very low (only 0.5007 QALYs). We attribute this to an issue in the model with the probability of death of the general population. Since the probability of dying from a well state is only the probability of death from old age, and the only other transition out of the well state is due to a non-fatal stroke (which does not depend on age), we have that the matrix eventually becomes non-stochastic. For example, in the surgical chain if we look at the transition probabilities from state 2, "well without stenosis":

$$p_{2,2} = 1 - 0.023 \times 0.2 - p(x),$$
$$p_{2,3} = 0.023 \times 0.2,$$
$$p_{2,4} = p(x).$$

If $x = 112$, then $p_{2,2}$ becomes negative and therefore the matrix is non-stochastic. In the medical chain, if $x = 111$, the transitions from "well with stenosis" (state 1) mean that $p_{1,1}$ becomes negative. Both of these issues are later amended within our own modified model of CEA.

For a 60-year-old, the benefit of CEA in our calculations is 0.4752 QALYs. In Figure 4.6a, each different line on the graph represents the benefit of CEA for a 60-year-old for a different comorbidity factor, c, of the function $p(x)$. This value of

c, where $c = 1, 2$ or 3, is the method that Nagaki *et al.* use to introduce the effects of comorbidity on benefit in their Markov model. The thicker dashed line represents the benefit when $c = 1$, which is what we use throughout our analysis. At the value $s = 0.03$, which is the original value for surgical risk, the benefit is just under 0.5 QALYs, confirming that the results from the model we re-created from Nagaki *et al.*'s article seem to correspond with their original results. To validate this further, we also reproduce a similar plot to Figure 4.6a to compare to the line corresponding to $c = 1$ (Figure 4.6b). This demonstrates that, using Nagaki *et al.*'s parameters, we are able to successfully reproduce their results.

4.1.6 Snapshot Benefit in Quality Adjusted Life Years

We can also use the transition matrices and utility values to calculate the snapshot benefit of CEA in expected QALYs. This is equivalent to the expected quality of outcome defined in Chapter 3. To see this, we consider the fatal and non-fatal outcomes of the model as two separate diseases, where the fatal outcome has a utility, or quality of outcome of 0, and the non-fatal outcome has a utility of 0.6. That is, we have the set of diseases,

$$N = \{1 \text{ (fatal outcome)}, 2 \text{ (non-fatal outcome)}\}$$

with $q(1) = 0$, and $q(2) = 0.6$. We can then calculate the appropriate probability of suffering negative consequences from the disease without treatment, $1 - p_i$, and with treatment, $1 - p_i - b_i$, for $i = 1, 2$.

Since we consider only the expected quality of outcome at a specific point in time, we can calculate the snapshot expected QALYs for any specified number of years t after surgery. To do so, we first need to calculate the probabilities of suffering negative consequences at that particular point in time, $\mathbb{P}^{(t)}$. We have established that the Markov chain is time inhomogeneous, so the expected QALYs can be calculated as follows.

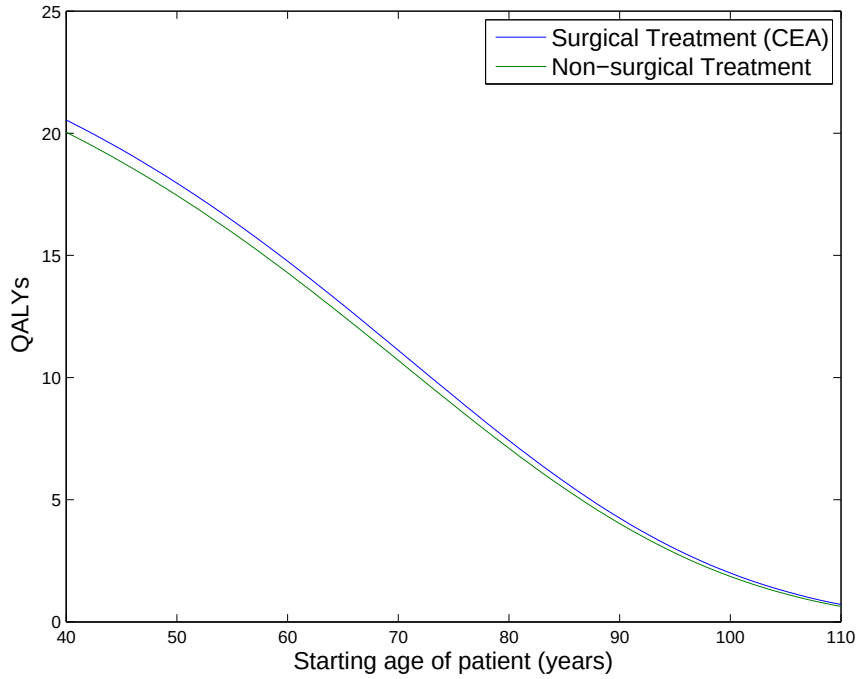


Figure 4.4: Expected lifetime QALYs for patients of varying ages, using a model for CAS by Nagaki *et al.* [11]. We compare patients receiving CEA, and those having medical treatment only.

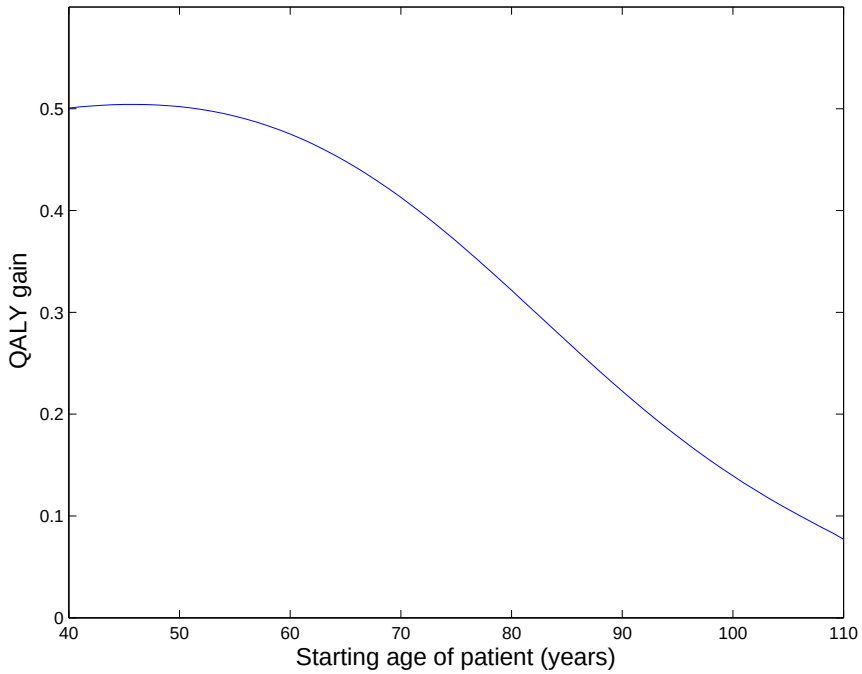
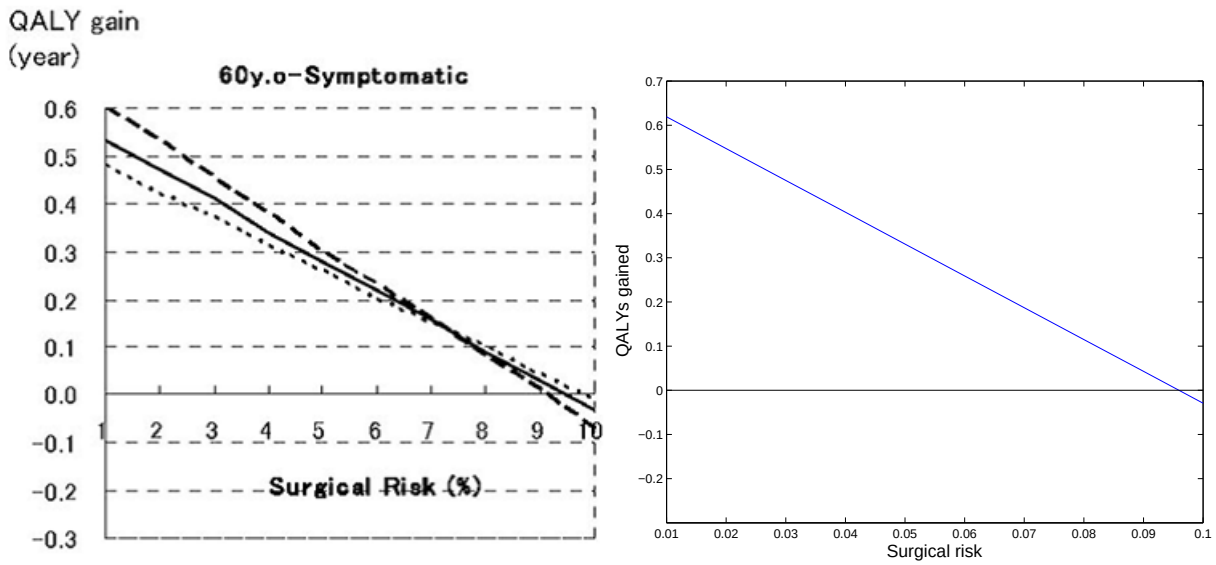


Figure 4.5: Lifetime benefit of CEA in expected QALY gain, for patients of varying ages, using a model for CAS by Nagaki *et al.* [11].



(a) Sensitivity analysis from the original source [11].

(b) Sensitivity analysis from our re-created results, using the original model.

Figure 4.6: Comparing CEA surgical risk sensitivity analysis for a 60-year-old patient, using a model for CAS by Nagaki *et al.* [11].

Definition 17. The **snapshot expected QALYs** t years after surgery is:

$$\begin{aligned}\mathbf{v}(t) &= \mathbb{P}^{(t)} \times \mathbf{u} \\ &= \mathbb{P}(0) \times \mathbb{P}(1) \times \mathbb{P}(2) \times \ldots \times \mathbb{P}(t) \times \mathbf{u}, \\ \mathbf{v}(T) &= 0, \qquad \text{for } T = 112 - age,\end{aligned}$$

where $\mathbb{P}(t)$ is the transition matrix corresponding to t years after the decision of whether to have surgery. As defined previously, $\mathbb{P}(0)$ corresponds to the transition probabilities for the surgical risk period, z days, and $\mathbb{P}(1)$ to the transitions for the remainder of the first year.

We can also use the appropriate probability matrix $\mathbb{P}^{(t)}$ to find p_1, p_2, b_1, and b_2. From our medical probability matrix, the probability of dying at time t, given that a patient started well with the disease, is ${}_m\mathbb{P}^{(t)}_{1,4}$. Since the probability of suffering negative consequences from the fatal outcome of the disease with no treatment, is

the probability of dying given no treatment, we have that ${}_m\mathbb{P}_{1,4}^{(t)} = 1 - p_1$. Therefore,

$$p_1 = 1 - {}_m\mathbb{P}_{1,4}^{(t)}.$$

We also have that ${}_m\mathbb{P}_{1,3}^{(t)}$ is the probability of having a stroke and not dying, given that a patient started well with the disease. That is,

$${}_m\mathbb{P}_{1,3}^{(t)} = P(\text{not dying}) \times P(\text{having a stroke}),$$

where the probability of not dying is the probability of not suffering negative consequences from the fatal outcome of the disease, and the probability of having a stroke is the probability of suffering negative consequences from the non-fatal outcome of the disease. That is,

$${}_m\mathbb{P}_{1,3}^{(t)} = p_1 \times (1 - p_2).$$

Therefore,

$$1 - p_2 = \frac{{}_m\mathbb{P}_{1,3}^{(t)}}{p_1}$$

$$p_2 = 1 - \frac{{}_m\mathbb{P}_{1,3}^{(t)}}{1 - {}_m\mathbb{P}_{1,4}^{(t)}}.$$

Since we know that $1 - p_i - b_i$ for $i = 1, 2$, is the probability of suffering negative consequences with treatment, we can use our surgical probability matrix to find b_i for $i = 1, 2$. Using similar reasoning as above, ${}_s\mathbb{P}_{1,4}^{(t)} = 1 - p_1 - b_1$, therefore,

$$b_1 = 1 - p_1 - {}_s\mathbb{P}_{1,4}^{(t)}$$

$$= {}_m\mathbb{P}_{1,4}^{(t)} - {}_s\mathbb{P}_{1,4}^{(t)}.$$

The probability of being in the post stroke state with treatment, given that a patient started well with the disease, is the probability of not dying and suffering from a stroke with treatment. That is,

$${}_s\mathbb{P}_{1,3}^{(t)} = (p_1 + b_1) \times (1 - p_2 - b_2).$$

Therefore,

$$\begin{aligned}
1 - p_2 - b_2 &= \frac{{}_s\mathbb{P}^{(t)}_{1,3}}{p_1 + b_1} \\
b_2 &= 1 - p_2 - \frac{{}_s\mathbb{P}^{(t)}_{1,3}}{1 - {}_m\mathbb{P}^{(t)}_{1,4} + {}_m\mathbb{P}^{(t)}_{1,4} - {}_s\mathbb{P}^{(t)}_{1,4}} \\
&= 1 - \left(1 - \frac{{}_m\mathbb{P}^{(t)}_{1,3}}{1 - {}_m\mathbb{P}^{(t)}_{1,4}}\right) - \frac{{}_s\mathbb{P}^{(t)}_{1,3}}{1 - {}_s\mathbb{P}^{(t)}_{1,4}} \\
&= \frac{{}_m\mathbb{P}^{(t)}_{1,3}}{1 - {}_m\mathbb{P}^{(t)}_{1,4}} - \frac{{}_s\mathbb{P}^{(t)}_{1,3}}{1 - {}_s\mathbb{P}^{(t)}_{1,4}}.
\end{aligned}$$

Now the expected quality of outcome, given that a patient does not have treatment (CEA), t years after surgery, is

$$\begin{aligned}
E(N) &= \sum_{S \subseteq N} P(S, N) q(S) \\
&= (1 - p_1)(1 - p_2)q(1)q(2) + p_1(1 - p_2)q(2)q(\varnothing) + (1 - p_1)p_2 q(1)q(\varnothing) + p_1 p_2 q(\varnothing) \\
&= p_1(1 - p_2)q(2) + p_1 p_2,
\end{aligned}$$

since we make the fundamental assumptions that the quality of outcome of death is 0, and that the quality of outcome of not suffering negative outcomes is 1; that is $q(1) = 0$, and $q(\varnothing) = 1$. Therefore,

$$\begin{aligned}
E(N) &= (1 - {}_m\mathbb{P}^{(t)}_{1,4}) \left(\frac{{}_m\mathbb{P}^{(t)}_{1,3}}{1 - {}_m\mathbb{P}^{(t)}_{1,4}}\right) u_3 + (1 - {}_m\mathbb{P}^{(t)}_{1,4}) \left(1 - \frac{{}_m\mathbb{P}^{(t)}_{1,3}}{1 - {}_m\mathbb{P}^{(t)}_{1,4}}\right) \\
&= {}_m\mathbb{P}^{(t)}_{1,3} u_3 + 1 - {}_m\mathbb{P}^{(t)}_{1,4} - {}_m\mathbb{P}^{(t)}_{1,3}.
\end{aligned}$$

The snapshot expected QALYs with no treatment, calculated using Definition 13, are

$$\mathbf{v}(t) = {}_m\mathbb{P}^{(t)} \times \mathbf{u}.$$

Therefore, the snapshot QALYs with no treatment, given that a patient started well with the disease are,

$${}_m\mathbb{P}^{(t)}_{1,\bullet} \times (1, 1, u_3, 0)^T,$$

where ${}_m\mathbb{P}^{(t)}_{1,\bullet}$ is the first row of the matrix. Therefore,

$$({}_m\mathbf{v})_1(t) = {}_m\mathbb{P}^{(t)}_{1,1} + {}_m\mathbb{P}^{(t)}_{1,3}u_3,$$

since we assume that, without treatment, a patient cannot become well without the disease. That is, we assume ${}_m\mathbb{P}^{(t)}_{1,2} = 0$. Therefore,

$$\begin{aligned}({}_m\mathbf{v})_1(t) &= 1 - {}_m\mathbb{P}^{(t)}_{1,4} - {}_m\mathbb{P}^{(t)}_{1,3} + {}_m\mathbb{P}^{(t)}_{1,3}u_3 \\ &= \mathrm{E(N)}.\end{aligned}$$

Now, the expected quality of outcome, given that a patient does have treatment (CEA), t years after surgery, is

$$\begin{aligned}E_N(N) &= \sum_{S\subseteq N} P_N(S,N)q(S) \\ &= (1-p_1-b_1)(1-p_2-b_2)q(1)q(2) + (p_1+b_1)(1-p_2-b_2)q(2)q(\varnothing) \\ &\qquad + (1-p_1-b_1)(p_2+b_2)q(1)q(\varnothing) + (p_1+b_1)(p_2+b_2)q(\varnothing) \\ &= (p_1+b_1)(1-p_2-b_2)q(2) + (p_1+b_1)(p_2+b_2) \\ &= (1-{}_s\mathbb{P}^{(t)}_{1,4})\frac{{}_s\mathbb{P}^{(t)}_{1,3}}{1-{}_s\mathbb{P}^{(t)}_{1,4}}u_3 + (1-{}_s\mathbb{P}^{(t)}_{1,4})\left(1-\frac{{}_s\mathbb{P}^{(t)}_{1,3}}{1-{}_s\mathbb{P}^{(t)}_{1,4}}\right) \\ &= {}_s\mathbb{P}^{(t)}_{1,3}u_3 + 1 - {}_s\mathbb{P}^{(t)}_{1,4} - {}_s\mathbb{P}^{(t)}_{1,3}.\end{aligned}$$

The snapshot expected QALYs with treatment (CEA), given that a patient starts well with the disease, t years after surgery, are

$$\begin{aligned}({}_s\mathbf{v})_1(t) &= {}_s\mathbb{P}^{(t)}_{1,\bullet} \times (1,1,u_3,0)^T \\ &= {}_s\mathbb{P}^{(t)}_{1,1} + {}_s\mathbb{P}^{(t)}_{1,3}u_3, \\ &\text{since } {}_s\mathbb{P}^{(t)}_{1,2} = 0. \\ \text{Therefore,}\quad ({}_s\mathbf{v})_1(t) &= 1 - {}_s\mathbb{P}^{(t)}_{1,4} - {}_s\mathbb{P}^{(t)}_{1,3} + {}_s\mathbb{P}^{(t)}_{1,3}u_3 \\ &= E_N(N).\end{aligned}$$

In other words, the snapshot expected QALYs are equivalent to the expected quality of outcome, when the disease in the lifetime model is considered as two

separate diseases: the fatal outcome as one disease, and the non-fatal outcome as the other.

Since we can define the snapshot expected QALYs t years after surgery, we can also define the snapshot net benefit t years after surgery.

Definition 18. The snapshot net benefit t years after surgery, is

$$\mathfrak{b}(t) = ({}_s\mathbf{v})_1(t) - ({}_m\mathbf{v})_1(t).$$

In Chapter 3, Assumption 1 states that

$$0 \leq p_i < p_i + b_i < 1.$$

Therefore, for the results from Chapter 3 to apply to the snapshot benefit, we need that

$$0 \leq 1 - {}_m\mathbb{P}_{1,4}^{(t)} < 1 - {}_s\mathbb{P}_{1,4}^{(t)} < 1, \quad \forall t,$$

and

$$0 \leq 1 - \frac{{}_m\mathbb{P}_{1,3}^{(t)}}{1 - {}_m\mathbb{P}_{1,4}^{(t)}} < 1 - \frac{{}_s\mathbb{P}_{1,3}^{(t)}}{1 - {}_s\mathbb{P}_{1,4}^{(t)}} < 1 \quad \forall t.$$

That is,

$$0 < {}_s\mathbb{P}_{1,4}^{(t)} < {}_m\mathbb{P}_{1,4}^{(t)} \leq 1,$$

and

$$0 < \frac{{}_s\mathbb{P}_{1,3}^{(t)}}{1 - {}_s\mathbb{P}_{1,4}^{(t)}} < \frac{{}_m\mathbb{P}_{1,3}^{(t)}}{1 - {}_m\mathbb{P}_{1,4}^{(t)}} \leq 1, \quad \forall t.$$

In other words, for the snapshot benefit to meet the requirements of Assumption 1, we need to assume that the probability of a patient being in the dead state after t years with treatment, is less than the probability that a patient is in the dead state after t years, without treatment. That is, treatment results in a positive benefit in terms of probability of death. We also need to assume that the proportion of patients in the post stroke state, that did not die after t years, with treatment, is less than the same proportion of patients without treatment. That is, treatment needs to result in a positive benefit in terms of the proportion of patients who have a non-fatal stroke.

Snapshot Benefit of CEA

For completeness, we can also calculate the snapshot expected QALYs for a 70-year-old patient for every time period t after surgery, and hence also the snapshot benefit in QALYs at each time period. We choose to explore the benefit for a 70-year-old patient since this is the age at which Nagaki *et al.* concentrate their analysis. Figure 4.7 depicts the snapshot expected QALYs at each year after the decision to have surgery, for both the CEA (surgical) and non-CEA (medical) chains, where the time period $t = 0$ refers to the 30 day surgical period. At $t = 0$ we notice that the medical snapshot QALYs are greater than the surgical snapshot QALYs, which can be explained by the surgical risk of CEA. The surgical snapshot QALYs are 0.9844 QALYs, compared to 0.9942 QALYs for the medical chain. This corresponds to the negative snapshot benefit we see in Figure 4.8 at $t = 0$; a benefit of -0.0098 QALYs. We also note that in Figure 4.8, the maximum snapshot benefit for a 70-year-old patient occurs at $t = 3$, where the benefit is 0.0494 QALYs. After this point, the snapshot benefit declines until eventually reaching 0. As mentioned previously, the probability of having a stroke eventually becomes lower in the medical chain, than in the surgical chain. This happens in the third year after surgery, explaining the decline of the snapshot benefit after this point in time.

We also examine the snapshot benefit in expected QALYs for 40-, 60- and 80-year-old patients, in Figures 4.9a, 4.9b and 4.9c respectively. For patients of all ages, similarly to the snapshot benefit for a 70-year-old, the benefit at $t = 0$ (the surgical risk period) is negative, due to the surgical risk. We also note that the maximum, again, occurs at $t = 3$ then declines from that point onwards. In Figure 4.9a, depicting the benefit for a 40-year-old, we note that after approximately 30 years, the snapshot benefit in QALYs becomes negative. As mentioned in the lifetime benefit analysis, this is due to the probability of death from a stroke becoming higher in the surgical chain than in the medical chain. The 40-year-old patient is expected to live for a longer period of time than older patients, so this negative

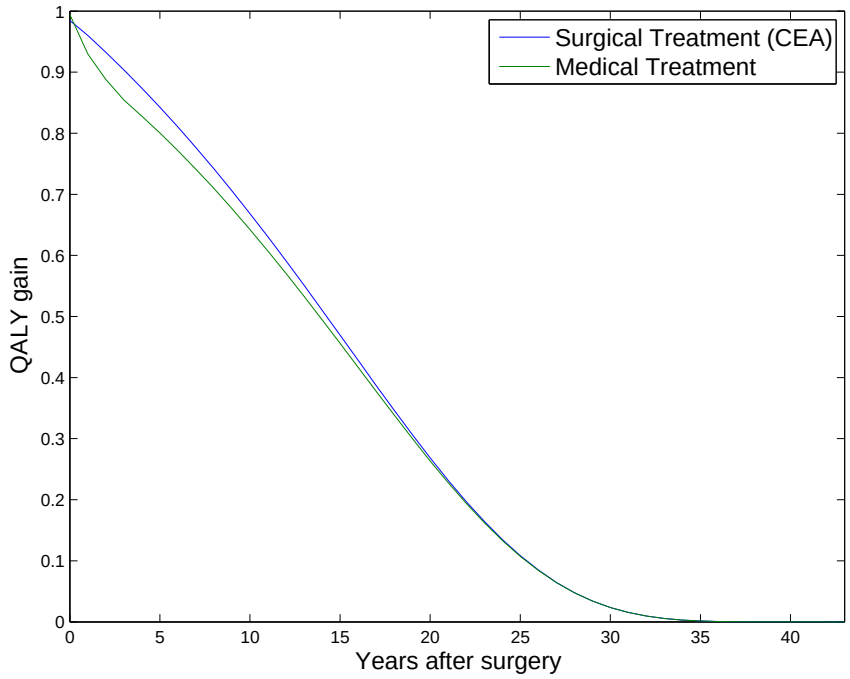


Figure 4.7: Snapshot expected QALYs for a 70-year-old patient with CAS, at each year after the decision to have CEA or continue with medical treatment only. Original model and parameters from Nagaki *et al.* [11].

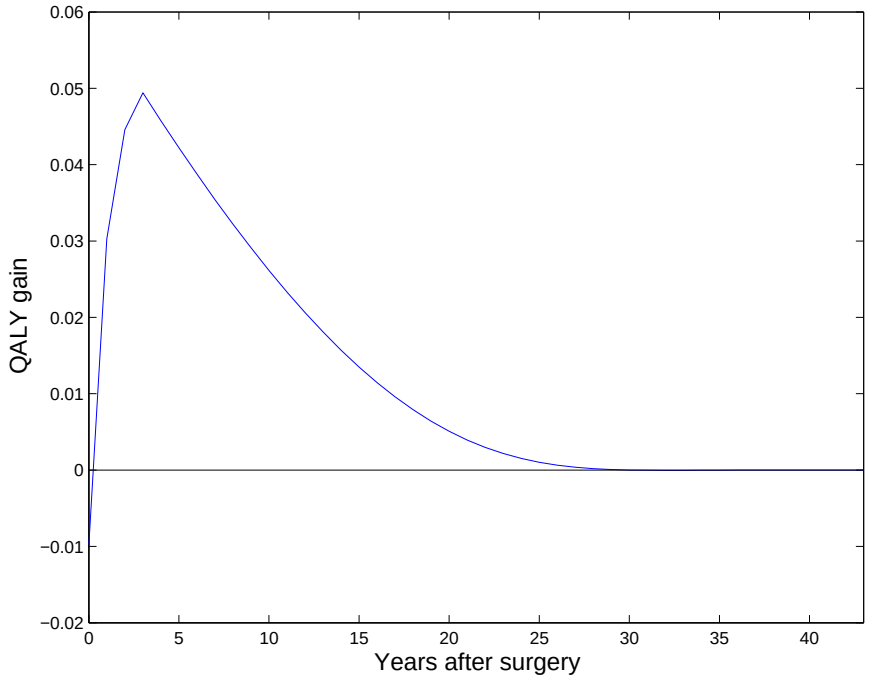
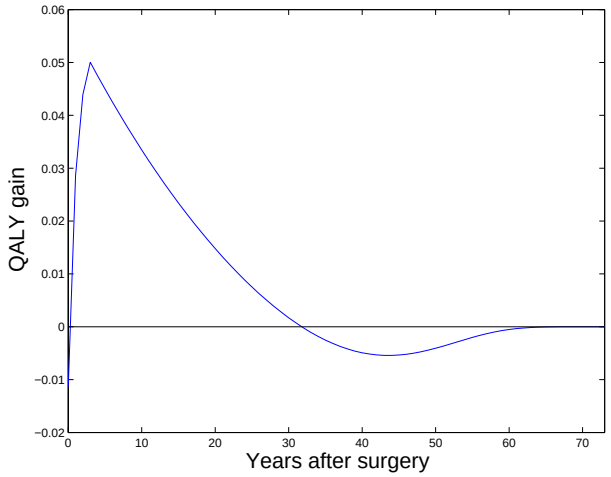
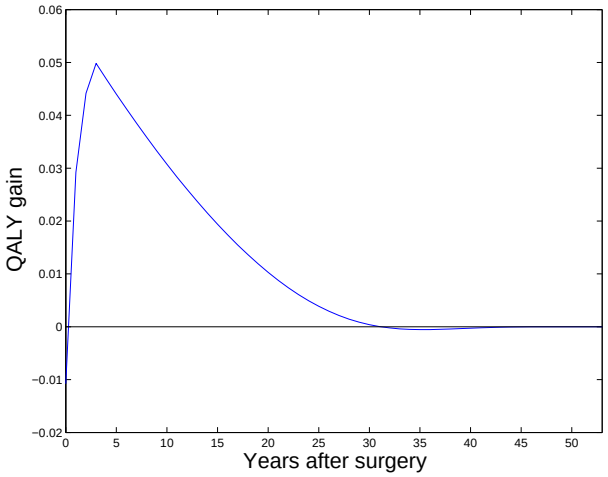


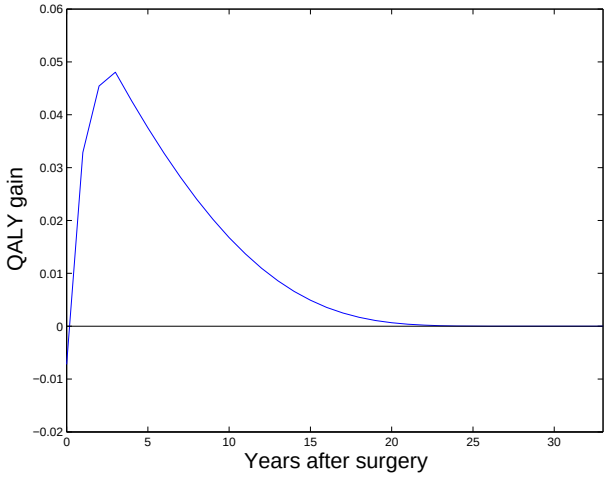
Figure 4.8: Snapshot benefit in QALY gain for a 70-year-old patient with CAS, at each year after the decision to have CEA or continue with medical treatment only. Original model and parameters from Nagaki *et al.* [11].



(a) 40-year-old patient.



(b) 60-year-old patient.



(c) 80-year-old patient.

Figure 4.9: Snapshot benefit in QALY gain for patients of varying ages with CAS, at each year after the decision to have CEA or continue with medical treatment only. Original model and parameters from Nagaki *et al.* [11].

benefit has more time to accumulate than in an older patient's lifetime (as can be seen in Figures 4.9b and 4.9c, the snapshot benefits for a 60-year-old and 80-year-old patient respectively).

We will visit the idea of the snapshot benefit in expected QALYs again in Chapter

6, where we will use it to prove theoretical results for the lifetime benefit of treatment. In any following benefit analyses, we will not analyse the snapshot benefit, and only mention it again for comparisons.

4.2 Issues with the Model

There are some clear issues with the current model that we aim to address before using it to build our multiple disease model. One of the main issues is the probability of a patient transitioning to the dead state, for example, from state 1 in the medical chain:

$$p_{1,4} = P(\text{have stroke} \cap \text{die}) + P(\text{die other causes}) = p(x).$$

This is saying that the probability of having a fatal event and the probability of dying from other causes are both encompassed in the age related annual probability of death of the general population, $p(x)$. However, people with the disease in question are morely likely to have a higher probability of death than the general population, so it is not sensible that their probability of death is the same. That is to say, the probability of a patient transitioning from "well with stenosis" to "dead" is likely to be more than $p(x)$. Furthermore, if the probability of having a fatal event, $P(\text{have stroke} \cap \text{die})$, is large then this calculation is saying that because of this, the patient is less likely to die of all other causes. This in general does not make sense.

Another issue with the current model, is that we assume that once a patient has had a stroke, they do not have another one. Again, this is unrealistic, as if a patient has suffered from a stroke, they are more likely to suffer from another, thus increasing their impairment and probability of dying or having another event in the next time period, as confirmed by Dr. Stephen Fitzgerald, a practicing physician. However, for simplicity, we do not consider varying levels of disablement, as this would make the initial computation and cross disease comparisons difficult. This is an idea which could be explored further in future research. We do, however, consider multiple events. That is, we consider that a patient can die from another

stroke from the "post stroke" state, but another non-fatal stroke does not change the utility value.

The next flaw in this model is that the surgical risk does not change according to the patient's age at the time of surgery. This causes the surgical month in older patients to be more beneficial than a non-surgical month. Clearly, this is not a reasonable assumption. Again, this is something that we do not yet change within the model, but it is something that can easily be modified; we only need to consult and research the literature to find more appropriate surgical risk estimates for older patients.

We also disagreed with some of the values that Nagaki *et al.* used in their transition probabilities. These were numbers that either were not sourced, or did not match the source material from which their other values were found. These values are something that can easily be modified, and we do so in the next section.

4.3 A Modified CEA Model

In our own, modified version of Nagaki *et al.*'s model of carotid endarterectomy (CEA) for carotid artery stenosis (CAS) we define the same state space as before, altering the the disease to the more specific 'CAS' instead of 'stenosis':

$$S = \{1 \text{ (well with CAS)}, 2 \text{ (well without CAS)}, 3 \text{ (post stroke)}, 4 \text{ (dead)}\}.$$

As mentioned previously, we do not agree with all of the values used in the original model. However, there are those values that we do agree with and can recreate ourselves, and we use these in our modified model.

The first value that we do not agree with, is the surgical risk s. The value that Nagaki *et al.* use for surgical risk, $s = 0.03$, is presented without a source or any other explanation. Therefore instead, we use the value $s = 0.062$ for patients with 70-99% stenosis, obtained from the pooled analysis of CEA clinical trial data [15] that Nagaki *et al.* use for other values in their model.

The other value that was not sourced,

$$P(\text{die}|\text{have stroke}) = d,$$

we were unable to obtain from the pooled analysis. This is essentially the probability of death from significant stroke. In the original model, Nagaki *et al.* use 20% for this value. We did, however, find sources from which an estimate for this probability might be found [8, 18].

One source, Stroke Statistics from The Stroke Center at University Hospital [18], reported that 7.6% of ischemic strokes resulted in death within 30 days. We only consider ischemic strokes in this case as we are only considering strokes that are severe enough to leave a patient 'disabled'. Upon further advice from Dr. Fitzgerald, we choose the value 10% for this probability, as he advised that this is a reasonable value for the probability of death from serious stroke. Many physicians use different values for their own risk assessments from personal experience. Therefore this value, and others such as surgical risk, are subject to change between physicians, and we use sensitivity analysis to address this uncertainty in a later section.

The main issue with the original single disease model is that the probability of having a stroke is not related to the probability of dying in a year. This means that as the probability of dying increases with age, the probability of having a stroke remains the same and the matrix becomes non-stochastic once the age of the patient becomes sufficiently high. To remedy this, we want to create a relation between the age related probability of death, and the probability of stroke (in the CEA model).

Consider that a patient is in the "well with CAS" state in the medical chain, or the "well without CAS" state in the surgical chain. Consider the different events a patient can have from this state, and let:

- FS be the event that a patient has a fatal stroke;
- nFS be the even that a patient has a non-fatal stroke, and;
- D be the event that a patient dies due to "other causes".

Then, we have that:

$$P(FS) = e \times d \qquad \text{and}$$
$$P(nFS) = e \times (1 - d),$$

where e is the probability of having a stroke, and d is the probability that the stroke is fatal. We also have that

$$P(D) \approx p(x),$$

the age related probability of death of the general population at age x. The number of people estimated to have CAS, from population-based studies, ranges from 0.5% to 8% [20]. Consequently, we assume that the proportion of $p(x)$ due to severe stroke from CAS is small enough that we can also assume that $p(x)$ is approximately equivalent to the probability of dying from causes other than severe stroke. Hence, we model the probability of a patient suffering a fatal stroke directly on top of $p(x)$.

We can now redefine our transition probabilities using the above. In the medical chain, we have:

$$\begin{aligned} p_{1,3} &= P(\text{“well with CAS”} \to \text{“post stroke”}) \\ &= P(nFS \cap D^c) \\ &= P(nFS) \times P(D^c) \qquad \text{(independence)} \\ &= e \times (1 - d) \times (1 - p(x)), \end{aligned}$$

and

$$\begin{aligned} p_{1,4} &= P(\text{“well with CAS”} \to \text{“dead”}) \\ &= P(D \cup FS) \\ &= P(D \setminus FS) + P(FS) \\ &= P(D \cap FS^c) + P(FS) \\ &= P(D) \times P(FS^c) + P(FS) \qquad \text{(independence)} \\ &= p(x) \times (1 - e \times d) + e \times d. \end{aligned}$$

This now ensures that the transition matrices are stochastic, and that a person who is suffering from CAS does have a greater probability of death than the general population. It also ensures that as the probability of death from causes other than stroke increases, the probability of stroke decreases.

In the surgical chain, the equivalent transition probabilities $p_{2,3}$ and $p_{2,4}$ become the same as their respective probabilities above, $p_{1,3}$ and $p_{1,4}$ in the medical chain.

We also now allow for a patient in the "post stroke" state to have fatal strokes, resulting in the probability of transitioning from "post stroke" to "dead" to now be:

$$p_{3,4} = p(x) \times (1 - e \times d) + e \times d,$$

using similar reasoning to above.

The last value we decide to alter in our modified model is the probability of stroke in the medical chain. Originally this was 1.7% per year, however we set this at 2.3% so that the supplementary surgical treatment (CEA) never becomes a 'worse' option than only the medical treatment. This will rectify the issue we have in the original model of surgery becoming less beneficial for a 40-year-old patient, than for a 50-year-old.

Thus, our final transition matrices, ${}_m\mathbb{P}$ for the medical chain and ${}_s\mathbb{P}$ for the surgical chain, are as follows:

$${}_m\mathbb{P}(y) = \begin{pmatrix} 1-p_{1,3}-p_{1,4} & 0 & e_m(y)(1-d)(1-p(a+y)) & p(a+y)(1-e_m(y)d) + e_m(y)d \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_m(y)d) + e_m(y)d \\ 0 & 0 & 0 & 1 \end{pmatrix},$$

$${}_s\mathbb{P}(y) = \begin{pmatrix} 0 & 1-s & s(1-d) & sd \\ 0 & 1-p_{2,3}-p_{2,4} & e_s(1-d)(1-p(a+y)) & p(a+y)(1-e_sd) + e_sd \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_sd) + e_sd \\ 0 & 0 & 0 & 1 \end{pmatrix},$$

where a is the starting age of the patient, y is the number of years after surgery,

$$e_m(y) = \begin{cases} 0.16 & \text{for } y = 0 \\ 0.08 & \text{for } y = 1 \\ 0.05 & \text{for } y = 2 \\ 0.023 & \text{for } y = 3, 4, 5, ..., \end{cases}$$

$e_s = 0.023$, $s = 0.062$ [15] and $p(x) = e^{-10.58+0.095x}$ [11] is the age related probability of death of the general population. Note that for the notation to remain simple, the age of the patient, a, is not included in the matrix notation $\mathbb{P}(y)$. However, in the rest of this thesis, the age of the patient will be stated whenever the probability matrices are mentioned.

We then use the same utility values,

$$\mathbf{u} = (u_1, u_2, u_3, u_4)^T = (1, 1, 0.6, 0)^T,$$

discounted at 3% each year as before, and the expected reward equations from Section 4.1.4 to calculate the expected lifetime benefit of CEA for patients of various ages. We can also calculate the snapshot benefit using these modified transition matrices.

4.3.1 Comparison of CEA Results

One of the alterations we make in our modified model is to ensure that the probability of death of the general population and the probability of stroke are related. This results in a vast difference in the benefit of CEA between the different starting ages of the patients, as can be seen in Figure 4.10. Now, that the probability of stroke also depends on the age of the patient, the benefit of CEA depends more on the age as well. Using the previous model for CEA, the benefit of surgery for a 40-year-old patient is calculated to be 0.5007 QALYs. In our modified Markov model, the benefit of surgery for a 40-year-old is approximately 1.1066 QALYs. For a 100-year-old, the benefit of surgery in the original model is 0.1394 QALYs, compared to 0.1108 QALYs in the modified model. That is, the benefit of surgery is less

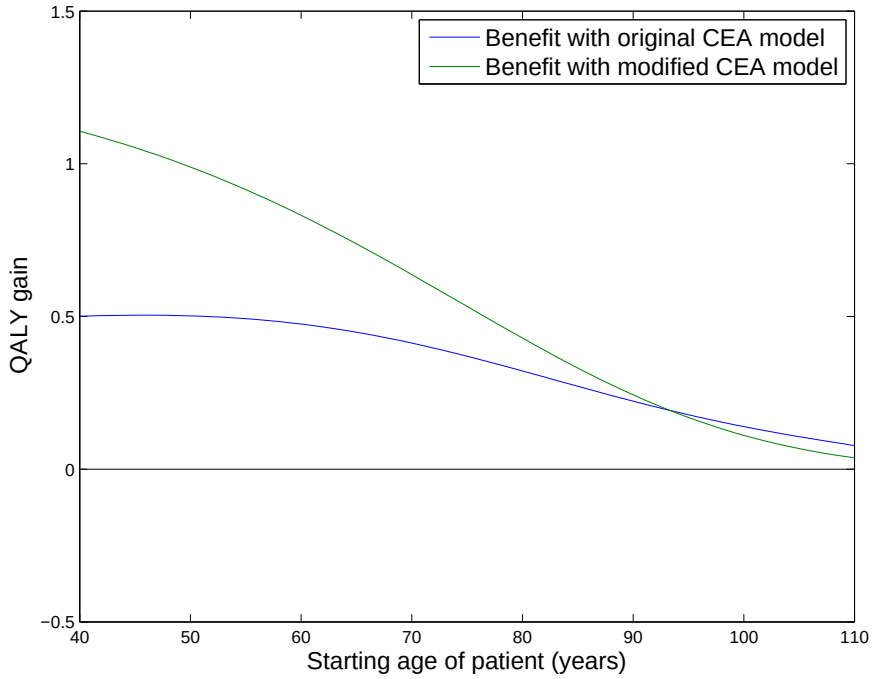


Figure 4.10: Benefit of CEA in expected lifetime QALYs gained, for patients of varying ages. Comparing an original model of the progression of CAS (from Nagaki *et al.* [11]) with our modified model.

in the modified model for an older patient. We believe that these are more realistic results, as performing major surgery on a younger patient should be significantly more beneficial than performing it on a 100-year-old patient.

4.3.2 Iatrogenic Loss and Ideal Benefit

To further analyse the results of our modified model, we can also investigate the iatrognic loss of CEA, defined as the loss of QALYs due to the treatment rather than the disease, as in Chapter 3. Here, we define the iatrogenic loss, $\boldsymbol{\ell}$, to be the difference in expected QALY outcome between risk-free CEA and normal-risk CEA. The QALYs due to risk-free CEA can be calculated by setting the surgical risk, $s = 0$, to remove the iatrogenic effect. The normal-risk CEA is calculated using the

normal surgical risk, $s = 0.062$. That is,

$$\boldsymbol{\ell} = ({}_s\mathbf{w}^I)_1 - ({}_s\mathbf{w})_1,$$

where

$$({}_s\mathbf{w}^I)_1 = \mathbb{E}[\text{QALYs with CEA}(s = 0)|\text{start in state 1}],$$

and

$$({}_s\mathbf{w})_1 = \mathbb{E}[\text{QALYs with CEA}(s = 0.062)|\text{start in state 1}],$$

since, as before, we assume that a patient begins will with CAS.

In Figure 4.11, we can see how the various elements contribute to the QALYs for patients from ages 40 to 110. The red and cyan lines depict the expected QALY outcome for a patient in the surgical chain with the usual risks ($s = 0.062$), and a patient in the medical chain respectively (as calculated earlier). The blue line represents the expected QALYs a patient would have obtained if they suffered from nothing other than the effects of age, and the green line shows the expected QALYs a patient having CEA surgery would have received if the surgery had no risks associated with it – that is, if $s = 0$. Therefore, the iatrogenic loss is the difference depicted by the green shading. For a 70-year-old patient, the iatrogenic loss is 0.2895 QALYs. We can compare this to the lifetime net benefit, $\mathbf{b}$, as calculated earlier, taking into account the surgical risk. The lifetime net benefit of CEA is 0.6373 QALYs, meaning that the iatrogenic loss of surgery is approximately 45% of the normal benefit. That is, if there were no risks associated with CEA, a 70 year old patient could be receiving 45% more benefit than they actually do.

In the original CEA model used by Nagaki *et al.*, the probability of having a stroke in the surgical chain eventually becomes less than in the medical chain. This could be considered an iatrogenic effect, and hence contribute to the iatrogenic loss of QALYs due to CEA. However, this is not a feature of our modified model, and complicates the calculations, so we only consider the surgical risk.

Another measure we could consider from the expected QALYs shown in Figure 4.11, is the ideal benefit, defined as the benefit of risk-free treatment as in

Chapter 3. That is, the ideal benefit is measured as the QALYs gained from surgery if the surgical risk is $s = 0$. That is,

$$\mathbf{b}^I = ({}_s\mathbf{w}^I)_1 - ({}_m\mathbf{w})_1.$$

We can also think of the ideal benefit as the sum of the net benefit and the iatrogenic loss. Therefore, we can also write:

$$\mathbf{b}^I = \mathbf{b} + \boldsymbol{\ell}.$$

Figure 4.11 shows the net benefit as the difference between the red and cyan lines (shaded pink), and the ideal benefit as the difference between the green and cyan lines (the green and pink shaded areas together). For example, the lifetime net benefit of CEA for a 70-year-old is 0.6373 QALYs and the lifetime ideal benefit is 0.9268 QALYs. Naturally, this is greater than the net benefit, as all risks associated with the surgery are ignored. This means that the iatrogenic loss is therefore approximately 31% of the ideal benefit for a 70-year-old. That is, a 70-year-old patient only receives approximately 69% of their ideal benefit, due to iatrogenic loss.

As we did in Chapter 3, it is also possible to calculate the iatrogenic loss and ideal benefit of treatment in terms of the snapshot expected QALYs, where the snapshot iatrogenic loss at time t is

$$\mathfrak{l}(t) = ({}_s\mathbf{v}^I)_1(t) - ({}_s\mathbf{v})_1(t),$$

and the snapshot ideal benefit is

$$\mathfrak{b}^I(t) = ({}_s\mathbf{v}^I)_1(t) - ({}_m\mathbf{v})_1(t).$$

However, we will not be including the snapshot benefit results, as we are focussed on the behaviour of the lifetime benefit.

4.3.3 Sensitivity Analyses

We perform sensitivity analyses by varying the values of surgical risk, probability of death from stroke, and utility of the post stroke state in our Markov models to assess the impact on the different benefit and loss measures.

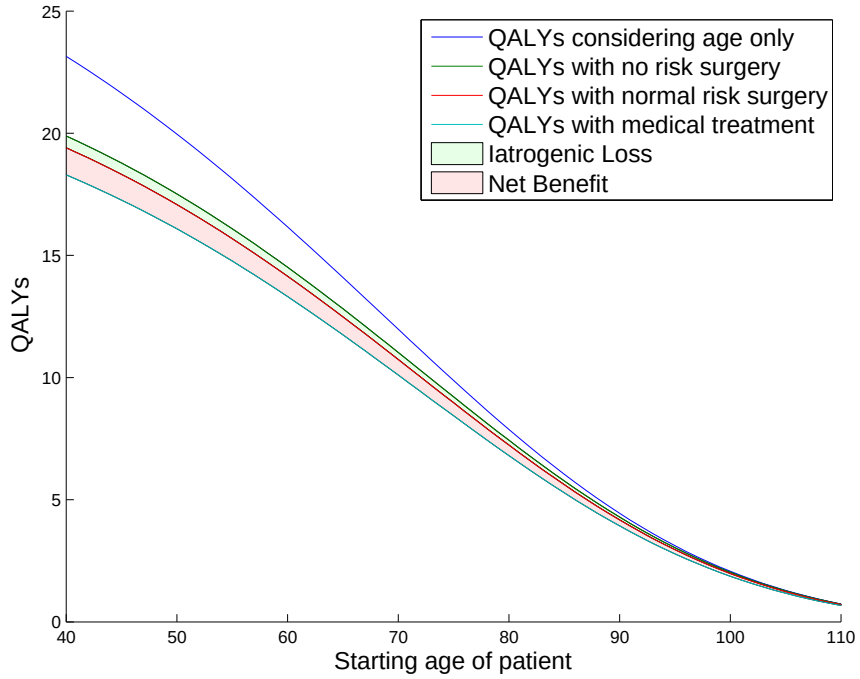
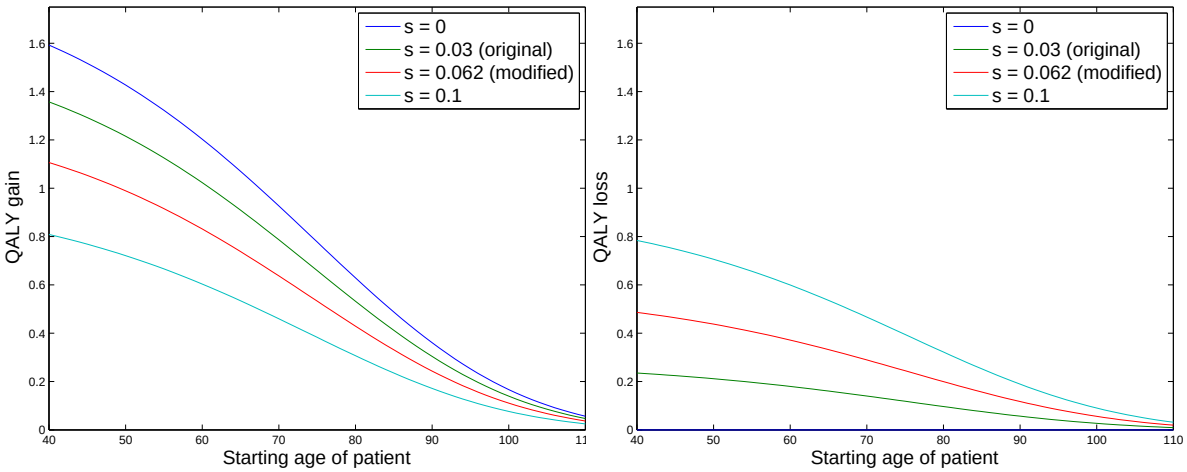


Figure 4.11: How the various options contribute to the lifetime QALYs for patients of varying ages suffering from CAS (using our modified model).

From our sensitivity analysis of the surgical risk, Figures 4.12a and 4.12b show that, as expected, decreasing the risk of surgery increases the net benefit and decreases the iatrogenic loss, respectively. Figure 4.12b shows that the loss is 0 when $s = 0$, and that as s increases, so too does the iatrogenic loss. Since the iatrogenic loss of CEA, $\boldsymbol{\ell}$, is the loss of QALYs caused by the surgical risk, this is expected. However, the ideal benefit, $\mathbf{b}^I$ is calculated using only $s = 0$, so is not affected by the change in surgical risk.

In Figure 4.13a, we see that a decrease in the probability of dying from a stroke, d, causes a decrease in the net benefit. Although this may seem counterintuitive at first, we can see in Figures 4.14a and 4.14b that decreasing d *increases* the expected QALYs in each chain, as we would expect. The net benefit decreases, since the QALY increase in the medical chain (Figure 4.14b) is greater than the increase in the surgical chain (Figure 4.14a), because more strokes occur.



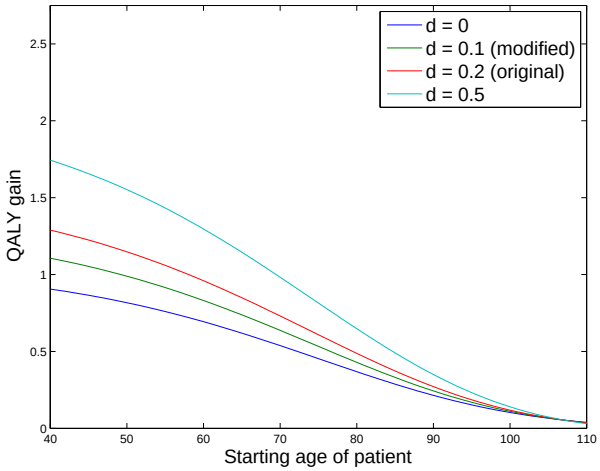
(a) Net benefit

(b) Iatrogenic loss

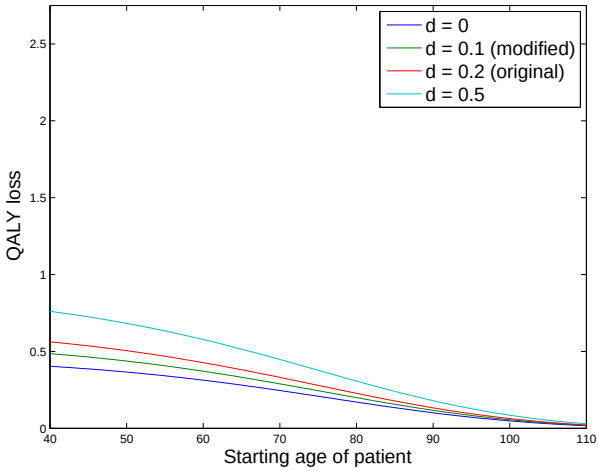
Figure 4.12: CEA sensitivity analysis: The effects of surgical risk on the QALY gain and loss for patients of varying ages undergoing CEA (modified model).

Figures 4.13b and 4.13c demonstrate that changing the value of d affects the iatrogenic loss and ideal benefit of CEA in the same way as it affects the net benefit. This can be explained using similar reasoning, since a decrease in d causes an increase in the expected QALYs of risk-free surgery (Figure 4.14c) as it does in normal-risk CEA and the medical chain shown before. However, the QALY increase in risk-free surgery is greater than in normal-risk surgery, which is greater than in the medical chain, therefore causing a decrease in both the iatrogenic loss and ideal benefit.

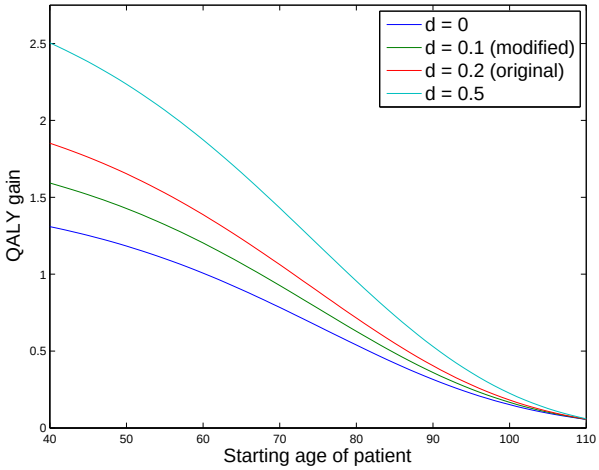
Even though in our new model we have increased the surgical risk and decreased the probability of dying from a stroke (both of which decrease the net benefit), the benefit of surgery is actually greater in the new model for patients approximately 93 years and younger. For 93-year-old patients, there is a 0.1972 QALY benefit in the modified model, compared to 0.1953 in the original. In our modified model, we now have the probability of stroke appearing in more transition probabilities, hence having a greater influence on a patient's health state at the end of a transition period. This causes CEA surgery to be more effective as it lowers the probability of a patient suffering from a stroke.



(a) Net benefit

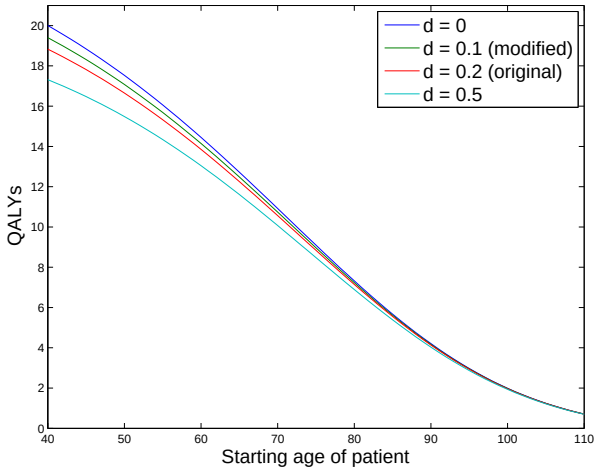


(b) Iatrogenic loss

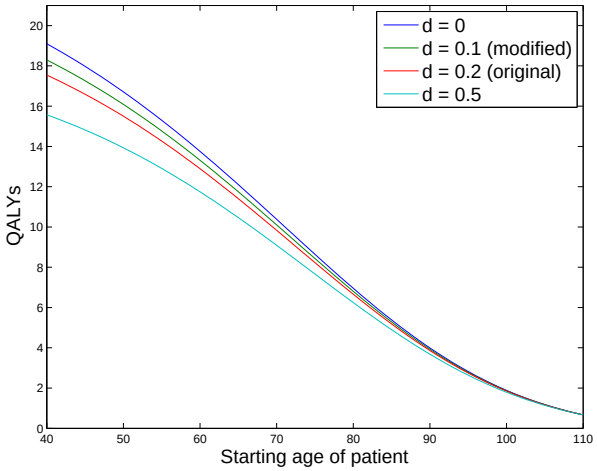


(c) Ideal benefit

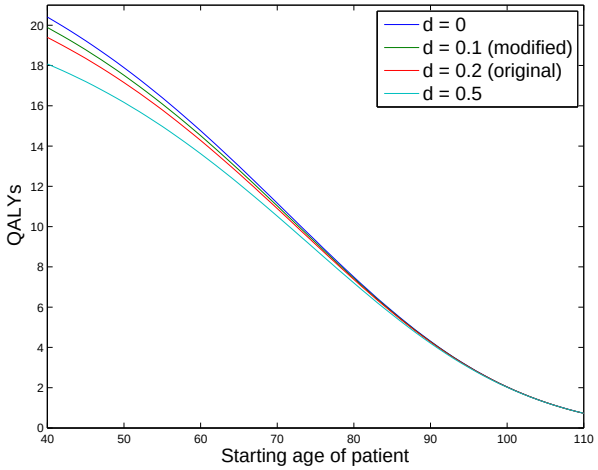
Figure 4.13: CEA sensitivity analysis: The effects of $P(\text{die} \mid \text{have stroke}) = d$ on the QALY gain and loss for patients of varying ages, with CAS (modified model).



(a) With CEA surgery



(b) Without CEA surgery



(c) risk-free CEA surgery

Figure 4.14: CEA sensitivity analysis: The effects of $P(\text{die} \mid \text{have stroke}) = d$ on the expected lifetime QALYs of patients of varying ages, with CAS (modified model).

In Figures 4.15a, 4.15b, and 4.15c, we can see the effects of altering the utility of the "post stroke" state. Since we keep the original value of 0.6 for this state in our modified model, it is interesting to see that there is a significant difference in the benefits for younger patients by altering the utility values by 0.2 each way. As we expect, considering more severe strokes (with a lowered state utility of 0.4) increases the net benefit, ideal benefit and the iatrogenic loss of CEA, and considering a less severe "post stroke" state (utility 0.8) decreases the net benefit, ideal benefit and iatrogenic loss, similar to the way that d affects them. As we could consider adding varying levels of the "post stroke" state in a future version of the model, it is also interesting to see the effects that this might have on the benefit of CEA.

Since we consider the results from this modified model to be appropriate, and the probabilities more realistic, we can adapt this model by generalising it to an arbitrary disease and its treatment, as the model is still simple enough to be easily adaptable.

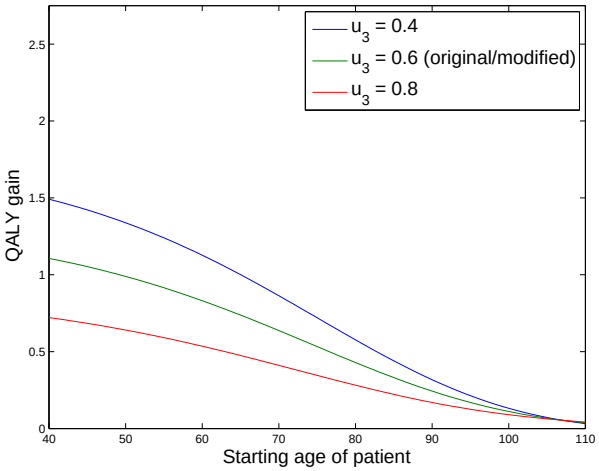
4.4 A General Model

Now that we are satisfied with the results of our modified model for carotid endarterectomy, we can generalise the health states and transition probabilities. For a general episodic disease and its treatment, the state space is:

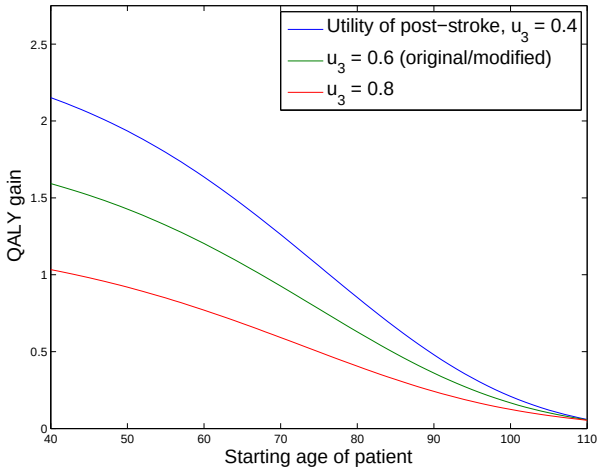
$$S = \{1 \text{ (well with } \textit{disease}), 2 \text{ (well without } \textit{disease}), 3 \text{ (post } \textit{event}), 4 \text{ (dead)}\},$$

where *disease* is the disease which we are treating, and *event* is the the episode or event associated with that disease. For example, for carotid artery stenosis (the disease), the event is a stroke.

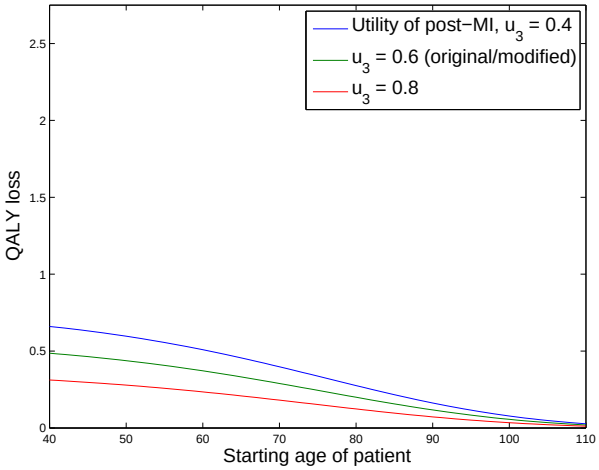
We are considering treatments similar to surgery, in that the treatment occurs only once and has some risk, s, associated with it. Therefore our transition probabilities from state 1 in our treatment chain will have the same format as in our CEA model, with different values. Since we are only considering episodic diseases,



(a) Net benefit



(b) Ideal benefit



(c) Iatrogenic loss

Figure 4.15: CEA sensitivity analysis: The effects of the post stroke state utility value, u_3, on QALY gain and loss of patients of varying ages, with CAS (modified model).

the format of the other general transition probabilities will also be the same as in our CEA model.

The general control chain has transition matrix:

$$ {}_m\mathbb{P}(y) = \begin{pmatrix} 1-p_{1,3}-p_{1,4} & 0 & e_m(y)(1-d)(1-p(a+y)) & p(a+y)(1-e_m(y)d)+e_m(y)d \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_m(y)d)+e_m(y)d \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

and the general treatment chain has matrix:

$$ {}_s\mathbb{P}(y) = \begin{pmatrix} 0 & 1-s & s(1-d) & sd \\ 0 & 1-p_{2,3}-p_{2,4} & e_s(y)(1-d)(1-p(a+y)) & p(a+y)(1-e_s(y)d)+e_s(y)d \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_s(y)d)+e_s(y)d \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

where a is the starting age of the patient, y is the number of years since treatment, $e_m(y)$ and $e_s(y)$ are the probabilities of having an event in year y in the control chain and treatment chain respectively, d is the probability of dying from a 'severe' event, and s is the treatment risk. In this general model, we also use the age related probability of death of the general population,

$$ p(x) = e^{-10.58+0.095x}, $$

where x is the age of the patient in years, obtained by regression analysis of death rates from Japanese Life Statistics data [11]. We use this function as it does not specifically model the probability of death from an event caused by the disease, therefore allowing us to model this death on top of the function.

We are also able to utilise the same expected QALY equations to calculate the benefit of the general treatment, being sure to use the correct treatment risk period,

z days:

$$\begin{aligned}
\mathbf{w}(0) &= \frac{z}{365} \times \frac{1}{2}(\mathbf{u}(0) + \mathbb{P}(0)\mathbf{u}(0)) + \mathbb{P}(0)\mathbf{w}(1), \\
\mathbf{w}(1) &= \frac{365 - z}{365} \times \frac{1}{2}(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)) + \mathbb{P}(1)\mathbf{w}(2) \quad \text{and} \\
\mathbf{w}(t) &= \frac{1}{2}(\mathbf{u}(t) + \mathbb{P}(t)\mathbf{u}(t)) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t = 2, ...T-1, \\
\mathbf{w}(T) &= \frac{1}{2}\mathbf{u}(T), \\
\mathbf{w}(t) &= \mathbf{0} \quad \text{for } t \geq T+1,
\end{aligned}$$

where $T = 112 - a$, as 112 years is the maximum age a patient can reach according to our model. We also have that $\mathbb{P}(t)$ is the transition matrix for the t^{th} time period, where time period 0 and time period 1 are both in the first year as before, and

$$\begin{aligned}
\mathbf{u}(0) &= \mathbf{u}(1) = \mathbf{u}, \\
\mathbf{u}(t) &= (1-f)^{(t-1)} \times \mathbf{u},
\end{aligned}$$

such that $\mathbf{u}(t)$ is the utility at time period t, and f is the discounting factor of the utility.

The lifetime benefit of treatment is the difference between the expected lifetime QALYs with and without treatment, given that a patient started in state 1. That is, if we let $({}_s\mathbf{w})_i(0)$ be the expected QALYs with treatment given that a patient started in state i, and $({}_m\mathbf{w})_i(0)$ be the expected QALYs without treatment given that a patient started in state i, then:

$$\text{benefit of treatment} = \mathbf{b} = ({}_s\mathbf{w})_1(0) - ({}_m\mathbf{w})_1(0),$$

where ${}_s\mathbf{w}$ and ${}_m\mathbf{w}$ can be calculated using the above equations, and backwards recursion.

The snapshot expected QALYs, and hence snapshot benefit, can also be calculated using the appropriate probability matrices and utility values. The snapshot

expected QALYs at time period t are:

$$\mathbf{v}(t) = \mathbb{P}(0) \times \mathbb{P}(1) \times \mathbb{P}(2) \times \ldots \times \mathbb{P}(t) \times \mathbf{u},$$
$$\mathbf{v}(T) = \mathbf{0}, \quad \text{for } T = 112 - a,$$

where $\mathbb{P}(t)$ is the transition matrix corresponding to the t^{th} time period. As before, $\mathbb{P}(0)$ corresponds to the transition matrix for the surgical risk period, z days, and $\mathbb{P}(1)$ to the transition matrix for the remainder of that year.

Therefore, the snapshot benefit in expected QALYs at time t are:

$$\mathfrak{b} = ({}_s\mathbf{v})_1(t) - ({}_m\mathbf{v})_1(t),$$

where $({}_s\mathbf{v})_1(t)$ and $({}_m\mathbf{v})_1(t)$ correspond to the first entry of the snapshot expected QALY vectors, after time t, with and without treatment respectively.

Ensuring to carefully define the states, what a 'severe' event entails for different diseases, and the treatment risk period (for example, 30 days in the CEA model), we can use this general model to track the progress of various individual diseases with their respective treatments, and hence find the individual benefit of each treatment over time.

4.5 Modelling a Different Individual Treatment

4.5.1 A Model of Coronary Artery Bypass Graft Surgery

Since the purpose of creating the individual model is to eventually use it to model multiple treatments at once, we adapt it to a treatment for a disease other than carotid artery stenosis. The second treatment we model is coronary artery bypass graft surgery (CABG), the surgical treatment for coronary artery disease (CAD). We choose this, as patients who are suffering from carotid artery stenosis (CAS) are also reasonably likely to have CAD. It then makes sense to combine the two models for CABG and CEA to create a 2-disease model in a later chapter.

Coronary artery disease most commonly causes myocardial infarctions, or heart attacks, in its sufferers; that is, the 'event' associated with CAD is myocardial infarction (MI). Therefore, for this treatment the adapted state space is:

$$S = \{1 \text{ (well with CAD)}, 2 \text{ (well without CAD)}, 3 \text{ (post MI)}, 4 \text{ (dead)}\}.$$

In this model, a patient in the state "well with CAD" is defined to have 'stable coronary artery disease (stable angina not severe enough to necessitate surgery on grounds of symptoms alone)' [21], and to have not yet had an MI. As with the previous model, the only way for a patient to be "well without CAD" is to have successful surgery; that is, surgery not resulting in MI or death. Finally, a patient is in "post MI" if they have suffered a myocardial infarction (MI) and are now in an impaired state.

Using a triallist's collaboration (of seven CABG trials) [21], we are able to source most of the values necessary for the model. These values are:

$$P(\text{have MI without CABG}) = \text{annual probability of event on medical treatment},$$
$$P(\text{have MI after CABG}) = \text{annual probability of event after CABG},$$
$$P(\text{have MI during CABG}) = s \quad \text{(surgical risk)}.$$

We use the hazard function (age related death function) $p(x)$ for the probability of dying from other causes, as before.

From the trial collaboration data [21], we are given that 10.3% of patients have a myocardial infarction or die within 30 days of surgery. As surgical risk is defined as MI or death within 30 days of surgery, we have

$$s = 0.103.$$

We are also given the probability of infarction or death at one year as 11.6% in the CABG group of the trials, and 8.0% in the medical treatment group. At 5 years the probability is 24.4% in the CABG group, and 30.7% in the medical treatment group [21].

Using these values, and a similar method to that in the CEA model, we are able to find the annual probability of infarction and death for both the surgical (CABG) and medical groups for this model:

$$r_{s1} = 0.116 - s = 0.013 \qquad \text{and} \qquad r_{s5} = 0.244.$$

Therefore,

$$\begin{aligned} (1 - r_s)^4 &= 1 - (r_{s5} - 0.116) \\ &= 1 - 0.244 + 0.116 \\ &= 0.872. \\ \text{Therefore} \qquad r_s &= 1 - 0.872^{1/4} \\ &\approx 0.0337, \end{aligned}$$

where r_s is the probability of infarction or death in a single year after successful CABG, after the first year.

Similarly,

$$r_{m1} = 0.08 \qquad \text{and} \qquad r_{m5} = 0.307.$$

Therefore,

$$\begin{aligned} (1 - r_m)^4 &= 1 - (r_{m5} - r_{m1}) \\ &= 1 - 0.307 + 0.08 \\ &= 0.773. \\ \text{Therefore} \qquad r_m &= 1 - 0.773^{1/4} \\ &\approx 0.0623, \end{aligned}$$

where r_m is the probability of infarction or death in a single year on medical treatment, after the first year of the trial.

That is, we have:

$$P(\text{have MI after CABG}) = \begin{cases} 0.013 & \text{for 0-1 year} \\ 0.034 & \text{for 1 year onwards,} \end{cases}$$

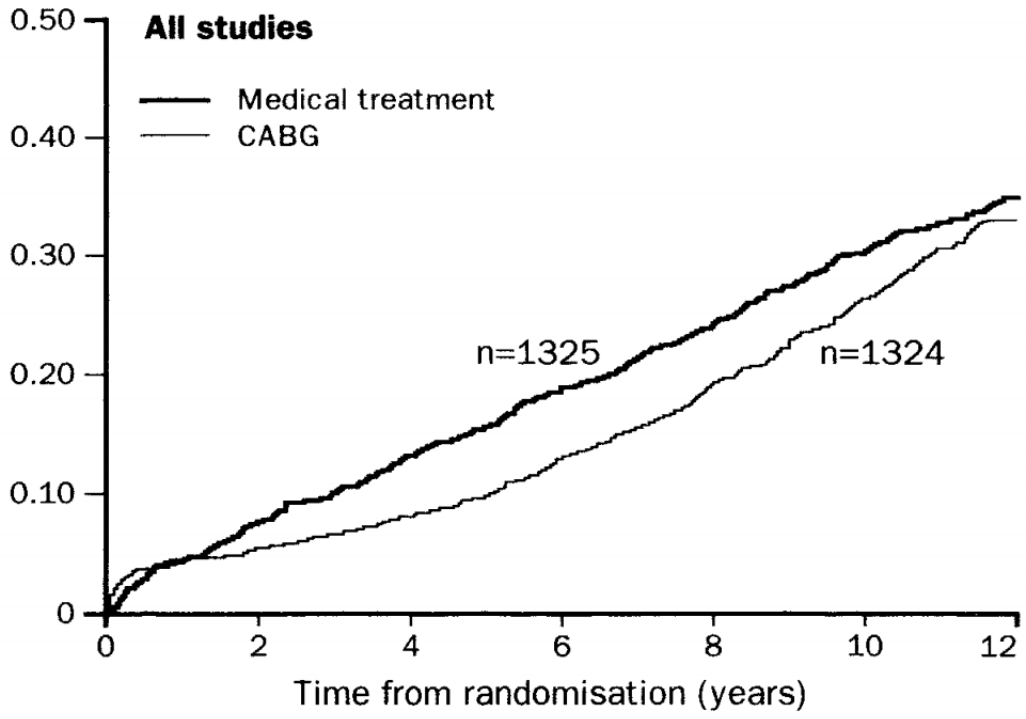


Figure 4.16: Kaplan-Meier survival curve for patients in clinical trials for CABG [21]. 1325 patients were allocated medical treatment, while 1324 were allocated surgery (CABG).

and

$$P(\text{have MI on medical treatment}) = \begin{cases} 0.08 & \text{for 0-1 year} \\ 0.062 & \text{for 1 year onwards.} \end{cases}$$

However, this assumes that after the first year, a Kaplan-Meier curve of MI incidents for both the CABG and medical treatment groups is approximately linear, which may not be the case. Since only a figure of the Kaplan-Meier survival curve, and not just the curve of the probability of infarction, is provided in the article (Figure 4.16), we are unable to use similar methods as in the CEA model to find the annual probabilities more accurately.

From Figure 4.16 we can see that the mortality probability for the medical treatment group seems to be approximately linear, so the assumption that the same is

true for MI probability is not unrealistic in this case. The survival curve for the CABG group, however, does not follow a linear trend; we can see that after accounting for surgical risk, the probability of infarction begins low, but increases as time goes on. Since the probability of infarction or death includes mortality, it is reasonable to assume that it follows a similar trend. However, since we do not have further data regarding the probability of infarction, we use the crude values we obtained above for $P(\text{have MI after CABG})$.

We also need to find the probability of death from myocardial infarction,

$$P(\text{die}|\text{have MI}).$$

As before, we obtain this from sources other than the CABG trial data because it does not depend on the surgery [13, 16]. However, there is limited data available for the probability of death from MI outside of hospitals. This leaves us unsure of the accuracy of the probability of death from MI in various articles. Another concern is that tests for myocardial infarctions in hospitals have become more sensitive, meaning that doctors are now able to detect more MIs than before. This may skew the results we are looking for, as we wish to only consider 'serious' myocardial infarctions (severe enough to leave the patient impaired, given that they did not die from the MI).

One article providing an in-hospital mortality after acute myocardial infarction reported that during their study, 7.99% of patients died within 30 days of admission to hospital [16]. We decided, upon advice from Dr. Fitzgerald, that using an approximate probability of death from MI of 8% is reasonable, and later use a sensitivity analysis to assess different values. We therefore have that the probability of a fatal myocardial infarction is,

$$P(\text{die}|\text{have MI}) = d = 0.08.$$

Ensuring that the probability of death and the probability of a MI are related as in our CEA model, our transition probability matrices for the CABG model are

then:

$$ {}_m\mathbb{P}(y) = \begin{pmatrix} 1-p_{1,3}-p_{1,4} & 0 & e_m(y)(1-d)(1-p(a+y)) & p(a+y)(1-e_m(y)d)+e_m(y)d \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_m(y)d)+e_m(y)d \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

and:

$$ {}_s\mathbb{P}(y) = \begin{pmatrix} 0 & 1-s & s(1-d) & sd \\ 0 & 1-p_{2,3}-p_{2,4} & e_s(y)(1-d)(1-p(a+y)) & p(a+y)(1-e_s(y)d)+e_s(y)d \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_s(y)d)+e_s(y)d \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

where, y is the number of years since surgery, a is the starting age of the patient,

$$ e_s(y) = \begin{cases} 0.013 & \text{for } y = 0 \\ 0.034 & \text{for } y = 1, 2, 3, ... \end{cases} $$

$$ e_s(y) = \begin{cases} 0.08 & \text{for } y = 0 \\ 0.062 & \text{for } y = 1, 2, 3, ... \end{cases} $$

$s = 0.103$, $d = 0.08$, and $p(x) = e^{-10.58+0.095x}$ is the age related probability of death of the general population.

4.5.2 The Benefit of CABG

We use the same method as before for calculating the expected QALYs for both of the medical and surgical chains, and hence the net benefit of treatment. To do this, we only need to alter the utility of being in the "post MI" state. Using the American Medical Association Guides to the Evaluation of Permanent Impairment [1] and consulting with Dr. Fitzgerald, we estimate that the impairment for a 'severe enough' myocardial infarction would be approximately 35% impairment of the whole person. Therefore, the utility we use for a patient in the "post MI" state is estimated to be

$$ 1 - \text{impairment} = 1 - 0.35 = 0.65. $$

Since we are still using utilities of 1 for the "well-" states, and 0 for death, we have that:

$$\mathbf{u} = (u_1, u_2, u_3, u_4)^T = (1, 1, 0.65, 0)^T.$$

Again, using the same lifetime benefit calculations as in the CEA model, with the CABG transition matrices and utilities instead, we obtain the results in Figure 4.17. This depicts a comparison of the lifetime benefit in quality adjusted life years (QALYs) between CEA (the green line) and CABG (the blue line). The figure shows that although CABG is more beneficial for patients who have the surgery before approximately 58 years of age, it has a steeper drop in benefit as the age that the patient has surgery increases.

To investigate this phenomenon, we consider how the net benefit accumulates through a patient's lifetime. For example, Figure 4.18 depicts the accumulation of net benefit in QALYs with CEA or CABG for a 70-year-old patient. We can see that, unlike for CEA, the net benefit of CABG is not immediately positive. That is, it only becomes positive after approximately five years after surgery. This we can attribute to the relatively high surgical risk in CABG: a 10.3% chance of a bad outcome compared to 6.2% in CEA.

We can also compare the snapshot benefit in expected QALYs of CEA and CABG, for a 70-year-old patient, as shown in Figure 4.19. As expected, since the surgical risk of CABG is higher than CEA, the snapshot benefit of CABG remains negative until $t = 3$, compared to only being negative for $t = 0$ for CEA. Unlike that of CEA, the snapshot benefit of CABG for a 70-year-old reaches its peak later in the patient's lifetime (at $t = 12$, rather than $t = 3$). The snapshot benefit of CABG also increases more gradually than that of CEA, and the maximum snapshot QALYs are less (0.0441 QALYs for CABG, compared to 0.0629 QALYs for CEA).

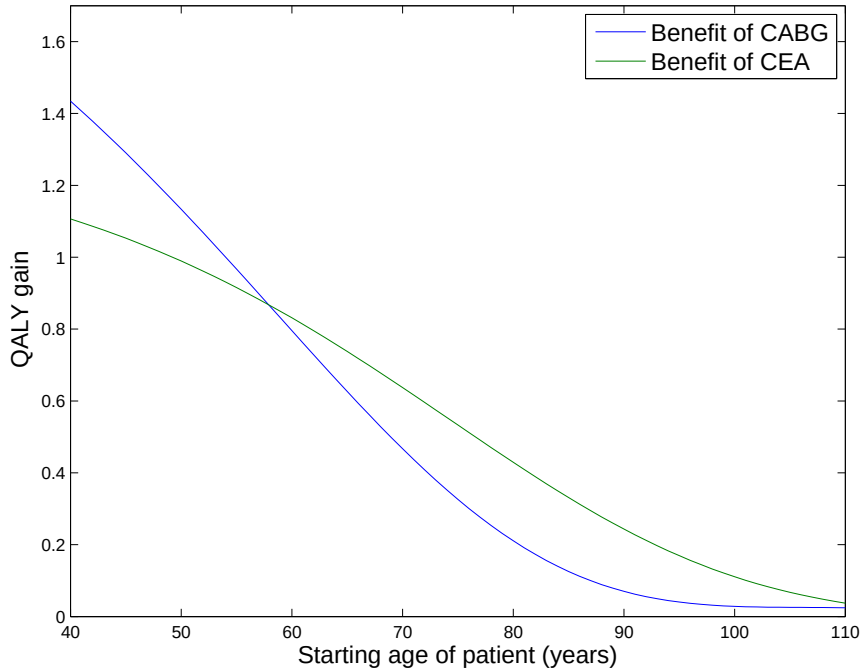


Figure 4.17: Net benefit for patients of varying ages, suffering either from CAD or CAS.

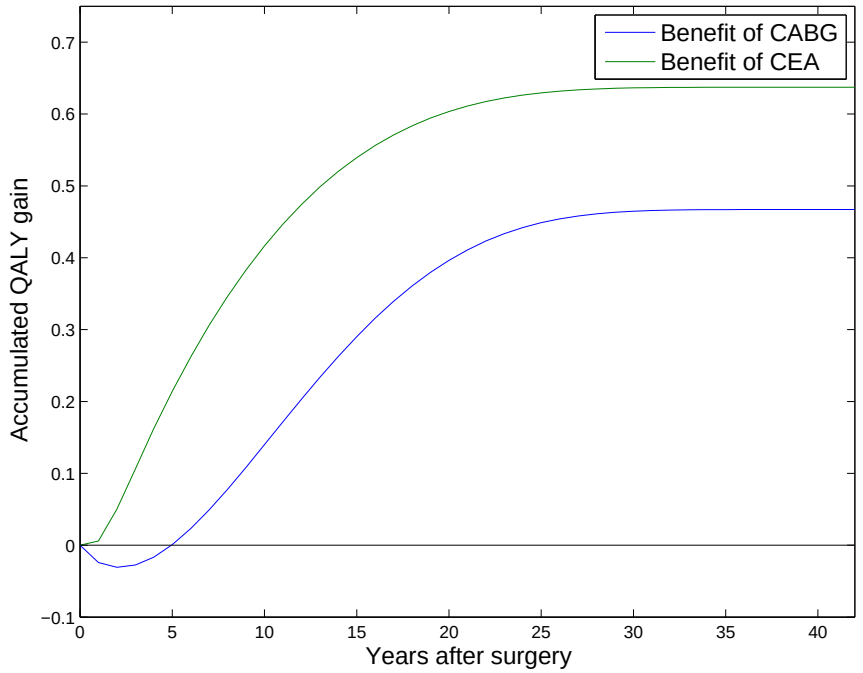


Figure 4.18: Accumulated net benefit each year after surgery, for a 70-year-old patient suffering either from CAD or CAS.

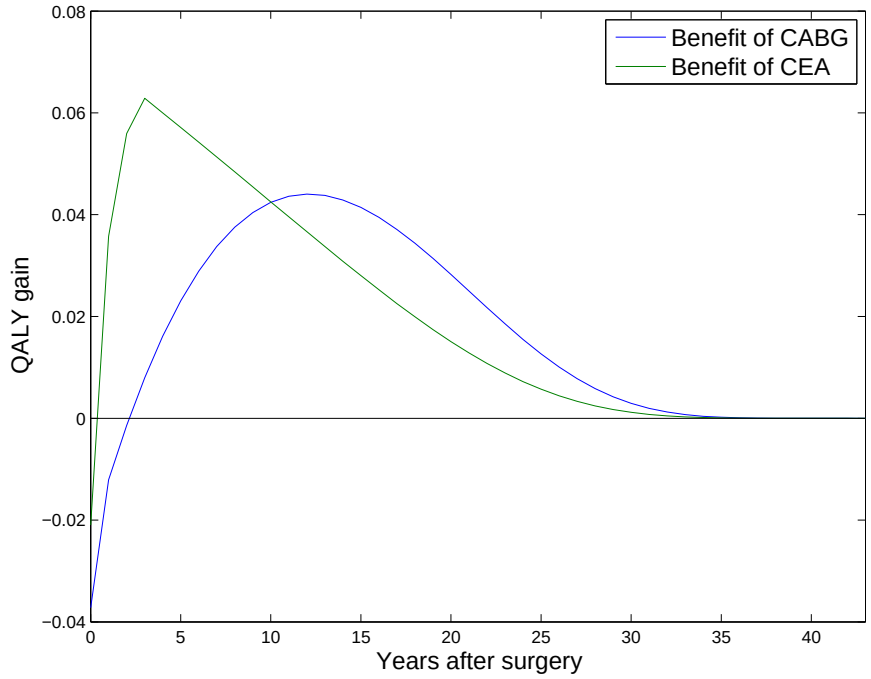


Figure 4.19: Snapshot net benefit each year after surgery, for a 70-year-old patient suffering either from CAD or CAS.

4.5.3 The Ideal Benefit and Iatrogenic Loss of CABG

As in the CEA model, we also look at how the surgical risk of CABG affects the benefit by considering the ideal benefit, $\mathbf{b}^I$, where

$$\mathbf{b}^I = \mathbf{b} + \boldsymbol{\ell},$$

and $\boldsymbol{\ell}$ is the iatrogenic loss, or loss of QALYs due to surgery, as before. Figure 4.20 shows how the varoius elements contribute to the lifetime expected QALYs for patients aged 40 to 110 years old. The iatrogenic loss for a 70-year-old patient undergoing CABG is 0.3980 QALYs, compared to 0.2895 QALYs for a 70-year-old having CEA. It is reasonable that the iatrogenic loss is higher in patients undergoing CABG as the surgical risk of CABG is $s = 0.103$ compared to $s = 0.062$ for CEA.

Recall that the ideal benefit is the benefit measured considering surgery carries no risk. That is,

$$\mathbf{b}^I = ({}_s\mathbf{w}^I)_1 - ({}_m\mathbf{w})_1.$$

The ideal benefit of CABG for a 70-year-old is 0.8651 QALYs, thus making the iatrogenic loss due to CABG approximately 46% of the ideal benefit. This means that a 70-year-old patient undergoing normal-risk CABG, with $s = 0.103$, is only receiving 54% of their potential benefit if the surgery were to carry no risk. The percentage loss of benefit due to surgical risk is much higher in patients undergoing CABG than those undergoing CEA, due to the high surgical risk of CABG.

In Figure 4.17, we saw that the net benefit of CABG was greater for younger patients than CEA, but became less beneficial for patients around 58 years old. We then speculated that this may have been due to the high surgical risk of CABG compared to CEA, meaning that for older patients there was a period of negative benefit in the first few years after surgery that took some years to become positive. However, Figure 4.21 demonstrates that even considering risk-free surgery for both CABG and CEA, CABG still becomes less beneficial than CEA for patients aged approximately 66 years old. We expect that this is due to the difference in how surgery affects the probability of having an event (either MI or stroke) in the CABG model, compared to in the CEA model.

Patients with carotid artery disease (CAD) undergoing CABG can expect to have a reduction in MI probability of 0.067 in the first year after surgery, and 0.028 for every year after that. In comparison, patients with coronary artery stenosis (CAS) undergoing CEA expect a reduction in stroke probability of 0.137 in the first year, 0.057 in the second, 0.027 in the third year and no reduction in stroke probability in the following years. That is, patients undergoing CABG benefit from a reduction in annual MI probability for the rest of their lifetime, however in the first few years after surgery, the reduction in MI is much less than the reduction in stroke that patients undergoing CEA benefit from.

This leads to patients undergoing CABG having to live longer to accrue the same benefit after surgery. However, in the CEA model, patients have an immediately large reduction in stroke probability, meaning that the benefits of CEA surgery are more up front than for CABG surgery. Patients undergoing CEA then eventually

return to having the same probability of stroke as patients receiving only medical treatment, meaning that patients living longer (younger patients) experience more years with no additional benefit. Hence, younger patients undergoing CABG receive more lifetime benefit than younger patients undergoing CEA, and older patients undergoing CABG receive less benefit than older patients undergoing CEA, even when surgical risk is not considered. The large surgical risk of CABG, compared to CEA, further exacerbates this situation, causing the age for which CABG becomes less beneficial than CEA to drop from 66 to 58 years old.

From Figure 4.22a, which shows the accumulation of the QALY differences for a 70-year-old patient undergoing CEA, we can see that there is no period of negative ideal benefit. This is to be expected, as there is no period of negative benefit in the accumulated net benefit of CEA either. However, we note that in approximately the first two years after CEA surgery, the iatrogenic loss of surgery is greater than the net benefit. In other words, the iatrogenic loss is more than half of the ideal benefit for two years after CEA surgery.

Figure 4.22b demonstrates that with risk-free CABG surgery, again, there is no period of negative benefit, compared with a period of five years for normal-risk surgery. As before, we expect this, as we hypothesised that the period of negative benefit was due to the high surgical risk of CABG, and the ideal benefit is calculated with no surgical risk. We can also note that, like in the CEA model, the accumulated iatrogenic loss of CABG is initially greater than the net benefit. However, this is for a period of 19 years after surgery, compared to approximately two years in the CEA model.

This means that the loss of benefit in QALYs due to the surgical risk, is greater than the net benefit that a 70-year-old patient is receiving from surgery, for almost 20 years after it is performed. This result, along with the five year period of negative benefit after surgery for a 70-year-old, leads to questions of whether CABG surgery is in fact worthwhile for older patients.

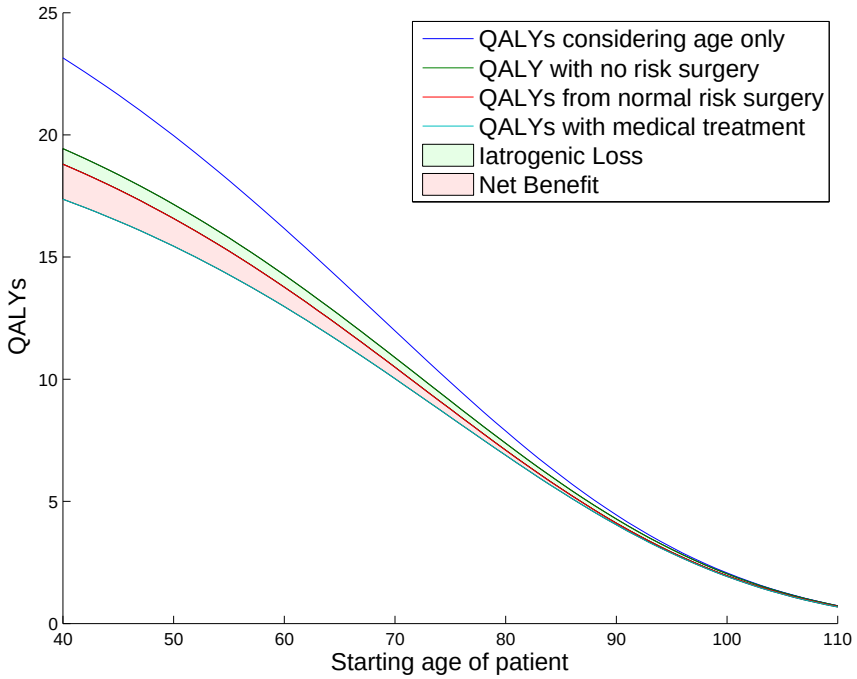


Figure 4.20: How the various options contribute to the lifetime QALYs for patients suffering from CAD.

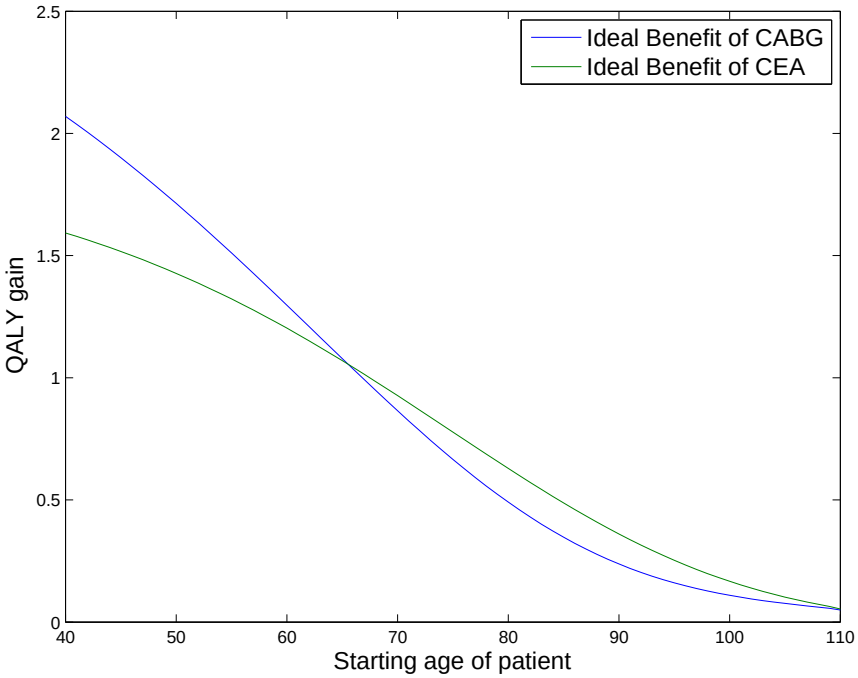
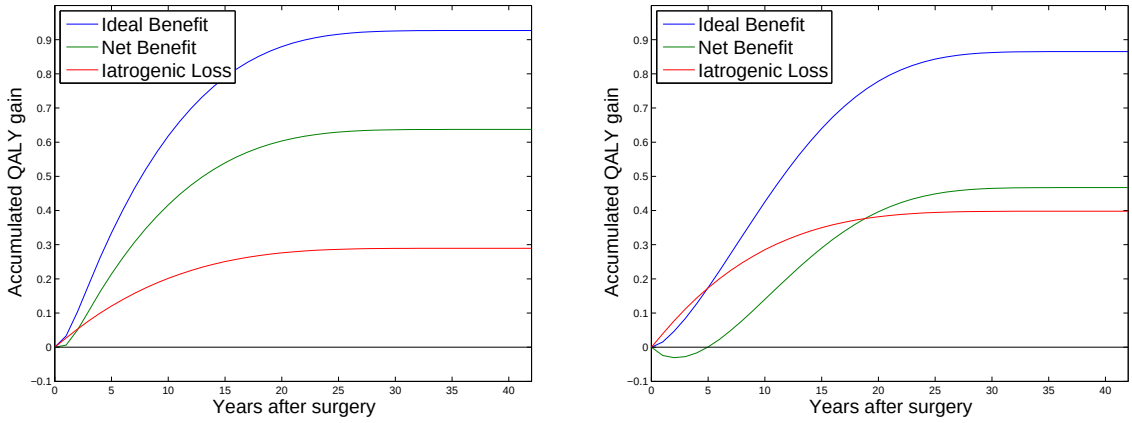


Figure 4.21: Comparison of the ideal benefits (in expected QALY gain) for patients of varying ages, suffering either from CAD or CAS.



(a) Catorid artery stenosis (CAS) (b) Coronary artery disease (CAD)

Figure 4.22: Accumulation of QALY loss and gain measures for a 70-year-old patient, suffering either from CAS or CAD.

4.5.4 Sensitivity Analyses

Figure 4.23 shows a surgical risk sensitivity analysis for the accumulated benefit of CABG. It demonstrates that even for a smaller surgical risk value than that of CEA ($s = 0.05$ compared to $s = 0.062$ for CEA), there is still a slight period of negative benefit in the first year after surgery, that patients undergoing CEA do not encounter. As mentioned previously, this is due to CEA being more beneficial than CABG in the first year after surgery. Recall that CEA lowers the probability of stroke in the first year vastly more than CABG reduces the probability of MI in the first year, meaning that patients undergoing CEA do not experience any period of negative benefit, after the first 30 days.

For completeness, we perform sensitivity analyses on the surgical risk in the overall lifetime net benefit for patients of different ages (Figure 4.24a) and also iatrogenic loss (Figures 4.24b). We also perform sensitivity analyses for the probability of dying from a myocardial infarction, d, (Figure 4.25a, 4.25b and 4.25c), and for the "post MI" utility value (Figures 4.26a, 4.26b, and 4.26c) on the net benefit, ideal benefit and iatrogenic loss of CABG, respectively.

As expected, an increase in the surgical risk results in a decrease of the net benefit of the surgery, and vice versa. Like in the CEA model, clearly increasing surgical risk increases the iatrogenic loss. We see that as the probability of death from MI increases, so too does the net benefit, ideal benefit and iatrogenic loss of CABG. Also, increasing the utility value of the "post MI" (decreasing the level of impairment of a myocardial infarction) decreases the net and ideal benefits, and iatrogenic loss of CABG, as was demonstrated in the CEA model.

These results demonstrate that the base Markov model for a once-off treatment, such as surgery, for an episodic disease can be successfully adapted to different diseases, as required, and produces sensible results for the lifetime benefit of such a treatment. Now that we have confirmed this, and produced models for different diseases, we can begin the process of using these to create a combined model for multiple treatments and diseases.

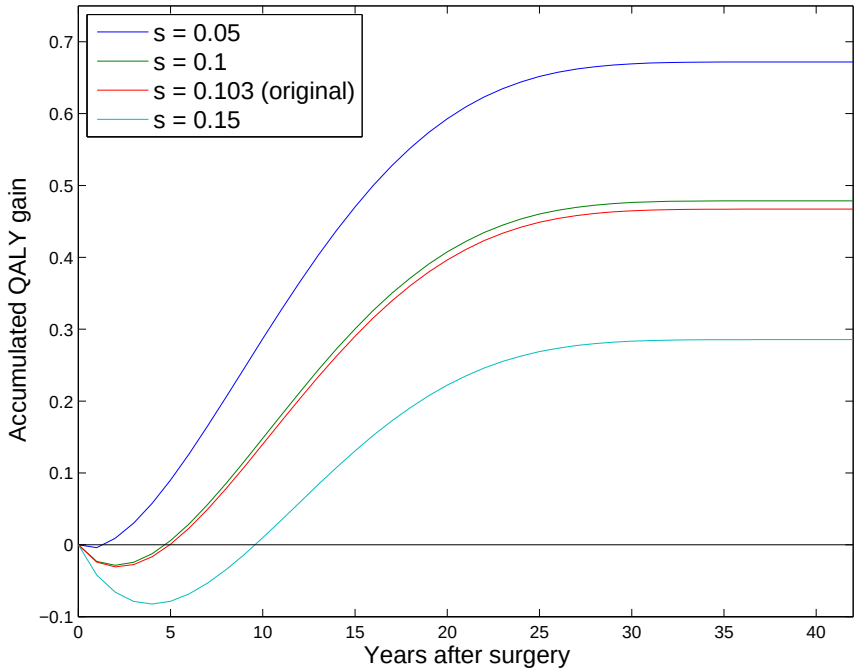
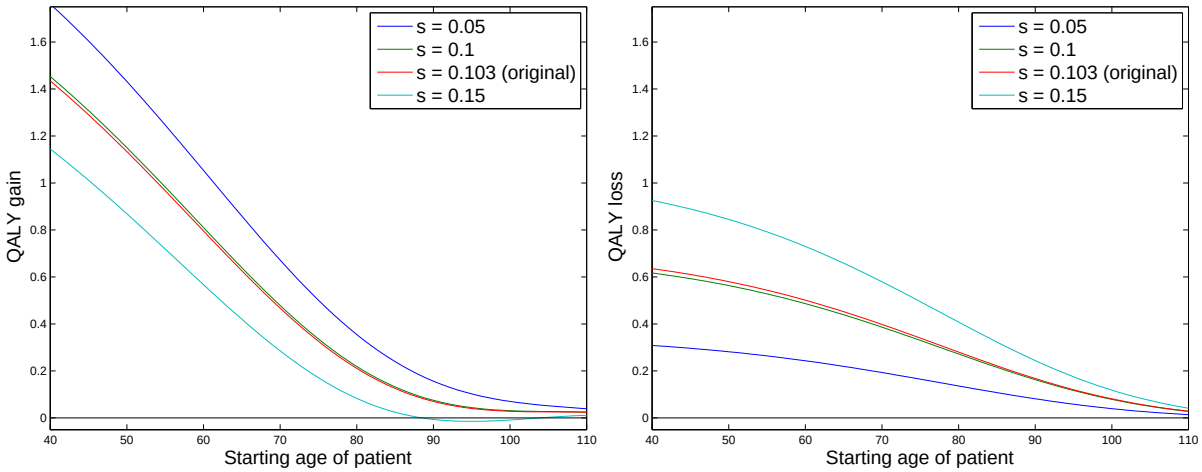


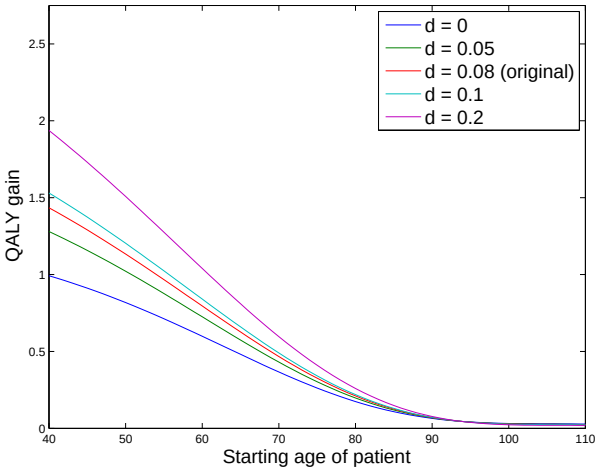
Figure 4.23: Sensitivity analysis: Effect of surgical risk on the accumulated net benefit, each year after surgery, for a 70-year-old patient undergoing CABG.



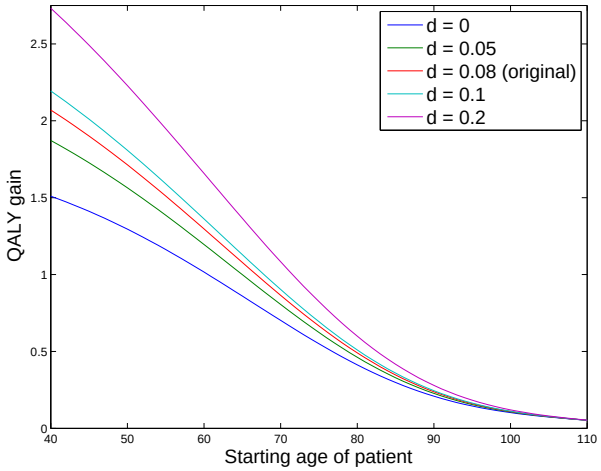
(a) Net benefit

(b) Iatrogenic loss

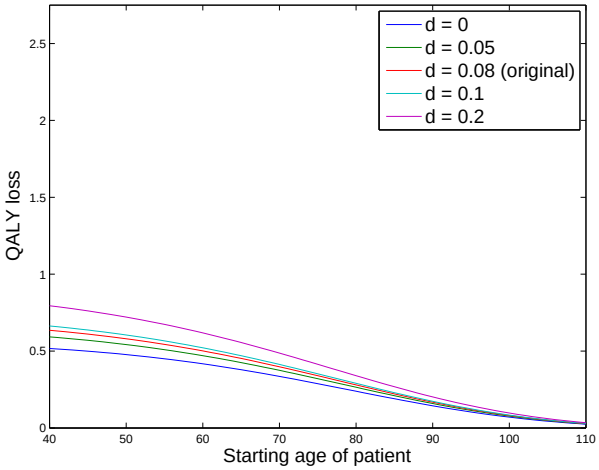
Figure 4.24: Sensitivity analysis: Effect of surgical risk on the expected lifetime QALY gain and loss, for patients of varying ages undergoing CABG.



(a) Net benefit

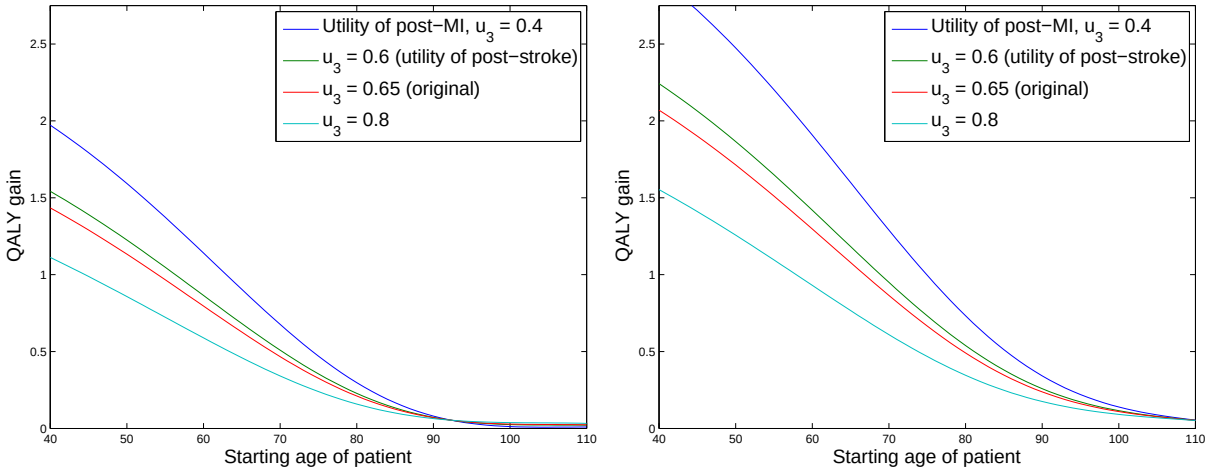


(b) Ideal benefit



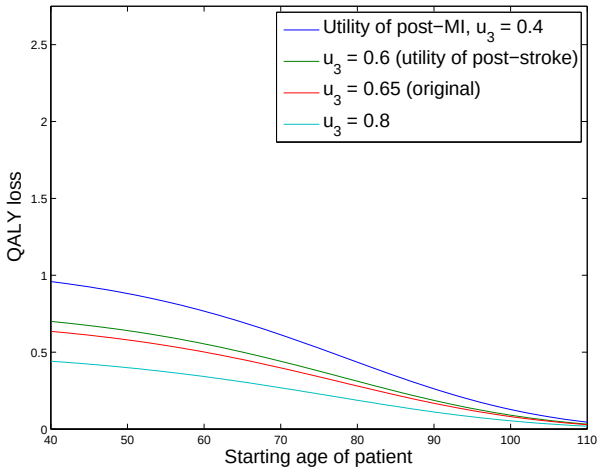
(c) Iatrogenic loss

Figure 4.25: Sensitivity analysis: Effect of $P(\text{die} \mid \text{have MI}) = d$ on the expected lifetime QALY gain and loss, for patients of varying ages, undergoing CABG.



(a) Net benefit

(b) Ideal benefit



(c) Iatrogenic loss

Figure 4.26: Sensitivity analysis: Effect of the post MI state utility value, u_3, on the expected lifetime QALY gain and loss, for patients of varying ages, undergoing CABG.

Chapter 5

Modelling Multiple Treatments Simultaneously

Our primary aim is to be able to calculate the combined benefits of various treatments over time. In Chapter 4 we have created a base model for a single treatment, and demonstrated that it can be adapted to different treatments. Using this base model, we aim to find a 'simple' and credible way to combine the state spaces, transition probabilities and utilities of multiple diseases and their treatments. This would then allow us to model the progression of both diseases simultaneously and hence the combined benefit of treatment.

5.1 Assumptions

Before being able to combine the individual models, we must first make some simplifying assumptions. We make the assumption of independence; that is, we assume that the treatment of one disease does not affect another disease. This allows us to calculate the product of probabilities without considering a measure of the interaction between diseases. We also assume that a patient has been recently diagnosed with each of the diseases, meaning that they are considering treatment for both. Lastly, we assume that if a patient does choose the path of surgery for both dis-

eases, these surgeries both occur at the same time: at the beginning of the chain. Clearly this last assumption is not reasonable if we wish to create a realistic model of multiple treatments. Nevertheless, to first assess the validity of our multiple treatment model, this makes combining the models much simpler.

5.2 Creating a Combined Model

As mentioned above, for a combined model we must consider the best way to combine the state spaces, the transition matrices and also the utility values of the individual models. For the combined state space, we use the Cartesian product of each individual state space. In our particular case, the two treatments we are considering are both surgical: carotid endarterectomy (CEA) for treating carotid artery stenosis (CAS), and coronary artery bypass graft surgery (CABG) for treating coronary artery disease (CAD). The state spaces associated with these treatments, respectively, are:

$$S_1 = \{1 \text{ (well with CAS)}, 2 \text{ (well without CAS)}, 3 \text{ (post stroke)}, 4 \text{ (dead)}\},$$

and

$$S_2 = \{1 \text{ (well with CAD)}, 2 \text{ (well without CAD)}, 3 \text{ (post MI)}, 4 \text{ (dead)}\}.$$

Since each of these consists of 4 states, the Cartesian product, $S* = S_1 \times S_2$, has 16 states:

1. Well with CAS and well with CAD,
2. Well with CAS and well without CAD,
3. Well with CAS and post-MI,
4. Well with CAS and dead,
5. Well without CAS and well with CAD,

6. Well without CAS and well without CAD,
7. Well without CAS and post-MI,
8. Well without CAS and dead,
9. Post-stroke and well with CAD,
10. Post-stroke and well without CAD,
11. Post-stroke and post-MI,
12. Post-stroke and dead,
13. Dead and well with CAD,
14. Dead and well without CAD,
15. Dead and post-MI,
16. Dead and dead.

A patient cannot be simultaneously dead and in another health state at the same time, therefore, all of the combined states that include "dead" are essentially part of the same health state: "dead". The transitions into these separate dead states correspond to *how* a patient died.

Due to this, we can combine all of these separate dead states into one all inclusive "dead" state. Since there are 7 dead states in our particular combined model (states 4, 8, 12, 13, 14, 15 and 16), collapsing these into one state results in 10 unique states in our new state space, S:

1. Well with CAS and well with CAD,
2. Well with CAS and well without CAD,
3. Well with CAS and post MI,

4. Well without CAS and well with CAD,
5. Well without CAS and well without CAD,
6. Well without CAS and post MI,
7. Post stroke and well with CAD,
8. Post stroke and well without CAD,
9. Post stroke and post MI,
10. Dead,

where "dead" is the last state as usual.

Consider combining two individual state spaces using the Cartesian product, one model with m states, and the other with n states, where the "dead" state in each is the last state: the m^{th} and n^{th} state respectively. Let the state spaces be labelled S_m and S_n, then for $S_m \times S_n$, the set of separate dead states before collapsing would be:

$$D = \{n, 2n, ..., (m-1)n, (m-1)n+1, ..., (m-1)n+(n-1), nm\}.$$

That is, taking the Cartesian product of the individual state spaces will result in $m \times n$ states with these specific $m+n-1$ separate dead states. Upon collapsing these into one encompassing dead state, the new combined state space will have $nm-(m+n)+2$ unique states, with "dead" being the last state. For an additional condition, the already collapsed state space for the first two conditions can be combined with the state space of the third condition, to create a new combined state space. This process can also be repeated for multiple conditions.

Now that we have our combined state space, we must also combine our transition matrices in a similar way. However, for our particular case, rather than just two treatment options (as in our individual model), a patient now has four different treatment paths to choose from:

1. Have both surgeries (CEA and CABG);
2. Have only CEA and continue with medical treatment only for CAD;
3. Have only CABG and continue with medical treatment only for CAS, or;
4. Continue to have only medical treatment for both CAS and CAD.

For k different conditions, there are 2^k different treatment options. For each of these options, there exists a different probability transition matrix, calculated by combining the individual matrices that correspond to each disease's treatment option. For example, let CAS be disease 1, and CAD be disease 2. Then consider a patient who is undergoing CEA for CAS and continuing with the medical treatment for CAD: the two corresponding matrices we combine are ${}_s\mathbb{P}_1$ and ${}_m\mathbb{P}_2$.

For each of these treatment options, we need the corresponding probability matrix to include every possible transition that a patient could undergo. Therefore, we use the Kronecker product to combine the appropriate individual treatment matrices, where the Kronecker product is defined in Definition 19.

Definition 19. If A is an $m \times n$ matrix and B is a $p \times q$ matrix, then the Kronecker product $A \otimes B$ is the $mp \times nq$ matrix:

$$A \otimes B = \begin{bmatrix} a_{11}B & \cdots & a_{1n}B \\ \vdots & \ddots & \vdots \\ a_{m1}B & \cdots & a_{mn}B \end{bmatrix}$$

For our particular model, taking the Kronecker product of two individual treatment matrices would result in a 16×16 combined treatment matrix. However, as with combining the state spaces, we now have multiple elements corresponding to the same state: "dead". To remedy this, we collapse our transition matrix to a 10×10 matrix, as we collapsed our state space to have 10 health states.

We must take care in collapsing the transition matrix, as these transitions all have physical meaning. In the combined matrix, the rows corresponding to the

individual dead states contain the probabilities of transitioning from each "dead" state into other "dead" states. However, the combined dead state is absorbing, just like state "Dead and dead", which is state 16 in our example. Therefore, we can remove all of the rows corresponding to a dead state (apart from the final row that is absorbing). If the two individual models have m and n states respectively, with state spaces S_m and S_n, then we remove rows $j \in D \setminus \{nm\}$, to be left with $nm - (m + n) + 2$ rows.

However, the columns contain the transition probabilities into each of the individual dead states, and these correspond to the various ways that a patient can die. That is, the probability of dying for all health states $i \in S$ is

$$P(X_{t+1} = \text{"dead"} | X_t = i) = \sum_{j \in D} P(X_{t+1} = j | X_t = i),$$

Therefore, instead of removing these columns, we sum the elements so that each entry, i, in the new column is the total probability of transitioning from state i, to the one "dead" state. We then replace the last column of our matrix with this new column, and remove the remaining columns that correspond to individual dead states. That is, considering two individual models with n and m states respectively, for all $i \in S$, we insert into the matrix

$$\mathbb{P}_{i,nm} = \sum_{j \in D} \mathbb{P}_{i,j}.$$

We then remove all columns $j \in D \setminus \{nm\}$, and are left with an $(nm - (m + n) + 2) \times (nm - (m + n) + 2)$, stochastic matrix. As with the state space, we can repeat this process for each additional disease added to the analysis.

In our particular model, we now have a 10×10 transition matrix, $\mathbb{P}$, for each treatment option such that

- $0 \leq \mathbb{P}_{i,j} \leq 1$ for $i, j \in S$ and,
- $\sum_{i \in S} \mathbb{P}_{i,j} = 1$ for all $j \in S$.

We have already established transition matrices for carotid artery stenosis (CAS) and coronary artery disease (CAD) in the previous chapters. As before, let CAS be disease 1 and CAD be disease 2, then:

$$ {}_m\mathbb{P}_1(y) = \begin{pmatrix} 1-p_{1,3}-p_{1,4} & 0 & e_{m_1}(y)(1-d_1)(1-p(a+y)) & p(a+y)(1-e_{m_1}(y)d_1)+e_{m_1}(y)d_1 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_{m_1}(y)d_1)+e_{m_1}(y)d_1 \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

$$ {}_s\mathbb{P}_1(y) = \begin{pmatrix} 0 & 1-s_1 & s_1(1-d_1) & s_1d_1 \\ 0 & 1-p_{2,3}-p_{2,4} & e_{s_1}(1-d_1)(1-p(a+y)) & p(a+y)(1-e_{s_1}d_1)+e_{s_1}d_1 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_{s_1}d_1)+e_{s_1}d_1 \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

$$ {}_m\mathbb{P}_2(y) = \begin{pmatrix} 1-p_{1,3}-p_{1,4} & 0 & e_{m_2}(y)(1-d_2)(1-p(a+y)) & p(a+y)(1-e_{m_2}(y)d_2)+e_{m_2}(y)d_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_{m_2}(y)d_2)+e_{m_2}(y)d_2 \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

and

$$ {}_s\mathbb{P}_2(y) = \begin{pmatrix} 0 & 1-s_2 & s_2(1-d_2) & s_2d_2 \\ 0 & 1-p_{2,3}-p_{2,4} & e_{s_2}(y)(1-d_2)(1-p(a+y)) & p(a+y)(1-e_{s_2}(y)d_2)+e_{s_2}(y)d_2 \\ 0 & 0 & 1-p_{3,4} & p(a+y)(1-e_{s_2}(y)d_2)+e_{s_2}(y)d_2 \\ 0 & 0 & 0 & 1 \end{pmatrix}, $$

where a is the starting age of the patient, y is the number of years after surgery,

$$ e_{m_1}(y) = \begin{cases} 0.16 & \text{for } y = 0 \\ 0.08 & \text{for } y = 1 \\ 0.05 & \text{for } y = 2 \\ 0.023 & \text{for } y = 3, 4, 5, ..., \end{cases} $$

$$ e_{s_2}(y) = \begin{cases} 0.013 & \text{for } y = 0 \\ 0.034 & \text{for } y = 1, 2, 3, ... \end{cases} $$

$$e_{m_2}(y) = \begin{cases} 0.08 & \text{for } y = 0 \\ 0.062 & \text{for } y = 1, 2, 3, ... \end{cases}$$

$e_{s_1} = 0.023$, $s_1 = 0.062$, $d_1 = 0.1$, $s_2 = 0.103$, $d_2 = 0.08$ and $p(x) = e^{-10.58+0.095x}$ is the age related probability of death of the general population. Therefore, the transition matrices for the different treatment options a patient can take are:

1. ${}_s\mathbb{P}_1 \otimes {}_s\mathbb{P}_2$, then collapsed as described above to become a 10×10 matrix for having both surgeries;

2. ${}_s\mathbb{P}_1 \otimes {}_m\mathbb{P}_2$, with rows and columns adjusted to have only one dead state, for having only CEA and continuing with medical treatment for CAD;

3. ${}_m\mathbb{P}_1 \otimes {}_s\mathbb{P}_2$, adjusted again, for having only CABG and continuing with medical treatment for CAS, or;

4. ${}_m\mathbb{P}_1 \otimes {}_m\mathbb{P}_2$, adjusted, for having only medical treatment for both CAS and CAD.

To then be able to calculate the expected lifetime quality adjusted life years for each treatment path, we need to have utility values for each of the combined states in our new state space, S. The utility of a health state is a value that describes how "well" a patient is while in that state, where 0 indicates death, and 1 indicates no impairment. There have been a number of attempts in the literature at combining utilities using various methods, which we have seen in Chapter 2, that include adding the impairments $(1 - \text{utility})$ of each state, and taking the minimum of the utility values of the individual health states that make up the combined state [17]. However, these have been shown to be mathematically flawed in Chapter 2.

Therefore, to calculate the utility of a combined state, we take the product of the utility values that correspond to the individual health states making up the combined state. For example, for state 9, "post stroke and post MI", the combined utility, u_9 is:

$$u_9 = 0.6 \times 0.65.$$

That is, if a patient suffers from a disabling stroke and now has a utility of 0.6, they are at 60% of their original health. If, on top of that, they also have a myocardial infarction, the patient is then at 65% of their 0.6 utility. Therefore, it is reasonable that the new combined utility is the product of the individual utilities.

This calculation also ensures that the utility values remain between 0 and 1, as they must by definition. To further validate this method of combining utility values, the American Medical Association Guides to the Evaluation of Permanent Impairments [1] also recommend that utility values be calculated this way.

Thus, the utility values of our particular combined state space are:

$$(u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10})^T = (1, 1, 0.65, 1, 1, 0.65, 0.6, 0.6, 0.39, 0)^T.$$

5.3 The Combined Benefit

In Chapter 4, the net benefit of an individual treatment, when considering the disease in isolation, is defined to be the difference in expected QALYs between the treatment chain and the control chain. In our particular case, since we are considering a patient who is suffering from two diseases, carotid artery stenosis and coronary artery disease, there are now four treatment options they can choose from:

1. Have both surgeries (CEA and CABG);

2. Have only CEA and continue with medical treatment only for CAD;

3. Have only CABG and continue with medical treatment only for CAS, or;

4. Continue to have only medical treatment for both CAS and CAD.

Using the same method of calculating the expected QALYs as mentioned in Chapter 4, we can calculate the outcome for each treatment path above. For indi-

vidual treatments, the expected QALYs are calculated with:

$$\begin{aligned}
\mathbf{w}(0) &= \frac{z}{365} \times \frac{1}{2}(\mathbf{u}(0) + \mathbb{P}(0)\mathbf{u}(0)) + \mathbb{P}(0)\mathbf{w}(1), \\
\mathbf{w}(1) &= \frac{365 - z}{365} \times \frac{1}{2}\left(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)\right) + \mathbb{P}(1)\mathbf{w}(2) \quad \text{and} \\
\mathbf{w}(t) &= \frac{1}{2}(\mathbf{u}(t) + \mathbb{P}(t)\mathbf{u}(t)) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t = 2, ...T-1, \\
\mathbf{w}(T) &= \frac{1}{2}\mathbf{u}(T), \\
\mathbf{w}(t) &= 0 \quad \text{for } t \geq T+1
\end{aligned}$$

where $N = 112 - a$, and z is the surgical risk period. We also have that $\mathbb{P}(t)$ is the transition matrix for the t^{th} time period, where time period 0 and time period 1 are both in the first year, and

$$\begin{aligned}
\mathbf{u}(0) &= \mathbf{u}(1) = \mathbf{u}, \\
\mathbf{u}(t) &= (1-f)^{(t-1)} \times \mathbf{u},
\end{aligned}$$

such that $\mathbf{u}(t)$ is the utility at time period t, and f is the discounting factor of the utility.

Since in both of our individual models, $z = 30$ days and the discounting factor is $f = 0.03$, we can use these again in the combined model. Therefore, using the equations above, with the corresponding 10×10 transition matrices, we can calculate the expected outcome in QALYs for each of the four treatment options. However, since we have multiple treatment paths to compare, rather than simply undergoing surgery or not, we can also include different methods of comparing these options.

The most obvious measure of benefit in the case of two diseases is to compare having both treatments, to having neither. This is the combined benefit, $\mathbf{B}^C$, as defined prevoiusly, where

$$\mathbf{B}^C = ({}_{s_1,s_2}\mathbf{w})_1(0) - ({}_{m_1,m_2}\mathbf{w})_1(0),$$

such that $({}_{s_1,s_2}\mathbf{w})_1(0)$ is the expected lifetime QALYs of having both surgeries, and $({}_{m_1,m_2}\mathbf{w})_1(0)$ is the expected lifetime QALYs of having neither surgery, both given

that a patient started in state 1, well with both diseases. This is what we refer to as the 'true' benefit of both treatments, and we show that this true benefit is less than the sum of the individual benefits of both treatments. That is,

$$\mathbf{B}^C < \mathbf{b}_1 + \mathbf{b}_2,$$

where $\mathbf{b}_i$ is the individual benefit of treatment i in isolation, given that a patient started in state 1, as calculated in Chapter 4. That is, we show that the true benefit is less than the perceived benefit of both treatments.

Another of our aims is to be able to compare how having multiple conditions impacts on the benefit of treating one of those conditions. Recall from Chapter 3 that Fitzgerald and Bean [4] defined two other ways of measuring the benefit of a treatment in the presence of multiple diseases: the withdrawal benefit, and the added benefit of a single treatment, given that a patient has more than one disease.

In our particular case, we are considering two conditions, therefore, without loss of generality, the withdrawal benefit of treatment 1 is:

$$\mathbf{B}_1^W = ({}_{s_1,s_2}\mathbf{w})_1(0) - ({}_{m_1,s_2}\mathbf{w})_1(0).$$

That is, the withdrawal benefit of treating disease 1 is the difference in expected QALYs between being treated for both diseases, and not treating disease 1 while still receiving treatment for disease 2.

The added benefit of treatment 1 is:

$$\mathbf{B}_1^A = ({}_{s_1,m_2}\mathbf{w})_1(0) - ({}_{m_1,m_2}\mathbf{w})_1(0).$$

That is, it is the difference in expected QALYs between treating only disease 1, and treating neither. The added benefit demonstrates the effect of other conditions on the 'true' benefit of a single treatment, given the other conditions are not treated. The withdrawal benefit demonstrates the effect of other conditions on the 'true' benefit of a single treatment, given the other conditions *are* treated. Since in most

real-life situations, other conditions are not left untreated, we assume that the withdrawal benefit is the most accurate way of measuring the true benefit of a single treatment in the presence of other conditions.

We can compare both the withdrawal and added benefit of CEA and CABG to the individual benefits of these surgeries in isolation to show that the individual benefit of a treating disease i, $\mathbf{b}_i$, is greater than the benefit of that treatment in the presence of other diseases. We also expect to see that for the individual treatments, the withdrawal benefit is greater than the added benefit.

Figure 5.1 shows the expected outcome in QALYs, of each treatment option in the combined model, compared to the outcome of the individual treatments in isolation. We can see that, since a patient is suffering from multiple diseases in our combined model, the expected QALYs from each treatment path is less than those expected if they were suffering from an individual disease. This figure also shows that with both diseases in our combined model, having both surgeries has the best outcome, while having neither has the worst outcome. This is to be expected since the isolated analysis in Chapter 4 showed that both surgical treatments were worthwhile. This demonstrates that our combined model produces valid and reasonable results.

From Figure 5.2, we can see that the combined benefit is significantly less than the sum of the individual benefits of treating each disease in isolation, as expected. That is, for our particular case we have demonstrated that:

$$\mathbf{B}^C < \mathbf{b}_1 + \mathbf{b}_2,$$

where $\mathbf{b}_1$ and $\mathbf{b}_2$ are the individual net benefits of having CEA given that a patient started well with CAS, and having CABG given that a patient started well with CAD, respectively. In Chapter 3 we have shown that for the general snapshot benefit,

$$\mathfrak{B}^C < \sum_i \mathfrak{b}_i,$$

where $\mathfrak{b}_i$ is the individual snapshot net benefit of treating disease i in isolation. In Chapter 6 we will show that the same result will follow for the general lifetime

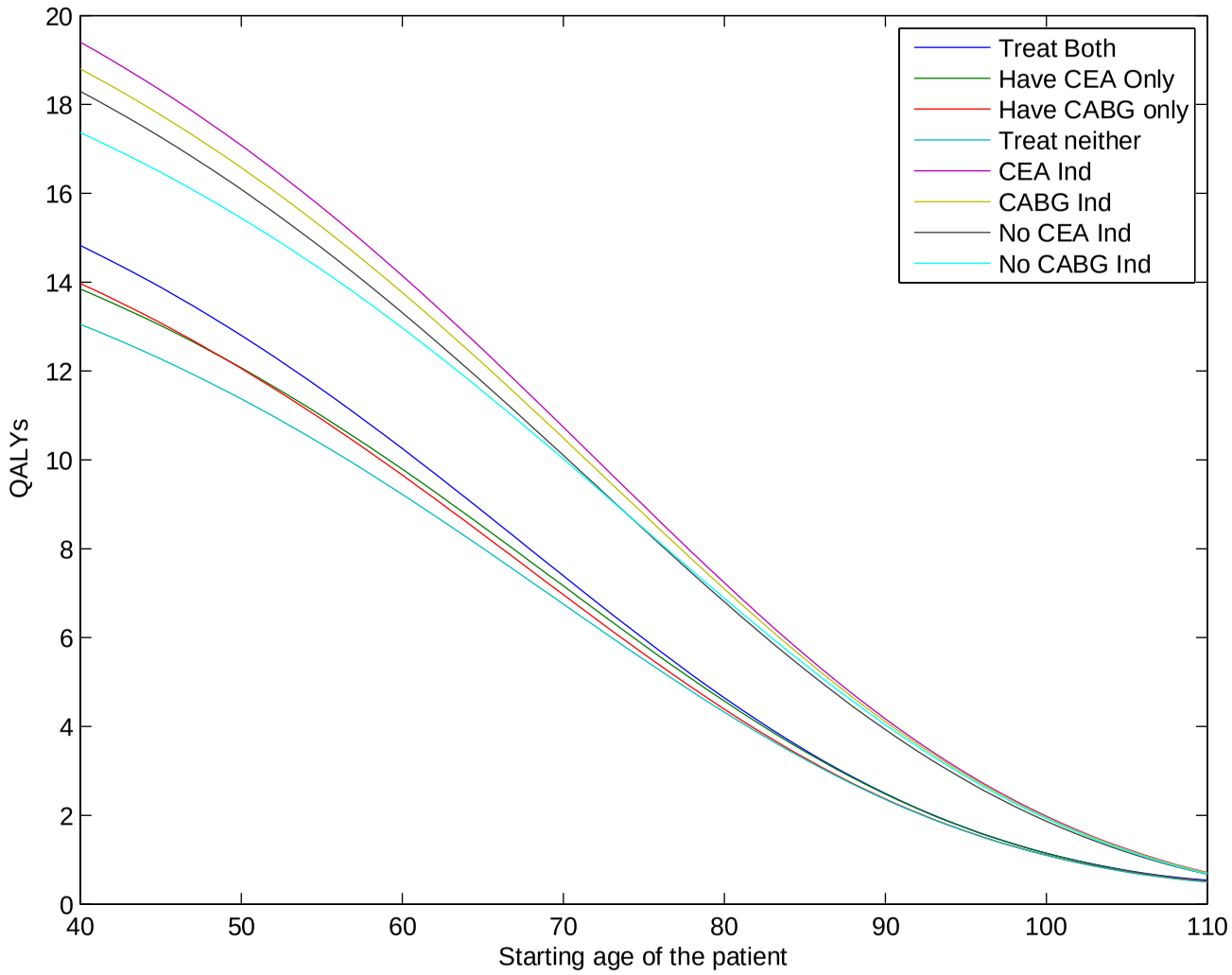


Figure 5.1: Comparison of the expected lifetime QALYs of different treatment paths. Patients are of varying ages and suffering from both CAS and CAD, CAS only, or CAD only.

benefit. That is, we show that

$$\mathbf{B}^C < \sum_i \mathbf{b}_i,$$

under certain conditions.

In Figure 5.2, we also see that

$$\begin{aligned} \mathbf{B}_1^W + \mathbf{B}_2^W &< \mathbf{b}_1 + \mathbf{b}_2, \\ \mathbf{B}_1^A + \mathbf{B}_2^A &< \mathbf{b}_1 + \mathbf{b}_2, \\ \text{and} \quad \mathbf{B}^C &< \mathbf{B}_1^W + \mathbf{B}_2^W, \end{aligned}$$

where $\mathbf{B}_1^W$ and $\mathbf{B}_2^W$ are the withdrawal benefits of CEA and CABG, resepectively, given that a patient started well with both diseases, and $\mathbf{B}_1^A$ and $\mathbf{B}_2^A$ are the added benefits of CEA and CABG, given a patient started well with both diseases. All of these results, again, we have shown are true in general for the snapshot benefit of multiple diseases in Chapter 3, and will show are true in general for the lifetime benefit of multiple diseases in Chapter 6.

Figures 5.3a and 5.3b show the different methods of measuring the benefit of CEA and CABG respectively. As mentioned above, we expect that for each disease, the individual benefit of treatment when the disease is in isolation, is greater than both the withdrawal and added benefits of the treatment when considered in the presence of other diseases. In both of these figures, we see that our combined model does demonstrate that this is true for our particular case. We also expect the withdrawal benefits to be greater than the added benefits, and again this is shown to be true in these figures.

In Chapter 4 we saw that the relatively high surgical risk for CABG resulted in a period of 'negative' benefit when we looked at the accumulation of net benefit in the years after surgery, for a 70-year-old patient. The high surgical risk of CABG also affects the early accumulation of the combined benefit of both surgeries, as we see a small period of negative benefit in Figure 5.4. In Figure 5.5b, we see this period of negative benefit again in the different measures of benefit of CABG. However,

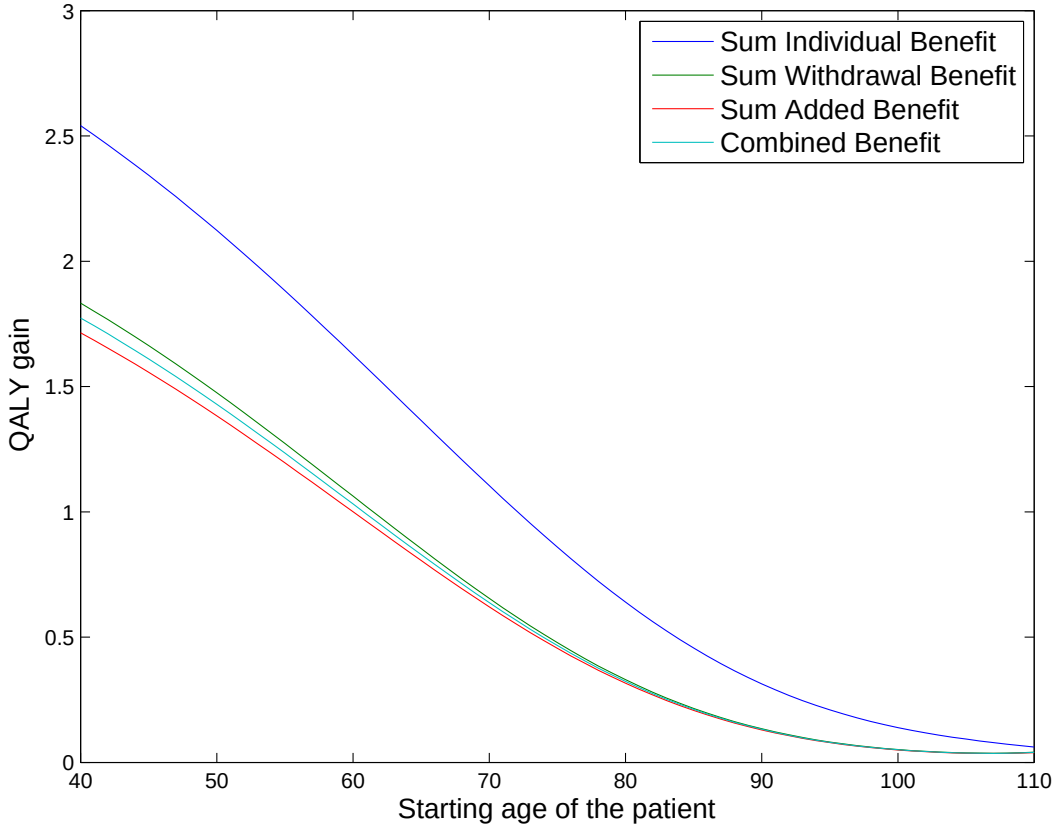
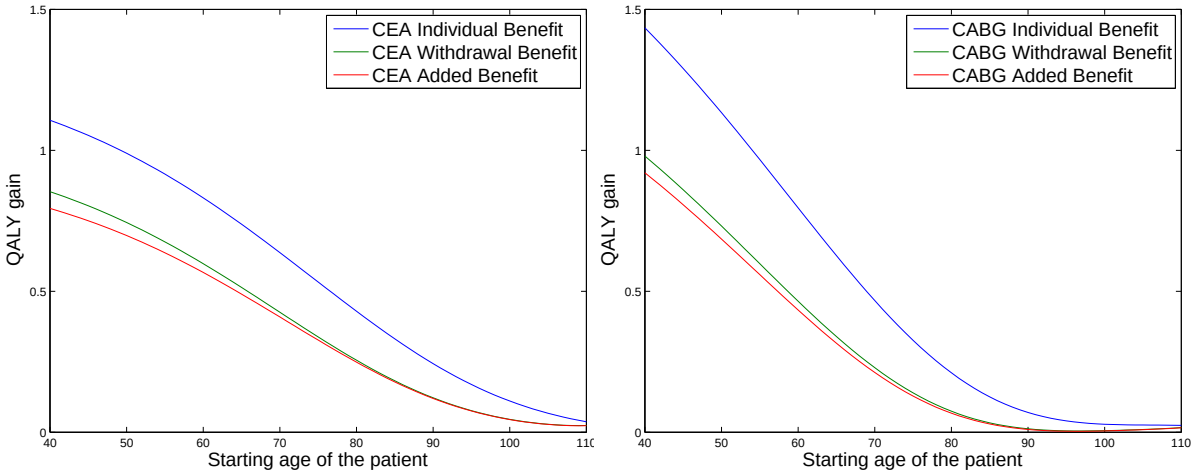


Figure 5.2: Comparison of the various measures of lifetime net benefit when having both CEA and CABG surgeries, for patients of varying ages.



(a) Comparing the benefits of CEA. (b) Comparing the benefits of CABG.

Figure 5.3: Comparison of the various measures of lifetime net benefit when having either CEA or CABG, for patients of varying ages.

as CEA did not have any period of negative benefit (see Figure 5.5a), it is less pronounced in the combined benefit.

5.3.1 Combining Ideal Benefit and Iatrogenic Loss

As with the net benefit, we are also interested in how the ideal benefit and iatrogenic loss combine when considering multiple conditions. We can combine these two measures using similar methods to those with which we combined the net benefit earlier. Let us define the combined ideal benefit as the difference in expected QALYs between having both surgeries with no surgical risk, and having neither surgery. That is,

$$\mathbf{B}^{I,C} = ({}_{s_1,s_2}\mathbf{w}^I)_1(0) - ({}_{m_1,m_2}\mathbf{w})_1(0).$$

Recall that the iatrogenic loss is defined as the loss of QALYs due to surgical risk, or the difference in expected QALYs between having risk-free surgery, and normal-risk surgery. Therefore, the combined iatrogenic loss of CEA and CABG is:

$$\boldsymbol{\ell}^C = ({}_{s_1,s_2}\mathbf{w}^I)_1(0) - ({}_{s_1,s_2}\mathbf{w})_1(0).$$

As with the combined net benefit, we expect to see that

$$\mathbf{B}^{I,C} < \mathbf{b}_1^I + \mathbf{b}_2^I$$

and

$$\boldsymbol{\ell}^C < \boldsymbol{\ell}_1 + \boldsymbol{\ell}_2$$

where $\mathbf{b}_i^I$ is the individual ideal benefit of disease i given that a patient started well with the disease, and $\boldsymbol{\ell}_i$ is the individual iatrogenic loss of treating disease i in isolation, given that a patient started well with the disease. That is, we aim to show that the ideal benefit and iatrogenic loss add up in the same way as the net benefit.

We can also calculate the withdrawal ideal benefit and iatrogenic loss, and added ideal benefit and iatrogenic loss. The withdrawal ideal benefit of surgery 1 is:

$$\mathbf{B}_1^{I,W} = ({}_{s_1,s_2}\mathbf{w}^I)_1(0) - ({}_{m_1,s_2}\mathbf{w}^I)_1(0).$$

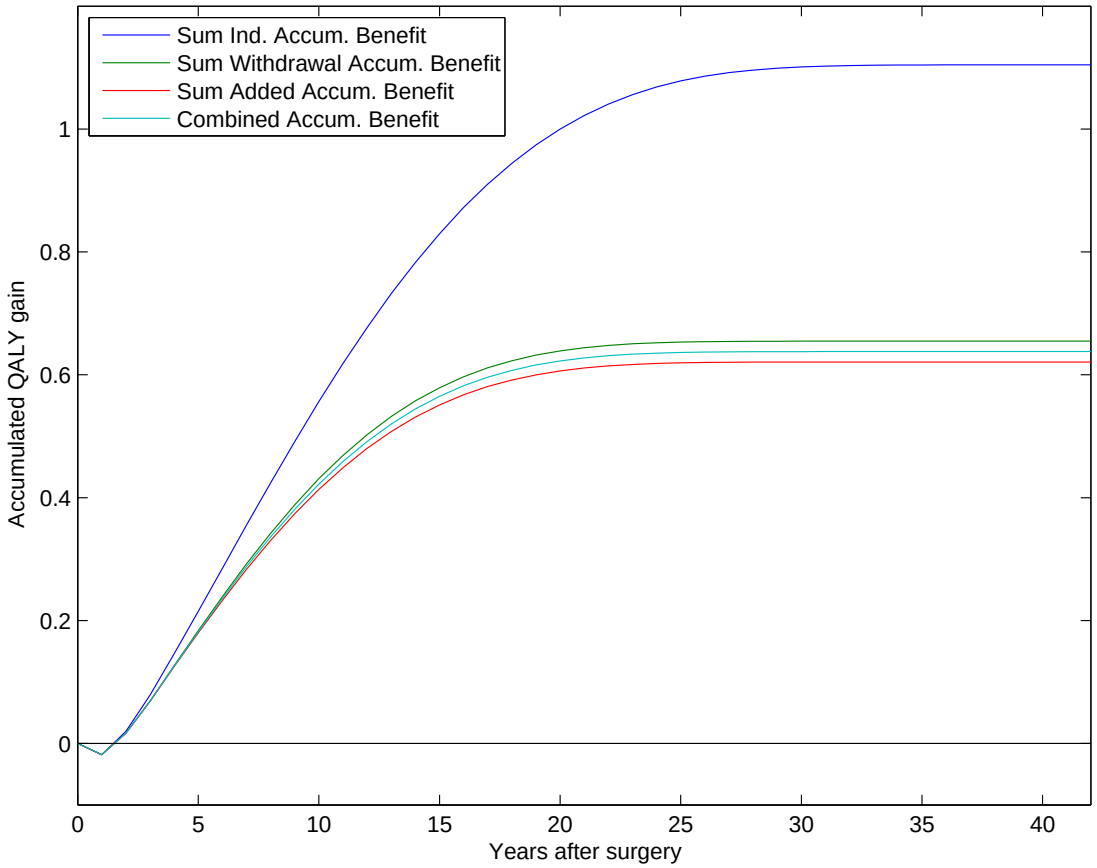
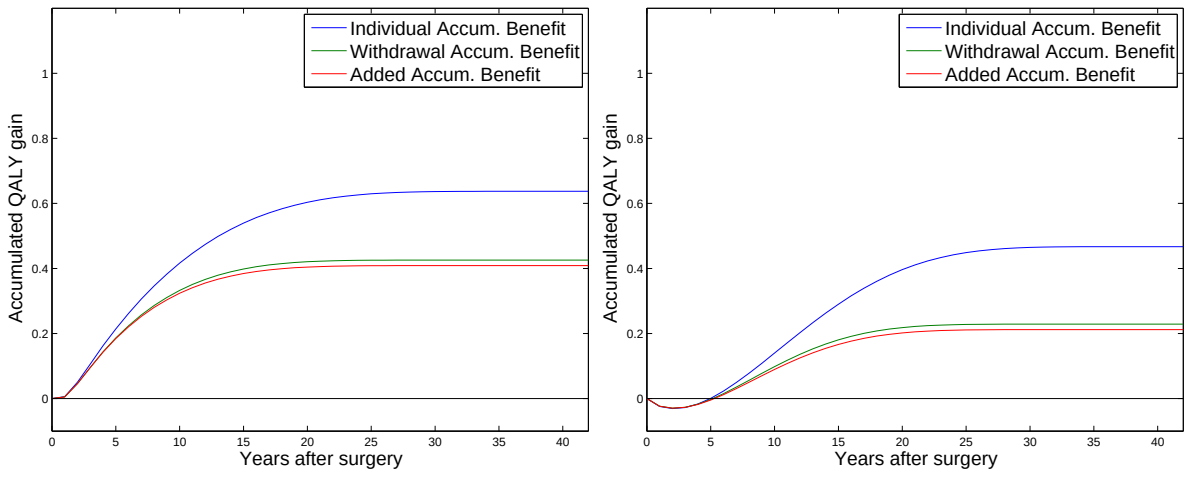


Figure 5.4: Comparison of the various measures of accumulated net benefit when having both CEA and CABG surgeries, for a 70-year-old patient.



(a) Accumulated net benefits of CEA (b) Accumulated net benefits of CABG

Figure 5.5: Comparison of the various measures of accumulated net benefit when having either CEA or CABG, for a 70-year-old patient.

That is, $\mathbf{B}_1^{I,W}$ is the difference in expected QALYs between having both surgeries with no risks, and having surgery for disease 2 with no risk, while undergoing only medical treatment for disease 1. The withdrawal iatrogenic loss of treating disease 1 is:

$$\boldsymbol{\ell}_1^W = ({}_{s_1,s_2}\mathbf{w}^I)_1(0) - ({}_{s_1,s_2^I}\mathbf{w})_1(0).$$

That is, it is the difference in expected QALYs between having both surgeries with no risk, and having normal-risk surgery for disease 1 and risk-free surgery for disease 2.

Similarly, we define the added ideal benefit of treating disease 1 as:

$$\mathbf{B}_1^{I,A} = ({}_{s_1,m_2}\mathbf{w}^I)_1(0) - ({}_{m_1,m_2}\mathbf{w})_1(0),$$

and the added iatrogenic loss of treating disease 1 as:

$$\boldsymbol{\ell}_1^A = ({}_{s_1,m_2}\mathbf{w}^I)_1(0) - ({}_{s_1,m_2}\mathbf{w})_1(0).$$

Comparing the added and withdrawal ideal benefits and iatrogenic losses to the individual measures in isolation, we again expect to see that the individual benefits are greater than the added and withdrawal benefits. We also expect that the added ideal benefit will be less than the withdrawal ideal benefit, and that the sum of the withdrawal ideal benefits is greater than the combined ideal benefit. We expect the same results with the withdrawal and added iatrogenic losses, as we did with the net benefit measures, as well.

From Figure 5.6 we can see that, as expected, the combined ideal benefit is much less than the sum of the individual ideal benefits. That is, our combined model has demonstrated that:

$$\mathbf{B}^{I,C} < \mathbf{b}_1^I + \mathbf{b}_2^I.$$

It also shows that

$$\begin{aligned}
\mathbf{B}_1^{I,W} + \mathbf{B}_2^{I,W} &< \mathbf{b}_1^I + \mathbf{b}_2^I, \\
\mathbf{B}_1^{I,A} + \mathbf{B}_2^{I,A} &< \mathbf{b}_1^I + \mathbf{b}_2^I, \\
\mathbf{B}_1^{I,A} + \mathbf{B}_2^{I,A} &< \mathbf{B}_1^{I,W} + \mathbf{B}_2^{I,W}, \\
\text{and} \quad \mathbf{B}^{I,C} &< \mathbf{B}_1^{I,W} + \mathbf{B}_2^{I,W},
\end{aligned}$$

as we expected. Figure 5.7 shows that the same is true for the combined iatrogenic loss measures. That is, it demonstrates that

$$\begin{aligned}
\boldsymbol{\ell}^C &< \boldsymbol{\ell}_1 + \boldsymbol{\ell}_2, \\
\boldsymbol{\ell}_1^W + \boldsymbol{\ell}_2^W &< \boldsymbol{\ell}_1 + \boldsymbol{\ell}_2, \\
\boldsymbol{\ell}_1^A + \boldsymbol{\ell}_2^A &< \boldsymbol{\ell}_1 + \boldsymbol{\ell}_2, \\
\boldsymbol{\ell}_1^A + \boldsymbol{\ell}_2^A &< \boldsymbol{\ell}_1^W + \boldsymbol{\ell}_2^W, \\
\text{and} \quad \boldsymbol{\ell}^C &< \boldsymbol{\ell}_1^W + \boldsymbol{\ell}_2^W.
\end{aligned}$$

Figures 5.8a and 5.8b show the different measures of ideal benefit and iatrogenic loss for CEA, respectively, in the presence of another condition. We see that the individual ideal benefit and iatrogenic loss in isolation are greater than both the withdrawal and added ideal benefit, and iatrogenic loss as expected. The same is true for CABG, as shown in Figures 5.9a and 5.9b.

Lastly, we investigate the accumulation of ideal benefit and iatrogenic loss for a 70-year-old patient undergoing both CEA and CABG and compare this to the accumulated net benefit of both CEA and CABG (Figure 5.10). As mentioned previously, there is a small period of negative net benefit, due to the high surgical risk of CABG. As in the individual models, the iatrogenic loss of treatment is greater than the net benefit for a period of a few years after surgery. In the combined model, this period lasts for approximately 10 years, compared to approximately 2 years in the individual CEA model, and 19 years in the individual CABG model.

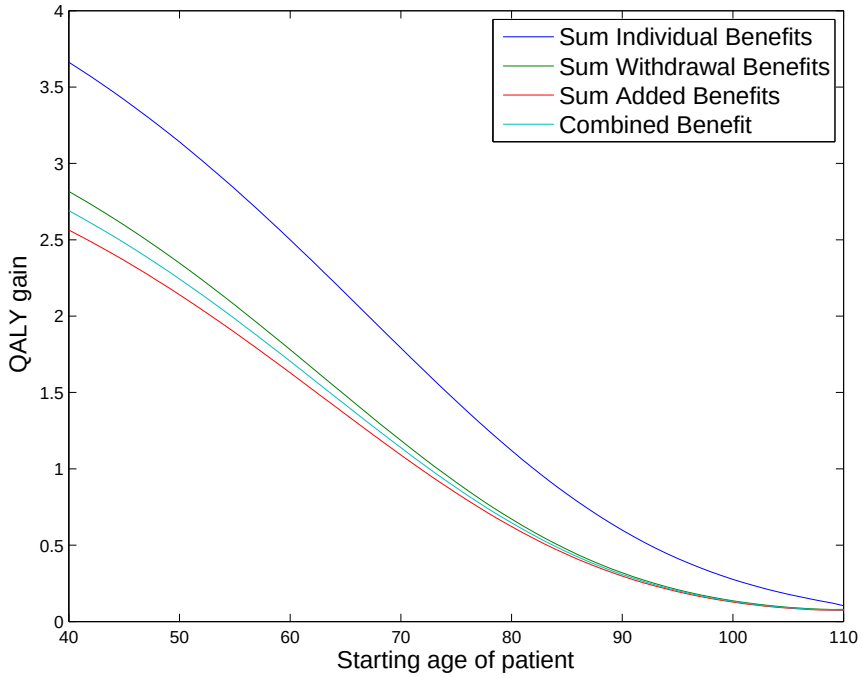


Figure 5.6: Comparison of the ideal lifetime benefits for patients of varying ages, undergoing both CEA and CABG.

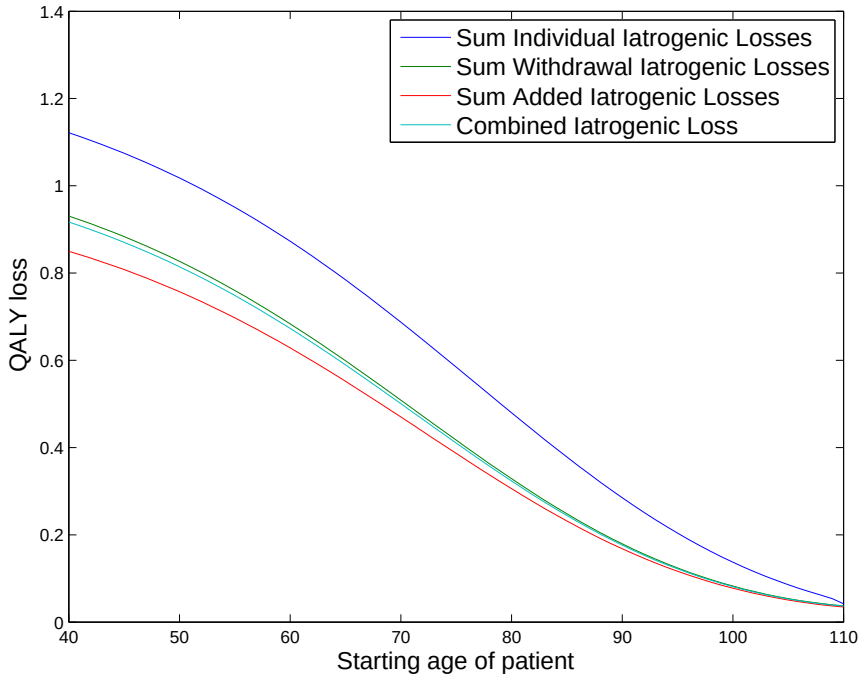
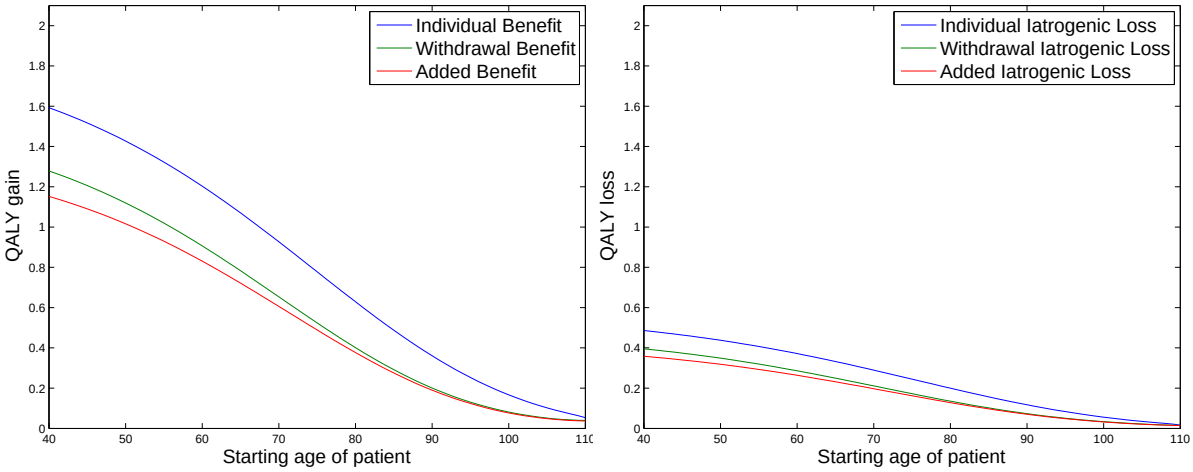
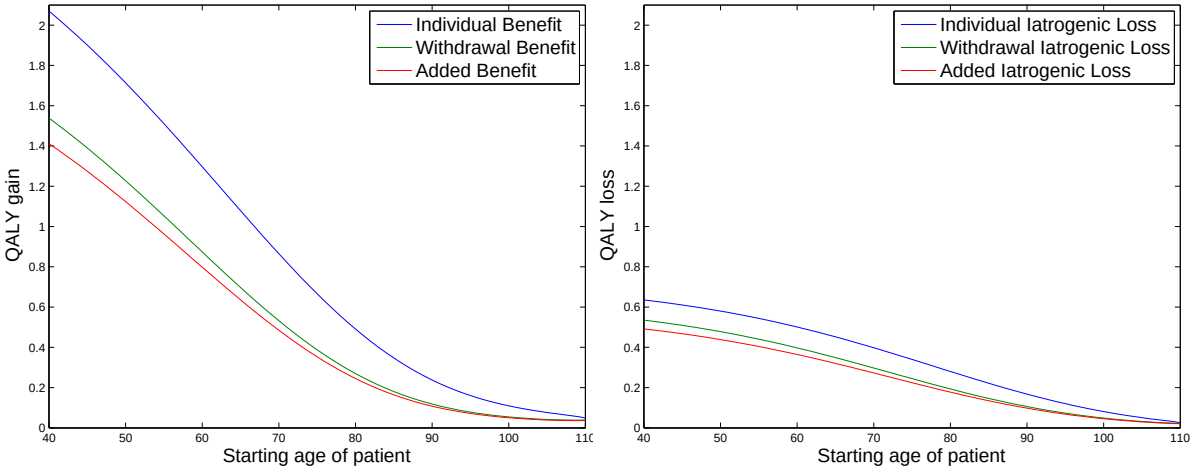


Figure 5.7: Comparison of the lifetime iatrogenic losses for patients of varying ages, undergoing both CEA and CABG.



(a) Ideal Benefit (b) Iatrogenic Loss

Figure 5.8: Comparison of QALY gains and losses of CEA, for patients of varying ages, suffering from both CAS and CAD.



(a) Ideal Benefit (b) Iatrogenic Loss

Figure 5.9: Comparison of QALY gains and losses of CABG, for patients of varying ages, suffering from both CAS and CAD.

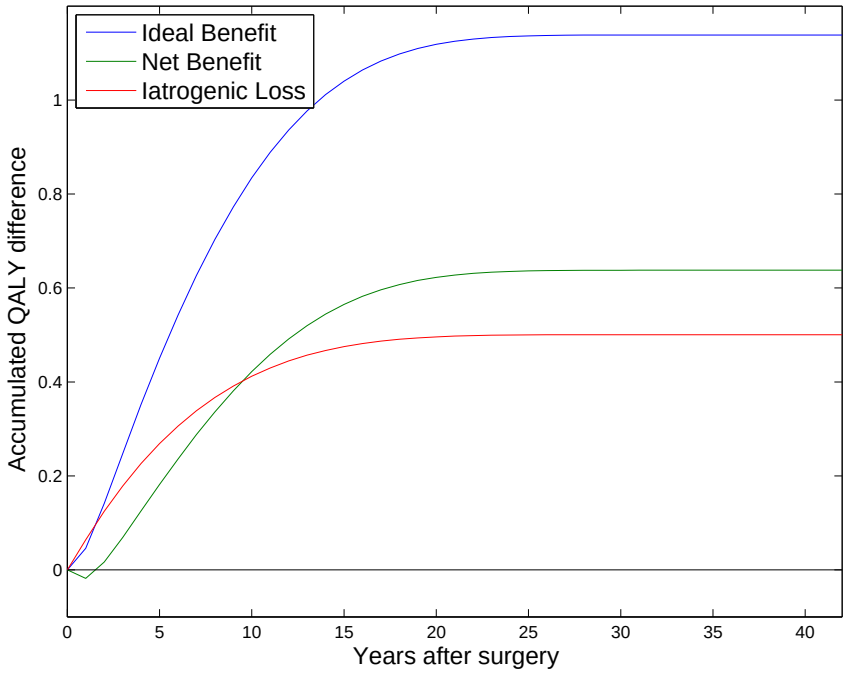
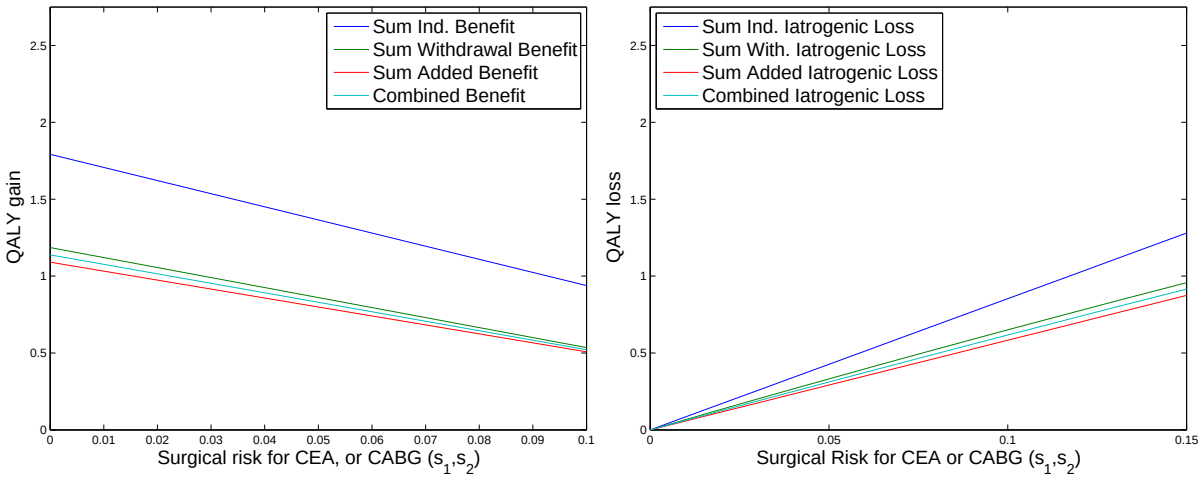


Figure 5.10: Accumulated QALY differences for a 70-year-old patient suffering from CAS and CAD, undergoing both CEA and CABG.

5.3.2 Sensitivity Analyses

Figures 5.11a and 5.11b show the effect of surgical risk on the net benefit and iatrogenic loss, respectively, for a 70-year-old of having both CEA and CABG. In this analysis, we only consider that $s_1 = s_2 = s$. As expected, as the surgical risk increases, the various net benefits of surgery decrease, and the iatrogenic loss of surgery increases. When $s = 0$ we have that the iatrogenic loss of surgery is 0 as well, which is to be expected as iatrogenic loss is defined as the loss of QALYs due to surgical risk.

Figures 5.12a, 5.12b and 5.12c show how altering the probability of death from stroke or myocardial infarction affects the net benefit, iatrogenic loss and ideal benefit of a 70-year-old patient respectively. Again, in this analysis $d_1 = d_2 = d$. As the probability of death, d, increases, so does the benefit of surgery. As in the individual models in Chapter 4, this initially may seem counterintuitive. However as we saw



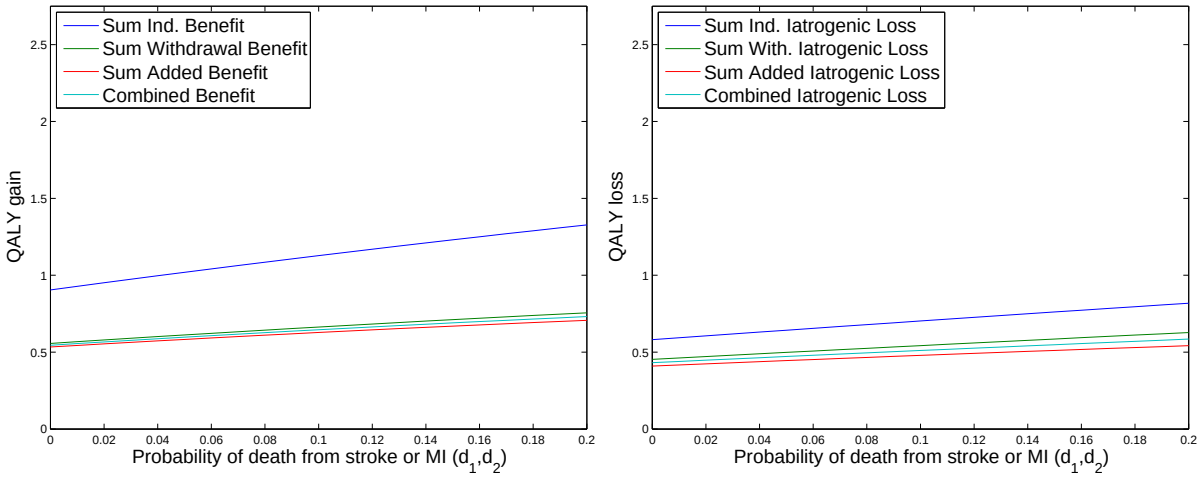
(a) Net Benefit (b) Iatrogenic Loss

Figure 5.11: Sensitivity analysis: Effect of surgical risks, s_1 and s_2, of CEA and CABG respectively, on the QALY gains and losses of a 70-year-old patient undergoing both CEA and CABG.

before, as d increases, the expected QALYs decrease. The increase in d decreases the expected QALYs less in the surgical chain than in the medical chain, due to surgery decreasing the probability of having a stroke or MI in the first place.

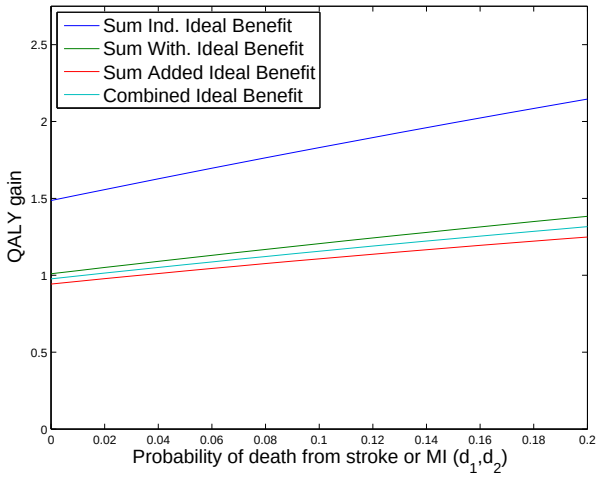
Lastly, Figures 5.13a, 5.13b and 5.13c demonstrate that as the utility of the post stroke and post MI states increase, the benefit of surgery decreases, where $u_1 = u_2 = u$. That is, if we consider that a stroke or a myocardial infarction is less severe, then the benefit of surgery decreases. Again, this may seem counterintuitive, but with similar reasoning to as above, it is a sensible outcome. If an event (stroke or MI) is less severe, meaning that the utility of the post event state is greater, then the surgery becomes less effective and hence less beneficial.

These results demonstrate that, as expected, the benefit of surgery when considering that a patient has more than one condition, is likely to be overestimated. That is, the benefit of surgery when considering a disease in isolation, is higher than the benefit taking into account another condition. We also demonstrate that the loss of QALYs due to surgery combine in a similar way to the benefit of surgery.



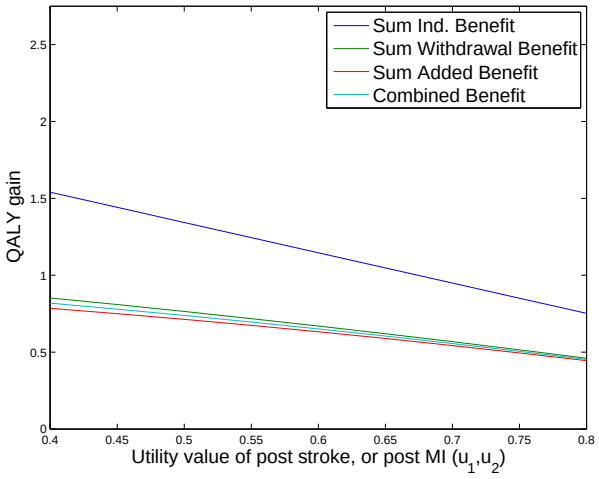
(a) Net Benefit

(b) Iatrogenic Loss

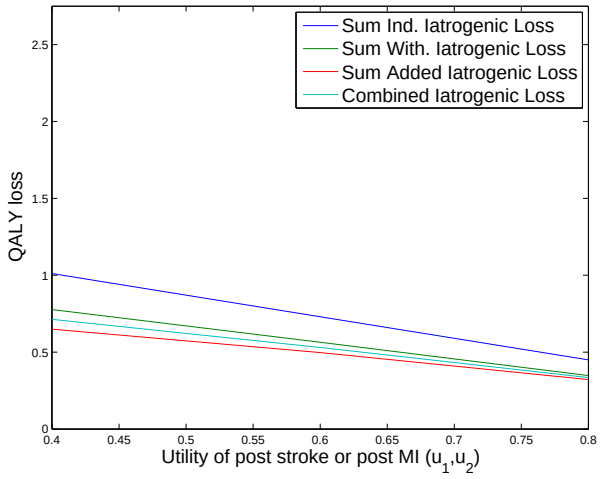


(c) Ideal Benefit

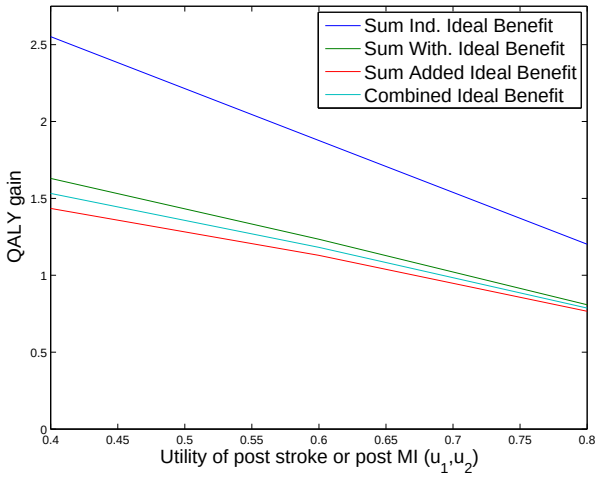
Figure 5.12: Sensitivity analysis: Effect of $P(\text{die} \mid \text{have stroke}) = d_1$ and $P(\text{die} \mid \text{have MI}) = d_2$, on the QALY gains and losses for a 70-year-old patient undergoing both CEA and CABG.



(a) Net Benefit



(b) Iatrogenic Loss



(c) Ideal Benefit

Figure 5.13: Sensitivity analysis: Effect of post stroke and post MI state utility values, $u_{1,3}$ and $u_{2,3}$, respectively, on the QALY gains and losses for a 70-year-old patient undergoing both CEA and CABG.

That is, the iatrogenic loss due to surgery, when considering multiple conditions, is also overestimated. In the following chapter we prove this result true in the general case of the lifetime benefit for multiple diseases.

Chapter 6

Theoretical Results for Lifetime Benefit and Loss

In the previous chapter we used examples to demonstrate that the lifetime benefit of an individual treatment measured in quality adjusted life years gained, in the presence of another disease, is less than the benefit measured considering only the single disease in isolation. We have also demonstrated that the combined benefit of multiple treatments is less than the sum of the individual benefits of the treatments in isolation, as predicted.

In this chapter, we prove theoretically that this is true for multiple diseases and their treatments, under some assumptions.

6.1 Snapshot Quality Adjusted Life Years

First, we show that the lifetime expected quality adjusted life years can be written as the sum of snapshot quality adjusted life years.

Recall from Section 4.1.6, Definition 17, that the snapshot QALYs after t years, given that a patient started in state j, is given by the j^{th} entry of $\mathbf{v}(t)$, where

$$\mathbf{v}(t) = \mathbb{P}(0) \times \mathbb{P}(1) \times \mathbb{P}(2) \times \ldots \times \mathbb{P}(t) \times \mathbf{u},$$

$$\mathbf{v}(T) = 0, \qquad \text{for } T = 112 - a, \tag{6.1}$$

where a is the starting age of the patient. Here, $\mathbb{P}(t)$ is the transition matrix corresponding to t years after the decision of whether to have surgery. As defined previously, $\mathbb{P}(0)$ corresponds to the transition probabilities for the surgical risk period, z days, and $\mathbb{P}(1)$ to the transitions for the remainder of the first year.

Also recall from Section 4.1.4, that the expected lifetime QALYs for a treatment path, given that a patient started in state j is given by the j^{th} entry of $\mathbf{w}(0)$, where

$$\begin{aligned}
\mathbf{w}(0) &= \frac{z}{365} \times \frac{1}{2}(\mathbf{u}(0) + \mathbb{P}(0)\mathbf{u}(0)) + \mathbb{P}(0)\mathbf{w}(1), \\
\mathbf{w}(1) &= \frac{365 - z}{365} \times \frac{1}{2}\left(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)\right) + \mathbb{P}(1)\mathbf{w}(2) \quad \text{and} \\
\mathbf{w}(t) &= \frac{1}{2}(\mathbf{u}(t) + \mathbb{P}(t)\mathbf{u}(t)) + \mathbb{P}(t)\mathbf{w}(t+1) \quad \text{for } t = 2, ...T - 1, \\
\mathbf{w}(T) &= \frac{1}{2}\mathbf{u}(T), \\
\mathbf{w}(t) &= \mathbf{0} \quad \text{for } t \geq T + 1.
\end{aligned} \tag{6.2}$$

Here, $T = 112 - a$ is the maximum time a person can live, given their starting age, a, and

$$\begin{aligned}
\mathbf{u}(0) &= \mathbf{u}(1) = \mathbf{u}, \\
\mathbf{u}(t) &= (1 - f)^{(t-1)} \times \mathbf{u} \qquad \text{for } t \geq 2,
\end{aligned}$$

where $\mathbf{u}(t)$ is the utility at time period t, and f is the discounting factor of the utility.

Using these recursive equations, we can then write the expected lifetime QALYs as a single equation.

Lemma 5. *The expected lifetime quality adjusted life years (QALYs) for a treatment path can be written as:*

$$\begin{aligned}
\mathbf{w}(0) = \frac{1}{2}\Bigg\{ &\frac{z}{365}\mathbf{u}(0) + \mathbb{P}(0)\left[\frac{z}{365}\mathbf{u}(0) + \frac{365 - z}{365}\mathbf{u}(1)\right] + \mathbb{P}(0)\mathbb{P}(1)\left[\frac{365 - z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right]\Bigg\} \\
&+ \frac{1}{2}\sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right].
\end{aligned}$$

Proof. We are given that:

$$\mathbf{w}(T) = \frac{1}{2}\mathbf{u}(T).$$

By substituting this into the expression for $W(T-1)$, we get:

$$\mathbf{w}(T-1) = \frac{1}{2}\left[\mathbf{u}(T-1) + \mathbb{P}(T-1)\mathbf{u}(T-1) + \mathbb{P}(T-1)\mathbf{u}(T)\right].$$

Repeating this process, we have:

$$\begin{aligned}
\mathbf{w}(T-2) &= \frac{1}{2}\left[\mathbf{u}(T-2) + \mathbb{P}(T-2)\mathbf{u}(T-2)\right] \\
&\quad + \mathbb{P}(T-2)\left\{\frac{1}{2}\left[\mathbf{u}(T-1) + \mathbb{P}(T-1)\mathbf{u}(T-1) + \mathbb{P}(T-1)\mathbf{u}(T)\right]\right\} \\
&= \frac{1}{2}\left\{\mathbf{u}(T-2) + \mathbb{P}(T-2)\left[\mathbf{u}(T-2) + \mathbf{u}(T-1)\right]\right\} \\
&\quad + \frac{1}{2}\mathbb{P}(T-2)\mathbb{P}(T-1)\left[\mathbf{u}(T-1) + \mathbf{u}(T)\right], \\
&= \frac{1}{2}\left\{\mathbf{u}(T-2) + \sum_{t=T-2}^{T-1}\left[\prod_{j=T-2}^{t} P(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right]\right\},
\end{aligned}$$

and hence,

$$\begin{aligned}
\mathbf{w}(T-3) &= \frac{1}{2}\left\{\mathbf{u}(T-3) + \mathbb{P}(T-3)\mathbf{u}(T-3)\right\} \\
&\quad + \frac{1}{2}\mathbb{P}(T-3)\left\{\mathbf{u}(T-2) + \sum_{t=T-2}^{T-1}\left[\prod_{j=T-2}^{t} P(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right]\right\} \\
&= \frac{1}{2}\left\{\mathbf{u}(T-3) + \mathbb{P}(T-3)\left[\mathbf{u}(T-3) + \mathbf{u}(T-2)\right]\right\} \\
&\quad + \frac{1}{2}\left\{\sum_{t=T-2}^{T-1}\left[\prod_{j=T-2}^{t} P(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right]\right\} \\
&= \frac{1}{2}\left\{\mathbf{u}(T-3) + \sum_{t=T-3}^{T-1}\left[\prod_{j=T-3}^{t} P(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right]\right\}.
\end{aligned}$$

We can apply this recursively until we get

$$\mathbf{w}(2) = \frac{1}{2}\left\{\mathbf{u}(2) + \sum_{t=2}^{T-1}\left[\prod_{j=2}^{t} \mathbb{P}(j)\left(\mathbf{u}(t) + \mathbf{u}(t+1)\right)\right]\right\}.$$

For the first year, we must take care when separating it into the treatment period and the remainder of the year. Therefore, we have that

$$\begin{aligned}
\mathbf{w}(1) &= \frac{365-z}{365} \times \frac{1}{2}\left(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)\right) + \mathbb{P}(1)\mathbf{w}(2) \\
&= \frac{365-z}{365} \times \frac{1}{2}\left(\mathbf{u}(1) + \mathbb{P}(1)\mathbf{u}(1)\right) \\
&\quad + \mathbb{P}(1)\frac{1}{2}\left\{\mathbf{u}(2) + \sum_{t=2}^{T-1}\left[\prod_{j=2}^{t}\mathbb{P}(j)\left(\mathbf{u}(t)+\mathbf{u}(t+1)\right)\right]\right\} \\
&= \frac{1}{2}\left\{\frac{365-z}{365}\mathbf{u}(1) + \mathbb{P}(1)\left(\frac{365-z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right)\right\} \\
&\qquad + \frac{1}{2}\mathbb{P}(1)\sum_{t=2}^{T-1}\left[\prod_{j=2}^{t}\mathbb{P}(j)\left(\mathbf{u}(t)+\mathbf{u}(t+1)\right)\right].
\end{aligned}$$

Finally,

$$\begin{aligned}
\mathbf{w}(0) &= \frac{z}{365} \times \frac{1}{2}(\mathbf{u}(0) + \mathbb{P}(0)\mathbf{u}(0)) + \mathbb{P}(0)\mathbf{w}(1) \\
&= \frac{1}{2}\left\{\frac{z}{365}\mathbf{u}(0) + \mathbb{P}(0)\left(\frac{z}{365}\mathbf{u}(0) + \frac{365-z}{365}\mathbf{u}(1)\right)\right\} \\
&\qquad + \frac{1}{2}\mathbb{P}(0)\mathbb{P}(1)\left(\frac{365-z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right) \\
&\qquad\quad + \frac{1}{2}\mathbb{P}(0)\mathbb{P}(1)\sum_{t=2}^{T-1}\left[\prod_{j=2}^{t}\mathbb{P}(j)\left(\mathbf{u}(t)+\mathbf{u}(t+1)\right)\right] \\
&= \frac{1}{2}\left\{\frac{z}{365}\mathbf{u}(0) + \mathbb{P}(0)\left(\frac{z}{365}\mathbf{u}(0) + \frac{365-z}{365}\mathbf{u}(1)\right)\right\} \\
&\qquad + \frac{1}{2}\mathbb{P}(0)\mathbb{P}(1)\left(\frac{365-z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right) \\
&\qquad\quad + \frac{1}{2}\sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)\left(\mathbf{u}(t)+\mathbf{u}(t+1)\right)\right].
\end{aligned}$$

□

Theorem 11. *The expected lifetime QALYs for a treatment path can be written as a sum of the snapshot QALYs. More specifically,*

$$\mathbf{w}(0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbf{v}(0) + \mathbf{v}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathbf{v}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

for $T \geq 2$, where $T = 112 - a$.

Proof. From Lemma 5, we have that

$$\mathbf{w}(0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u}(0) + \mathbb{P}(0)\left[\frac{z}{365}\mathbf{u}(0) + \frac{365-z}{365}\mathbf{u}(1)\right] + \mathbb{P}(0)\mathbb{P}(1)\left[\frac{365-z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right]\right\} + \frac{1}{2}\sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right].$$

Substituting $\mathbf{u}(i)$ for all i, we get

$$\begin{aligned}\mathbf{w}(0) &= \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbb{P}(0)\left[\frac{z}{365}\mathbf{u} + \frac{365-z}{365}\mathbf{u}\right] + \mathbb{P}(0)\mathbb{P}(1)\left[\frac{365-z}{365}\mathbf{u} + \mathbf{u}\times(1-f)\right]\right\} \\ &\quad + \frac{1}{2}\sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)(\mathbf{u}\times(1-f)^{t-1} + \mathbf{u}\times(1-f)^{t})\right]. \\ &= \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbb{P}(0)\mathbf{u} + \frac{365-z}{365}\mathbb{P}(0)\mathbb{P}(1)\mathbf{u} + \mathbb{P}(0)\mathbb{P}(1)\mathbf{u}\times(1-f)\right\} \\ &\quad + \frac{1}{2}\sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)\mathbf{u}\left((1-f)^{t-1} + (1-f)^{t}\right)\right].\end{aligned}$$

Substituting in $\mathbf{v}(t)$ for all t, we find that

$$\mathbf{w}(0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbf{v}(0) + \mathbf{v}(1)\left[\frac{365-z}{365} + (1-f)\right]\right\} + \frac{1}{2}\sum_{t=2}^{T-1}\left[\mathbf{v}(t)((1-f)^{t-1} + (1-f)^{t})\right];$$

that is,

$$\mathbf{w}(0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbf{v}(0) + \mathbf{v}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathbf{v}(t)\left(\sum_{j=t-1}^{t}(1-f)^{j}\right)\right]\right\}.$$

□

6.2 Individual Benefits

Therefore, by defining the snapshot benefits in QALYs, we can write the expected lifetime benefit of treatment QALYs gained, as a sum of these snapshot benefits.

Definition 20. The **snapshot net benefit** in expected QALYs, for an individual disease in isolation, after t years is:

$$\mathfrak{b}(t) = ({}_s\mathbf{v})_1(t) - ({}_m\mathbf{v})_1(t),$$

where $({}_s\mathbf{v})_1(t)$ is the snapshot expected QALYs after t years, with treatment, and $({}_m\mathbf{v})_1(t)$ is the snapshot expected QALYs after t years, without treatment, given that a patient started well with the disease.

The **snapshot ideal benefit** in expected QALYs, for an individual disease in isolation, after t years is:

$$\mathfrak{b}^I(t) = ({}_s\mathbf{v}^I)_1(t) - ({}_m\mathbf{v})_1(t),$$

where $({}_s\mathbf{v}^I)_1(t)$ is the snapshot expected QALYs with risk-free treatment, after t years, given that a patient started well with the disease.

The **snapshot iatrogenic loss** in expected QALYs, for an individual disease in isolation, after t years is:

$$\mathfrak{l}(t) = ({}_s\mathbf{v}^I)_1(t) - ({}_s\mathbf{v})_1(t).$$

Theorem 12. *The expected lifetime net benefit, ideal benefit, and iatrogenic loss of treatment in QALYs, for an individual disease in isolation, can be written as a sum of the snapshot net benefits, ideal benefits and iatrogenic losses in QALYs, respectively.*

$$\mathbf{b} = \frac{1}{2}\left\{\mathfrak{b}(0) + \mathfrak{b}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{b}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

$$\mathbf{b}^I = \frac{1}{2}\left\{\mathfrak{b}^I(0) + \mathfrak{b}^I(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{b}^I(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

and,

$$\boldsymbol{\ell} = \frac{1}{2}\left\{\mathfrak{l}(0) + \mathfrak{l}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{l}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Proof.

$$\mathbf{b} = ({}_s\mathbf{w})_1(0) - ({}_m\mathbf{w})_1(0)$$

and ${}_s\mathbf{w}(0) - {}_m\mathbf{w}(0)$

$$= \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + {}_s\mathbf{v}(0) + {}_s\mathbf{v}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[{}_s\mathbf{v}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}$$
$$- \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + {}_m\mathbf{v}(0) + {}_m\mathbf{v}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[{}_m\mathbf{v}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}$$

(by Theorem 11)

$$= \frac{1}{2}\left\{{}_s\mathbf{v}(0) - {}_m\mathbf{v}(0) + ({}_s\mathbf{v}(1) - {}_m\mathbf{v}(1))\left[\frac{365-z}{365} + (1-f)\right]\right.$$
$$\left. + \sum_{t=2}^{T-1}\left[({}_s\mathbf{v}(t) - {}_m\mathbf{v}(t))\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Therefore, $\mathbf{b} = \frac{1}{2}\left\{({}_s\mathbf{v})_1(0) - ({}_m\mathbf{v})_1(0) + (({}_s\mathbf{v})_1(1) - ({}_m\mathbf{v})_1(1))\left[\frac{365-z}{365} + (1-f)\right]\right.$
$$\left. + \sum_{t=2}^{T-1}\left[(({}_s\mathbf{v})_1(t) - ({}_m\mathbf{v})_1(t))\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}$$
$$= \frac{1}{2}\left\{\mathfrak{b}(0) + \mathfrak{b}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{b}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

By replacing ${}_s\mathbf{v}(t)$ with ${}_s\mathbf{v}^I(t)$ in the proof above, and following the steps verbatim, the result for ideal benefit follows.

$$\mathbf{b}^I = \frac{1}{2}\left\{\mathfrak{b}^I(0) + \mathfrak{b}^I(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{b}^I(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

The iatrogenic loss is,

$$\boldsymbol{\ell} = ({}_s\mathbf{w}^I)_1 - ({}_s\mathbf{w})_1,$$

therefore, from Theorem 11:

$$\boldsymbol{\ell} = \frac{1}{2}\left\{({}_s\mathbf{v}^I)_1(0) - ({}_s\mathbf{v})_1(0) + (({}_s\mathbf{v}^I)_1(1) - ({}_s\mathbf{v})_1(1))\left[\frac{365-z}{365} + (1-f)\right]\right.$$
$$\left. + \sum_{t=2}^{T-1}\left[(({}_s\mathbf{v}^I)_1(t) - ({}_s\mathbf{v})_1(t))\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}$$

$$= \frac{1}{2}\left\{\mathfrak{l}(0) + \mathfrak{l}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{l}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

□

6.3 Benefit in the Presence of Multiple Diseases

We can also show that when considering multiple diseases, the lifetime benefit in QALYs can still be written as a sum of the relevant snapshot benefits in QALYs. Therefore, since the snapshot benefits in QALYs are equivalent to the benefit in expected quality of outcome, as described in Chapter 3, we can show that the results from Chapter 3 also apply to the lifetime benefit in QALYs.

Definition 21. Consider a set of diseases, N. Let the expected lifetime QALYs of treating those diseases $P \subseteq N$ be

$$\mathbf{w}_P(N;0),$$

calculated using equations (6.2), and the snapshot QALYs of treating $P \subseteq N$ at time t be

$$\mathbf{v}_P(N;t),$$

calculated using equations (6.1), where $\mathbf{u}$ represents the utility values of the combined health states, and $\mathbb{P}$ is the relevant combined transition matrix.

Theorem 13. *The expected lifetime QALYs of treating diseases $P \subseteq N$ can be written as a sum of the snapshot QALYs of treating diseases $P \subseteq N$. More specifically,*

$$\mathbf{w}_P(N;0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbf{v}_P(N;0) + \mathbf{v}_P(N;1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathbf{v}_P(N;i)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Proof. We use the same equations (6.2) for calculating the expected lifetime QALYs of treating multiple diseases, as we do for an individual disease, the only difference

being the larger combined utility value vector, and relevant combined transition matrices. Therefore, from Lemma 5,

$$\mathbf{w}_P(N;0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u}(0) + \mathbb{P}(0)\left[\frac{z}{365}\mathbf{u}(0) + \frac{365-z}{365}\mathbf{u}(1)\right] + \mathbb{P}(0)\mathbb{P}(1)\left[\frac{365-z}{365}\mathbf{u}(1) + \mathbf{u}(2)\right] + \sum_{t=2}^{T-1}\left[\prod_{j=0}^{t}\mathbb{P}(j)(\mathbf{u}(t) + \mathbf{u}(t+1))\right]\right\},$$

where $\mathbf{u}$ contains the utility values of the combined health states of all diseases, N, and $\mathbb{P}$ is the relevant combined transition matrix of treating diseases $P \subseteq N$. It therefore follows from the proof of Theorem 11, that the expected lifetime QALYs of treating diseases $P \subseteq N$ can be written as a sum of the snapshot QALYs of treating diseases $P \subseteq N$. That is,

$$\mathbf{w}_P(N;0) = \frac{1}{2}\left\{\frac{z}{365}\mathbf{u} + \mathbf{v}_P(N;0) + \mathbf{v}_P(N;1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathbf{v}_P(N;t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

□

Definition 22. Consider that a patient is suffering from a set of diseases, N. The **combined lifetime benefit** in QALYs is the difference in expected lifetime QALYs between treating all diseases, and treating none. Mathematically,

$$\mathbf{B}^C = (\mathbf{w}_N)_1(N;0) - (\mathbf{w}_\varnothing)_1(N;0).$$

The **added lifetime benefit** of treating disease i is the difference in expected lifetime QALYs between treating disease i, and treating no diseases. Mathematically,

$$\mathbf{B}_i^A = (\mathbf{w}_i)_1(N;0) - (\mathbf{w}_\varnothing)_1(N;0).$$

The **withdrawal lifetime benefit** of treating disease i is the difference in expected lifetime QALYs between treating all diseases, N, and treating all except disease i. Mathematically,

$$\mathbf{B}_i^W = (\mathbf{w}_N)_1(N;0) - (\mathbf{w}_{N\setminus\{i\}})_1(N;0).$$

Definition 23. For a set of diseases, N, the **combined snapshot benefit** in QALYs, at time t, is:

$$\mathfrak{B}^C(t) = (\mathbf{v}_N)_1(N;t) - (\mathbf{v}_\varnothing)_1(N;t).$$

The **added snapshot benefit** in QALYs, of disease i, at time t, is:

$$\mathfrak{B}_i^A(t) = (\mathbf{v}_i)_1(N;t) - (\mathbf{v}_\varnothing)_1(N;t).$$

The **withdrawal snapshot benefit** is QALYs, of disease i, at time t, is:

$$\mathfrak{B}_i^W(t) = (\mathbf{v}_N)_1(N;t) - (\mathbf{v}_{N\setminus\{i\}})_1(N;t).$$

The lifetime benefits, considering multiple diseases, can also be written in terms of the sums of the relevant snapshot benefits.

Theorem 14.

$$\mathbf{B}^C = \frac{1}{2}\left\{\mathfrak{B}^C(0) + \mathfrak{B}^C(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}^C(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

$$\mathbf{B}_i^A = \frac{1}{2}\left\{\mathfrak{B}_i^A(0) + \mathfrak{B}_i^A(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}_i^A(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

and,

$$\mathbf{B}_i^W = \frac{1}{2}\left\{\mathfrak{B}_i^W(0) + \mathfrak{B}_i^W(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}_i^W(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Proof. From Theorem 11,

$$\begin{aligned}
\mathbf{B}^C = \frac{1}{2}\Bigg\{ & \frac{z}{365}\mathbf{u} + (\mathbf{v}_N)_1(N;0) + (\mathbf{v}_N)_1(N;1)\left[\frac{365-z}{365} + (1-f)\right] \\
& + \sum_{t=2}^{T-1}\left[(\mathbf{v}_N)_1(N;t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\Bigg\} \\
& - \frac{1}{2}\Bigg\{ \frac{z}{365}\mathbf{u} + (\mathbf{v}_\varnothing)_1(N;0) + (\mathbf{v}_\varnothing)_1(N;1)\left[\frac{365-z}{365} + (1-f)\right] \\
& + \sum_{t=2}^{T-1}\left[(\mathbf{v}_\varnothing)_1(N;t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\Bigg\} \\
= \frac{1}{2}\Bigg\{ & (\mathbf{v}_N)_1(N;0) - (\mathbf{v}_\varnothing)_1(N;0) + ((\mathbf{v}_N)_1(N;1) - (\mathbf{v}_\varnothing)_1(N;1))\left[\frac{365-z}{365} + (1-f)\right] \\
& + \sum_{t=2}^{T-1}\left[((\mathbf{v}_N)_1(N;t) - (\mathbf{v}_\varnothing)_1(N;t))\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\Bigg\} \\
= \frac{1}{2}\Bigg\{ & \mathfrak{B}^C(0) + \mathfrak{B}^C(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}^C(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\Bigg\}.
\end{aligned}$$

Similarly, by replacing the relevant expected QALY terms, the result follows for both the added benefit and withdrawal benefit. □

Recall that the snapshot expected QALYs of a disease is equivalent to the expected quality of outcome described in Chapter 3, if we consider the separate fatal and non-fatal outcomes as separate diseases.

Theorem 15. *If Assumptions 1 and 2 (from Chapter 3) hold for the snapshot expected QALYs of the fatal and non-fatal outcomes of all diseases $i \in N$, at all times $0 \leq t \leq T$, then*

$$\sum_{i\in N}\mathbf{B}_i^A \leq \mathbf{B}^C \leq \sum_{i\in N}\mathbf{B}_i^W \leq \sum_{i\in N}\mathbf{b}_i.$$

Proof.

$$\mathbf{B}_i^A = \frac{1}{2}\left\{\mathfrak{B}_i^A(0) + \mathfrak{B}_i^A(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}_i^A(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

Therefore,

$$\sum_{i\in N}\mathbf{B}_i^A = \frac{1}{2}\sum_{i\in N}\left\{\mathfrak{B}_i^A(0)+\mathfrak{B}_i^A(1)\left[\frac{365-z}{365}+(1-f)\right]+\sum_{t=2}^{T-1}\left[\mathfrak{B}_i^A(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Since in Chapter 3 we proved, under Assumptions 1 and 2, that for the expected quality of outcome,

$$\sum_{i\in N}\mathfrak{B}_i^A \leq \mathfrak{B}^C,$$

we can extend this result to the snapshot benefits in QALYs, as we proved in Chapter 4 that these are equivalent when the diseases are broken down into their fatal and non-fatal counterparts. Therefore,

$$\begin{aligned}\sum_{i\in N}\mathbf{B}_i^A &\leq \frac{1}{2}\left\{\mathfrak{B}^C(0)+\mathfrak{B}^C(1)\left[\frac{365-z}{365}+(1-f)\right]+\sum_{t=2}^{T-1}\left[\mathfrak{B}^C(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}\\ &= \mathbf{B}^C.\end{aligned}$$

Using similar reasoning, the other inequalities follow. So we have that, under Assumptions 1 and 2,

$$\sum_{i\in N}\mathbf{B}_i^A \leq \mathbf{B}^C \leq \sum_{i\in N}\mathbf{B}_i^W \leq \sum_{i\in N}\mathbf{b}_i.$$

□

Definition 24. Consider a set of diseases, N. Let the expected lifetime QALYs of treating those diseases $P \subseteq N$ with risk-free treatment be

$$\mathbf{w}_P^I(N;0),$$

and the snapshot QALYs of treating those diseases $P \subseteq N$ with risk-free treatment, at time t, be

$$\mathbf{v}_P^I(N;t).$$

We can also consider treating some diseases with risk-free treatment, while treating others with normal-risk treatment.

Definition 25. Consider a set of diseases, N, with $P, S \subseteq N$ such that $P \cap S = \varnothing$. Let the expected lifetime QALYs of treating those diseases P with normal-risk treatment, and S with risk-free treatment, be

$$\mathbf{w}_{P,S}(N; 0),$$

and the snapshot QALYs of treating those diseases P with normal-risk treatment, and S with risk-free treatment, at time t, be

$$\mathbf{v}_{P,S}(N; t).$$

We can then clearly define the ideal benefits and iatrogenic losses in terms of the expected lifetime QALYs and snapshot QALYs.

Definition 26. Consider that a patient is suffering from a set of diseases, N. The **combined lifetime ideal benefit** in QALYs is,

$$\mathbf{B}^{I,C} = (\mathbf{w}^I_N)_1(N; 0) - (\mathbf{w}_\varnothing)_1(N; 0).$$

The **added lifetime ideal benefit** of treating disease i is,

$$\mathbf{B}^{I,A}_i = (\mathbf{w}^I_i)_1(N; 0) - (\mathbf{w}_\varnothing)_1(N; 0).$$

The **withdrawal lifetime ideal benefit** of treating disease i is,

$$\mathbf{B}^{I,W}_i = (\mathbf{w}^I_N)_1(N; 0) - (\mathbf{w}^I_{N\setminus\{i\}})_1(N; 0).$$

Definition 27. Consider that a patient is suffering from a set of diseases, N. The **combined snapshot ideal benefit** in QALYs at time j is,

$$\mathfrak{B}^{I,C}(j) = (\mathbf{v}^I_N)_1(N; j) - (\mathbf{v}_\varnothing)_1(N; j).$$

The **added snapshot ideal benefit** of treating disease i at time j is,

$$\mathfrak{B}^{I,A}_i(j) = (\mathbf{v}^I_i)_1(N; j) - (\mathbf{v}_\varnothing)_1(N; j).$$

The **withdrawal lifetime ideal benefit** of treating disease i at time j is,

$$\mathfrak{B}^{I,W}_i(j) = (\mathbf{v}^I_N)_1(N; j) - (\mathbf{v}^I_{N\setminus\{i\}})_1(N; j).$$

Then, the ideal lifetime benefits in QALYs can also be written as sums of the relevant ideal snapshot benefits in QALYs.

Theorem 16.

$$\mathbf{B}^{I,C} = \frac{1}{2}\left\{\mathfrak{B}^{I,C}(0) + \mathfrak{B}^{I,C}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}^{I,C}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

$$\mathbf{B}_i^{I,A} = \frac{1}{2}\left\{\mathfrak{B}_i^{I,A}(0) + \mathfrak{B}_i^{I,A}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}_i^{I,A}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

and,

$$\mathbf{B}_i^{I,W} = \frac{1}{2}\left\{\mathfrak{B}_i^{I,W}(0) + \mathfrak{B}_i^{I,W}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{B}_i^{I,W}(t)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Proof. Since we can write the expected lifetime QALYs as a sum of snapshot QALYs, the proof follows exactly the steps of the proof of Theorem 12, replacing the relevant expected QALY terms for each the combined, added and withdrawal ideal benefits.

□

Theorem 17. *If Assumptions 1 and 2 hold for the snapshot expected quality of outcomes, at all times* $0 \leq t \leq T$*, then*

$$\sum_{i\in N}\mathbf{B}_i^{I,A} \leq \mathbf{B}^{I,C} \leq \sum_{i\in N}\mathbf{B}_i^{I,W} \leq \sum_{i\in N}\mathbf{b}_i^{I}.$$

Proof. The proof follows directly from the results of Chapter 3, Theorem 16, and following the steps of Theorem 15, using ideal benefits everywhere instead. Therefore,

$$\sum_{i\in N}\mathbf{B}_i^{I,A} \leq \mathbf{B}^{I,C} \leq \sum_{i\in N}\mathbf{B}_i^{I,W} \leq \sum_{i\in N}\mathbf{b}_i^{I}.$$

□

Definition 28. Consider that a patient is suffering from a set of diseases, N. The **combined lifetime iatrogenic loss** in QALYs is,

$$\mathbf{L}^{C} = (\mathbf{w}_N^I)_1(N;0) - (\mathbf{w}_N)_1(N;0).$$

The **added lifetime iatrogenic loss** of treating disease i is,

$$\mathbf{L}_i^A = (\mathbf{w}_i^I)_1(N;0) - (\mathbf{w}_i)_1(N;0).$$

The **withdrawal lifetime iatrogenic loss** of treating disease i is,

$$\mathbf{L}_i^W = (\mathbf{w}_N^I)_1(N;0) - (\mathbf{w}_{i,N\setminus\{i\}})_1(N;0).$$

Definition 29. Consider that a patient is suffering from a set of diseases, N. The **combined snapshot iatrogenic loss** in QALYs at time j is,

$$\mathfrak{L}^C(j) = (\mathbf{v}_N^I)_1(N;j) - (\mathbf{v}_N)_1(N;j).$$

The **added snapshot iatrogenic loss** of treating disease i at time j is,

$$\mathfrak{L}_i^A(j) = (\mathbf{v}_i^I)_1(N;j) - (\mathbf{v}_i)_1(N;j).$$

The **withdrawal snapshot iatrogenic loss** of treating disease i at time j is,

$$\mathfrak{L}_i^W(j) = (\mathbf{v}_N^I)_1(N;j) - (\mathbf{v}_{i,N\setminus\{i\}})_1(N;j).$$

Theorem 18.

$$\mathbf{L}^{I,C} = \frac{1}{2}\left\{\mathfrak{L}^{I,C}(0) + \mathfrak{L}^{I,C}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{L}^{I,C}(i)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

$$\mathbf{L}_i^{I,A} = \frac{1}{2}\left\{\mathfrak{L}_i^{I,A}(0) + \mathfrak{L}_i^{I,A}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{L}_i^{I,A}(i)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\},$$

and,

$$\mathbf{L}_i^{I,W} = \frac{1}{2}\left\{\mathfrak{L}_i^{I,W}(0) + \mathfrak{L}_i^{I,W}(1)\left[\frac{365-z}{365} + (1-f)\right] + \sum_{t=2}^{T-1}\left[\mathfrak{L}_i^{I,W}(i)\left(\sum_{j=t-1}^{t}(1-f)^j\right)\right]\right\}.$$

Proof. Again, the proof follows exactly the steps of the proof of Theorem 12, replacing the relevant expected QALY terms for each the combined, added and withdrawal iatrogenic losses. □

Theorem 19. *If Assumptions 1 and 2 hold, then*

$$\sum_{i \in N} \mathbf{L}_i^A < \mathbf{L}^C \leq \sum_{i \in N} \mathbf{L}_i^W \leq \sum_{i \in N} \boldsymbol{\ell}_i.$$

Proof. The proof follows directly from Chapter 3, Theorem 18 and again following the arguments in the proof of Theorem 15, using iatrogenic loss in place of net benefit. □

6.3.1 Considering Negative Early Benefits

In Chapter 3, we made some assumptions about the snapshot benefit and snapshot expected outcome of treatment, at a certain point in time, to ensure that only sensible treatments were considered. However, as we have seen in Chapter 4, these assumptions are not necessarily met at all points in time. Since each individual disease in our lifetime model can be considered as two separate diseases (fatal and non-fatal) in the snapshot model, we have that Assumption 2 is not necessarily being met in the early stages after treatment. In particular, since the snapshot benefit for each disease is negative at the beginning of the process, the assumption that $E(N) < E_N(N)$ does not hold, where $N = \{1 \text{ (fatal outcome)}, 2 \text{ (non-fatal outcome)}\}$.

In Figure 6.1, for both CEA and CABG, we see that this means the individual snapshot benefit of surgery for a 70-year-old patient is not positive immediately after surgery. For CABG, the benefit remains negative until $t = 3$, while the benefit of CEA is negative for only the surgical period, $t = 0$. However, we also know that the individual lifetime benefits of both CEA and CABG, as calculated in Chapter 4, are positive, and hence the treatments are considered sensible; the lifetime benefit of CEA is 0.6373 QALYs, and the lifetime benefit of CABG is 0.4671 QALYs.

Earlier in this chapter, we saw that the lifetime benefit is a sum of the snapshot benefits over the years, adjusted by the appropriate constants. Since the negative benefits in our example are small and only temporary, the positive benefits that the patient experiences for the rest of their lifetime outweigh them.

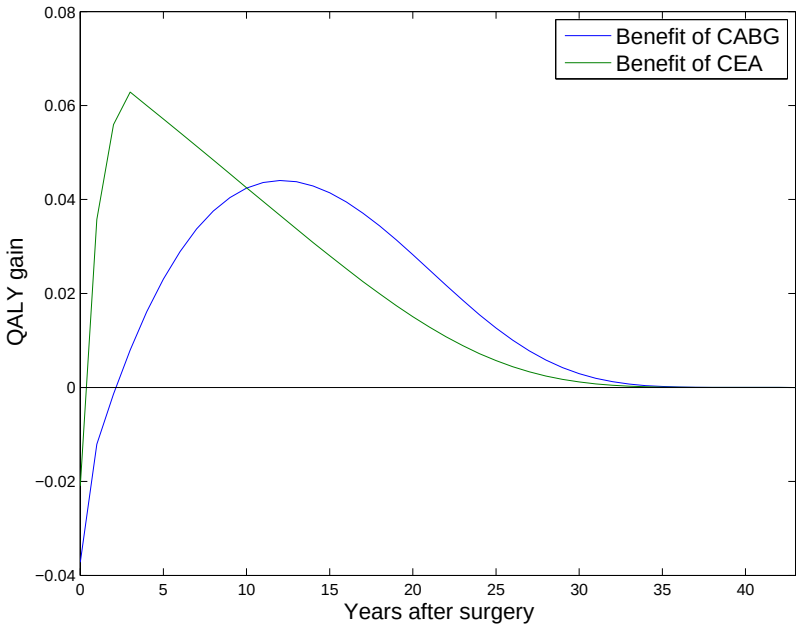


Figure 6.1: Snapshot net benefit each year after surgery, for a 70-year-old patient undergoing either CABG or CEA.

For situations where all of the snapshot benefits obey Assumptions 1 and 2, we have that the claims of Theorems 15, 17, 19 must hold. However, for situations in which the early snapshot benefits do not obey Assumption 2, these claims do not necessarily hold. Therefore, we cannot prove the results claimed in Theorems 15, 17, 19 in these cases. Nonetheless, we do believe that these results do hold in general, as long as the snapshot benefits are sufficiently positive for a sufficient amount of time, which should be the case for any sensible treatment.

Chapter 7

Conclusion

Treatment benefit data is usually obtained from clinical trials, performed on patients in a specific controlled setting. These patients typically have few medical problems other than the disease being treated, to ensure bias in the results is minimised. Despite this, patients who receive this treatment in reality may have multiple diseases, or comorbidities, which could affect the actual benefit.

To study the effect of this, we have developed a model that has allowed us to accurately calculate the lifetime benefit of treating multiple conditions simultaneously. Using this model, and two particular comorbidities, we have confirmed that the lifetime benefit of treatment in the presence of other diseases is less than if we consider the diseases separately. We have also shown that treatment risk, when measured in the same way as benefit, behaves similarly to benefit when considering multiple conditions. That is, we have proven for a set of diseases N, that the relationship

$$C \leq \sum_{i \in N} W_i \leq \sum_{i \in N} Ind_i \tag{7.1}$$

holds for benefits and risks measured in various ways, where W_i, and Ind_i refer to the withdrawal and individual measures respectively, and C refers to the combined measure. To prove these results theoretically for multiple comorbidities, we extended existing theoretical results for snapshot benefits.

7.1 A Snapshot Analysis of Benefit

In Chapter 3 we introduced and extended results by Fitzgerald and Bean [4], for considering multiple comorbidities when measuring the benefit of treatment at a specific point in time (the snapshot benefit). Fitzgerald and Bean first defined the snapshot net benefit of treatment in terms of the probability of outcome, and proved that the combined net benefit, of treating all of a set of diseases N, is less than the sum of the individual net benefits. They also introduced two methods of measuring the benefit of an individual treatment in the presence of multiple comorbidities: the 'withdrawal' net benefit and the 'added' net benefit. The withdrawal net benefit considered the benefit of treating a disease given that *all* other diseases were treated, and the added net benefit considered the benefit of treatment given that *none* of the other diseases were treated. Using these definitions, they proved that for the snapshot net benefit measured in probability of outcome, the benefit in the presence of comorbidities is less than the reported benefit in isolation.

We then extended these results to prove that the relationship between the different benefit measures follows equation (7.1), where the inequalities between the measures is strict. In other words, when considering different methods of measuring the benefit of treating all diseases in the presence of comorbidities, the benefit is always less than considering only the diseases in isolation. We consider the withdrawal benefit to be the best method of measuring the benefit of a single treatment in the presence of comorbidities; however, the sum of the withdrawal benefits is still greater than the combined benefit of treating all diseases simultaneously. That is, even when considering the effect of comorbidities on each single treatment, the benefit of treating all diseases is still overstated if we do not consider all treatments together. Thus, we conclude that the interaction between treatment outcomes also has an effect on the total benefit.

We then introduced the concepts of ideal benefit and iatrogenic loss, where the ideal benefit is the benefit considering that the treatment has no risks involved, and

the iatrogenic loss is the loss of potential benefit due to treatment. Using the same methods as for the net benefit in terms of the probability of outcome, we defined the combined and withdrawal, ideal benefits and iatrogenic losses. Using these, we proved that the same relationships held for these measures, as they did for the net benefits before (equation 7.1), again with strict inequalities. That is, we proved that when considering multiple comorbidities, the risk of treatment behaves similarly to the benefit, as predicted. We also proved that removing this risk from the benefit calculation has no effect on the relationship between the different ways of considering the benefit of treating all diseases, where the benefit is the reduction in probability of a bad outcome.

However, it is more meaningful to consider the quality of a patient's outcome, rather than just the likelihood of a bad outcome. To do this, we extended upon Fitzgerald and Bean's definition of the snapshot net benefit in expected quality of outcome. Firstly, we made some assumptions to ensure that only sensible treatments were allowed, then we defined the combined, withdrawal and individual benefits and iatrogenic losses of treatment in terms of expected quality of outcome, as we did in terms of probability of outcome. Using these definitions, we proved that similar inequalities hold for the expected quality measures, as for the probability measures. In the expected quality of outcome environment, the inequalities were not all strict, however, due to looser assumptions.

In other words, we proved theoretically that for a patient with multiple comorbidities, for the benefit measured in both expected quality of outcome and probability of outcome, the snapshot benefits and risks of treatment are overstated if the effect of comorbidities is ignored. More specifically,

$$B^C < \sum_{i \in N} Ind_i.$$

We also proved that even when considering individual benefits in the presence of comorbidities, the sum of the these is still greater than the combined benefit of all

treatments simultaneously. That is,

$$B^C < \sum_{i \in N} W_i.$$

This suggests that the interaction between treatment benefits also has an effect on the true measure of benefit.

7.2 Results for Lifetime Benefit

However, treatment benefits captured at a particular point in time are not always indicative of the actual benefit that a patient may receive over their lifetime. For this reason, in Chapter 4 we developed a model that tracked the progression of a disease over time, with and without treatment. From this, we calculated the lifetime benefit of treatment in expected quality adjusted life years (QALYs). To begin with, we utilised an already developed discrete-time Markov model of carotid endarterectomy (CEA) on patients with carotid artery stenosis (CAS). We then improved the model by modifying the transition probabilities to more accurately model the interactions between the age related probability of death, and the probability of stroke. With this modified model, we calculated the expected QALYs for a patient with CEA and without CEA using Markov expected reward equations. Thus, we were able to calculate the net benefit, ideal benefits and iatrogenic loss of CEA surgery in lifetime expected QALYs for patients of varying ages. As expected, the benefit of surgery was greater in younger patients, as was the iatrogenic loss.

We also considered the snapshot benefit of CEA in QALYs, at a particular time t after surgery. We demonstrated that this snapshot benefit is equivalent to the snapshot benefit in expected quality of outcome as defined in Chapter 3, if we consider the fatal and non-fatal outcomes of the disease as two separate diseases. The results from this snapshot analysis for a 70-year-old patient, showed that the benefit of CEA was not positive at every point in time, t, after surgery (negative for $t = 0$); that is, our assumption of sensible treatments was not always met in the

snapshot case, despite the positive lifetime benefit.

After developing this model for calculating the benefit of an individual treatment in isolation, we then generalised the parameters and applied it to a different disease. We decided to find the benefit of coronary artery bypass graft surgery (CABG) as treatment for coronary artery disease (CAD), and compare the results to those obtained for the benefit of CEA. We found that the lifetime benefit of CABG varied much more across different ages than the benefit of CEA; the benefit of CABG for a 40-year-old patient was greater, however became less for patients who had the surgery at approximately 60 years old or later. To further analyse this outcome, we looked at how the lifetime benefit accumulated over a 70-year-old patient's lifetime. Due to the higher surgical risk, and lower initial benefit in terms of reduction in probability of heart attack, the accumulated benefit of CABG in QALYs remained negative for 5 years after surgery, whereas the accumulated benefit of CEA was positive after the first year. The snapshot benefits in QALYs of CABG for a 70-year-old were not always positive, and in fact remained negative until $t = 3$, again showing that our assumptions ensuring sensible treatments were not met at all time points.

In Chapter 5, we used this general model of an individual disease to create a Markov model capable of modelling multiple diseases simultaneously. In doing so, we considered the best ways to combine the state spaces, transition matrices and utility values of each of the new combined health states. To begin with, we used a simple Cartesian product of the individual state spaces and essentially collapsed all of the resulting individual dead states into one all-encompassing dead state. To combine the transition matrices, we used the Kronecker product, and again collapsed all of the relevant transition probabilities for the individual dead states, into the one dead state. To ensure reasonable utility values, we took the product of the utilities of the individual health states that made up the resulting combined state.

We then used this combined model, and our two particular diseases to find the expected outcome in QALYs of the four different treatment options for patients suf-

fering from both CAS and CAD. Using these, we calculated the relevant withdrawal and combined net benefits, ideal benefits and iatrogenic losses. The results showed that for these particular diseases and their treatments, the lifetime benefits and iatrogenic losses satisfied the inequalities in equation (7.1). That is, for this particular example, the benefits and risks behaved as we expected, further demonstrating that the benefit of treatment is overstated when the effects of multiple conditions, and their treatments, are not considered.

In Chapter 3, we proved theoretically for the snapshot benefit, that the benefit of treatment is overestimated if a patient has multiple comorbidities. However, for this proof to hold, we made some assumptions about the expected quality of outcome to ensure that treatment is always beneficial. In Chapter 4, we then showed that the snapshot benefits in expected quality of outcome are equivalent to the snapshot benefits in QALYs, if we consider the fatal and non-fatal outcomes of a disease as two separate diseases. Using these outcomes, in Chapter 6 we proved theoretically, under the assumptions made earlier, that the lifetime benefits and iatrogenic losses of treatment, considering multiple comorbidities, obey the same inequalities as the snapshot benefits. To facilitate this, we first proved that the lifetime expected QALYs could be written as a sum of the snapshot expected QALYs. This allowed us to use the results proved in Chapter 3 for the snapshot benefits in expected quality of outcome, to prove the same relationship between the lifetime benefits and losses in QALYs, shown in equation (7.1).

In proving these results, we needed to assume that all treatments were sensible according to the requirements in Chapter 3. That is, all snapshot benefits must be positive. However, in Chapter 4 we saw that for our particular cases, the snapshot benefits did not necessarily meet these assumptions at every point in time after surgery, despite the lifetime benefits still obeying the theorised inequalities. Nevertheless, we hypothesise that these inequalities *do* hold in general, for treatments in which the positive snapshot benefits outweigh the negative, which should be true for sensible treatments.

Overall, in this thesis we have developed a model capable of showing the progression of multiple diseases simultaneously. We also introduced the concepts of net benefit (benefit with normal-risk treatment), ideal benefit (benefit with risk-free treatment), and iatrogenic loss. Using our model, we demonstrated that when considering two particular diseases and their treatments, the lifetime benefits and iatrogenic loss are overstated if calculated without considering the other diseases.

Furthermore, we proved that for sensible treatments, the benefit of treating multiple conditions is always less than the sum of the individual treatment benefits. This is true when considering the total benefit as the sum of withdrawal benefits or the combined benefit, for both net and ideal benefits. We also proved that the benefit of treating multiple conditions is not only affected by the effect of comorbidities, it is also affected by the interactions between treatment benefits. Since we proved that the sum of the withdrawal benefits is greater than the combined benefit of treating all diseases, we showed that even when considering the effects of multiple comorbidities on the benefit of a single treatment, the benefit of treating all diseases is still overstated if we do not consider treating them all at once. We proved that this relationship is also true for the iatrogenic loss of treatments. That is, the loss due to treatment, or risk of treatment, is affected by comorbidities in the same way as the benefit is affected.

Treatments are usually approved based on a cost-effectiveness analysis, which typically approves treatment if the benefit justifies the cost, according to some comparitive measure. However, since the monetary costs of treatment are usually additive, and we have demonstrated that benefits are less than additive, these analyses may be approving treatments which may not be "worth" receiving when considering a more accurate measure of combined benefit.

7.3 Limitations and Further Research

Although the work in this thesis has improved upon the already existing models used to calculate the benefit of treatment while considering multiple comorbidities, it still has some limitations.

One key limitation is an assumption made at the beginning of Chapter 5, which states that the surgeries must both occur at the same time: at the beginning of the chain. However, this assumption is clearly not realistic, as two major surgeries cannot both occur at once. After one major surgery, a patient must be allowed time to recover, to ensure that a second surgery does not become too dangerous. To remedy this, the model could be easily altered to allow for having the second surgery at a different point in time to the first surgery. When considering surgeries at varying times, we expect that the expected lifetime QALYs will be less than having both surgeries together. This is since we are losing the immediate benefit in the reduction of the probability of a debilitating event. For our particular combined model of CEA and CABG, we can see that it would be most beneficial to undergo CEA immediately, as the difference in stroke probability between the surgical and medical chain is much greater than the difference in MI probability for CABG.

Even though this would be more realistic than having both surgeries simultaneously, there are still further considerations that could be made to ensure an even more realistic model. For example, after surgery for the first disease, a patient could decline in health from the second disease and have their probability of an event increase, thus making surgery more beneficial. As mentioned earlier, having another surgery too soon after the first would likely increase the risk of a bad outcome. Therefore, another consideration could be to quantify this extra risk and account for it in a model considering surgeries at varying times.

A second limitation is that in our model, we consider only severe strokes and myocardial infarctions that leave the patient with the same utility. Realistically, a stroke or MI could have varying severity levels, leaving the patient in health states

with different utility values. To account for this, more "post event" states could be included in the individual models before creating the combined model. However, we must consider that if we were to do this, the number of states would increase, and the benefit could take much longer to calculate, the more diseases that are added. Therefore, a discussion on the trade-off between model complexity and computation time could be included in further research for this model. If these extra states do not significantly alter the overall lifetime benefit of treatment, or other results, then they may not be necessary for acceptable accuracy.

We also do not consider that the surgical risk would vary for patients of different ages; for example, the surgery would likely carry more risk for an 80-year-old than a 40-year-old patient. This limitation could be amended by further research into the effects of age on the outcome of surgery, to determine a more accurate, age related surgical risk value, and hence more accurate benefit.

Lastly, when we first introduce the individual Markov model, the type of model we utilise only accounts for certain types of conditions: episodic diseases. However, there are many other types of diseases from which a patient could be suffering. For example, we could also consider diseases that are degenerative in nature, such as dementia, that cause a patient to become more impaired over time rather than causing a specific impairing event. Again, further research could be conducted into a method of combining models of varying types of diseases, so that a more accurate lifetime benefit, and hence the best treatment option could be determined for specific patients.

Our research into the effects of multiple comorbidities on the actual benefit of treatment could lead to the possibility of accurate personalised benefit calculations. We have shown current benefit predictions overestimate the true benefit of treatment, since many patients will have more than one condition that needs to be treated. Thus, if our model could be further refined to include various types of diseases and possibly more accurate parameters, physicians may be able to make more informed decisions for each individual patient.

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