



Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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ABSTRACT

Objective

An economic model was developed to evaluate the cost-effectiveness of hawthorn extract as an adjunctive treatment for heart failure in Australia.

Methods

A Markov model of chronic heart failure was developed using the New York Heart Association (NYHA) classification system. Classes I to IV make up the four health states. Patients may remain in the same NYHA class over time, experience an improvement of symptoms and an improvement in NYHA class, or a deterioration and worsening of NYHA class. Each NYHA class has its own decision tree. Within the decision tree some patients have been admitted to hospital and some have not, some will then die, and some will survive. Model inputs were derived from the published medical literature, and the output was Quality Adjusted Life Years (QALYs). Probabilistic Sensitivity Analysis was conducted. The Expected Value of Perfect Information (EVPI) and the Expected Value of Partial Perfect Information (EVPPI) were conducted to establish the value of further research and the ideal target for such research.

Results

The new treatment increased costs by \$1866.78 and resulted in a gain of 0.02 QALYs. The incremental cost-effectiveness ratio was \$85,160.33 per QALY. The CEAC indicated at a threshold of \$40,000 the new treatment had a 0.29 probability of being cost-effective. The average incremental NMB was -\$1791.64, the average NMB for the standard treatment was \$92,067.49, and for the new treatment \$90,275.84. Additional research is potentially cost-effective if research is not proposed to cost more than \$325 million. Utilities is the most important target parameter group for further research.

Conclusions

Hawthorn extract is not currently considered to be cost-effective in as an adjunctive treatment for heart failure in Australia. Further research in the area of utilities is warranted.

INTRODUCTION

Heart failure is a major public health concern for all Western countries¹. In the United States and Europe it is the most common principal diagnosis for adults admitted to hospital aged 65 years and over. In the United States around 2% of the population have heart failure (approximately 5 million people), and each year there are 500, 000 new cases diagnosed². The estimated prevalence in Sweden is 1.5-2%, approximately 135, 000 to 180, 000 people³.

Australian data regarding the public health significance and epidemiology of heart failure is currently limited. Estimates rely on information from large-scale population studies conducted in the United States and Europe¹. It is estimated there are approximately 300,000 Australians living with chronic heart failure, and approximately 30,000 new cases diagnosed each year, with incidence rates and prevalence rising significantly with age^{4,5}. In Australia, chronic cardiovascular diseases are associated with health care costs of over five billion dollars, and estimates put the cost of heart failure at around one billion dollars⁶. The mortality, morbidity and health care costs of heart failure are therefore significant⁴.

Heart failure is a syndrome with a range of signs and symptoms, diagnosis is based on such signs and symptoms, including dyspnoea and fatigue, and appropriate investigations, such as echocardiogram, which confirm the presence or absence of heart failure and help determine its aetiology¹.

Current treatment aims to relieve and stabilise symptoms and prolong survival by stopping, stabilizing or reversing the progression of heart failure⁷. There are a variety of strategies used in Australia, including non-pharmacological management, pharmacological management, lifestyle changes, and the use of supportive devices, surgery, and palliative care^{6,8}. The pharmacological approach depends on the type of heart failure and extent of the symptoms.

Despite the availability of strategies to treat and manage the chronic disease, the disability and suffering associated with heart failure is devastating⁷. Given this, and the large economic burden, it is reasonable to examine options not currently

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3 considered standard therapy. Research examining the use of complementary and
4 alternative medicine, particularly the use of hawthorn extract is showing promising
5 results.
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10 Hawthorn extract is a popular herbal medicine used worldwide, particularly for its
11 cardiovascular properties⁹. Hawthorn extract has positive inotropic, anti-
12 inflammatory and anti-oxidative properties; causes peripheral and coronary
13 vasodilation; and protects against ischaemia induced arrhythmias⁹. A recent
14 systematic review concluded hawthorn extract can provide significant benefits to
15 heart failure patients as an adjunct to conventional treatment and a recent cost-
16 effectiveness study conducted in Germany concluded hawthorn is a cost-effective
17 treatment option especially in the early stages of heart failure¹⁰⁻¹².
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25 Economic evaluation is a structured method for examining the costs and
26 consequences involved with alternative methods of treatments and/or programs, in
27 order to inform which is the best alternative from a particular viewpoint¹³. The goal
28 is to improve the use of health care resources and improve patient care¹⁴. When
29 conducted rigorously, such formal analysis allows recommendation to be made with
30 transparency regarding the methods, data sources and assumptions¹³. This further
31 allows the process to be replicated, reviewed and even challenged.
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38 Models allow complex situations to be organised into a single coherent form that can
39 be used to make decisions based on comprehensive consideration of the alternative
40 interventions by capturing the essential relationships between the factors included in
41 the model and outcomes^{15 16}. Markov models define diseases using clinically
42 relevant and economically important health states, between which patients move
43 based on the natural history of the disease, and to which cost and effectiveness
44 outcomes are ascribed¹⁶.
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51 The aim of this study was the construction and application of an economic decision
52 model to evaluate hawthorn treatment as an adjunct to recommended pharmacological
53 treatment versus recommended pharmacological management for chronic heart failure
54 in Australia. The analysis has been conducted using a health sector perspective.
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METHODS

Model Description

A four state Markov model of chronic heart failure was developed based on the New York Heart Association (NYHA) classification system using Microsoft Excel® (see Figure 1). Classes I to IV make up four discrete health states included in the model (See Table 1 for a description of the NYHA classes). A decision tree completes the model. Each NYHA class has its own decision tree. Within the decision tree patients could be hospitalised for worsening heart failure. Patients also either survived or died.

Progression through the model

A simulated cohort of 1000 patients aged 60 entered the model with NYHA class II heart failure and progressed through the model. Patients progress through the model in one month cycles for a duration of 5 years. After one month, patients either remained in NYHA class II or improved to NYHA class I or deteriorated. In turn, for each class of heart failure patients were either hospitalised or not hospitalised for worsening heart failure. Patients who were hospitalised or not hospitalised either survived or died. Death was a possibility from any class of heart failure. The patients accrued costs and benefits of treatment in each of the states for each cycle.

Per patient costs were required for each NYHA class. Costs were assumed to be the same for standard treatment and standard treatment with hawthorn extract, except for the additional cost of hawthorn extract. Patient health was considered as a single index utility on a zero to one scale, where 0 represents death and 1 represents perfect health. This allows the calculation of Quality Adjusted Life Years (QALYs) when combined with the mortality data and the calculation of cost per QALY ratios.

Two cohorts were modeled, one receiving standard pharmacological treatment and the other receiving standard pharmacological treatment with hawthorn extract as an adjunct. The two cohorts will progress through the model in slightly different ways and as such there will be a difference in the accumulation of costs and QALYS. It is

the differences in costs and QALYs that will determine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment.

A discount rate of 3% per year was applied to the costs and benefits. This rate is a standard choice in the literature.

Table 1. NYHA grading of symptoms in chronic heart failure.

NYHA Class	Description
Class I	No symptoms and limitations in ordinary physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms such as fatigue, shortness of breath, and angina.
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
Class IV	Severely limited. Experiences symptoms even at rest.

Model Construction

Disease Progression

Transition probabilities for movement between NYHA classes of heart failure were estimated from the published literature detailing the large scale international Study of the Effects of Nebivolol Intervention on Outcomes and Re-hospitalisation in Seniors with Heart Failure (SENIORS) and personal correspondence with authors^{17 18}. A thorough literature search was conducted to identify disease progression data for each NYHA class. The search yielded a limited number of studies, of which only one was considered suitable for inclusion.

Disease progression between the Markov states was assumed to be the same for standard treatment and for standard treatment with hawthorn extract, as we were unable to identify any data to indicate that hawthorn extract altered progression through the classes of heart failure. We have incorporated a difference in mortality and a difference in the hospitalisation rate between the standard treatment and the standard treatment with hawthorn extract as an adjunct, which in turn will impact on the cost and QALY outcomes.

Data Sources

Mortality

Baseline mortality was derived from Australian Bureau of Statistics general population mortality data.

The mortality rate for cardiovascular causes was derived from the published literature detailing one year mortality among unselected patients with NYHA class II-IV heart failure in Switzerland¹⁹. The mortality rate increased with progression from NYHA class I to NYHA class IV, and varied depending on whether the patient was hospitalised or not. A thorough search of the literature was made to identify data for each NYHA class individually, nothing was identified and the above study was the closest to ideal. Hospitalisation was considered a major factor in cost estimation, so data broken down by hospitalisation status was considered to represent the population of heart failure patients well. Also, unselected patients were considered to represent the patient cohort more accurately than studies that focused on hospitalised patients only. As data for NYHA class I was not included, an assumption was made that mortality for NYHA class I was the same as the general population mortality.

Health Status

Estimates of health status were derived from the same source as the transition probabilities^{17,20}. Data concerning utilities for heart failure is extremely limited, a study was identified that had specifically had developed utilities for heart failure in terms of both hospitalisation and NYHA class. However, we were unable to obtain the required data despite personal correspondence with the authors. The estimated health status used was considered the next best data source.

Health status was assumed to be the same for standard treatment and standard treatment with hawthorn extract. Hospitalisation was assumed to result in a health state lower than non-hospitalisation and a -0.1 disutility was applied to hospitalisation to reflect this.

Effect of Hawthorn

The relative risk of mortality and relative risk of hospitalisation with hawthorn extract was derived from the Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in congestive heart failure (SPICE) trial, a large scale, international, randomised, placebo-controlled, double-blind study designed to investigate the influence of hawthorn extract on mortality of patients with congestive heart failure NYHA class II

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3 and III with at least moderately impaired left ventricular function²¹. To date there
4 have only been two studies to examine the effect of hawthorn extract on heart failure
5 progression in terms of mortality and hospitalisation. Most studies have focused on
6 symptoms and exercise capability. SPICE enrolled nearly 3000 patients, and the
7 Hawthorn Extract Randomised Blinded Chronic Heart Failure (HERB CHF) trial
8 enrolled 120 patients^{22 23}. Meta-analysis was not considered appropriate, therefore
9 the data from SPICE was incorporated into the model.
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14 15 16 Costs

17 No Australian data was available to estimate the hospitalisation rate and number of
18 hospitalisations, this information was derived from a United States study²⁴.
19 The estimated length of stay in hospital data was obtained from Victorian Department
20 of Health for 2010-2011, it was unavailable for each NYHA class, so it was assumed
21 to be the same for all classes²⁵.
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23 The cost of a hospital admission per day was derived from the Queensland
24 Government/ Queensland Health Casemix Funding Model 2008-2009 Component
25 Prices Summary²⁶.
26

27 Outpatient costs included General Practitioner (GP) visits, pathology,
28 echocardiograms, and specialist visits. Estimates of the number of GP and specialist
29 visits came from a combination of Australian sources and overseas studies due to the
30 difficulty in finding complete Australian estimates. The costs came directly from the
31 Medicare Benefits Schedule and the Queensland Government/ Queensland Health
32 Casemix Funding Model 2008-2009 Component Prices Summary^{26 27}.
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34 The information for which medications are taken for each NYHA class have been
35 taken from the National Heart Foundation guidelines for the treatment of chronic
36 heart failure in Australia⁵. Information for the optimal dosages prescribed has been
37 taken from the Australian Therapeutic Guidelines. Individual drug pricing was
38 obtained from the most recently available online version of the Medicare Benefits
39 Schedule. The initial version of the model has incorporated the assumption that
40 medications are taken in 100% of patients and that dosing is optimal. The model
41 however can be altered to consider different scenarios of medication prescription and
42 consumption.
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56 The dosage was assumed to be 900mg daily, consistent with the dosage used in the
57 two most recent trials of hawthorn extract, the SPICE trial and the HERB-CHF trial²¹
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^{23 28}. An online search was conducted for standardised monopreparations of hawthorn leaf with flower available for purchase.

The model parameters have been listed in Table 2.

Table 2. Parameters used in the Decision Model

Parameter Description	Baseline Estimate	Variation/ SE (SD)	Distribution	Reference
Transition Probabilities		n/a	Dirichlet (Refer to Appendix 1 for method)	¹⁷
Stable NYHA class I	0.977			
Deteriorate NYHA class I to II	0.019			
Deteriorate NYHA class I to III	0.004			
Stable NYHA class II	0.981			
Improve NYHA class II to I	0.008			
Deteriorate NYHA class II to III	0.010			
Deteriorate NYHA class II to IV	0.001			
Stable NYHA class III	0.960			
Improve NYHA class III to II	0.034			
Deteriorate NYHA class III to IV	0.006			
Stable NYHA class IV	0.945			
Improve NYHA class IV to III	0.055			
Hospitalisation		n/a	n/a	²⁴
probability for hospitalisation Class I	0.01518800			
probability no hospitalisation Class I	0.98481200			
probability for hospitalisation Class II	0.02397800			
probability no hospitalisation Class II	0.97602200			
probability for hospitalisation Class III	0.02397800			
probability no hospitalisation Class III	0.97602200			

Class III				
probability for hospitalisation Class IV	0.15397000			
probability no hospitalisation Class IV	0.84603000			
Length of stay in hospital estimate	4.9 days	Alpha 0.1 Beta 316.81	Gamma	²⁵
Relative Risk of Hospitalisation with Hawthorn Extract	1.03651200	0.080800494	Lognormal	²⁸
Costs		n/a	n/a	^{26 27 29}
Cost of hospitalisation NYHA class I	\$2,957.08			
Cost of hospitalisation NYHA class II	\$4,435.63			
Cost of hospitalisation NYHA class III	\$4,435.63			
Cost of hospitalisation NYHA class IV	\$5,914.17			
Total cost of NYHA class I with hospitalisation	\$3,141.60			
Total cost of NYHA class II with hospitalisation	\$4,639.95			
Total cost of NYHA class III with hospitalisation	\$4,684.53			
Total cost of NYHA class IV with hospitalisation	\$6,176.17			
Cost of NYHA class I no hospitalisation	\$130.30			
Cost of NYHA class II no hospitalisation	\$150.11			
Cost of NYHA class III no hospitalisation	\$194.69			
Cost of NYHA class IV no hospitalisation	\$207.79			
Mortality				
Standardised Death Rate	6.0 per 1000	n/a	n/a	³⁰
Excess Mortality			Beta	¹⁹
probability of excess mortality given hospitalisation class II	0.01087776	Alpha 0.35916667	Beta 2.55750000	

probability of excess mortality given no hospitalisation class II	0.002620782	Alpha 0.43166667	Beta 13.485000	
probability of excess mortality given hospitalisation class III	0.01791369	Alpha 0.79666667	Beta 3.28666667	
probability of excess mortality given no hospitalisation class III	0.00674466	Alpha 0.72833333	Beta 8.60500000	
probability of excess mortality given hospitalisation class IV	0.05333974	Alpha 0.96416667	Beta 1.03583333	
probability of excess mortality given no hospitalisation class IV	0.00719464	Alpha 0.16583333	Beta 1.83416667	
Relative Risk of Mortality with Hawthorn Extract	0.90336300	0.09507420	Lognormal	²⁸
Utility			Beta	¹⁷
Utility of NYHA class I no hospitalisation	0.815	Alpha 395.88	Beta 89.86	
Utility of NYHA class II no hospitalisation	0.72	Alpha 661.95	Beta 257.42	
Utility of NYHA class III no hospitalisation	0.59	Alpha 359.8075	Beta 250.0357	
Utility of NYHA class IV no hospitalisation	0.508	Alpha 51.77	Beta 50.1394	

Probabilistic Sensitivity Analysis

Uncertainty is addressed in the model using probabilistic sensitivity analysis.

Statistical distributions were assigned to key model parameters to examine second-order uncertainty in the estimation of the parameter. Uncertainty was propagated through the model using Monte Carlo simulation, drawing parameter values at random 1000 times from the particular distributions. This generates a joint density of cost and QALY outcomes that summaries uncertainties in all model parameters.

Net Monetary Benefit

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3 The incremental net monetary benefit was calculated. The difference between the
4 average net benefit of the standard treatment and the average net benefit of the
5 standard treatment with hawthorn as an adjunct is equal to the incremental net benefit.
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7 The net benefit for each treatment is the increase in effectiveness multiplied by the
8 amount the decision maker is willing to pay per QALY (\$40,000), less the increase in
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10 cost.
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13 14 15 **The Expected Value of Perfect Information/ Expected Value of Partial Perfect** 16 **Information (EVPI/ EVPPI)** 17

18 The results of the modeling will indicate whether, based on the currently available
19 information, the new treatment should be recommended. This decision is always
20 associated with a level of uncertainty, which raises the question of whether it is
21 appropriate to conduct further research to better examine the potential value of the
22 new treatment, and whether we can identify where this research needs to be directed.
23 EVPI and EVPPI analysis have been used to address these questions.
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29 EVPI analysis is a combination of the cost of making the wrong decision in terms of
30 forgone health benefit and wasted resources, and the probability of making a wrong
31 decision. This equates to the expected cost of uncertainty. With all uncertainty
32 removed there would be economic savings from making the best decision and EVPI is
33 a monetary value of these savings. EVPI provides an upper bound for spending on
34 further research that reduces uncertainty in the decision. EVPPI follows the same
35 principles, but examines individual parameters³¹.
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43 For the model it has been assumed the life of technology is 10 years and the number
44 of eligible patients per annum has been estimated at 30, 000. This estimate is derived
45 from the estimate of 30, 000 new cases of chronic heart failure per annum.
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49 **RESULTS**

50 For the standard treatment and standard treatment with hawthorn extract as an adjunct
51 the total cost per patient was \$4,887.82 and \$6754.59 QALYs were 2.40 and 2.42
52 respectively. This was an incremental cost of \$1866.78 and 0.02 QALYs, and the
53 incremental cost-effectiveness ratio was \$85,160.33 per QALY. A Cost-
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3 Effectiveness Plane shows the joint density of cost and QALY outcomes from the
4 Monte Carlo simulations (See Appendix 2). The variation in the model parameters
5 can be seen in a series of histograms for each of the probabilistic parameters (See
6 Appendix 3).
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10 11 **Cost-Effectiveness Acceptability Curve (CEAC)**

12 Figure 2 shows the uncertainty around this estimate as a cost-effectiveness
13 acceptability curve (CEAC). At a willingness to pay threshold of \$40,000, the new
14 treatment has a 0.29 probability of being cost-effective. The probability of being cost
15 effective rises as the willingness to pay threshold rises, for a threshold between
16 \$500,000 and \$1,000,000 the probability is 0.48.
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22 **Net Monetary Benefit (NMB)**

23 For a threshold of \$40,000, the average incremental NMB is -\$1791.64, the average
24 NMB for the standard treatment is \$92,067.49, and for the new treatment \$90,275.84.
25 The new intervention has a negative incremental net benefit, and would not offer
26 good value for money for a decision maker.
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32 **Expected Value of Perfect Information (EVPI)**

33 The population EVPI has been plotted in Figure 3 for a cost-effectiveness threshold
34 between \$0 and \$200, 000 per QALY. The threshold was continued in the analysis up
35 to a threshold of \$500,000 per QALY, however this did not alter the slope of the
36 curve, so the results up to \$200, 000 have been shown.
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42 If the population EVPI represented in Figure 3 exceeds the expected costs of
43 additional research, then it is potentially cost-effective to conduct further research.
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47 At a threshold of \$40,000 additional research is potentially cost-effective if research is
48 not proposed to cost more than \$325 million.
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52 If we proposed additional research would cost \$100 million, it can be seen from
53 Figure 3 that this research would be potentially cost-effective at a threshold of just
54 under \$16,000. Even at a threshold of \$0 per QALY research would potentially be
55 cost-effective as long as the cost of research did not exceed \$15 million.
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The EVPI has indicated further research is potentially cost-effective. The Expected Value of Partial Perfect Information (EVPPPI) was examined to establish where further research would be of most benefit.

The Expected Value of Partial Perfect Information (EVPPPI)

The EVPPPI was examined for six parameters/ groups of parameters, Transitions, Average Length of stay, Excess Mortality (cardiovascular mortality), Relative Risk of Hawthorn, Utilities, and the Relative Risk of Hospitalisation.

The results of the EVPPPI analysis can be seen in Figure 4 (and Table 3). From both the table and figure it can be seen that all parameters and parameter groups have significant EVPPPI, but the impact varies. Utilities (\$439,471,050.98) has the highest EVPPPI, and is therefore the most important target parameter/ parameter group for further research.

Table 3. Partial EVPI Values for Parameters/ Parameter Groups

Parameters	Partial EVPI
Transitions	\$7,153,571.92
Average Length of stay	\$96,900,062.41
Excess Mortality	\$105,833,952.26
Relative Risk Hawthorn	\$86,323,972.20
Utilities	\$439,471,050.98
Relative Risk Hospitalisation	\$56,991,399.70

DISCUSSION

In this modelling study we examined the cost-effectiveness of hawthorn extract in addition to standard treatment for heart failure in Australia. This treatment is not considered cost-effective given the current evidence. This is the first known attempt to examine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment of chronic heart failure in Australia.

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3 EVPI analysis indicated that further research was likely to be of benefit, and EVPPI
4 analysis indicated that research ideally should be targeted toward Utilities. The
5 potential costs of further research and the particular type or types that may be required
6 are of crucial importance to the final decision. Further research to examine Utilities
7 will likely rely on primary data from randomized controlled trials such as the
8 Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival
9 Study (EPHESUS) and the Study of the Effects of Nebivolol Intervention on
10 Outcomes and Rehospitalisation in Seniors with Heart Failure Study (SENIORS)^{17 32}.
11 Alternatively such research would require the initiation of novel research with utilities
12 as a main outcome. This is costly research and this would certainly need to be
13 estimated before any research was undertaken.
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23 A limitation of this study was the relatively sparse data available for the Australian
24 context. There is scarce data on the incidence and prevalence of heart failure.
25 Estimates rely on information from a small number of large-scale population studies
26 conducted in the United States and Europe¹. The study of mortality in Australia is
27 complex, heart failure is considered a 'mode of death' not a 'cause of death'. Studies
28 examining mortality in terms of the underlying cause of death risk underestimating
29 mortality with condition such as heart failure. Mortality statistics are complicated by
30 multiple co-morbidities, which make the underlying cause of death difficult to
31 identify. Lack of consensus about the diagnosis of heart failure also complicates
32 recording of the cause of death, indeed complicating any examination of heart failure.
33 It is difficult to isolate costs for heart failure. Heart failure is grouped by the
34 Australian Institute of Health and Welfare as an 'other cardiovascular disease'. The
35 exact contribution of heart failure to the burden of cardiovascular disease is at best an
36 estimate.
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48 Another limitation was the availability of evidence of the effectiveness of hawthorn
49 extract. There are numerous studies supporting its use, however, very few studies that
50 examine final outcomes such as hospitalisation and mortality. Previously conducted
51 studies focus on reported outcomes including maximal workload, exercise tolerance,
52 pressure-heart rate product, 6-min walk test, and left-ventricular ejection fraction.
53 There are suggestions in the literature that the use of hawthorn extract can actually
54 decrease the use of standard pharmacological therapy and alter the progression of
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3 heart failure, but little rigorous evidence to support this ¹⁰. If such evidence was
4 available this would change the costs and benefits of hawthorn extract, and potentially
5 change the cost-effectiveness of hawthorn extract as an adjunct to standard
6 pharmacological treatment.
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11 Should further evidence become available, the model can easily be updated and the
12 results re-examined.
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14 15 **CONCLUSION**

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17 Our analysis indicates that based on currently available evidence, hawthorn extract is
18 not cost-effective in addition to standard pharmacological treatment for chronic heart
19 failure in Australia. EVPI and EVPPi analysis indicates that further research is
20 warranted, particularly in the area of utilities, pending an assessment of the estimated
21 costs of such research.
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29 public, commercial or not-for-profit sectors.
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33 **Competing Interests** None.
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37 **Contributors** EF carried out the data collection and economic analysis. EF was
38 responsible for the original draft. All authors contributed equally to all other aspects
39 including drafting and revising, and approved the final manuscript.
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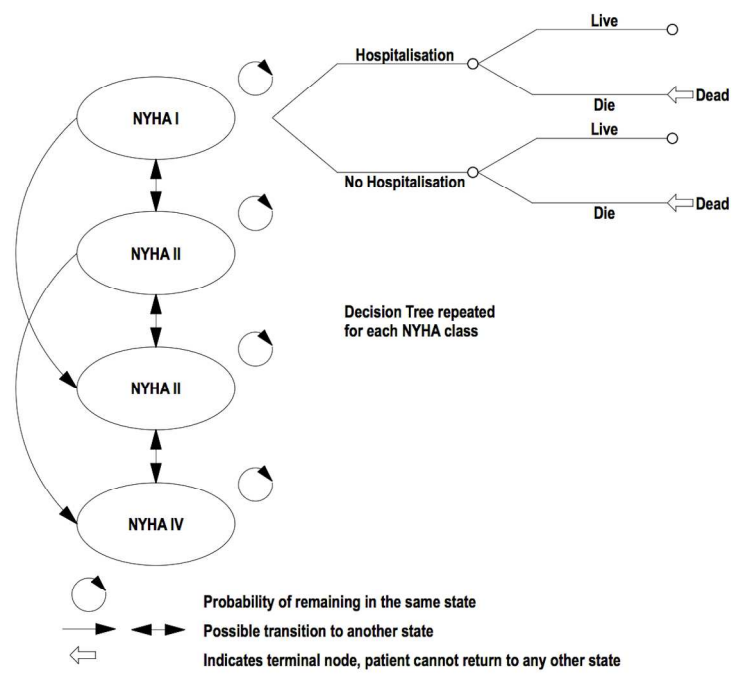


Figure 1. Markov model and decision tree showing transitions between potential health states for chronic heart failure.

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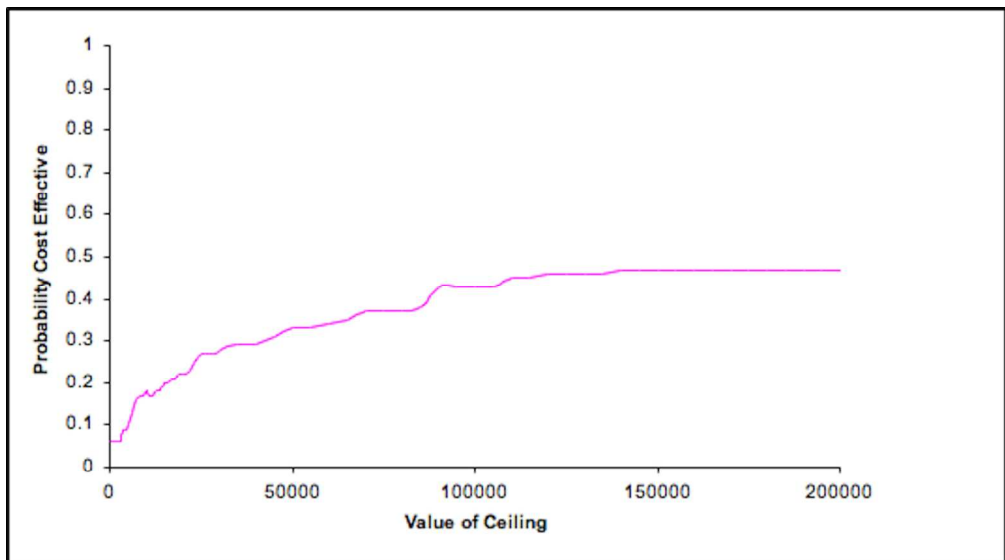


Figure 1. Cost-Effectiveness Acceptability Curve for the New Intervention
162x90mm (300 x 300 DPI)

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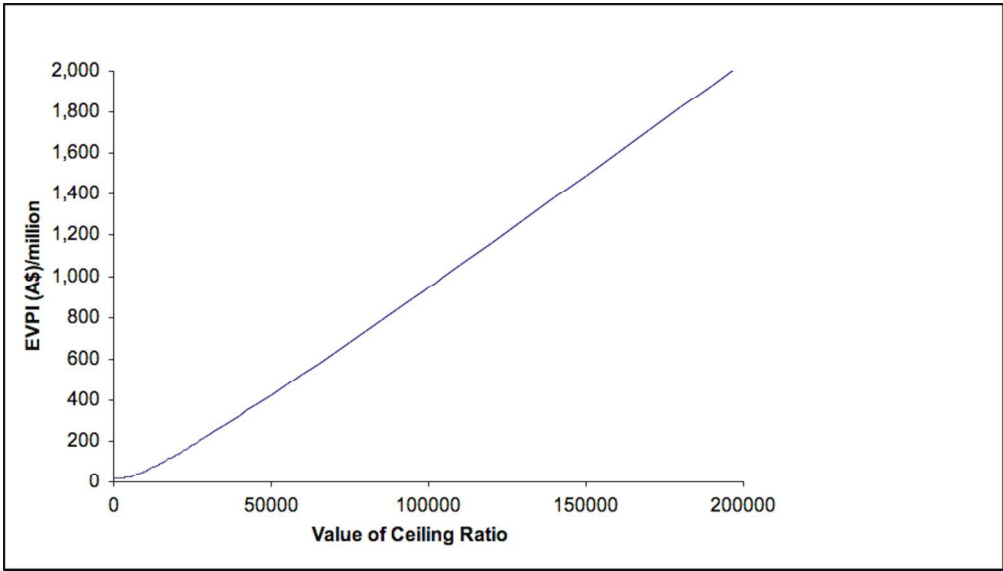


Figure 1. Population Expected Value of Perfect Information (EVPI) Curve
Note. The EVPI values have been divided by 1 million to make figure easier to read.

161x91mm (300 x 300 DPI)

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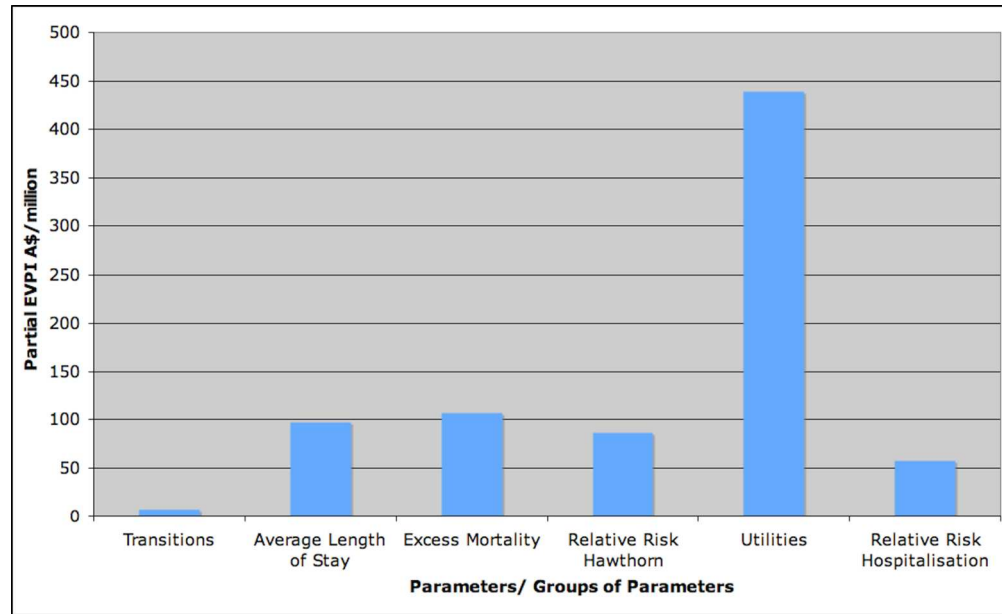


Figure 1. Expected Value of Perfect Information for Parameters

Note. The Partial EVPI values have been divided by 1 million to make figure easier to read.

149x91mm (300 x 300 DPI)

Appendix 1. Calculation of the Transition Probabilities for the Markov Model

<i>transition matrix</i>	NYHA I	NYHA II	NYHA III	NYHA IV	Check
NYHA I	0.977	0.019	0.004	0.000	1.000
NYHA II	0.008	0.981	0.010	0.001	1.000
NYHA III	0.000	0.034	0.960	0.006	1.000
NYHA IV	0.000	0.000	0.055	0.945	1.000
					0.000

Probabilistic version

1. Observed counts

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	59.597	1.159	0.244	0	61
NYHA II	9.6	1177.2	12	1.2	1200
NYHA III	0	28.016	791.04	4.944	824
NYHA IV	0	0	2.365	40.635	43
					2128

2. Estimated probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.977	0.019	0.004	0	1
NYHA II	0.008	0.981	0.010	0.001	1
NYHA III	0	0.034	0.960	0.006	1
NYHA IV	0	0	0.055	0.945	1

3. Random number table

	NYHA I	NYHA II	NYHA III	NYHA IV
NYHA I	0.24	0.44	0.87	0.66
NYHA II	0.91	0.62	0.99	0.21
NYHA III	0.72	0.91	0.27	0.46
NYHA IV	0.26	0.18	0.92	0.46

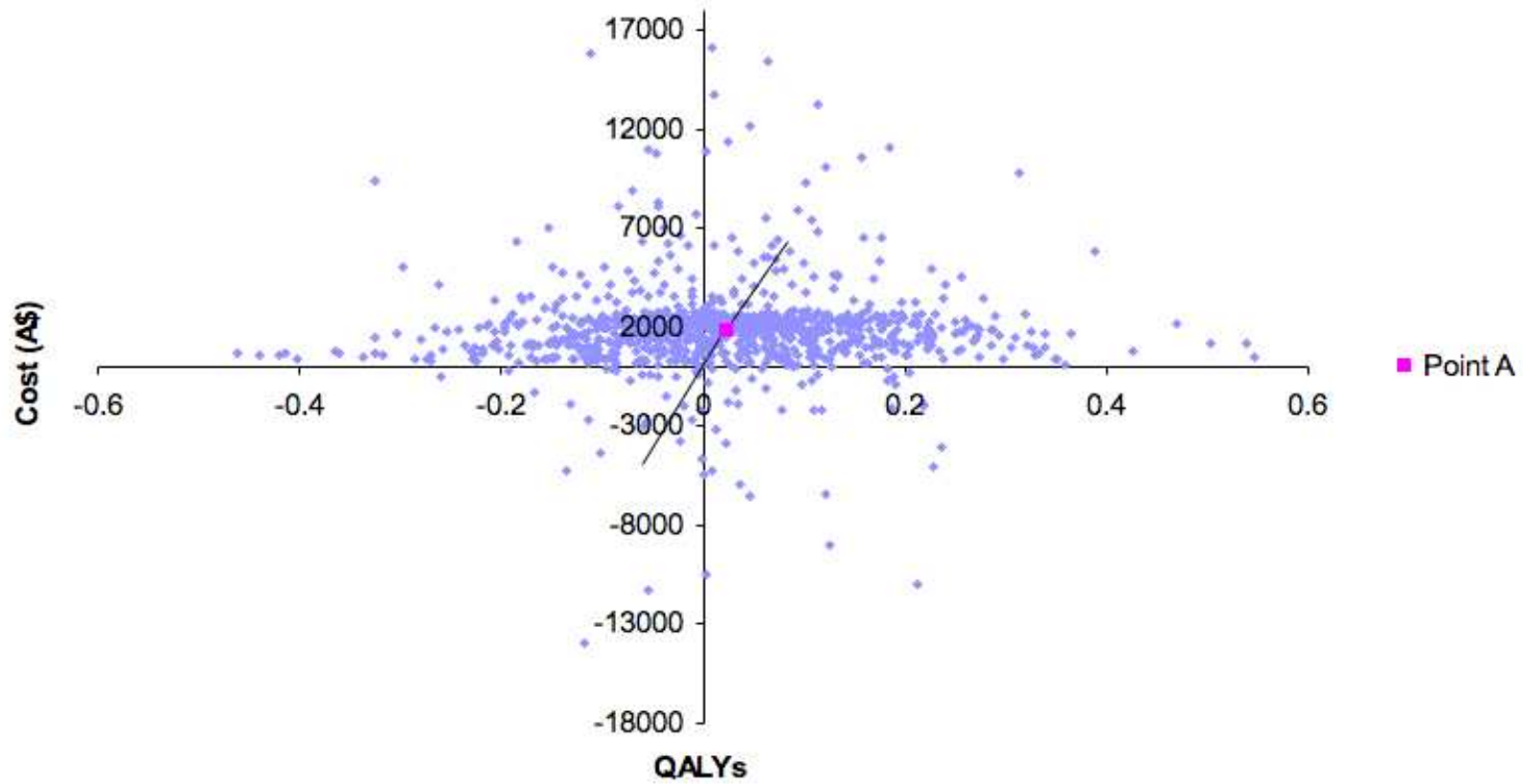
4. Cumulative gamma/normal functions

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	53.905	0.730	0.568	0	55
NYHA II	13.845	1188.106	20.983	0.342	1223
NYHA III	0	35.377	773.741	4.390	814
NYHA IV	0	0	4.735	39.593	44

5. Random dirichlet probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.976	0.013	0.010	0	1.00
NYHA II	0.011	0.971	0.017	0.000	1.00
NYHA III	0	0.043	0.951	0.005	1.00
NYHA IV	0	0	0.107	0.893	1.00

Appendix 2. Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model



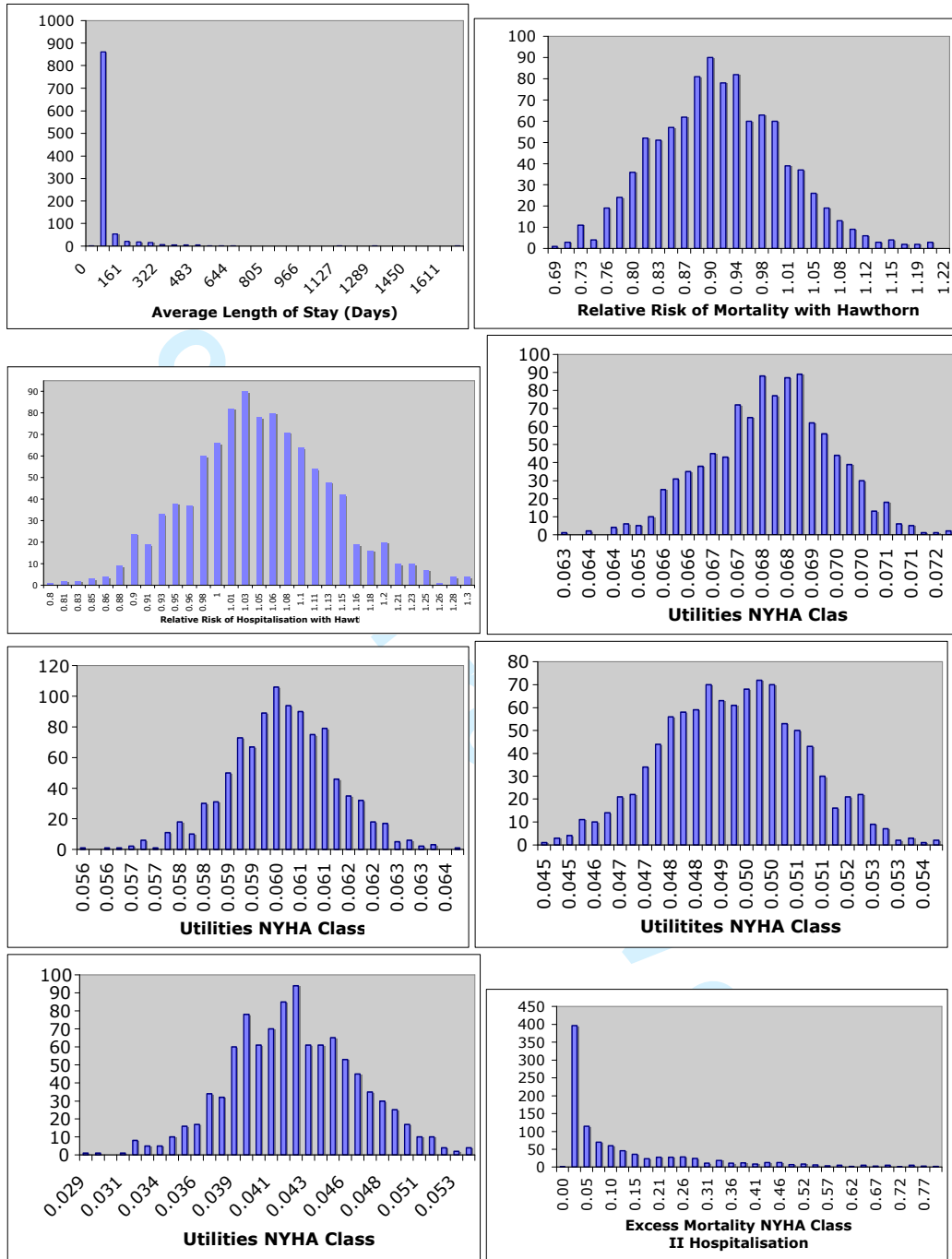
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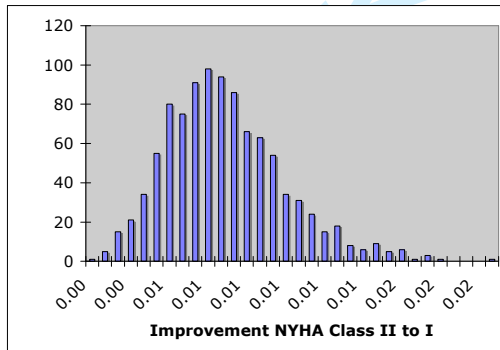
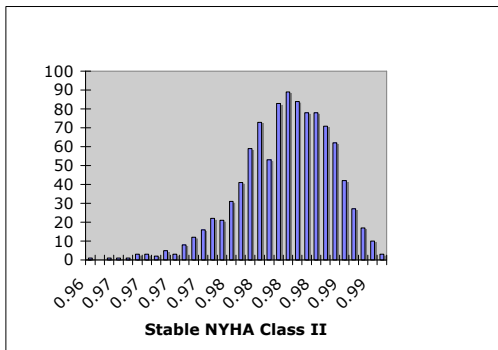
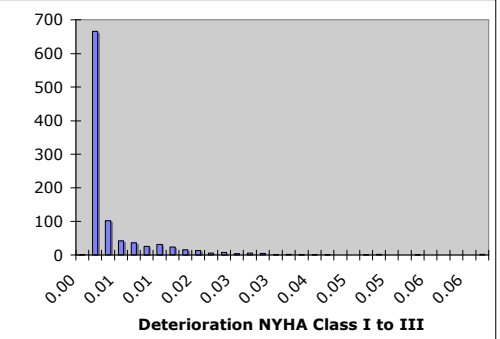
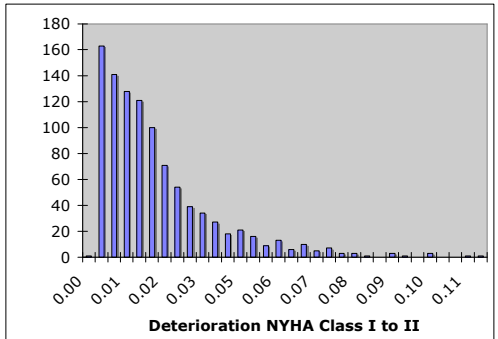
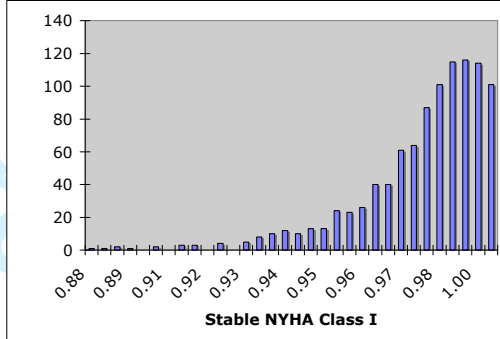
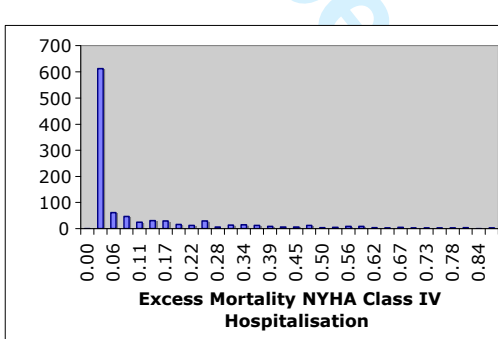
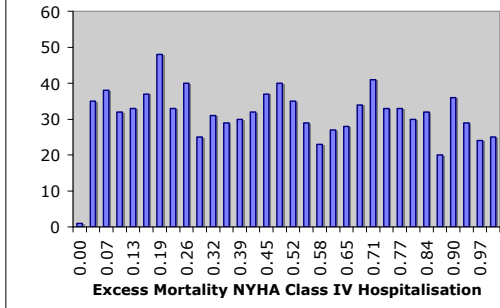
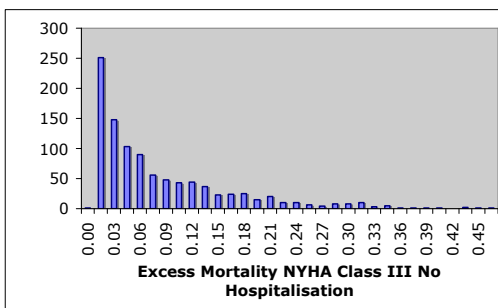
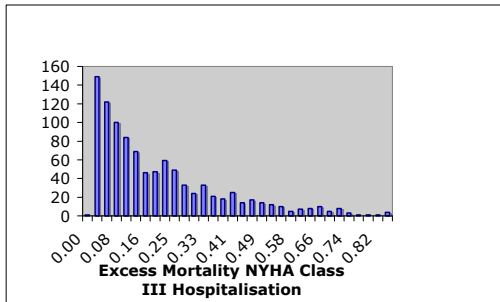
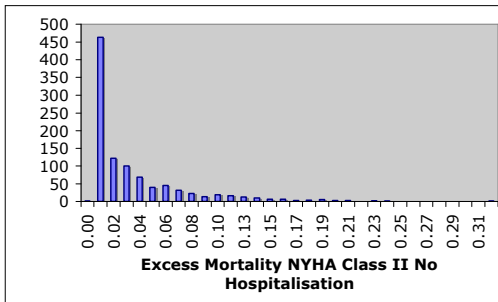
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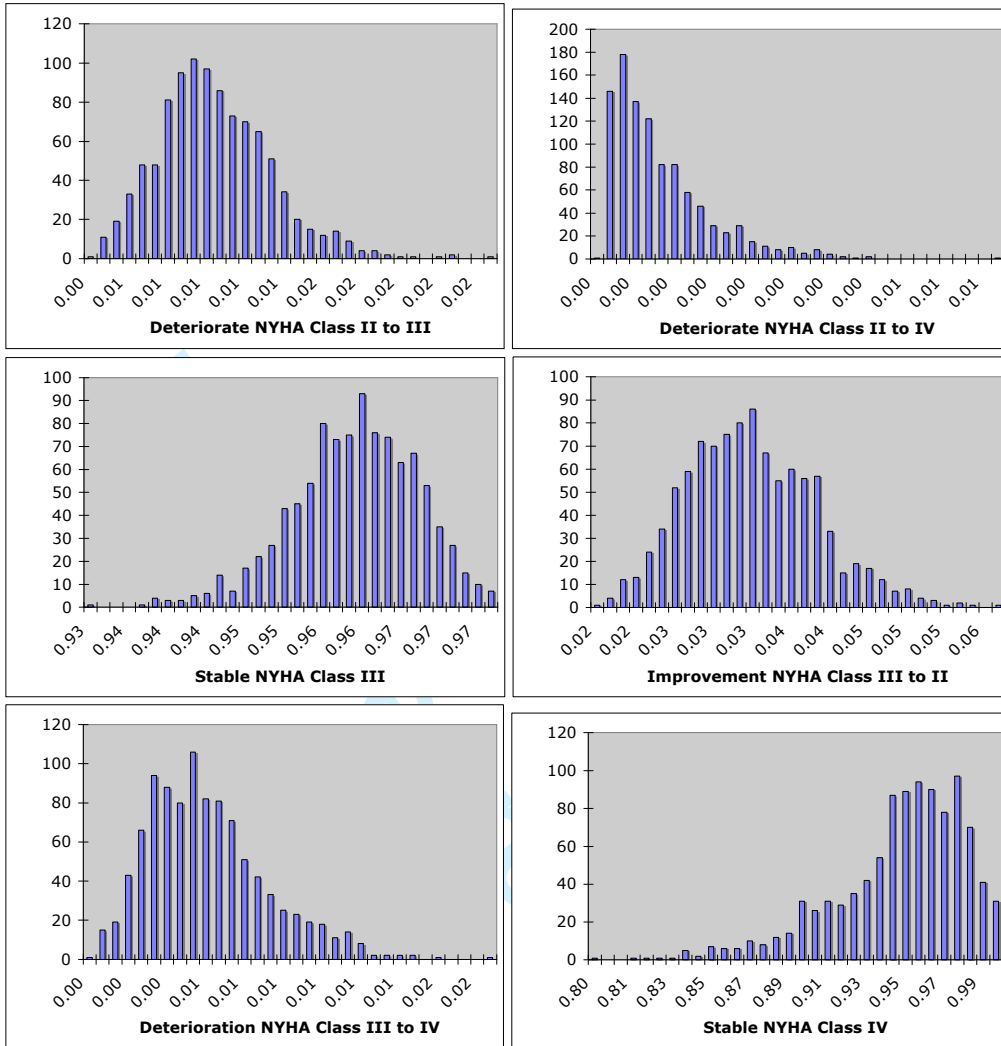
Appendix 3. Histograms of Individual Parameters



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EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction; Methods	
(6) The form of economic evaluation used is stated	Introduction; Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	Presented in table form and in written form
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from multiple sources
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	Meta-analysis was not used
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for	NA	As the study is

inflation or currency conversion are given		looking for relative cost, then inflation would be comparable between the different treatments
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods-Model construction; Discussion	Based on current cost estimates
(23) The discount rate(s) is stated	Methods	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	
(28) The choice of variables for sensitivity analysis is justified	Methods	
(29) The ranges over which the variables are varied are stated	Methods, Table 2	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	Results	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results Discussion; Conclusion	
(34) Conclusions follow from the data reported	Discussion; Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion; Conclusion	



Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Secondary Subject Heading:	Complementary medicine, Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, Heart failure < CARDIOLOGY, COMPLEMENTARY MEDICINE

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Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Keywords: complementary therapies, heart failure, cost-benefit analysis, crataegus extract

Word count: 4546

ABSTRACT

Objective

An economic model was developed to evaluate the cost-effectiveness of hawthorn extract as an adjunctive treatment for heart failure in Australia.

Methods

A Markov model of chronic heart failure was developed to compare the costs and outcomes of standard treatment and standard treatment with hawthorn extract using the New York Heart Association (NYHA) classification system. Health states were defined by the New York Heart Association (NYHA) classification system and death Classes I to IV make up the four health states. For any given cycle patients could may remain in the same NYHA class over time, experience an improvement of symptoms and an improvement or deterioration in NYHA class, be hospitalised or die or a deterioration and worsening of NYHA class. Each NYHA class has its own decision tree. Within the decision tree some patients have been admitted to hospital and some have not, some will then die, and some will survive. Model inputs were derived from the published medical literature, and the output was Quality Adjusted Life Years (QALYs). Probabilistic Sensitivity Analysis was conducted. The Expected Value of Perfect Information (EVPI) and the Expected Value of Partial Perfect Information (EVPPPI) were conducted to establish the value of further research and the ideal target for such research.

Results

Hawthorn extract ~~The new treatment~~ increased costs by \$1866.78 and resulted in a gain of 0.02 QALYs. The incremental cost-effectiveness ratio was \$85,160.33 per QALY. The CEAC indicated at a threshold of \$40,000 the new treatment had a 0.29 probability of being cost-effective. The average incremental NMB was -\$1791.64, the average NMB for the standard treatment was \$92,067.49, and for hawthorn extract ~~the new treatment~~ \$90,275.84. Additional research is potentially cost-effective if research is not proposed to cost more than \$325 million. Utilities is the most important target parameter group for further research.

Conclusions

Hawthorn extract is not currently considered to be cost-effective in as an adjunctive treatment for heart failure in Australia. Further research in the area of utilities is warranted.

INTRODUCTION

Heart failure is a major public health concern for all Western countries ¹. In the United States and Europe it is the most common principal diagnosis for adults admitted to hospital aged 65 years and over. In the United States around 2% of the population have heart failure (approximately 5 million people), and each year there are 500, 000 new cases diagnosed ². The estimated prevalence in Sweden is 1.5-2%, approximately 135, 000 to 180, 000 people ³.

Australian data regarding the public health significance and epidemiology of heart failure is currently limited. Estimates rely on information from large-scale population studies conducted in the United States and Europe ¹. It is estimated there are approximately 300,000 Australians living with chronic heart failure, and approximately 30,000 new cases diagnosed each year, with incidence rates and prevalence rising significantly with age ^{4,5}. In Australia, chronic cardiovascular diseases are associated with health care costs of over five billion dollars, and estimates put the cost of heart failure at around one billion dollars ⁶. The mortality, morbidity and health care costs of heart failure are therefore significant ⁴.

Heart failure is a syndrome with a range of signs and symptoms, diagnosis is based on such signs and symptoms, including dyspnoea and fatigue, and appropriate investigations, such as echocardiogram, which confirm the presence or absence of heart failure and help determine its aetiology ¹.

Current treatment aims to relieve and stabilise symptoms and prolong survival by stopping, stabilizing or reversing the progression of heart failure ⁷. There are a variety of strategies used in Australia, including non-pharmacological management, pharmacological management, lifestyle changes, and the use of supportive devices,

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3 surgery, and palliative care⁶⁸. The pharmacological approach depends on the type of
4 heart failure and extent of the symptoms.
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8 Despite the availability of strategies to treat and manage the chronic disease, the
9 disability and suffering associated with heart failure is devastating⁷. Given this, and
10 the large economic burden, it is reasonable to examine options not currently
11 considered standard therapy. Research examining the use of complementary and
12 alternative medicine, particularly the use of hawthorn extract is showing promising
13 results.
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19 Hawthorn extract is a popular herbal medicine used worldwide, particularly for its
20 cardiovascular properties⁹. Hawthorn extract has positive inotropic, anti-
21 inflammatory and anti-oxidative properties; causes peripheral and coronary
22 vasodilation; and protects against ischaemia induced arrhythmias⁹. A recent
23 systematic review concluded hawthorn extract can provide significant benefits to
24 heart failure patients as an adjunct to conventional treatment and a recent cost-
25 effectiveness study conducted in Germany concluded hawthorn is a cost-effective
26 treatment option especially in the early stages of heart failure¹⁰⁻¹².
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35 Economic evaluation is a structured method for examining the costs and
36 consequences involved with alternative methods of treatments and/or programs, in
37 order to inform which is the best alternative from a particular viewpoint¹³. The goal
38 is to improve the use of health care resources and improve patient care¹⁴. When
39 conducted rigorously, such formal analysis allows recommendation to be made with
40 transparency regarding the methods, data sources and assumptions¹³. This further
41 allows the process to be replicated, reviewed and even challenged.
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48 Models allow complex situations to be organised into a single coherent form that can
49 be used to make decisions based on comprehensive consideration of the alternative
50 interventions by capturing the essential relationships between the factors included in
51 the model and outcomes^{15 16}. Markov models define diseases using clinically
52 relevant and economically important health states, between which patients move
53 based on the natural history of the disease, and to which cost and effectiveness
54 outcomes are ascribed¹⁶.
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There are numerous examples of cost-effectiveness modeling in heart failure that examine conventional medicine. Pharmacological, behavioural and surgical interventions have all been investigated and many found to be cost-effective^{17 18}. Pharmacological agents that have cost-effectiveness evidence include angiotensin converting enzyme inhibitors (ACEIs), digoxin, and beta-blockers such as carvedilol and nebivolol. Multidisciplinary heart failure management, in the form of a team, usually made up of a nurse co-ordinator and support from medical staff and allied health including dieticians and physiotherapy, has also shown to be cost-effective through reductions in hospitalisation and length of stay^{17 19}. Surgical options including heart transplant, through intensive education and maximal medical therapy, have demonstrated a range of cost-effectiveness values. Cardiac resynchronisation therapy with or without an implantable cardioverter-defibrillator, has shown to be cost-effective from a healthcare perspective^{17 20}. Most of the recent evidence involves Markov modeling. The models in any area of health vary in terms of the Markov states chosen, for example when representing the severity of heart failure, hospitalisations and NYHA classes of heart failure are both utilised. It is difficult to summarise the multitude of evidence and compare models as different model structures and methods are used, which potentially leads to different outcomes²¹.

The increasing number of published health economic evaluations is not yet reflected in CAM^{22 23 24}. A systematic review examined whether CAM demonstrated cost-effectiveness through economic evaluations²⁵. This was based on 56 economic evaluations, 39 full economic evaluations and 14 of appropriate quality for further assessment. There was good evidence for the cost-effectiveness of several therapies in comparison to usual care, acupuncture for migraine, manual therapy for neck pain, spa therapy for Parkinson's, self-administered stress management for cancer patients undergoing chemotherapy, pre- and post-operative oral nutritional supplementation for lower gastrointestinal tract surgery, biofeedback for patients with "functional" disorders (eg, irritable bowel syndrome), and guided imagery, relaxation therapy, and a potassium rich diet for cardiac patients. There were a number of therapies that were cost-effective compared to usual care, and evidence to suggest CAM could be cost effective as a complement to usual care²⁵.

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It has been several years since this review, but a literature search suggests the situation today is similar. It is possible to identify economic evaluation of CAM, however there are few full economic evaluations. An example of such an evaluation, is a study examining therapeutic massage, exercise, and lessons in the Alexander technique for treating persistent back pain²⁶. Costs included those to the National Health Service (NHS) and to participants. Outcome measures included the Roland-Morris disability score, days in pain, and quality adjusted life years (QALYs). Results included incremental cost effectiveness ratios and cost effectiveness acceptability curves. Massage, lessons in the Alexander technique, and an exercise prescription all provided benefits to patients over a 12-month period. A series of six lessons in the Alexander technique combined with an exercise prescription was the most effective and cost effective option for the NHS²⁶.

Some economic evaluations of CAM have incorporated decision modeling. A recent study examined the cost-effectiveness of adding acupuncture to usual care for chronic low back pain, from a societal perspective, using a Markov model²⁷. This led to a gain of 0.13 QALYs at an incremental cost of KRW 459,637, resulting in an incremental cost per QALY gained of KRW 3,421,394, well below the recommended threshold based on the per capita gross domestic product in Korea (KRW 20,000,000). The probability of collaborative treatment being cost-effective was 72.3%. The EVPI analysis suggested further research to reduce the uncertainty around the cost-effectiveness of collaborative treatment was of reasonable value. The authors concluded acupuncture plus usual care was more cost-effective than usual care for these patients²⁷.

The aim of this study was the construction and application of an economic decision model to evaluate hawthorn treatment as an adjunct to recommended pharmacological treatment versus recommended pharmacological management for chronic heart failure in Australia. The analysis has been conducted using a health sector perspective.

METHODS

Model Description

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3 A four state Markov model of chronic heart failure was developed based on the New
4 York Heart Association (NYHA) classification system using Microsoft Excel® (see
5 Figure 1). Classes I to IV make up four discrete health states included in the model
6 (See Table 1 for a description of the NYHA classes). A decision tree completes the
7 model. Each NYHA class has its own decision tree. Within the decision tree
8 patients could be hospitalised for worsening heart failure. Patients also either
9 survived or died.
10

16 **Progression through the model**

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18 A simulated cohort of 1000 patients aged 60 entered the model with NYHA class II
19 heart failure and progressed through the model. Patients progress through the model
20 in one month cycles for a duration of 5 years. After one month, patients either
21 remained in NYHA class II or improved to NYHA class I or deteriorated.
22 In turn, for each class of heart failure patients were either hospitalised or not
23 hospitalised for worsening heart failure. Patients who were hospitalised or not
24 hospitalised either survived or died. Death was a possibility from any class of heart
25 failure. The patients accrued costs and benefits of treatment in each of the states for
26 each cycle.
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35 Per patient costs were required for each NYHA class. Costs were assumed to
36 be the same for standard treatment and standard treatment with hawthorn extract,
37 except for the additional cost of hawthorn extract. Patient health was considered as a
38 single index utility on a zero to one scale, where 0 represents death and 1 represents
39 perfect health. This allows the calculation of Quality Adjusted Life Years (QALYs)
40 when combined with the mortality data and the calculation of cost per QALY ratios.
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46 Two cohorts were modeled, one receiving standard pharmacological treatment and the
47 other receiving standard pharmacological treatment with hawthorn extract as an
48 adjunct. The two cohorts will progress through the model in slightly different ways
49 and as such there will be a difference in the accumulation of costs and QALYS. It is
50 the differences in costs and QALYs that will determine the cost-effectiveness of
51 hawthorn extract in addition to standard pharmacological treatment.
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A discount rate of 3% per year was applied to the costs and benefits. This rate is a standard choice in the literature.

Table 1. NYHA grading of symptoms in chronic heart failure.

NYHA Class	Description
Class I	No symptoms and limitations in ordinary physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms such as fatigue, shortness of breath, and angina.
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
Class IV	Severely limited. Experiences symptoms even at rest.

Model Construction

Disease Progression

Transition probabilities for movement between NYHA classes of heart failure were estimated from the published literature detailing the large scale international Study of the Effects of Nebivolol Intervention on Outcomes and Re-hospitalisation in Seniors with Heart Failure (SENIORS) and personal correspondence with authors^{18,28}. A thorough literature search was conducted to identify disease progression data for each NYHA class. Data was considered relevant if transition probabilities were provided for each NYHA class. The databases searched were Medline, CINAHL and the Cochrane Library. Search terms used included 'New York Heart Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'decision model', 'chronic heart failure', and 'heart failure'.

The search yielded a limited number of studies, of which only the above study was considered suitable for inclusion.

Disease progression between the Markov states was assumed to be the same for standard treatment and for standard treatment with hawthorn extract, as we were unable to identify reliable data to indicate that hawthorn extract altered progression through the classes of heart failure. Transition probabilities were fixed over time. We have incorporated a difference in mortality and a difference in the hospitalisation rate between the standard treatment and the standard treatment with hawthorn extract as an adjunct, which in turn will impact on the cost and QALY outcomes.

Data Sources

Mortality

Baseline mortality was derived from Australian Bureau of Statistics general population mortality data.

Mortality data was of interest if it was provided for each NYHA class and if it concerned the excess mortality from heart failure and/or cardiovascular causes. The databases searched were Medline, CINAHL and the Cochrane Library. Search terms used included 'New York Heart Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'decision model', 'chronic heart failure', 'heart failure', 'mortality'.

The mortality rate for cardiovascular causes was derived from the published literature detailing one-year mortality among unselected patients with NYHA class II-IV heart failure in Switzerland²⁹. The mortality rate increased with progression from NYHA class I to NYHA class IV, and varied depending on whether the patient was hospitalised or not. A thorough search of the literature was made to identify data for each NYHA class individually, nothing was identified and the above study was the closest to ideal. Hospitalisation was considered a major factor in cost estimation, so data broken down by hospitalisation status was considered to represent the population of heart failure patients well. Also, unselected patients were considered to represent the patient cohort more accurately than studies that focused on hospitalised patients only. As data for NYHA class I was not included, an assumption was made that mortality for NYHA class I was the same as the general population mortality.

Health Status

Estimates of health status were derived from the same source as the transition probabilities^{18 20}. Data concerning utilities for heart failure is extremely limited, a study was identified that had specifically had developed utilities for heart failure in terms of both hospitalisation and NYHA class. However, we were unable to obtain the required data despite personal correspondence with the authors. The estimated health status used was considered the next best data source.

Health status was assumed to be the same for standard treatment and standard treatment with hawthorn extract. Hospitalisation was assumed to result in a health

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3 state lower than non-hospitalisation and a -0.1 disutility was applied to hospitalisation
4 to reflect this.
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8 Effect of Hawthorn

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10 A literature search identified the existing research for the use of hawthorn extract in
11 the treatment of heart failure. The search included electronic databases (Medline,
12 PubMed, CAM on PubMed, AMED, Econolit, DynaMed, CINAHL, Cochrane
13 Database of Systematic Reviews), hand searches of the literature, including hard
14 copies of journals, and a search of the reference lists of the articles and publications
15 found through electronic and hand searches. Personal communication with authors
16 and experts including manufacturers and researchers in the field was also necessary to
17 identify other sources of information and research that may not have been found using
18 any other methods.

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20 A wide range of search terms was used including: 'heart failure', 'chronic heart
21 failure', 'systolic heart failure', and 'congestive heart failure', 'hawthorn',
22 'Crataegus', 'Crataegus oxyacantha', 'Crataegus monogyna', 'whitethorn',
23 weissdorn', 'Crataegus laevigata', 'WS 1442', 'LI 132', 'complementary',
24 'alternative', 'medicine' and 'therapy'. There were several studies written in German,
25 these were translated into English and then examined.

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28 Publicly accessible trials registers were also searched. The Australian New Zealand
29 Clinical Trials Registry (ANZCTR) was searched, no studies were identified. The
30 World Health Organisation International Clinical Trials Registry Platform was
31 searched, no new relevant trials were identified. The search terms used were:
32 'hawthorn extract', 'hawthorn', 'crataegus', 'WS1442', 'whitehorn', 'heart failure'.

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35 There were no planned exclusion criteria at this stage for the patient population as any
36 of the studies found have the potential to contribute valuable information to inform
37 the model development.

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52 The relative risk of mortality and relative risk of hospitalisation with hawthorn extract
53 was derived from the Survival and Prognosis: Investigation of Crataegus Extract WS
54 1442 in congestive heart failure (SPICE) trial, a large scale, international, randomised,
55 placebo-controlled, double-blind study designed to investigate the influence of
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3 hawthorn extract on mortality of patients with congestive heart failure NYHA class II
4 and III with at least moderately impaired left ventricular function³⁰. To date there
5 have only been two studies to examine the effect of hawthorn extract on heart failure
6 progression in terms of mortality and hospitalisation. Most studies have focused on
7 symptoms and exercise capability. SPICE enrolled ~~2681~~~~nearly 3000~~ patients, and the
8 Hawthorn Extract Randomised Blinded Chronic Heart Failure (HERB CHF) trial
9 enrolled 120 patients^{31 32}. Meta-analysis was not considered appropriate, therefore
10 the data from SPICE was incorporated into the model.
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17 18 Costs

19 No Australian data was available to estimate the hospitalisation rate and number of
20 hospitalisations, this information was derived from a United States study³³.
21 The estimated length of stay in hospital data was obtained from Victorian Department
22 of Health for 2010-2011, it was unavailable for each NYHA class, so it was assumed
23 to be the same for all classes³⁴.
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28 The cost of a hospital admission per day was derived from the Queensland
29 Government/ Queensland Health Casemix Funding Model 2008-2009 Component
30 Prices Summary (\$3,775 per day)^{35 26}.
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33 Outpatient costs included General Practitioner (GP) visits, pathology (urea, creatinine,
34 electrolytes), echocardiograms, and specialist visits. Estimates of the number of GP
35 and specialist visits came from a combination of Australian sources and overseas
36 studies due to the difficulty in finding complete Australian estimates. It was
37 estimated that NYHA class I had 6 GP visits per year, and the remaining NYHA
38 classes had 12 visits per year at \$34.30 per visit. Pathology was assumed to be
39 required every 3 months at a cost of \$17.80. An Echocardiogram was assumed to be
40 performed every two years (\$230.65). A specialist visit was assumed to occur twice
41 per year (\$290 initial visit, \$194 repeat visit). If hospitalized, it was assumed patients
42 had an extra 3 specialist visits and 2 GP visits per year. The costs came directly from
43 the Medicare Benefits Schedule and the Queensland Government/ Queensland Health
44 Casemix Funding Model 2008-2009 Component Prices Summary^{35 36}.
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53 The information for which medications are taken for each NYHA class have been
54 taken from the National Heart Foundation guidelines for the treatment of chronic
55 heart failure in Australia⁵. Information for the optimal dosages prescribed has been
56 taken from the Australian Therapeutic Guidelines. Individual drug pricing was
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obtained from the most recently available online version of the Medicare Benefits Schedule. The initial version of the model has incorporated the assumption that medications are taken in 100% of patients and that dosing is optimal. The model however can be altered to consider different scenarios of medication prescription and consumption.

The dosage was assumed to be 900mg daily, consistent with the dosage used in the two most recent trials of hawthorn extract, the SPICE trial and the HERB-CHF trial³⁰^{32 37}. An online search was conducted for standardised monopreparations of hawthorn leaf with flower available for purchase. [Cardiomax® retails for A\\$25.95.](#)

[The transition parameters are listed in Table 2.](#) The model parameters have been listed in Table 3. [Appendix 1 details the calculation of transition probabilities for the model.](#)

[Table 2. Transition Parameters used in the Decision Model](#)

<i>Transition Matrix</i>	NYHA I	NYHA II	NYHA III	NYHA IV	Distribution
NYHA I	0.977	0.019	0.004	0.000	Dirichlet
NYHA II	0.008	0.981	0.010	0.001	Dirichlet
NYHA III	0.000	0.034	0.960	0.006	Dirichlet
NYHA IV	0.000	0.000	0.055	0.945	Dirichlet

Table 3. Parameters used in the Decision Model

Probabilistic Parameters				
Parameter Description	Baseline Estimate	Variation/ SE (SD)	Distribution	Reference
Hospitalisation				
Length of stay in hospital estimate	4.9 days	Alpha 0.1 Beta 316.81	Gamma	³⁴
Relative Risk of Hospitalisation with Hawthorn Extract	1.03651200	0.080800494	Lognormal	³⁷
Mortality				
Excess Mortality			Beta	²⁹
probability of excess mortality given hospitalisation class II	0.01087776	Alpha 0.35916667	Beta 2.55750000	
probability of excess mortality	0.002620782	Alpha 0.43166667	Beta 13.485000	

given no hospitalisation class II				
probability of excess mortality given hospitalisation class III	0.01791369	Alpha 0.79666667	Beta 3.28666667	
probability of excess mortality given no hospitalisation class III	0.00674466	Alpha 0.72833333	Beta 8.60500000	
probability of excess mortality given hospitalisation class IV	0.05333974	Alpha 0.96416667	Beta 1.03583333	
probability of excess mortality given no hospitalisation class IV	0.00719464	Alpha 0.16583333	Beta 1.83416667	
Relative Risk of Mortality with Hawthorn Extract	0.90336300	0.09507420	Lognormal	³⁷
Utility			Beta	¹⁸
Utility of NYHA class I no hospitalisation	0.815	Alpha 395.88	Beta 89.86	
Utility of NYHA class II no hospitalisation	0.72	Alpha 661.95	Beta 257.42	
Utility of NYHA class III no hospitalisation	0.59	Alpha 359.8075	Beta 250.0357	
Utility of NYHA class IV no hospitalisation	0.508	Alpha 51.77	Beta 50.1394	
Fixed Parameters				
Parameter Description	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
Hospitalisation				³⁵
Probability for hospitalisation	0.01518800	0.02397800	0.02397800	0.15397000
Probability no hospitalisation	0.98481200	0.97602200	0.97602200	0.84603000
Costs				^{35 36 38}
Cost of hospitalisation	\$2,957.08	\$4,435.63	\$4,435.63	\$5,914.17
Total cost for each NYHA class with hospitalisation	\$3,141.60	\$4,639.95	\$4,684.53	\$6,176.17
Cost of each class with no hospitalisation	\$130.30	\$150.11	\$194.69	\$207.79
Mortality				³⁹

Standardised Death Rate	6.0 per 1000	6.0 per 1000	6.0 per 1000	6.0 per 1000
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Probabilistic Sensitivity Analysis

Uncertainty is addressed in the model using probabilistic sensitivity analysis. Statistical distributions were assigned to key model parameters to examine second-order uncertainty in the estimation of the parameter. Uncertainty was propagated through the model using Monte Carlo simulation, drawing parameter values at random 1000 times from the particular distributions. This generates a joint density of cost and QALY outcomes that summarises uncertainty in all model parameters.

Net Monetary Benefit

The incremental net monetary benefit was calculated. The difference between the average net benefit of the standard treatment and the average net benefit of the standard treatment with hawthorn as an adjunct is equal to the incremental net benefit. The net benefit for each treatment is the increase in effectiveness multiplied by the amount the decision maker is willing to pay per QALY (\$40,000), less the increase in cost.

The Expected Value of Perfect Information/ Expected Value of Partial Perfect Information (EVPI/ EVPPI)

The results of the modeling will indicate whether, based on the currently available information, the new treatment should be recommended. This decision is always associated with a level of uncertainty, which raises the question of whether it is appropriate to conduct further research to better examine the potential value of the new treatment, and whether we can identify where this research needs to be directed. EVPI and EVPPI analysis have been used to address these questions.

EVPI analysis is a combination of the cost of making the wrong decision in terms of forgone health benefit and wasted resources, and the probability of making a wrong decision. This equates to the expected cost of uncertainty. With all uncertainty removed there would be economic savings from making the best decision and EVPI is a monetary value of these savings. EVPI provides an upper bound for spending on

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3 further research that reduces uncertainty in the decision. EVPPI follows the same
4 principles, but examines individual parameters⁴⁰.
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8 For the model it has been assumed the life of technology is 10 years and the number
9 of eligible patients per annum has been estimated at 30, 000. This estimate is derived
10 from the estimate of 30, 000 new cases of chronic heart failure per annum.
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13 14 15 **RESULTS**

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17 For the standard treatment and standard treatment with hawthorn extract as an adjunct
18 the total cost per patient was \$4,887.82 and \$6754.59 QALYs were 2.40 and 2.42
19 respectively. This was an incremental cost of \$1866.78 and 0.02 QALYs, and the
20 incremental cost-effectiveness ratio was \$85,160.33 per QALY. A Cost-
21 Effectiveness Plane shows the joint density of cost and QALY outcomes from the
22 Monte Carlo simulations (See Appendix 2). The variation in the model parameters
23 can be seen in a series of histograms for each of the probabilistic parameters (See
24 Appendix 3).
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32 **Cost-Effectiveness Acceptability Curve (CEAC)**

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34 Figure 2 shows the uncertainty around this estimate as a cost-effectiveness
35 acceptability curve (CEAC). At a willingness to pay threshold of \$40,000, the ~~new~~
36 treatment with hawthorn extract has a 0.29 probability of being cost-effective. The
37 probability of being cost effective rises as the willingness to pay threshold rises, for a
38 threshold between \$500,000 and \$1,000,000 the probability is 0.48.
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43 **Net Monetary Benefit (NMB)**

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45 For a threshold of \$40,000, the average incremental NMB is -\$1791.64, the average
46 NMB for the standard treatment is \$92,067.49, and for the standard treatment with
47 hawthorn as an adjunct~~new treatment~~ \$90,275.84. The treatment with hawthorn
48 extract~~new intervention~~ has a negative incremental net benefit, and would not offer
49 good value for money for a decision maker.
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55 **Expected Value of Perfect Information (EVPI)**

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3 The population EVPI has been plotted in Figure 3 for a cost-effectiveness threshold
4 between \$0 and \$200, 000 per QALY. The threshold was continued in the analysis up
5 to a threshold of \$500,000 per QALY, however this did not alter the slope of the
6 curve, so the results up to \$200, 000 have been shown.
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11 If the population EVPI represented in Figure 3 exceeds the expected costs of
12 additional research, then it is potentially cost-effective to conduct further research.
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16 At a threshold of \$40,000 additional research is potentially cost-effective if research is
17 not proposed to cost more than \$325 million.
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21 If we proposed additional research would cost \$100 million, it can be seen from
22 Figure 3 that this research would be potentially cost-effective at a threshold of just
23 under \$16,000. Even at a threshold of \$0 per QALY research would potentially be
24 cost-effective as long as the cost of research did not exceed \$15 million.
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29 The EVPI has indicated further research is potentially cost-effective. The Expected
30 Value of Partial Perfect Information (EVPPI) was examined to establish where further
31 research would be of most benefit.
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34 35 36 **The Expected Value of Partial Perfect Information (EVPPI)**

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38 The EVPPI was examined for six parameters/ groups of parameters, Transitions,
39 Average Length of stay, Excess Mortality (cardiovascular mortality), Relative Risk of
40 Hawthorn, Utilities, and the Relative Risk of Hospitalisation.
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45 The results of the EVPPI analysis can be seen in Figure 4 (and Table 4). From both
46 the table and figure it can be seen that all parameters and parameter groups have
47 significant EVPPI, but the impact varies. Utilities (\$439,471,050.98) has the highest
48 EVPPI, and is therefore the most important target parameter/ parameter group for
49 further research.
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56 **Table 4. Partial EVPI Values for Parameters/ Parameter Groups**

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58 Parameters Partial EVPI
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Transitions	\$7,153,571.92
Average Length of stay	\$96,900,062.41
Excess Mortality	\$105,833,952.26
Relative Risk Hawthorn	\$86,323,972.20
Utilities	\$439,471,050.98
Relative Risk Hospitalisation	\$56,991,399.70

DISCUSSION

In this modelling study we examined the cost-effectiveness of hawthorn extract in addition to standard treatment for heart failure in Australia. This treatment is not considered cost-effective given the current evidence. This is the first known attempt to examine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment of chronic heart failure in Australia. Economic evaluation has been conducted examining hawthorn extract and standard heart failure treatment in Germany and this research indicates hawthorn extract was cost-effective in the study context, however, these studies were not considered rigorous enough for the data to be used in this study^{10 41}.

EVPI analysis indicated that further research was likely to be of benefit, and EVPPI analysis indicated that research ideally should be targeted toward Utilities. The potential costs of further research and the particular type or types that may be required are of crucial importance to the final decision. Further research to examine Utilities will likely rely on primary data from randomized controlled trials such as the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure Study (SENIORS)^{18 42}. Alternatively such research would require the initiation of novel research with utilities as a main outcome. This is costly research and this would certainly need to be estimated before any research was undertaken.

A limitation of this study was the relatively sparse data available for the Australian context. There is scarce data on the incidence and prevalence of heart failure.

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3 Estimates rely on information from a small number of large-scale population studies
4 conducted in the United States and Europe ¹. The study of mortality in Australia is
5 complex, heart failure is considered a 'mode of death' not a 'cause of death'. Studies
6 examining mortality in terms of the underlying cause of death risk underestimating
7 mortality with condition such as heart failure. Mortality statistics are complicated by
8 multiple co-morbidities, which make the underlying cause of death difficult to
9 identify. Lack of consensus about the diagnosis of heart failure also complicates
10 recording of the cause of death, indeed complicating any examination of heart failure.
11 It is difficult to isolate costs for heart failure. Heart failure is grouped by the
12 Australian Institute of Health and Welfare as an 'other cardiovascular disease'. The
13 exact contribution of heart failure to the burden of cardiovascular disease is at best an
14 estimate.
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25 Another limitation was the availability of evidence of the effectiveness of hawthorn
26 extract. There are numerous studies supporting its use, however, very few studies that
27 examine final outcomes such as hospitalisation and mortality^{12,30,32}. Previously
28 conducted studies focus on reported outcomes including maximal workload, exercise
29 tolerance, pressure-heart rate product, 6-min walk test, and left-ventricular ejection
30 fraction. There are suggestions in the literature that the use of hawthorn extract can
31 actually decrease the use of standard pharmacological therapy and alter the
32 progression of heart failure, but little rigorous evidence to support this ¹⁰. If the use of
33 standard pharmaceuticals was decreased, and/or disease progression was altered and
34 patients improved their NYHA class to a greater extent or remained in the less
35 symptomatic classes for longer such evidence was available this would
36 decrease~~change the~~ costs ~~and benefits of hawthorn extract,~~ and potentially change the
37 cost-effectiveness in favour of adding~~of~~ hawthorn extract as an adjunct to standard
38 pharmacological treatment.
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50 Should further evidence become available, the model can easily be updated and the
51 results re-examined.
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53 54 CONCLUSION

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3 Our analysis indicates that based on currently available evidence, hawthorn extract is
4 not cost-effective in addition to standard pharmacological treatment for chronic heart
5 failure in Australia. EVPI and EVPPI analysis indicates that further research is
6 warranted, particularly in the area of utilities, pending an assessment of the estimated
7 costs of such research.
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14 public, commercial or not-for-profit sectors.
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18 **Competing Interests** None.
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20

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22 research. EF carried out the data collection and economic analysis. EF was
23 responsible for the original draft. All authors contributed equally to all other aspects
24 including drafting and revising, and approved the final manuscript.
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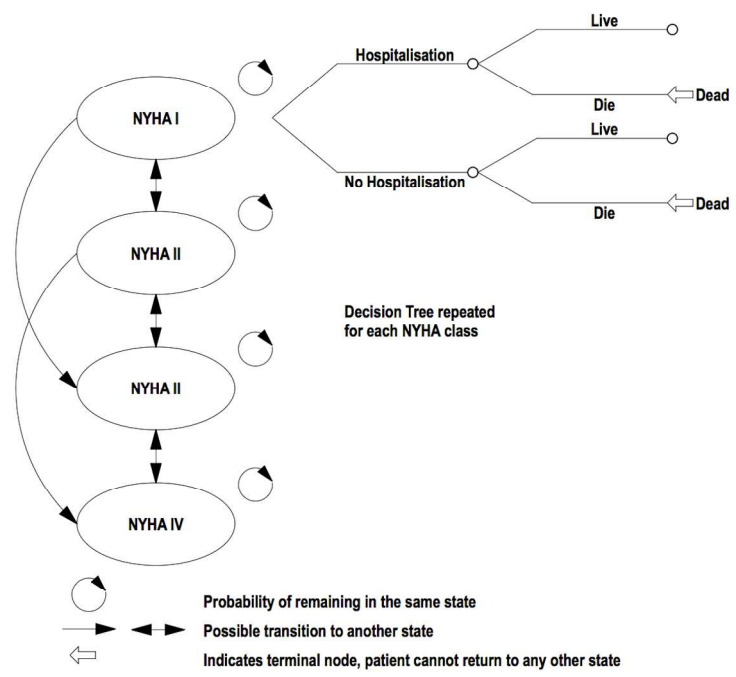


Figure 1. Markov model and decision tree showing transitions between potential health states for chronic heart failure.

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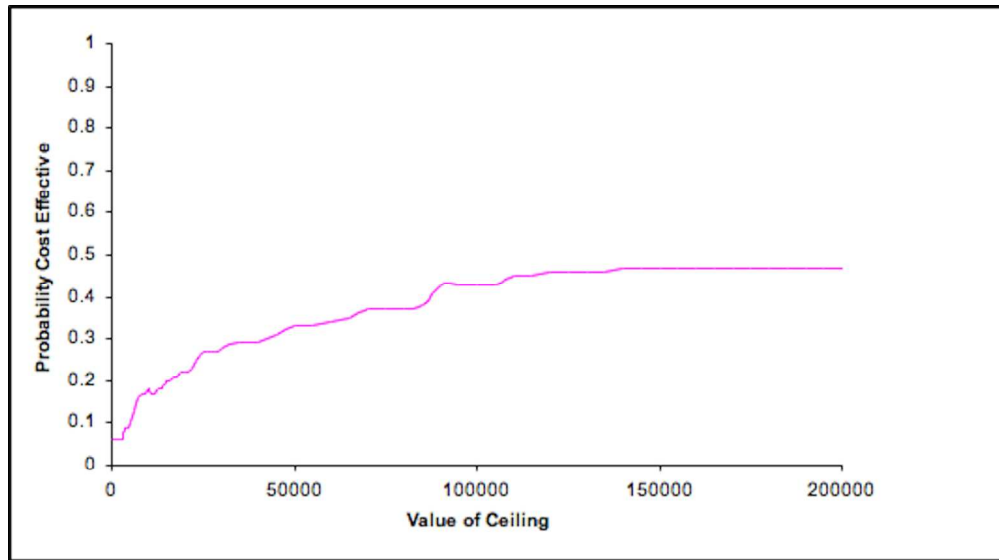


Figure 1. Cost-Effectiveness Acceptability Curve for the New Intervention 162x90mm (300 x 300 DPI)

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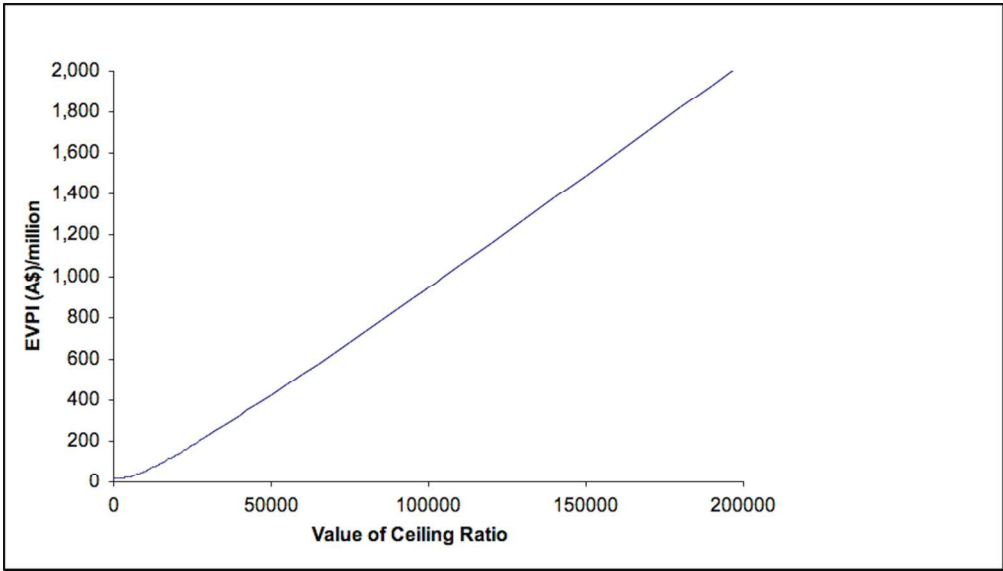


Figure 1. Population Expected Value of Perfect Information (EVPI) Curve
Note. The EVPI values have been divided by 1 million to make figure easier to read.

161x91mm (300 x 300 DPI)

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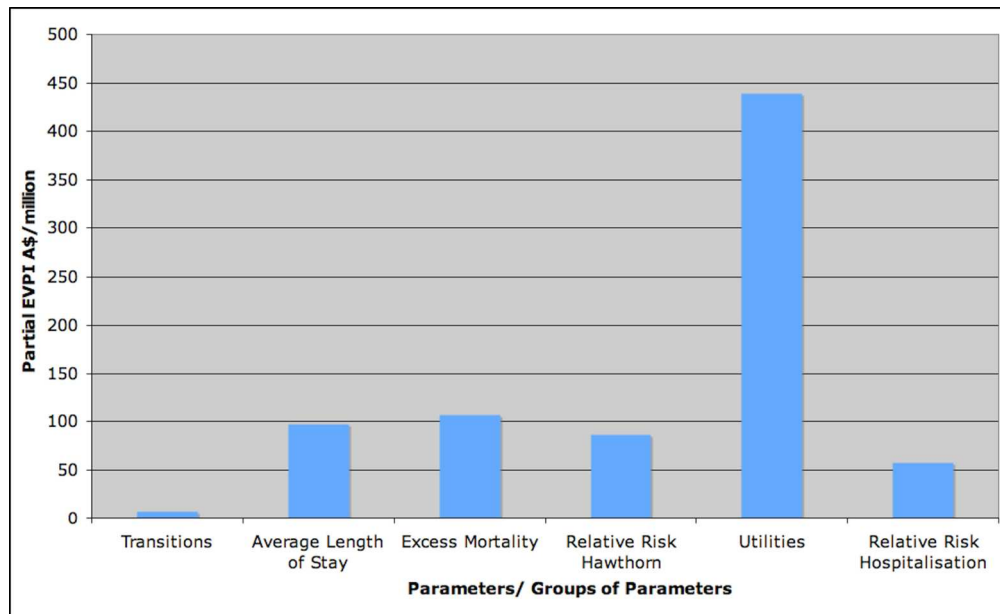


Figure 1. Expected Value of Perfect Information for Parameters
 Note. The Partial EVPI values have been divided by 1 million to make figure easier to read.

149x91mm (300 x 300 DPI)

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Appendix 1. Calculation of the Transition Probabilities for the Markov Model

<i>transition matrix</i>	NYHA I	NYHA II	NYHA III	NYHA IV	Check
NYHA I	0.977	0.019	0.004	0.000	1.000
NYHA II	0.008	0.981	0.010	0.001	1.000
NYHA III	0.000	0.034	0.960	0.006	1.000
NYHA IV	0.000	0.000	0.055	0.945	1.000
					0.000

Probabilistic version

1. Observed counts

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	59.597	1.159	0.244	0	61
NYHA II	9.6	1177.2	12	1.2	1200
NYHA III	0	28.016	791.04	4.944	824
NYHA IV	0	0	2.365	40.635	43
					2128

2. Estimated probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.977	0.019	0.004	0	1
NYHA II	0.008	0.981	0.010	0.001	1
NYHA III	0	0.034	0.960	0.006	1
NYHA IV	0	0	0.055	0.945	1

3. Random number table

	NYHA I	NYHA II	NYHA III	NYHA IV
NYHA I	0.24	0.44	0.87	0.66
NYHA II	0.91	0.62	0.99	0.21
NYHA III	0.72	0.91	0.27	0.46
NYHA IV	0.26	0.18	0.92	0.46

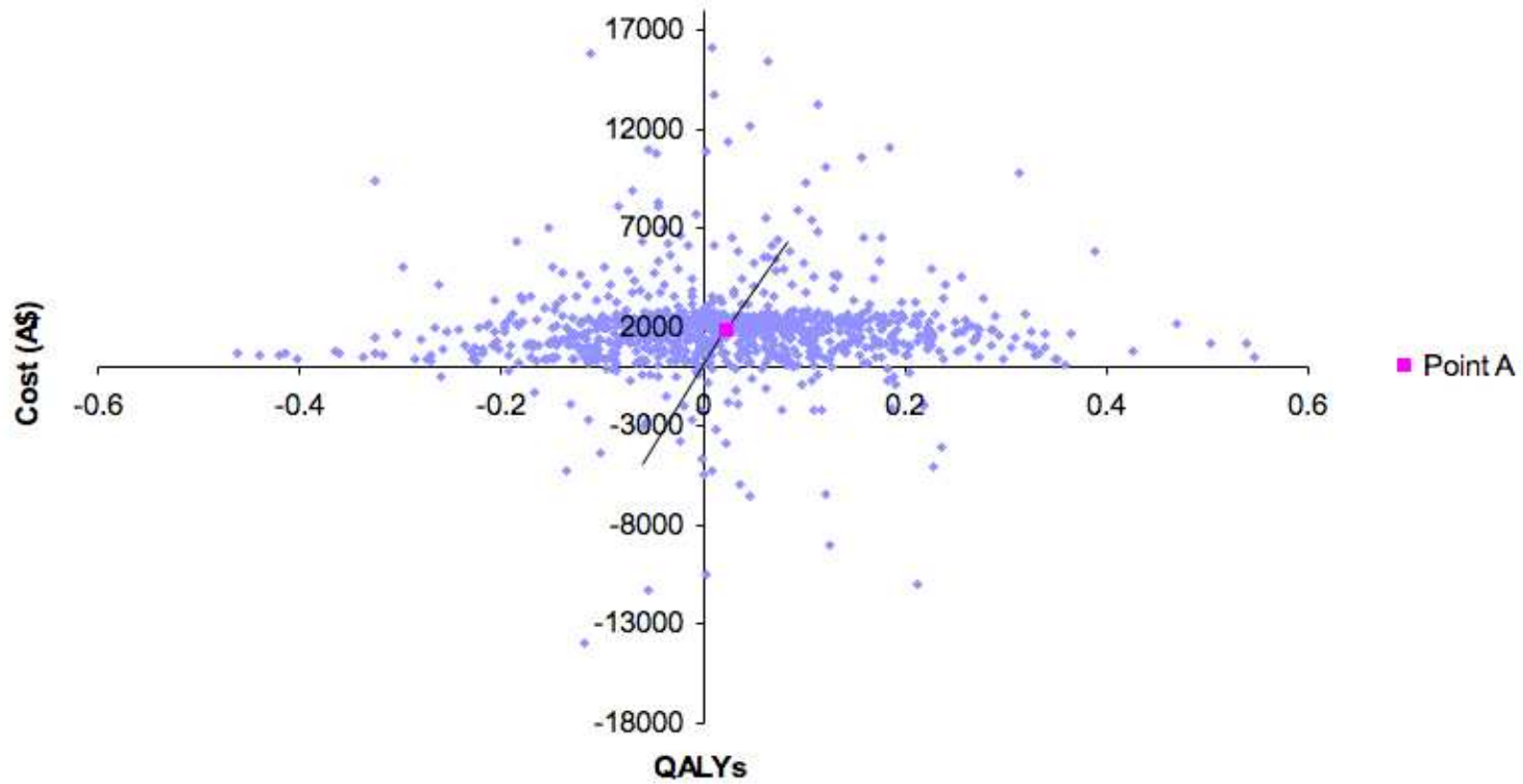
4. Cumulative gamma/normal functions

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	53.905	0.730	0.568	0	55
NYHA II	13.845	1188.106	20.983	0.342	1223
NYHA III	0	35.377	773.741	4.390	814
NYHA IV	0	0	4.735	39.593	44

5. Random dirichlet probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.976	0.013	0.010	0	1.00
NYHA II	0.011	0.971	0.017	0.000	1.00
NYHA III	0	0.043	0.951	0.005	1.00
NYHA IV	0	0	0.107	0.893	1.00

Appendix 2. Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model



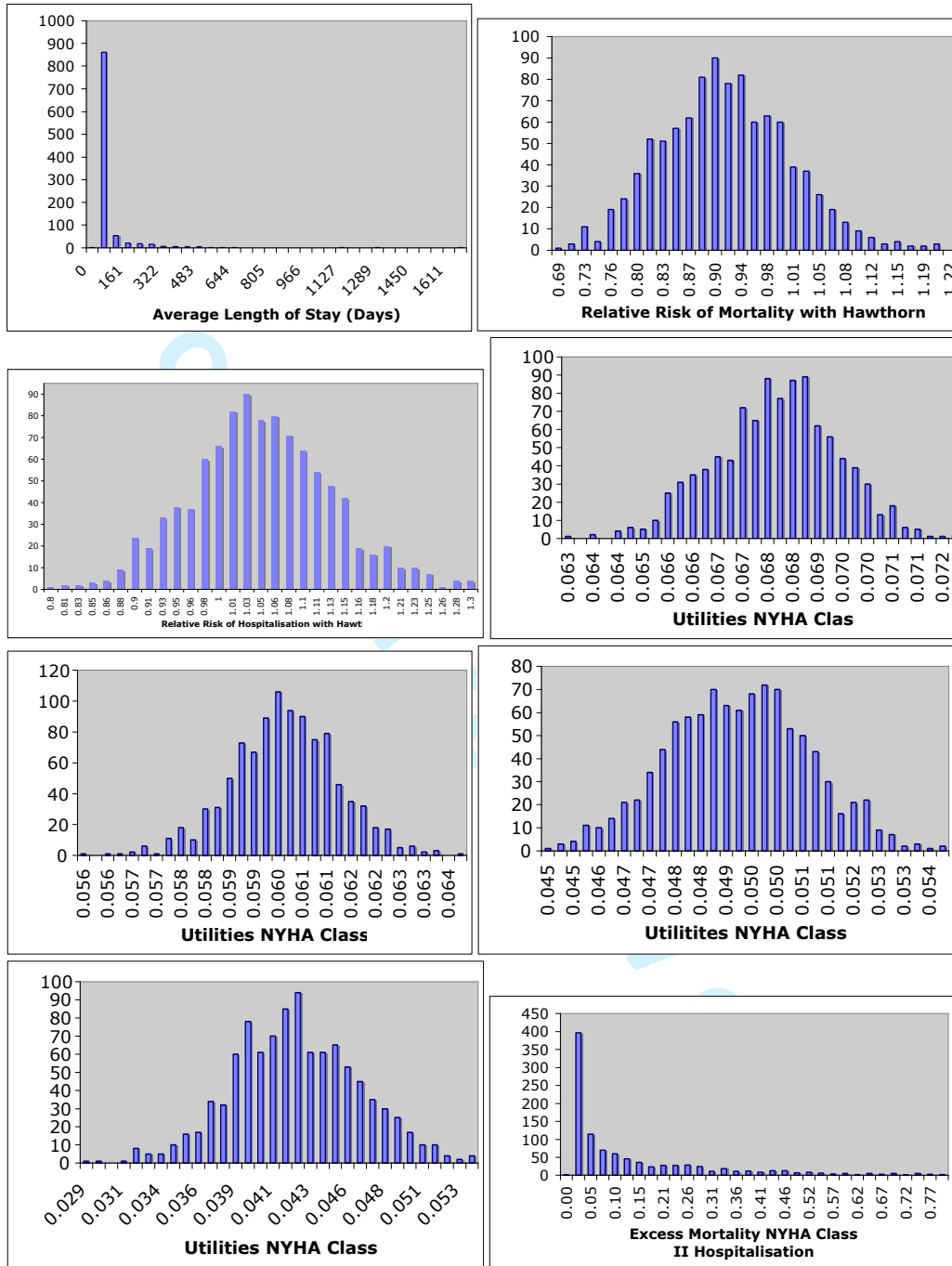
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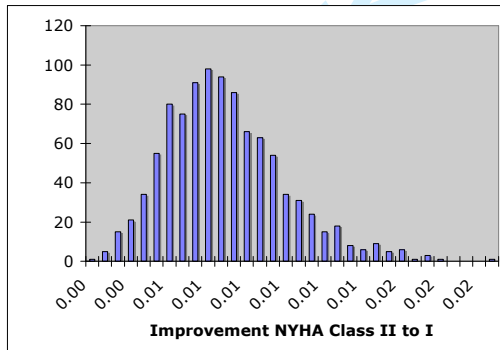
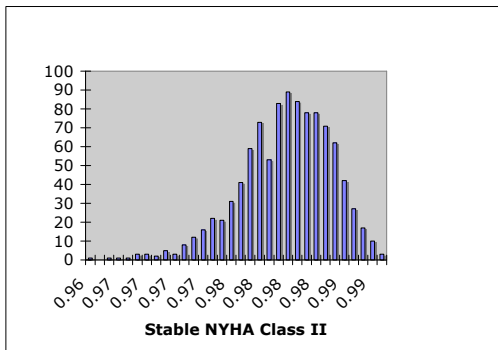
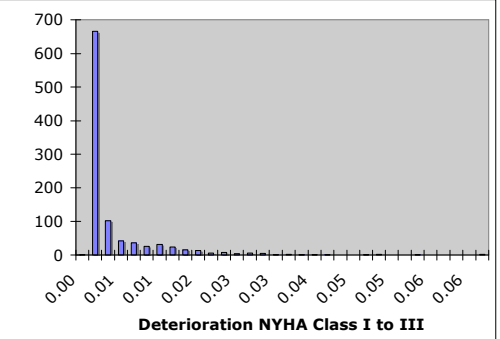
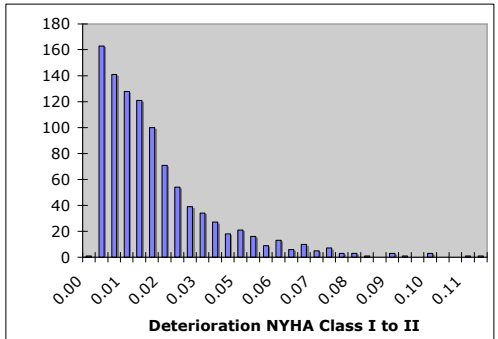
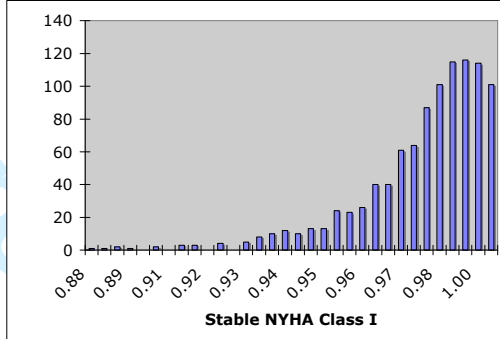
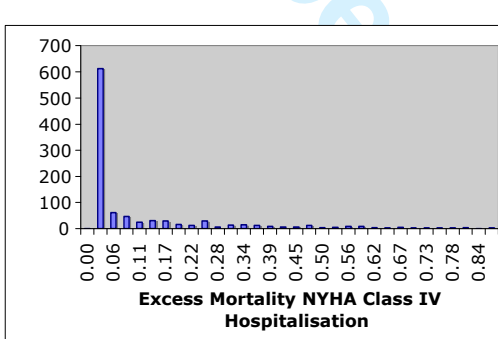
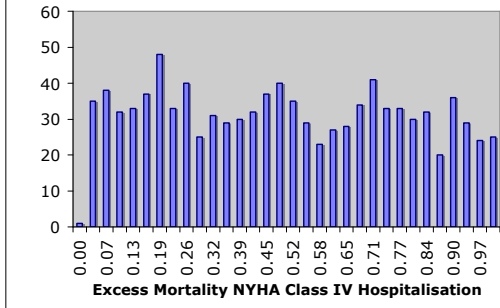
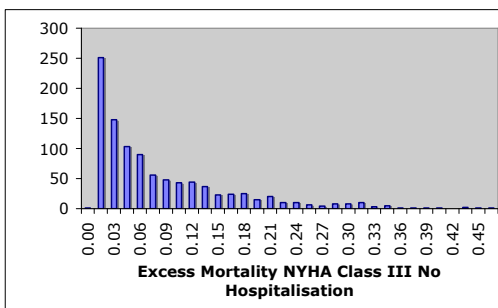
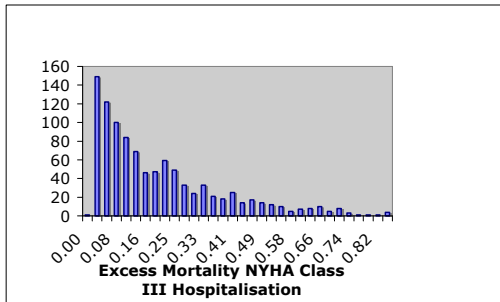
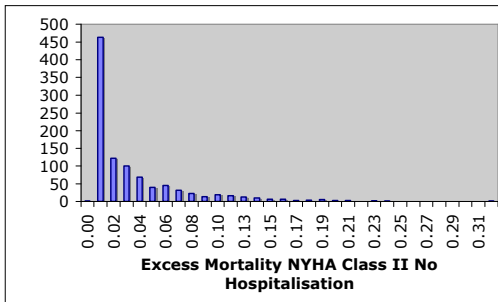
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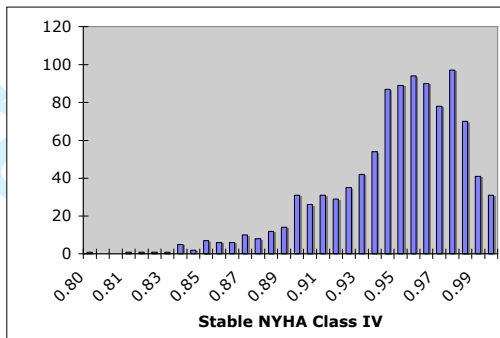
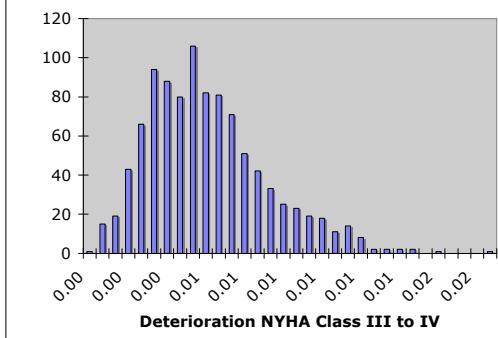
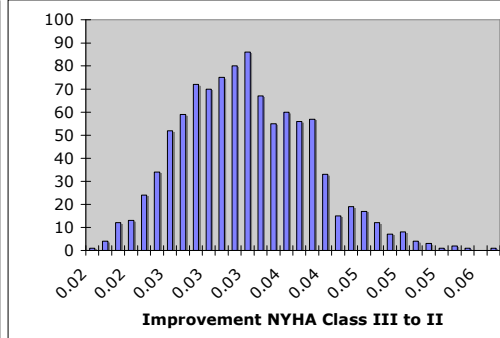
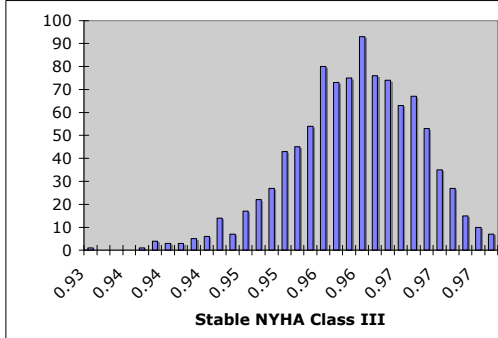
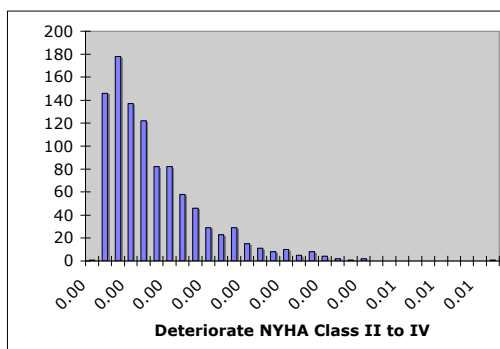
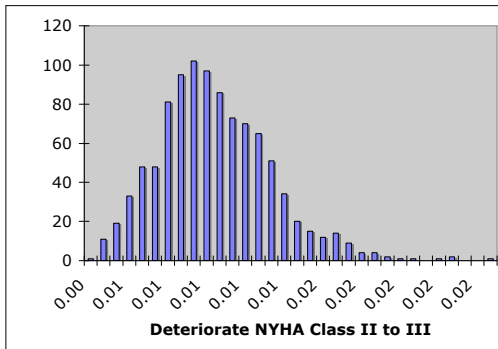
Appendix 3. Histograms of Individual Parameters



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EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction; Methods	
(6) The form of economic evaluation used is stated	Introduction; Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	Presented in table form and in written form
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from multiple sources
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	Meta-analysis was not used
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for	NA	As the study is

inflation or currency conversion are given		looking for relative cost, then inflation would be comparable between the different treatments
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods-Model construction; Discussion	Based on current cost estimates
(23) The discount rate(s) is stated	Methods	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	
(28) The choice of variables for sensitivity analysis is justified	Methods	
(29) The ranges over which the variables are varied are stated	Methods, Table 2	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	Results	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results Discussion; Conclusion	
(34) Conclusions follow from the data reported	Discussion; Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion; Conclusion	



Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Keywords:	HEALTH ECONOMICS, Heart failure < CARDIOLOGY, COMPLEMENTARY MEDICINE

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Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Keywords: complementary therapies, heart failure, cost-benefit analysis, crataegus extract

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ABSTRACT

Objective

An economic model was developed to evaluate the cost-effectiveness of hawthorn extract as an adjunctive treatment for heart failure in Australia.

Methods

A Markov model of chronic heart failure was developed to compare the costs and outcomes of standard treatment and standard treatment with hawthorn extract. Health states were defined by the New York Heart Association (NYHA) classification system and death. For any given cycle patients could remain in the same NYHA class, experience an improvement or deterioration in NYHA class, be hospitalised or die. Model inputs were derived from the published medical literature, and the output was Quality Adjusted Life Years (QALYs). Probabilistic Sensitivity Analysis was conducted. The Expected Value of Perfect Information (EVPI) and the Expected Value of Partial Perfect Information (EVPPI) were conducted to establish the value of further research and the ideal target for such research.

Results

Hawthorn extract increased costs by \$1866.78 and resulted in a gain of 0.02 QALYs. The incremental cost-effectiveness ratio was \$85,160.33 per QALY. The CEAC indicated at a threshold of \$40,000 the new treatment had a 0.29 probability of being cost-effective. The average incremental NMB was -\$1791.64, the average NMB for the standard treatment was \$92,067.49, and for hawthorn extract \$90,275.84.

Additional research is potentially cost-effective if research is not proposed to cost more than \$325 million. Utilities is the most important target parameter group for further research.

Conclusions

Hawthorn extract is not currently considered to be cost-effective in as an adjunctive treatment for heart failure in Australia. Further research in the area of utilities is warranted.

INTRODUCTION

Heart failure is a major public health concern for all Western countries¹. In the United States and Europe it is the most common principal diagnosis for adults admitted to hospital aged 65 years and over. In the United States around 2% of the population have heart failure (approximately 5 million people), and each year there are 500,000 new cases diagnosed². The estimated prevalence in Sweden is 1.5-2%, approximately 135,000 to 180,000 people³.

Australian data regarding the public health significance and epidemiology of heart failure is currently limited. Estimates rely on information from large-scale population studies conducted in the United States and Europe¹. It is estimated there are approximately 300,000 Australians living with chronic heart failure, and approximately 30,000 new cases diagnosed each year, with incidence rates and prevalence rising significantly with age^{4,5}. In Australia, chronic cardiovascular diseases are associated with health care costs of over five billion dollars, and estimates put the cost of heart failure at around one billion dollars⁶. The mortality, morbidity and health care costs of heart failure are therefore significant⁴.

Heart failure is a syndrome with a range of signs and symptoms, diagnosis is based on such signs and symptoms, including dyspnoea and fatigue, and appropriate investigations, such as echocardiogram, which confirm the presence or absence of heart failure and help determine its aetiology¹.

Current treatment aims to relieve and stabilise symptoms and prolong survival by stopping, stabilizing or reversing the progression of heart failure⁷. There are a variety of strategies used in Australia, including non-pharmacological management, pharmacological management, lifestyle changes, and the use of supportive devices, surgery, and palliative care^{6,8}. The pharmacological approach depends on the type of heart failure and extent of the symptoms.

Despite the availability of strategies to treat and manage the chronic disease, the disability and suffering associated with heart failure is devastating⁷. Given this, and the large economic burden, it is reasonable to examine options not currently

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3 considered standard therapy. Research examining the use of complementary and
4 alternative medicine, particularly the use of hawthorn extract is showing promising
5 results.
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10 Hawthorn extract is a popular herbal medicine used worldwide, particularly for its
11 cardiovascular properties⁹. Hawthorn extract has positive inotropic, anti-
12 inflammatory and anti-oxidative properties; causes peripheral and coronary
13 vasodilation; and protects against ischaemia induced arrhythmias⁹. A recent
14 systematic review concluded hawthorn extract can provide significant benefits to
15 heart failure patients as an adjunct to conventional treatment and a recent cost-
16 effectiveness study conducted in Germany concluded hawthorn is a cost-effective
17 treatment option especially in the early stages of heart failure¹⁰⁻¹².
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25 Economic evaluation is a structured method for examining the costs and
26 consequences involved with alternative methods of treatments and/or programs, in
27 order to inform which is the best alternative from a particular viewpoint¹³. The goal
28 is to improve the use of health care resources and improve patient care¹⁴. When
29 conducted rigorously, such formal analysis allows recommendation to be made with
30 transparency regarding the methods, data sources and assumptions¹³. This further
31 allows the process to be replicated, reviewed and even challenged.
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38 Models allow complex situations to be organised into a single coherent form that can
39 be used to make decisions based on comprehensive consideration of the alternative
40 interventions by capturing the essential relationships between the factors included in
41 the model and outcomes^{15 16}. Markov models define diseases using clinically
42 relevant and economically important health states, between which patients move
43 based on the natural history of the disease, and to which cost and effectiveness
44 outcomes are ascribed¹⁶.
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51 There are numerous examples of cost-effectiveness modeling in heart failure that
52 examine conventional medicine. Pharmacological, behavioural and surgical
53 interventions have all been investigated and many found to be cost-effective^{17 18}.
54 Pharmacological agents that have cost-effectiveness evidence include angiotensin
55 converting enzyme inhibitors (ACEIs), digoxin, and beta-blockers such as carvedilol
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3 and nebivolol. Multidisciplinary heart failure management, in the form of a team,
4 usually made up of a nurse co-ordinator and support from medical staff and allied
5 health including dieticians and physiotherapy, has also shown to be cost-effective
6 through reductions in hospitalisation and length of stay^{17 19}. Surgical options
7 including heart transplant, through intensive education and maximal medical therapy,
8 have demonstrated a range of cost-effectiveness values. Cardiac resynchronisation
9 therapy with or without an implantable cardioverter-defibrillator, has shown to be
10 cost-effective from a healthcare perspective^{17 20}. Most of the recent evidence
11 involves Markov modeling.
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20 The increasing number of published health economic evaluations is not yet reflected
21 in CAM^{21 22 23}. A systematic review examined whether CAM demonstrated cost-
22 effectiveness through economic evaluations²⁴. There was good evidence for the cost-
23 effectiveness of several therapies in comparison to usual care, acupuncture for
24 migraine, manual therapy for neck pain, spa therapy for Parkinson's, self-administered
25 stress management for cancer patients undergoing chemotherapy, pre- and post-
26 operative oral nutritional supplementation for lower gastrointestinal tract surgery,
27 biofeedback for patients with "functional" disorders (eg, irritable bowel syndrome),
28 and guided imagery, relaxation therapy, and a potassium rich diet for cardiac patients
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There remain very few full economic evaluations today. One such evaluation
examined therapeutic massage, exercise, and lessons in the Alexander technique for
treating persistent back pain²⁵. Massage, lessons in the Alexander technique, and an
exercise prescription all provided benefits to patients over a 12-month period. Six
lessons in the Alexander technique combined with an exercise prescription was the
most cost effective option for the NHS²⁵. Some economic evaluations of CAM have
incorporated decision modeling. Recently, the cost-effectiveness of adding
acupuncture to usual care for chronic low back pain was examined, using a Markov
model²⁶. The result was an incremental cost per QALY gained of KRW 3,421,394,
well below the threshold of KRW 20,000,000. Acupuncture plus usual care was more
cost-effective than usual care for these patients. The probability of collaborative
treatment being cost-effective was 72.3%. EVPI analysis suggested further research

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3 was of reasonable value²⁶. This highlights the need for full economic evaluations in
4 many areas of CAM.
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8 The aim of this study was the construction and application of an economic decision
9 model to evaluate hawthorn treatment as an adjunct to recommended pharmacological
10 treatment versus recommended pharmacological management for chronic heart failure
11 in Australia. The analysis has been conducted using a health sector perspective.
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14 15 16 **METHODS**

17 18 **Model Description**

19 A four state Markov model of chronic heart failure was developed based on the New
20 York Heart Association (NYHA) classification system using Microsoft Excel® (see
21 Figure 1). Classes I to IV make up four discrete health states included in the model
22 (See Table 1 for a description of the NYHA classes). A decision tree completes the
23 model. Each NYHA class has its own decision tree. Within the decision tree
24 patients could be hospitalised for worsening heart failure. Patients also either
25 survived or died.
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32 33 **Progression through the model**

34 A simulated cohort of 1000 patients aged 60 entered the model with NYHA class II
35 heart failure and progressed through the model. Patients progress through the model
36 in one month cycles for a duration of 5 years. After one month, patients either
37 remained in NYHA class II or improved to NYHA class I or deteriorated.
38 In turn, for each class of heart failure patients were either hospitalised or not
39 hospitalised for worsening heart failure. Patients who were hospitalised or not
40 hospitalised either survived or died. Death was a possibility from any class of heart
41 failure. The patients accrued costs and benefits of treatment in each of the states for
42 each cycle.
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50 Per patient costs were required for each NYHA class. Costs were assumed to
51 be the same for standard treatment and standard treatment with hawthorn extract,
52 except for the additional cost of hawthorn extract. Patient health was considered as a
53 single index utility on a zero to one scale, where 0 represents death and 1 represents
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perfect health. This allows the calculation of Quality Adjusted Life Years (QALYs) when combined with the mortality data and the calculation of cost per QALY ratios.

Two cohorts were modeled, one receiving standard pharmacological treatment and the other receiving standard pharmacological treatment with hawthorn extract as an adjunct. The two cohorts will progress through the model in slightly different ways and as such there will be a difference in the accumulation of costs and QALYS. It is the differences in costs and QALYS that will determine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment.

A discount rate of 3% per year was applied to the costs and benefits. This rate is a standard choice in the literature.

Table 1. NYHA grading of symptoms in chronic heart failure.

NYHA Class	Description
Class I	No symptoms and limitations in ordinary physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms such as fatigue, shortness of breath, and angina.
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
Class IV	Severely limited. Experiences symptoms even at rest.

Model Construction

Disease Progression

Transition probabilities for movement between NYHA classes of heart failure were estimated from the published literature detailing the large scale international Study of the Effects of Nebivolol Intervention on Outcomes and Re-hospitalisation in Seniors with Heart Failure (SENIORS) and personal correspondence with authors^{18,27}. A thorough literature search was conducted to identify disease progression data for each NYHA class, between January 2004 and December 2009. Data was considered relevant if transition probabilities were provided for each NYHA class. The databases searched were Medline, CINAHL and the Cochrane Library. Search terms used included 'New York Heart Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'chronic heart failure', and 'heart failure'.

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3 The search yielded a limited number of studies (17 in Medline, 3 in CINAHL and 3 in
4 the Cochrane library), of which only the above study was considered suitable for
5 inclusion.
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8 Disease progression between the Markov states was assumed to be the same for
9 standard treatment and for standard treatment with hawthorn extract, as we were
10 unable to identify reliable data to indicate that hawthorn extract altered progression
11 through the classes of heart failure. Transition probabilities were fixed over time. We
12 have incorporated a difference in mortality and a difference in the hospitalisation rate
13 between the standard treatment and the standard treatment with hawthorn extract as
14 an adjunct, which in turn will impact on the cost and QALY outcomes.
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20 21 **Data Sources**

22 23 24 Mortality

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26 Baseline mortality was derived from Australian Bureau of Statistics general
27 population mortality data.
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30 Mortality data was of interest if it was provided for each NYHA class and if it
31 concerned the excess mortality from heart failure and/or cardiovascular causes. The
32 databases searched were Medline, CINAHL and the Cochrane Library, between
33 January 2004 and December 2009. Search terms used included 'New York Heart
34 Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'chronic heart
35 failure', 'heart failure', 'mortality'. 83 papers were identified in Medline, 198 in
36 CINAHL and 411 in Cochrane.
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41 The mortality rate for cardiovascular causes was derived from the published literature
42 detailing one-year mortality among unselected patients with NYHA class II-IV heart
43 failure in Switzerland²⁸. The mortality rate increased with progression from NYHA
44 class I to NYHA class IV, and varied depending on whether the patient was
45 hospitalised or not. A thorough search of the literature was made to identify data for
46 each NYHA class individually, nothing was identified and the above study was the
47 closest to ideal. Hospitalisation was considered a major factor in cost estimation, so
48 data broken down by hospitalisation status was considered to represent the population
49 of heart failure patients well. Also, unselected patients were considered to represent
50 the patient cohort more accurately than studies that focused on hospitalised patients
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3 only. As data for NYHA class I was not included, an assumption was made that
4 mortality for NYHA class I was the same as the general population mortality.
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7 8 Health Status

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10 Estimates of health status were derived from the same source as the transition
11 probabilities^{18 20}. Data concerning utilities for heart failure is extremely limited, a
12 study was identified that had specifically had developed utilities for heart failure in
13 terms of both hospitalisation and NYHA class. However, we were unable to obtain
14 the required data despite personal correspondence with the authors. The estimated
15 health status was considered the next best data source.
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19 Health status was assumed to be the same for standard treatment and standard
20 treatment with hawthorn extract. Hospitalisation was assumed to result in a health
21 state lower than non-hospitalisation and a -0.1 disutility was applied to hospitalisation
22 to reflect this.
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27 28 Effect of Hawthorn

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30 A literature search identified the existing research for the use of hawthorn extract in
31 the treatment of heart failure, between January 2004 and January 2010. The search
32 included electronic databases (Medline,(472 papers) AMED (129 papers), Econlit (0
33 papers), CINAHL (15 papers), Cochrane Database of Systematic Reviews (71
34 papers)), hand searches of the literature, including hard copies of journals, and a
35 search of the reference lists of the articles and publications found through electronic
36 and hand searches. Personal communication with authors and experts including
37 manufacturers and researchers in the field was also necessary to identify other sources
38 of information and research that may not have been found using any other methods.
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46 A wide range of search terms was used including: 'heart failure', 'chronic heart
47 failure', 'systolic heart failure', and 'congestive heart failure', 'hawthorn',
48 'Crataegus', 'Crataegus oxyacantha', 'Crataegus monogyna', 'whitethorn',
49 'weissdorn', 'Crataegus laevigata', 'WS 1442', 'LI 132', 'complementary',
50 'alternative', 'medicine' and 'therapy'. There were several studies written in German,
51 these were translated into English and then examined.
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3 Publicly accessible trials registers were also searched, and information was current up
4 to December 2011. The Australian New Zealand Clinical Trials Registry (ANZCTR)
5 was searched, no studies were identified. The World Health Organisation
6 International Clinical Trials Registry Platform was searched, no new relevant trials
7 were identified. The search terms used were: 'hawthorn extract', 'hawthorn',
8 'crataegus', 'WS1442', 'whitehorn', 'heart failure'.
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14 There were no planned exclusion criteria at this stage for the patient population as any
15 of the studies found have the potential to contribute valuable information to inform
16 the model development.
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21 The relative risk of mortality and relative risk of hospitalisation with hawthorn extract
22 was derived from the Survival and Prognosis: Investigation of Crataegus Extract WS
23 1442 in congestive heart failure (SPICE) trial, a large scale, international, randomised,
24 placebo-controlled, double-blind study designed to investigate the influence of
25 hawthorn extract on mortality of patients with congestive heart failure NYHA class II
26 and III with at least moderately impaired left ventricular function²⁹. To date there
27 have only been two studies to examine the effect of hawthorn extract on heart failure
28 progression in terms of mortality and hospitalisation. Most studies have focused on
29 symptoms and exercise capability. SPICE enrolled 2681 patients, and the Hawthorn
30 Extract Randomised Blinded Chronic Heart Failure (HERB CHF) trial enrolled 120
31 patients^{30 31}. Meta-analysis was not considered appropriate, therefore the data from
32 SPICE was incorporated into the model.
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43 Costs

44 No Australian data was available to estimate the hospitalisation rate and number of
45 hospitalisations, this information was derived from a United States study³².
46 The estimated length of stay in hospital data was obtained from Victorian Department
47 of Health for 2010-2011, it was unavailable for each NYHA class, so it was assumed
48 to be the same for all classes³³.
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52 The cost of a hospital admission per day was derived from the Queensland
53 Government/ Queensland Health Casemix Funding Model 2008-2009 Component
54 Prices Summary (\$3,775 per day)³⁴.
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3 Outpatient costs included General Practitioner (GP) visits, pathology (urea, creatinine,
4 electrolytes), echocardiograms, and specialist visits. Estimates of the number of GP
5 and specialist visits came from a combination of Australian sources and overseas
6 studies due to the difficulty in finding complete Australian estimates. It was
7 estimated that NYHA class I had 6 GP visits per year, and the remaining NYHA
8 classes had 12 visits per year at \$34.30 per visit. Pathology was assumed to be
9 required every 3 months at a cost of \$17.80. An Echocardiogram was assumed to be
10 performed every two years (\$230.65). A specialist visit was assumed to occur twice
11 per year (\$290 initial visit, \$194 repeat visit). If hospitalized, it was assumed patients
12 had an extra 3 specialist visits and 2 GP visits per year. The costs came directly from
13 the Medicare Benefits Schedule and the Queensland Government/ Queensland Health
14 Casemix Funding Model 2008-2009 Component Prices Summary^{34 35}.

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16 The information for which medications are taken for each NYHA class have been
17 taken from the National Heart Foundation guidelines for the treatment of chronic
18 heart failure in Australia⁵. Information for the optimal dosages prescribed has been
19 taken from the Australian Therapeutic Guidelines. Individual drug pricing was
20 obtained from the most recently available online version of the Medicare Benefits
21 Schedule. The initial version of the model has incorporated the assumption that
22 medications are taken in 100% of patients and that dosing is optimal. The model
23 however can be altered to consider different scenarios of medication prescription and
24 consumption.

25
26 The dosage was assumed to be 900mg daily, consistent with the dosage used in the
27 two most recent trials of hawthorn extract, the SPICE trial and the HERB-CHF trial²⁹
28^{31 36}. An online search was conducted for standardised monopreparations of hawthorn
29 leaf with flower available for purchase. Cardiomax® retails for A\$25.95 for 30 x
30 450mg tablets (this equates to a 15 day supply, the cost for one month is \$51.90).

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32 The transition parameters are listed in Table 2. The model parameters have been
33 listed in Table 3. Appendix 1 details the calculation of transition probabilities for the
34 model.
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Table 2. Transition Parameters used in the Decision Model

Transition Matrix	NYHA I	NYHA II	NYHA III	NYHA IV	Distribution
NYHA I	0.977	0.019	0.004	0.000	Dirichlet
NYHA II	0.008	0.981	0.010	0.001	Dirichlet
NYHA III	0.000	0.034	0.960	0.006	Dirichlet
NYHA IV	0.000	0.000	0.055	0.945	Dirichlet

Table 3. Parameters used in the Decision Model

Probabilistic Parameters				
Parameter Description	Baseline Estimate	Variation/ SE (SD)	Distribution	Reference
Hospitalisation				
Length of stay in hospital estimate	4.9 days	Alpha 0.1 Beta 316.81	Gamma	³³
Relative Risk of Hospitalisation with Hawthorn Extract	1.03651200	0.080800494	Lognormal	³⁶
Mortality				
Excess Mortality			Beta	²⁸
probability of excess mortality given hospitalisation class II	0.01087776	Alpha 0.35916667	Beta 2.55750000	
probability of excess mortality given no hospitalisation class II	0.002620782	Alpha 0.43166667	Beta 13.485000	
probability of excess mortality given hospitalisation class III	0.01791369	Alpha 0.79666667	Beta 3.28666667	
probability of excess mortality given no hospitalisation class III	0.00674466	Alpha 0.72833333	Beta 8.60500000	
probability of excess mortality given hospitalisation class IV	0.05333974	Alpha 0.96416667	Beta 1.03583333	
probability of excess mortality given no hospitalisation class IV	0.00719464	Alpha 0.16583333	Beta 1.83416667	
Relative Risk of Mortality with	0.90336300	0.09507420	Lognormal	³⁶

Hawthorn Extract				
Utility			Beta	¹⁸
Utility of NYHA class I no hospitalisation	0.815	Alpha 395.88	Beta 89.86	
Utility of NYHA class II no hospitalisation	0.72	Alpha 661.95	Beta 257.42	
Utility of NYHA class III no hospitalisation	0.59	Alpha 359.8075	Beta 250.0357	
Utility of NYHA class IV no hospitalisation	0.508	Alpha 51.77	Beta 50.1394	
Fixed Parameters				
Parameter Description	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
Hospitalisation				³²
Probability for hospitalisation	0.01518800	0.02397800	0.02397800	0.15397000
Probability no hospitalisation	0.98481200	0.97602200	0.97602200	0.84603000
Costs				^{34 35 37}
Cost of hospitalisation	\$2,957.08	\$4,435.63	\$4,435.63	\$5,914.17
Total cost for each NYHA class with hospitalisation	\$3,141.60	\$4,639.95	\$4,684.53	\$6,176.17
Cost of each class with no hospitalisation	\$130.30	\$150.11	\$194.69	\$207.79
Mortality				³⁸
Standardised Death Rate	6.0 per 1000	6.0 per 1000	6.0 per 1000	6.0 per 1000

Probabilistic Sensitivity Analysis

Uncertainty is addressed in the model using probabilistic sensitivity analysis. Statistical distributions were assigned to key model parameters to examine second-order uncertainty in the estimation of the parameter. Uncertainty was propagated through the model using Monte Carlo simulation, drawing parameter values at random 1000 times from the particular distributions. This generates a joint density of cost and QALY outcomes that summarises uncertainty in all model parameters.

Net Monetary Benefit

The incremental net monetary benefit was calculated. The difference between the average net benefit of the standard treatment and the average net benefit of the standard treatment with hawthorn as an adjunct is equal to the incremental net benefit.

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3 The net benefit for each treatment is the increase in effectiveness multiplied by the
4 amount the decision maker is willing to pay per QALY (\$40,000), less the increase in
5 cost.
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8 9 10 **The Expected Value of Perfect Information/ Expected Value of Partial Perfect** 11 **Information (EVPI/ EVPPI)** 12

13 The results of the modeling will indicate whether, based on the currently available
14 information, the new treatment should be recommended. This decision is always
15 associated with a level of uncertainty, which raises the question of whether it is
16 appropriate to conduct further research to better examine the potential value of the
17 new treatment, and whether we can identify where this research needs to be directed.
18 EVPI and EVPPI analysis have been used to address these questions.
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24 EVPI analysis is a combination of the cost of making the wrong decision in terms of
25 forgone health benefit and wasted resources, and the probability of making a wrong
26 decision. This equates to the expected cost of uncertainty. With all uncertainty
27 removed there would be economic savings from making the best decision and EVPI is
28 a monetary value of these savings. EVPI provides an upper bound for spending on
29 further research that reduces uncertainty in the decision. EVPPI follows the same
30 principles, but examines individual parameters³⁹.
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38 For the model it has been assumed the life of technology is 10 years and the number
39 of eligible patients per annum has been estimated at 30, 000. This estimate is derived
40 from the estimate of 30, 000 new cases of chronic heart failure per annum.
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44 **RESULTS**

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46 For the standard treatment and standard treatment with hawthorn extract as an adjunct
47 the total cost per patient was \$4,887.82 and \$6754.59 QALYs were 2.40 and 2.42
48 respectively. This was an incremental cost of \$1866.78 and 0.02 QALYs, and the
49 incremental cost-effectiveness ratio was \$85,160.33 per QALY. A Cost-
50 Effectiveness Plane shows the joint density of cost and QALY outcomes from the
51 Monte Carlo simulations (See Figure 2). In Figure 2, point A is the ICER. The
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3 variation in the model parameters can be seen in a series of histograms for each of the
4 probabilistic parameters (See Appendix 2).
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8 **Cost-Effectiveness Acceptability Curve (CEAC)**

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10 Figure 3 shows the uncertainty around this estimate as a cost-effectiveness
11 acceptability curve (CEAC). At a willingness to pay threshold of \$40,000, the
12 treatment with hawthorn extract has a 0.29 probability of being cost-effective. The
13 probability of being cost effective rises as the willingness to pay threshold rises, for a
14 threshold between \$500,000 and \$1,000,000 the probability is 0.48.
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19 **Net Monetary Benefit (NMB)**

20 For a threshold of \$40,000, the average incremental NMB is -\$1791.64, the average
21 NMB for the standard treatment is \$92,067.49, and for the standard treatment with
22 hawthorn as an adjunct \$90,275.84. The treatment with hawthorn extract has a
23 negative incremental net benefit, and would not offer good value for money for a
24 decision maker.
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30 **Expected Value of Perfect Information (EVPI)**

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32 The population EVPI has been plotted in Figure 4 for a cost-effectiveness threshold
33 between \$0 and \$200, 000 per QALY. The threshold was continued in the analysis up
34 to a threshold of \$500,000 per QALY, however this did not alter the slope of the
35 curve, so the results up to \$200, 000 have been shown.
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41 If the population EVPI represented in Figure 4 exceeds the expected costs of
42 additional research, then it is potentially cost-effective to conduct further research.
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46 At a threshold of \$40,000 additional research is potentially cost-effective if research is
47 not proposed to cost more than \$325 million.
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51 If we proposed additional research would cost \$100 million, it can be seen from
52 Figure 4 that this research would be potentially cost-effective at a threshold of just
53 under \$16,000. Even at a threshold of \$0 per QALY research would potentially be
54 cost-effective as long as the cost of research did not exceed \$15 million.
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The EVPI has indicated further research is potentially cost-effective. The Expected Value of Partial Perfect Information (EVPPPI) was examined to establish where further research would be of most benefit.

The Expected Value of Partial Perfect Information (EVPPPI)

The EVPPPI was examined for six parameters/ groups of parameters, Transitions, Average Length of stay, Excess Mortality (cardiovascular mortality), Relative Risk of Hawthorn, Utilities, and the Relative Risk of Hospitalisation.

The results of the EVPPPI analysis can be seen in Figure 5 (and Table 4). From both the table and figure it can be seen that all parameters and parameter groups have significant EVPPPI, but the impact varies. Utilities (\$439,471,050.98) has the highest EVPPPI, and is therefore the most important target parameter/ parameter group for further research.

Table 4. Partial EVPI Values for Parameters/ Parameter Groups

Parameters	Partial EVPI
Transitions	\$7,153,571.92
Average Length of stay	\$96,900,062.41
Excess Mortality	\$105,833,952.26
Relative Risk Hawthorn	\$86,323,972.20
Utilities	\$439,471,050.98
Relative Risk Hospitalisation	\$56,991,399.70

DISCUSSION

In this modelling study we examined the cost-effectiveness of hawthorn extract in addition to standard treatment for heart failure in Australia. This treatment is not considered cost-effective given the current evidence. This is the first known attempt to examine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment of chronic heart failure in Australia. Economic evaluation has been conducted examining hawthorn extract and standard heart failure treatment in Germany and this research indicates hawthorn extract was cost-effective in the

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3 study context, however, these studies were not considered rigorous enough for the
4 data to be used in this study^{10 40}.

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8 EVPI analysis indicated that further research was likely to be of benefit, and EVPPI
9 analysis indicated that research ideally should be targeted toward Utilities. The
10 potential costs of further research and the particular type or types that may be required
11 are of crucial importance to the final decision. Further research to examine Utilities
12 will likely rely on primary data from randomized controlled trials such as the
13 Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival
14 Study (EPHESUS) and the Study of the Effects of Nebivolol Intervention on
15 Outcomes and Rehospitalisation in Seniors with Heart Failure Study (SENIORS)^{18 41}.
16 Alternatively such research would require the initiation of novel research with utilities
17 as a main outcome. This is costly research and this would certainly need to be
18 estimated before any research was undertaken.
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28 The models in any area of health vary in terms of the Markov states chosen, for
29 example when representing the severity of heart failure, hospitalisations and NYHA
30 classes of heart failure are both utilised. It is difficult to summarise the multitude of
31 evidence and compare models as different model structures and methods are used,
32 which potentially leads to different outcomes⁴².
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38 The literature searches conducted for this study were comprehensive, although not to
39 the standard of a systematic review. It is also often seen that the keywords chosen for
40 CAM studies are not always uniform. The combination of these two factors may
41 mean we have missed some of the research available. Our search was not reliant on
42 databases alone, much of our information came from personal correspondence and a
43 thorough search of reference lists, minimizing the impact of the above limitations.
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49 A limitation of this study was the relatively sparse data available for the Australian
50 context. There is scarce data on the incidence and prevalence of heart failure.
51 Estimates rely on information from a small number of large-scale population studies
52 conducted in the United States and Europe¹. The study of mortality in Australia is
53 complex, heart failure is considered a 'mode of death' not a 'cause of death'. Studies
54 examining mortality in terms of the underlying cause of death risk underestimating
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3 mortality with condition such as heart failure. Mortality statistics are complicated by
4 multiple co-morbidities, which make the underlying cause of death difficult to
5 identify. Lack of consensus about the diagnosis of heart failure also complicates
6 recording of the cause of death, indeed complicating any examination of heart failure.
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8 It is difficult to isolate costs for heart failure. Heart failure is grouped by the
9 Australian Institute of Health and Welfare as an 'other cardiovascular disease'. The
10 exact contribution of heart failure to the burden of cardiovascular disease is at best an
11 estimate.
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18 Another limitation was the availability of evidence of the effectiveness of hawthorn
19 extract. There are numerous studies supporting its use, however, very few studies that
20 examine final outcomes such as hospitalisation and mortality^{12,30,32}. Previously
21 conducted studies focus on reported outcomes including maximal workload, exercise
22 tolerance, pressure-heart rate product, 6-min walk test, and left-ventricular ejection
23 fraction. There are suggestions in the literature that the use of hawthorn extract can
24 actually decrease the use of standard pharmacological therapy and alter the
25 progression of heart failure, but little rigorous evidence to support this¹⁰. If the use of
26 standard pharmaceuticals was decreased, and/or disease progression was altered and
27 patients improved their NYHA class to a greater extent or remained in the less
28 symptomatic classes for longer this would decrease costs and potentially change the
29 cost-effectiveness in favour of adding hawthorn extract as an adjunct to standard
30 pharmacological treatment.
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41 Should further evidence become available, the model can easily be updated and the
42 results re-examined.
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45 **CONCLUSION**

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47 Our analysis indicates that based on currently available evidence, hawthorn extract is
48 not cost-effective in addition to standard pharmacological treatment for chronic heart
49 failure in Australia. EVPI and EVPPI analysis indicates that further research is
50 warranted, particularly in the area of utilities, pending an assessment of the estimated
51 costs of such research.
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8 **Competing Interests** None.
9

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11 **Contributors** EF, NG and JA were responsible for the conception and design of the
12 research. EF carried out the data collection and economic analysis. EF was
13 responsible for the original draft. All authors contributed equally to all other aspects
14 including drafting and revising, and approved the final manuscript.
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Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia

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Word count: 4546

ABSTRACT**Objective**

An economic model was developed to evaluate the cost-effectiveness of hawthorn extract as an adjunctive treatment for heart failure in Australia.

Methods

A Markov model of chronic heart failure was developed to compare the costs and outcomes of standard treatment and standard treatment with hawthorn extract. Health states were defined by the New York Heart Association (NYHA) classification system and death. For any given cycle patients could remain in the same NYHA class, experience an improvement or deterioration in NYHA class, be hospitalised or die. Model inputs were derived from the published medical literature, and the output was Quality Adjusted Life Years (QALYs). Probabilistic Sensitivity Analysis was conducted. The Expected Value of Perfect Information (EVPI) and the Expected Value of Partial Perfect Information (EVPPPI) were conducted to establish the value of further research and the ideal target for such research.

Results

Hawthorn extract increased costs by \$1866.78 and resulted in a gain of 0.02 QALYs. The incremental cost-effectiveness ratio was \$85,160.33 per QALY. The CEAC indicated at a threshold of \$40,000 the new treatment had a 0.29 probability of being cost-effective. The average incremental NMB was -\$1791.64, the average NMB for the standard treatment was \$92,067.49, and for hawthorn extract \$90,275.84. Additional research is potentially cost-effective if research is not proposed to cost more than \$325 million. Utilities is the most important target parameter group for further research.

Conclusions

Hawthorn extract is not currently considered to be cost-effective in as an adjunctive treatment for heart failure in Australia. Further research in the area of utilities is warranted.

INTRODUCTION

Heart failure is a major public health concern for all Western countries¹. In the United States and Europe it is the most common principal diagnosis for adults admitted to hospital aged 65 years and over. In the United States around 2% of the population have heart failure (approximately 5 million people), and each year there are 500,000 new cases diagnosed². The estimated prevalence in Sweden is 1.5-2%, approximately 135,000 to 180,000 people³.

Australian data regarding the public health significance and epidemiology of heart failure is currently limited. Estimates rely on information from large-scale population studies conducted in the United States and Europe¹. It is estimated there are approximately 300,000 Australians living with chronic heart failure, and approximately 30,000 new cases diagnosed each year, with incidence rates and prevalence rising significantly with age^{4,5}. In Australia, chronic cardiovascular diseases are associated with health care costs of over five billion dollars, and estimates put the cost of heart failure at around one billion dollars⁶. The mortality, morbidity and health care costs of heart failure are therefore significant⁴.

Heart failure is a syndrome with a range of signs and symptoms, diagnosis is based on such signs and symptoms, including dyspnoea and fatigue, and appropriate investigations, such as echocardiogram, which confirm the presence or absence of heart failure and help determine its aetiology¹.

Current treatment aims to relieve and stabilise symptoms and prolong survival by stopping, stabilizing or reversing the progression of heart failure⁷. There are a variety of strategies used in Australia, including non-pharmacological management, pharmacological management, lifestyle changes, and the use of supportive devices, surgery, and palliative care^{6,8}. The pharmacological approach depends on the type of heart failure and extent of the symptoms.

Despite the availability of strategies to treat and manage the chronic disease, the disability and suffering associated with heart failure is devastating⁷. Given this, and the large economic burden, it is reasonable to examine options not currently

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6 considered standard therapy. Research examining the use of complementary and
7 alternative medicine, particularly the use of hawthorn extract is showing promising
8 results.
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11 Hawthorn extract is a popular herbal medicine used worldwide, particularly for its
12 cardiovascular properties⁹. Hawthorn extract has positive inotropic, anti-
13 inflammatory and anti-oxidative properties; causes peripheral and coronary
14 vasodilation; and protects against ischaemia induced arrhythmias⁹. A recent
15 systematic review concluded hawthorn extract can provide significant benefits to
16 heart failure patients as an adjunct to conventional treatment and a recent cost-
17 effectiveness study conducted in Germany concluded hawthorn is a cost-effective
18 treatment option especially in the early stages of heart failure¹⁰⁻¹².
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25 Economic evaluation is a structured method for examining the costs and
26 consequences involved with alternative methods of treatments and/or programs, in
27 order to inform which is the best alternative from a particular viewpoint¹³. The goal
28 is to improve the use of health care resources and improve patient care¹⁴. When
29 conducted rigorously, such formal analysis allows recommendation to be made with
30 transparency regarding the methods, data sources and assumptions¹³. This further
31 allows the process to be replicated, reviewed and even challenged.
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37 Models allow complex situations to be organised into a single coherent form that can
38 be used to make decisions based on comprehensive consideration of the alternative
39 interventions by capturing the essential relationships between the factors included in
40 the model and outcomes^{15 16}. Markov models define diseases using clinically
41 relevant and economically important health states, between which patients move
42 based on the natural history of the disease, and to which cost and effectiveness
43 outcomes are ascribed¹⁶.
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49 There are numerous examples of cost-effectiveness modeling in heart failure that
50 examine conventional medicine. Pharmacological, behavioural and surgical
51 interventions have all been investigated and many found to be cost-effective^{17 18}.
52 Pharmacological agents that have cost-effectiveness evidence include angiotensin
53 converting enzyme inhibitors (ACEIs), digoxin, and beta-blockers such as carvedilol
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6 and nebivolol. Multidisciplinary heart failure management, in the form of a team,
7 usually made up of a nurse co-ordinator and support from medical staff and allied
8 health including dieticians and physiotherapy, has also shown to be cost-effective
9 through reductions in hospitalisation and length of stay^{17 19}. Surgical options
10 including heart transplant, through intensive education and maximal medical therapy,
11 have demonstrated a range of cost-effectiveness values. Cardiac resynchronisation
12 therapy with or without an implantable cardioverter-defibrillator, has shown to be
13 cost-effective from a healthcare perspective^{17 20}. Most of the recent evidence
14 involves Markov modeling. ~~The models in any area of health vary in terms of the~~

15 ~~Markov states chosen, for example when representing the severity of heart failure,~~
16 ~~hospitalisations and NYHA classes of heart failure are both utilised. It is difficult to~~
17 ~~summarise the multitude of evidence and compare models as different model~~
18 ~~structures and methods are used, which potentially leads to different outcomes.²¹~~

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27 The increasing number of published health economic evaluations is not yet reflected
28 in CAM^{21 22 23}. A systematic review examined whether CAM demonstrated cost-
29 effectiveness through economic evaluations²⁴. ~~This was based on 56 economic~~
30 ~~evaluations, 39 full economic evaluations and 14 of appropriate quality for further~~
31 ~~assessment.~~ There was good evidence for the cost-effectiveness of several therapies
32 in comparison to usual care, acupuncture for migraine, manual therapy for neck pain,
33 spa therapy for Parkinson's, self-administered stress management for cancer patients
34 undergoing chemotherapy, pre- and post-operative oral nutritional supplementation
35 for lower gastrointestinal tract surgery, biofeedback for patients with "functional"
36 disorders (eg, irritable bowel syndrome), and guided imagery, relaxation therapy, and
37 a potassium rich diet for cardiac patients. ~~There were a number of therapies that~~
38 ~~were cost effective compared to usual care, and evidence to suggest CAM could be~~
39 ~~cost effective as a complement to usual care.²⁴~~

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48 ~~It has been several years since this review, but a literature search suggests the~~
49 ~~situation today is similar. It is possible to identify economic evaluation of CAM,~~
50 ~~however there remain very few full economic evaluations today. One An example~~
51 ~~of such an evaluation, is a study examining therapeutic massage, exercise, and~~
52 ~~lessons in the Alexander technique for treating persistent back pain^{25 6}. Costs~~
53 ~~included those to the National Health Service (NHS) and to participants. Outcome~~
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6 ~~measures included the Roland Morris disability score, days in pain, and quality~~
7 ~~adjusted life years (QALYs). Results included incremental cost effectiveness ratios~~
8 ~~and cost effectiveness acceptability curves.~~ Massage, lessons in the Alexander
9 technique, and an exercise prescription all provided benefits to patients over a 12-
10 month period. ~~A series of~~ six lessons in the Alexander technique combined with an
11 exercise prescription was the most ~~effective and~~ cost effective option for the NHS ^{25,6}.

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16 Some economic evaluations of CAM have incorporated decision modeling. ~~RA~~
17 ~~recently, study examined~~ the cost-effectiveness of adding acupuncture to usual care
18 for chronic low back pain ~~; was examined from a societal perspective~~, using a Markov
19 model ^{26,7}. ~~The is led to a gain of 0.13 QALYs at an incremental cost of KRW~~
20 ~~459,637, result wasting in~~ an incremental cost per QALY gained of KRW 3,421,394,
21 well below the ~~recommended~~ threshold ~~of based on the per capita gross domestic~~
22 ~~product in Korea (KRW 20,000,000). Acupuncture plus usual care was more~~
23 ~~cost-effective than usual care for these patients.~~ The probability of collaborative
24 treatment being cost-effective was 72.3%. ~~The~~ EVPI analysis suggested further
25 research ~~to reduce the uncertainty around the cost-effectiveness of collaborative~~
26 ~~treatment~~ was of reasonable value. ~~The authors concluded~~ ²⁶. ~~This highlights the need~~
27 ~~for full economic evaluations in many areas of CAM.~~

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36 The aim of this study was the construction and application of an economic decision
37 model to evaluate hawthorn treatment as an adjunct to recommended pharmacological
38 treatment versus recommended pharmacological management for chronic heart failure
39 in Australia. The analysis has been conducted using a health sector perspective.

40 41 42 43 **METHODS**

44 45 **Model Description**

46 A four state Markov model of chronic heart failure was developed based on the New
47 York Heart Association (NYHA) classification system using Microsoft Excel® (see
48 Figure 1). Classes I to IV make up four discrete health states included in the model
49 (See Table 1 for a description of the NYHA classes). A decision tree completes the
50 model. Each NYHA class has its own decision tree. Within the decision tree
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6 patients could be hospitalised for worsening heart failure. Patients also either
7 survived or died.
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9 10 **Progression through the model**

11 A simulated cohort of 1000 patients aged 60 entered the model with NYHA class II
12 heart failure and progressed through the model. Patients progress through the model
13 in one month cycles for a duration of 5 years. After one month, patients either
14 remained in NYHA class II or improved to NYHA class I or deteriorated.
15 In turn, for each class of heart failure patients were either hospitalised or not
16 hospitalised for worsening heart failure. Patients who were hospitalised or not
17 hospitalised either survived or died. Death was a possibility from any class of heart
18 failure. The patients accrued costs and benefits of treatment in each of the states for
19 each cycle.
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27 Per patient costs were required for each NYHA class. Costs were assumed to
28 be the same for standard treatment and standard treatment with hawthorn extract,
29 except for the additional cost of hawthorn extract. Patient health was considered as a
30 single index utility on a zero to one scale, where 0 represents death and 1 represents
31 perfect health. This allows the calculation of Quality Adjusted Life Years (QALYs)
32 when combined with the mortality data and the calculation of cost per QALY ratios.
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37 Two cohorts were modeled, one receiving standard pharmacological treatment and the
38 other receiving standard pharmacological treatment with hawthorn extract as an
39 adjunct. The two cohorts will progress through the model in slightly different ways
40 and as such there will be a difference in the accumulation of costs and QALYS. It is
41 the differences in costs and QALYS that will determine the cost-effectiveness of
42 hawthorn extract in addition to standard pharmacological treatment.
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47 A discount rate of 3% per year was applied to the costs and benefits. This rate is a
48 standard choice in the literature.
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53 **Table 1. NYHA grading of symptoms in chronic heart failure.**

54 NYHA	55 Description
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Class	
Class I	No symptoms and limitations in ordinary physical activity.
Class II	Slight limitation of physical activity. Ordinary physical activity results in mild symptoms such as fatigue, shortness of breath, and angina.
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms.
Class IV	Severely limited. Experiences symptoms even at rest.

Model Construction

Disease Progression

Transition probabilities for movement between NYHA classes of heart failure were estimated from the published literature detailing the large scale international Study of the Effects of Nebivolol Intervention on Outcomes and Re-hospitalisation in Seniors with Heart Failure (SENIORS) and personal correspondence with authors^{18,27}. A thorough literature search was conducted to identify disease progression data for each NYHA class, [between January 2004 and December 2009](#). Data was considered relevant if transition probabilities were provided for each NYHA class. The databases searched were Medline, CINAHL and the Cochrane Library. Search terms used included 'New York Heart Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'chronic heart failure', and 'heart failure'.

The search yielded a limited number of studies ([17 in Medline, 3 in CINAHL and 3 in the Cochrane library](#)), of which only the above study was considered suitable for inclusion.

Disease progression between the Markov states was assumed to be the same for standard treatment and for standard treatment with hawthorn extract, as we were unable to identify reliable data to indicate that hawthorn extract altered progression through the classes of heart failure. Transition probabilities were fixed over time. We have incorporated a difference in mortality and a difference in the hospitalisation rate between the standard treatment and the standard treatment with hawthorn extract as an adjunct, which in turn will impact on the cost and QALY outcomes.

Data Sources

Mortality

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6 Baseline mortality was derived from Australian Bureau of Statistics general
7 population mortality data.

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9 Mortality data was of interest if it was provided for each NYHA class and if it
10 concerned the excess mortality from heart failure and/or cardiovascular causes. The
11 databases searched were Medline, CINAHL and the Cochrane Library, between
12 January 2004 and December 2009. Search terms used included 'New York Heart
13 Association', 'NYHA', 'NYHA class', 'class', 'Markov model', 'chronic heart
14 failure', 'heart failure', 'mortality'. 83 papers were identified in Medline. 198 in
15 CINAHL and 411 in Cochrane.

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19 The mortality rate for cardiovascular causes was derived from the published literature
20 detailing one-year mortality among unselected patients with NYHA class II-IV heart
21 failure in Switzerland²⁸. The mortality rate increased with progression from NYHA
22 class I to NYHA class IV, and varied depending on whether the patient was
23 hospitalised or not. A thorough search of the literature was made to identify data for
24 each NYHA class individually, nothing was identified and the above study was the
25 closest to ideal. Hospitalisation was considered a major factor in cost estimation, so
26 data broken down by hospitalisation status was considered to represent the population
27 of heart failure patients well. Also, unselected patients were considered to represent
28 the patient cohort more accurately than studies that focused on hospitalised patients
29 only. As data for NYHA class I was not included, an assumption was made that
30 mortality for NYHA class I was the same as the general population mortality.

31 32 33 34 35 36 37 38 Health Status

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40 Estimates of health status were derived from the same source as the transition
41 probabilities^{18 20}. Data concerning utilities for heart failure is extremely limited, a
42 study was identified that had specifically had developed utilities for heart failure in
43 terms of both hospitalisation and NYHA class. However, we were unable to obtain
44 the required data despite personal correspondence with the authors. The estimated
45 health status used was considered the next best data source.

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49 Health status was assumed to be the same for standard treatment and standard
50 treatment with hawthorn extract. Hospitalisation was assumed to result in a health
51 state lower than non-hospitalisation and a -0.1 disutility was applied to hospitalisation
52 to reflect this.
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Effect of Hawthorn

A literature search identified the existing research for the use of hawthorn extract in the treatment of heart failure, [between January 2004 and January 2010](#). The search included electronic databases (Medline, ~~PubMed~~, ~~CAM on PubMed~~, [\(472 papers\)](#) AMED [\(129 papers\)](#), Econlit [\(0 papers\)](#), ~~DynaMed~~, CINAHL [\(15 papers\)](#), Cochrane Database of Systematic Reviews [\(71 papers\)](#)), hand searches of the literature, including hard copies of journals, and a search of the reference lists of the articles and publications found through electronic and hand searches. Personal communication with authors and experts including manufacturers and researchers in the field was also necessary to identify other sources of information and research that may not have been found using any other methods.

A wide range of search terms was used including: ‘heart failure’, ‘chronic heart failure’, ‘systolic heart failure’, and ‘congestive heart failure’, ‘hawthorn’, ‘Crataegus’, ‘Crataegus oxyacantha’, ‘Crataegus monogyna’, ‘whitethorn’, ‘weissdorn’, ‘Crataegus laevigata’, ‘WS 1442’, ‘LI 132’, ‘complementary’, ‘alternative’, ‘medicine’ and ‘therapy’. There were several studies written in German, these were translated into English and then examined.

Publicly accessible trials registers were also searched, [and information was current up to December 2011](#). The Australian New Zealand Clinical Trials Registry (ANZCTR) was searched, no studies were identified. The World Health Organisation International Clinical Trials Registry Platform was searched, no new relevant trials were identified. The search terms used were: ‘hawthorn extract’, ‘hawthorn’, ‘crataegus’, ‘WS1442’, ‘whitehorn’, ‘heart failure’.

There were no planned exclusion criteria at this stage for the patient population as any of the studies found have the potential to contribute valuable information to inform the model development.

The relative risk of mortality and relative risk of hospitalisation with hawthorn extract was derived from the Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in congestive heart failure (SPICE) trial, a large scale, international, randomised, placebo-controlled, double-blind study designed to investigate the influence of

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6 hawthorn extract on mortality of patients with congestive heart failure NYHA class II
7 and III with at least moderately impaired left ventricular function²⁹. To date there
8 have only been two studies to examine the effect of hawthorn extract on heart failure
9 progression in terms of mortality and hospitalisation. Most studies have focused on
10 symptoms and exercise capability. SPICE enrolled 2681 patients, and the Hawthorn
11 Extract Randomised Blinded Chronic Heart Failure (HERB CHF) trial enrolled 120
12 patients^{30 31}. Meta-analysis was not considered appropriate, therefore the data from
13 SPICE was incorporated into the model.
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19 Costs

20 No Australian data was available to estimate the hospitalisation rate and number of
21 hospitalisations, this information was derived from a United States study³².
22 The estimated length of stay in hospital data was obtained from Victorian Department
23 of Health for 2010-2011, it was unavailable for each NYHA class, so it was assumed
24 to be the same for all classes³³.
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28 The cost of a hospital admission per day was derived from the Queensland
29 Government/ Queensland Health Casemix Funding Model 2008-2009 Component
30 Prices Summary (\$3,775 per day)³⁴.
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33 Outpatient costs included General Practitioner (GP) visits, pathology (urea, creatinine,
34 electrolytes), echocardiograms, and specialist visits. Estimates of the number of GP
35 and specialist visits came from a combination of Australian sources and overseas
36 studies due to the difficulty in finding complete Australian estimates. It was
37 estimated that NYHA class I had 6 GP visits per year, and the remaining NYHA
38 classes had 12 visits per year at \$34.30 per visit. Pathology was assumed to be
39 required every 3 months at a cost of \$17.80. An Echocardiogram was assumed to be
40 performed every two years (\$230.65). A specialist visit was assumed to occur twice
41 per year (\$290 initial visit, \$194 repeat visit). If hospitalized, it was assumed patients
42 had an extra 3 specialist visits and 2 GP visits per year. The costs came directly from
43 the Medicare Benefits Schedule and the Queensland Government/ Queensland Health
44 Casemix Funding Model 2008-2009 Component Prices Summary^{34 35}.
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50 The information for which medications are taken for each NYHA class have been
51 taken from the National Heart Foundation guidelines for the treatment of chronic
52 heart failure in Australia⁵. Information for the optimal dosages prescribed has been
53 taken from the Australian Therapeutic Guidelines. Individual drug pricing was
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obtained from the most recently available online version of the Medicare Benefits Schedule. The initial version of the model has incorporated the assumption that medications are taken in 100% of patients and that dosing is optimal. The model however can be altered to consider different scenarios of medication prescription and consumption.

The dosage was assumed to be 900mg daily, consistent with the dosage used in the two most recent trials of hawthorn extract, the SPICE trial and the HERB-CHF trial²⁹³¹³⁶. An online search was conducted for standardised monopreparations of hawthorn leaf with flower available for purchase. Cardiomax® retails for A\$25.95 [for 30 x 450mg tablets \(this equates to a 15 day supply, the cost for one month is \\$51.90\)](#).

The transition parameters are listed in Table 2. The model parameters have been listed in Table 3. Appendix 1 details the calculation of transition probabilities for the model.

Table 2. Transition Parameters used in the Decision Model

<i>Transition Matrix</i>	NYHA I	NYHA II	NYHA III	NYHA IV	Distribution
NYHA I	0.977	0.019	0.004	0.000	Dirichlet
NYHA II	0.008	0.981	0.010	0.001	Dirichlet
NYHA III	0.000	0.034	0.960	0.006	Dirichlet
NYHA IV	0.000	0.000	0.055	0.945	Dirichlet

Table 3. Parameters used in the Decision Model

Probabilistic Parameters				
Parameter Description	Baseline Estimate	Variation/ SE (SD)	Distribution	Reference
Hospitalisation				
Length of stay in hospital estimate	4.9 days	Alpha 0.1 Beta 316.81	Gamma	³³
Relative Risk of Hospitalisation with Hawthorn Extract	1.03651200	0.080800494	Lognormal	³⁶
Mortality				
Excess Mortality			Beta	²⁸

probability of excess mortality given hospitalisation class II	0.01087776	Alpha 0.35916667	Beta 2.55750000	
probability of excess mortality given no hospitalisation class II	0.002620782	Alpha 0.43166667	Beta 13.485000	
probability of excess mortality given hospitalisation class III	0.01791369	Alpha 0.79666667	Beta 3.28666667	
probability of excess mortality given no hospitalisation class III	0.00674466	Alpha 0.72833333	Beta 8.60500000	
probability of excess mortality given hospitalisation class IV	0.05333974	Alpha 0.96416667	Beta 1.03583333	
probability of excess mortality given no hospitalisation class IV	0.00719464	Alpha 0.16583333	Beta 1.83416667	
Relative Risk of Mortality with Hawthorn Extract	0.90336300	0.09507420	Lognormal	³⁶
Utility			Beta	¹⁸
Utility of NYHA class I no hospitalisation	0.815	Alpha 395.88	Beta 89.86	
Utility of NYHA class II no hospitalisation	0.72	Alpha 661.95	Beta 257.42	
Utility of NYHA class III no hospitalisation	0.59	Alpha 359.8075	Beta 250.0357	
Utility of NYHA class IV no hospitalisation	0.508	Alpha 51.77	Beta 50.1394	
Fixed Parameters				
Parameter Description	NYHA class I	NYHA class II	NYHA class III	NYHA class IV
Hospitalisation				³²
Probability for hospitalisation	0.01518800	0.02397800	0.02397800	0.15397000
Probability no hospitalisation	0.98481200	0.97602200	0.97602200	0.84603000
Costs				^{34 35 37}
Cost of hospitalisation	\$2,957.08	\$4,435.63	\$4,435.63	\$5,914.17

Total cost for each NYHA class with hospitalisation	\$3,141.60	\$4,639.95	\$4,684.53	\$6,176.17
Cost of each class with no hospitalisation	\$130.30	\$150.11	\$194.69	\$207.79
Mortality				³⁸
Standardised Death Rate	6.0 per 1000	6.0 per 1000	6.0 per 1000	6.0 per 1000

Probabilistic Sensitivity Analysis

Uncertainty is addressed in the model using probabilistic sensitivity analysis. Statistical distributions were assigned to key model parameters to examine second-order uncertainty in the estimation of the parameter. Uncertainty was propagated through the model using Monte Carlo simulation, drawing parameter values at random 1000 times from the particular distributions. This generates a joint density of cost and QALY outcomes that summarises uncertainty in all model parameters.

Net Monetary Benefit

The incremental net monetary benefit was calculated. The difference between the average net benefit of the standard treatment and the average net benefit of the standard treatment with hawthorn as an adjunct is equal to the incremental net benefit. The net benefit for each treatment is the increase in effectiveness multiplied by the amount the decision maker is willing to pay per QALY (\$40,000), less the increase in cost.

The Expected Value of Perfect Information/ Expected Value of Partial Perfect Information (EVPI/ EVPPI)

The results of the modeling will indicate whether, based on the currently available information, the new treatment should be recommended. This decision is always associated with a level of uncertainty, which raises the question of whether it is appropriate to conduct further research to better examine the potential value of the new treatment, and whether we can identify where this research needs to be directed. EVPI and EVPPI analysis have been used to address these questions.

EVPI analysis is a combination of the cost of making the wrong decision in terms of forgone health benefit and wasted resources, and the probability of making a wrong

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6 decision. This equates to the expected cost of uncertainty. With all uncertainty
7 removed there would be economic savings from making the best decision and EVPI is
8 a monetary value of these savings. EVPI provides an upper bound for spending on
9 further research that reduces uncertainty in the decision. EVPPI follows the same
10 principles, but examines individual parameters³⁹.

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15 For the model it has been assumed the life of technology is 10 years and the number
16 of eligible patients per annum has been estimated at 30, 000. This estimate is derived
17 from the estimate of 30, 000 new cases of chronic heart failure per annum.

20 21 **RESULTS**

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23 For the standard treatment and standard treatment with hawthorn extract as an adjunct
24 the total cost per patient was \$4,887.82 and \$6754.59 QALYs were 2.40 and 2.42
25 respectively. This was an incremental cost of \$1866.78 and 0.02 QALYs, and the
26 incremental cost-effectiveness ratio was \$85,160.33 per QALY. A Cost-
27 Effectiveness Plane shows the joint density of cost and QALY outcomes from the
28 Monte Carlo simulations (See [Figure Appendix 2](#)). [In Figure 2, point A is the ICER.](#)
29 The variation in the model parameters can be seen in a series of histograms for each
30 of the probabilistic parameters (See Appendix [23](#)).

31 32 **Cost-Effectiveness Acceptability Curve (CEAC)**

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37 Figure [32](#) shows the uncertainty around this estimate as a cost-effectiveness
38 acceptability curve (CEAC). At a willingness to pay threshold of \$40,000, the
39 treatment with hawthorn extract has a 0.29 probability of being cost-effective. The
40 probability of being cost effective rises as the willingness to pay threshold rises, for a
41 threshold between \$500,000 and \$1,000,000 the probability is 0.48.

42 43 **Net Monetary Benefit (NMB)**

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46 For a threshold of \$40,000, the average incremental NMB is -\$1791.64, the average
47 NMB for the standard treatment is \$92,067.49, and for the standard treatment with
48 hawthorn as an adjunct \$90,275.84. The treatment with hawthorn extract has a
49 negative incremental net benefit, and would not offer good value for money for a
50 decision maker.
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Expected Value of Perfect Information (EVPI)

The population EVPI has been plotted in Figure 43 for a cost-effectiveness threshold between \$0 and \$200, 000 per QALY. The threshold was continued in the analysis up to a threshold of \$500,000 per QALY, however this did not alter the slope of the curve, so the results up to \$200, 000 have been shown.

If the population EVPI represented in Figure 43 exceeds the expected costs of additional research, then it is potentially cost-effective to conduct further research.

At a threshold of \$40,000 additional research is potentially cost-effective if research is not proposed to cost more than \$325 million.

If we proposed additional research would cost \$100 million, it can be seen from Figure 43 that this research would be potentially cost-effective at a threshold of just under \$16,000. Even at a threshold of \$0 per QALY research would potentially be cost-effective as long as the cost of research did not exceed \$15 million.

The EVPI has indicated further research is potentially cost-effective. The Expected Value of Partial Perfect Information (EVPPI) was examined to establish where further research would be of most benefit.

The Expected Value of Partial Perfect Information (EVPPI)

The EVPPI was examined for six parameters/ groups of parameters, Transitions, Average Length of stay, Excess Mortality (cardiovascular mortality), Relative Risk of Hawthorn, Utilities, and the Relative Risk of Hospitalisation.

The results of the EVPPI analysis can be seen in Figure 54 (and Table 4). From both the table and figure it can be seen that all parameters and parameter groups have significant EVPPI, but the impact varies. Utilities (\$439,471,050.98) has the highest EVPPI, and is therefore the most important target parameter/ parameter group for further research.

Table 4. Partial EVPI Values for Parameters/ Parameter Groups

Parameters	Partial EVPI
Transitions	\$7,153,571.92
Average Length of stay	\$96,900,062.41
Excess Mortality	\$105,833,952.26
Relative Risk Hawthorn	\$86,323,972.20
Utilities	\$439,471,050.98
Relative Risk Hospitalisation	\$56,991,399.70

DISCUSSION

In this modelling study we examined the cost-effectiveness of hawthorn extract in addition to standard treatment for heart failure in Australia. This treatment is not considered cost-effective given the current evidence. This is the first known attempt to examine the cost-effectiveness of hawthorn extract in addition to standard pharmacological treatment of chronic heart failure in Australia. Economic evaluation has been conducted examining hawthorn extract and standard heart failure treatment in Germany and this research indicates hawthorn extract was cost-effective in the study context, however, these studies were not considered rigorous enough for the data to be used in this study^{10 40}.

EVPI analysis indicated that further research was likely to be of benefit, and EVPPI analysis indicated that research ideally should be targeted toward Utilities. The potential costs of further research and the particular type or types that may be required are of crucial importance to the final decision. Further research to examine Utilities will likely rely on primary data from randomized controlled trials such as the Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) and the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure Study (SENIORS)^{18 41}. Alternatively such research would require the initiation of novel research with utilities as a main outcome. This is costly research and this would certainly need to be estimated before any research was undertaken.

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6 The models in any area of health vary in terms of the Markov states chosen, for
7 example when representing the severity of heart failure, hospitalisations and NYHA
8 classes of heart failure are both utilised. It is difficult to summarise the multitude of
9 evidence and compare models as different model structures and methods are used,
10 which potentially leads to different outcomes ⁴².

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15 The literature searches conducted for this study were comprehensive, although not to
16 the standard of a systematic review. It is also often seen that the keywords chosen for
17 CAM studies are not always uniform. The combination of these two factors may
18 mean we have missed some of the research available. Our search was not reliant on
19 databases alone, much of our information came from personal correspondence and a
20 thorough search of reference lists, minimizing the impact of the above limitations.

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25 A limitation of this study was the relatively sparse data available for the Australian
26 context. There is scarce data on the incidence and prevalence of heart failure.
27 Estimates rely on information from a small number of large-scale population studies
28 conducted in the United States and Europe ¹. The study of mortality in Australia is
29 complex, heart failure is considered a 'mode of death' not a 'cause of death'. Studies
30 examining mortality in terms of the underlying cause of death risk underestimating
31 mortality with condition such as heart failure. Mortality statistics are complicated by
32 multiple co-morbidities, which make the underlying cause of death difficult to
33 identify. Lack of consensus about the diagnosis of heart failure also complicates
34 recording of the cause of death, indeed complicating any examination of heart failure.
35 It is difficult to isolate costs for heart failure. Heart failure is grouped by the
36 Australian Institute of Health and Welfare as an 'other cardiovascular disease'. The
37 exact contribution of heart failure to the burden of cardiovascular disease is at best an
38 estimate.
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48 Another limitation was the availability of evidence of the effectiveness of hawthorn
49 extract. There are numerous studies supporting its use, however, very few studies that
50 examine final outcomes such as hospitalisation and mortality^{12,30,32}. Previously
51 conducted studies focus on reported outcomes including maximal workload, exercise
52 tolerance, pressure-heart rate product, 6-min walk test, and left-ventricular ejection
53 fraction. There are suggestions in the literature that the use of hawthorn extract can
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6 actually decrease the use of standard pharmacological therapy and alter the
7 progression of heart failure, but little rigorous evidence to support this ¹⁰. If the use of
8 standard pharmaceuticals was decreased, and/or disease progression was altered and
9 patients improved their NYHA class to a greater extent or remained in the less
10 symptomatic classes for longer this would decrease costs and potentially change the
11 cost-effectiveness in favour of adding hawthorn extract as an adjunct to standard
12 pharmacological treatment.
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18 Should further evidence become available, the model can easily be updated and the
19 results re-examined.
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21 **CONCLUSION**

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24 Our analysis indicates that based on currently available evidence, hawthorn extract is
25 not cost-effective in addition to standard pharmacological treatment for chronic heart
26 failure in Australia. EVPI and EVPPI analysis indicates that further research is
27 warranted, particularly in the area of utilities, pending an assessment of the estimated
28 costs of such research.
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34 public, commercial or not-for-profit sectors.
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38 **Competing Interests** None.
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41 **Contributors** EF, NG and JA were responsible for the conception and design of the
42 research. EF carried out the data collection and economic analysis. EF was
43 responsible for the original draft. All authors contributed equally to all other aspects
44 including drafting and revising, and approved the final manuscript.
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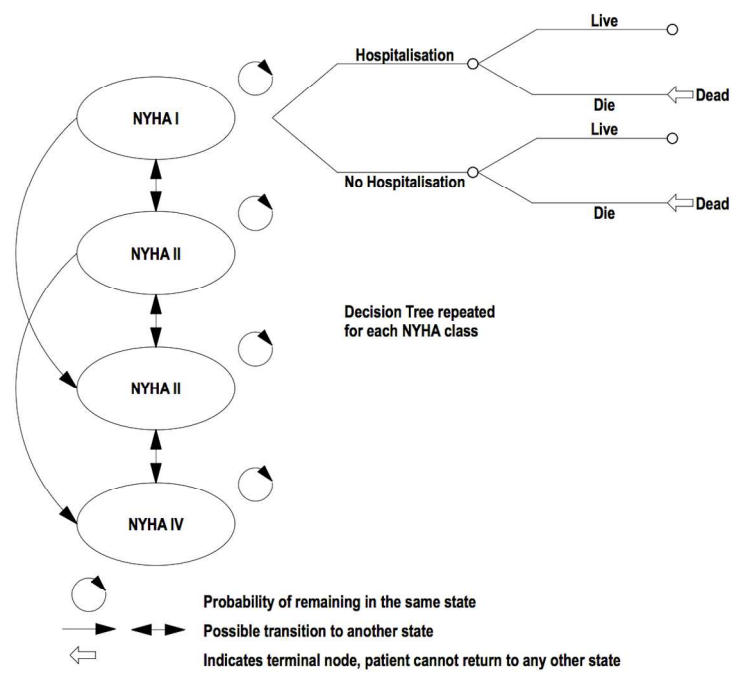
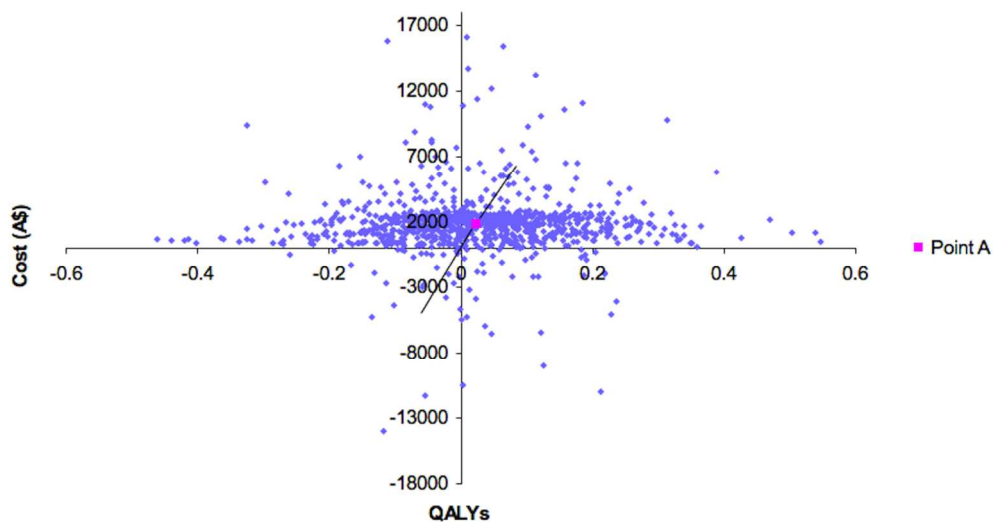


Figure 1. Markov model and decision tree showing transitions between potential health states for chronic heart failure.

451x317mm (300 x 300 DPI)

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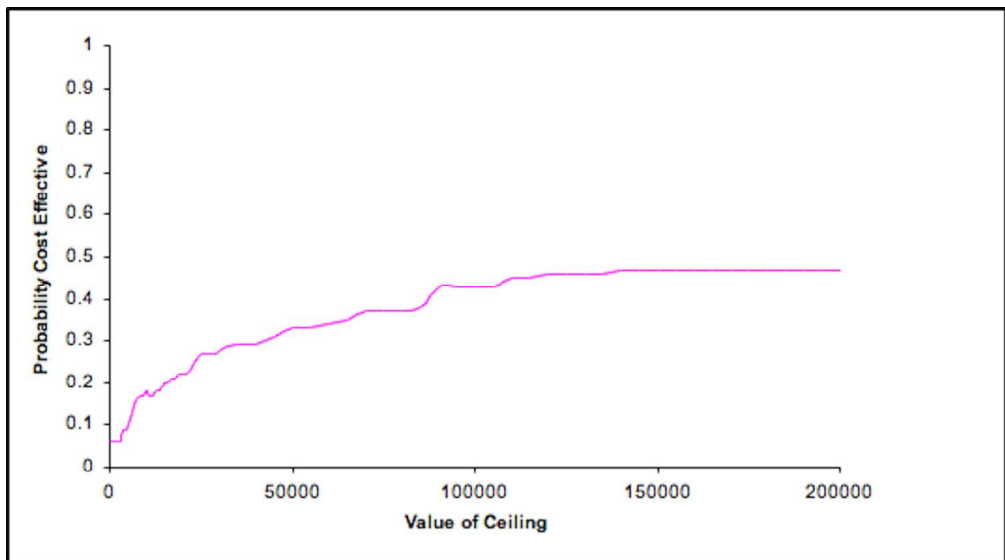


Cost Effectiveness Plane
150x84mm (300 x 300 DPI)

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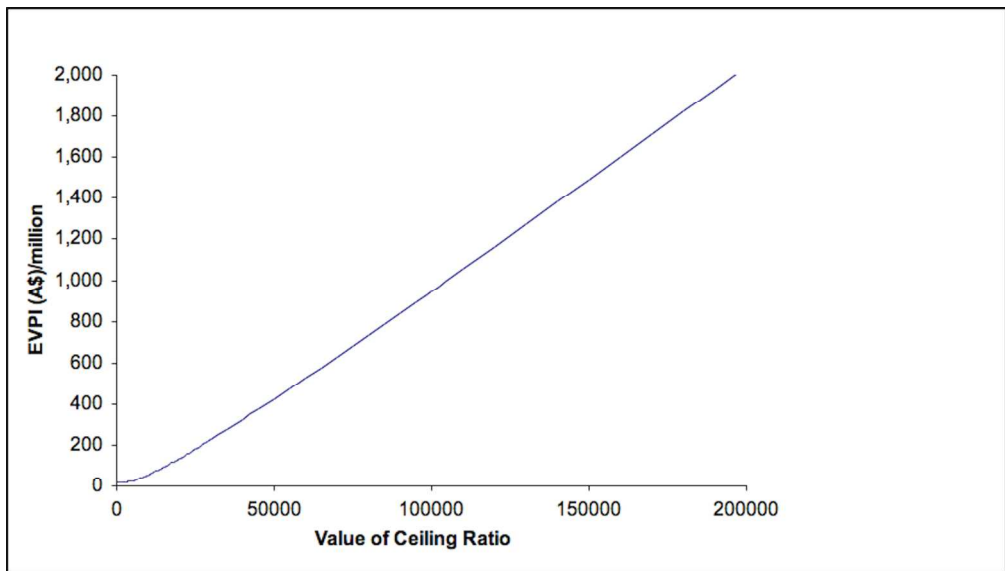
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Cost Effectiveness Acceptability Curve (CEAC)
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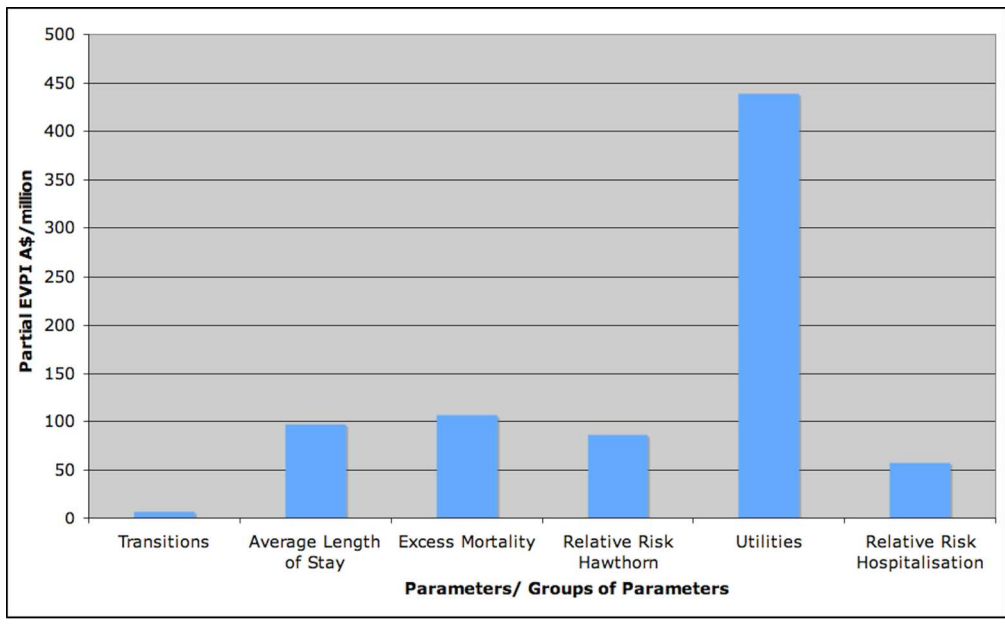
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Expected Value of Perfect Information (EVPI)
161x91mm (300 x 300 DPI)

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Expected Value of Partial Perfect Information (EVPPi)
149x91mm (300 x 300 DPI)

Review only

Appendix 1. Calculation of the Transition Probabilities for the Markov Model

<i>transition matrix</i>	NYHA I	NYHA II	NYHA III	NYHA IV	Check
NYHA I	0.977	0.019	0.004	0.000	1.000
NYHA II	0.008	0.981	0.010	0.001	1.000
NYHA III	0.000	0.034	0.960	0.006	1.000
NYHA IV	0.000	0.000	0.055	0.945	1.000
					0.000

Probabilistic version

1. Observed counts

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	59.597	1.159	0.244	0	61
NYHA II	9.6	1177.2	12	1.2	1200
NYHA III	0	28.016	791.04	4.944	824
NYHA IV	0	0	2.365	40.635	43
					2128

2. Estimated probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.977	0.019	0.004	0	1
NYHA II	0.008	0.981	0.010	0.001	1
NYHA III	0	0.034	0.960	0.006	1
NYHA IV	0	0	0.055	0.945	1

3. Random number table

	NYHA I	NYHA II	NYHA III	NYHA IV
NYHA I	0.24	0.44	0.87	0.66
NYHA II	0.91	0.62	0.99	0.21
NYHA III	0.72	0.91	0.27	0.46
NYHA IV	0.26	0.18	0.92	0.46

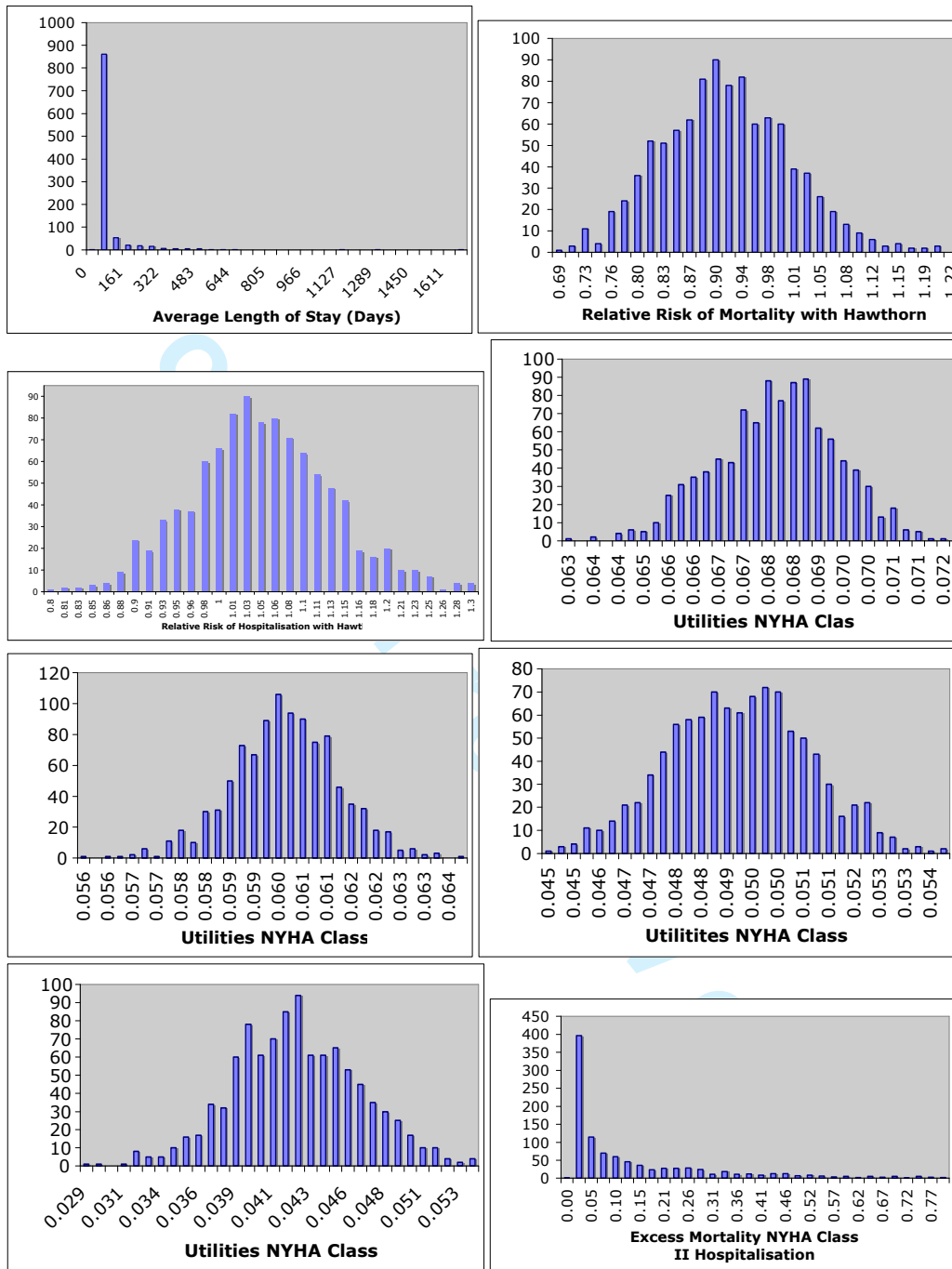
4. Cumulative gamma/normal functions

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	53.905	0.730	0.568	0	55
NYHA II	13.845	1188.106	20.983	0.342	1223
NYHA III	0	35.377	773.741	4.390	814
NYHA IV	0	0	4.735	39.593	44

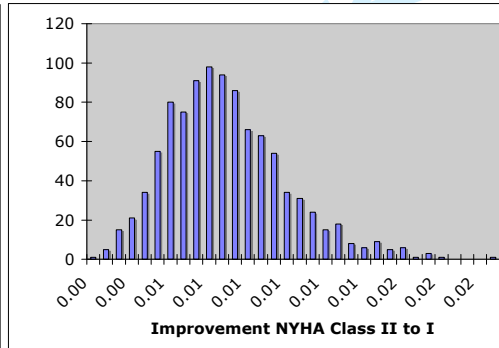
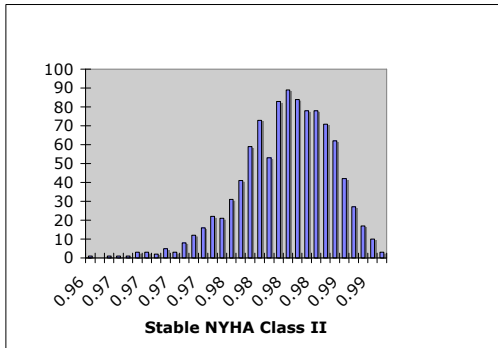
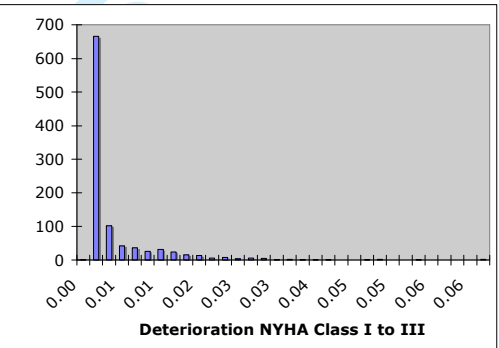
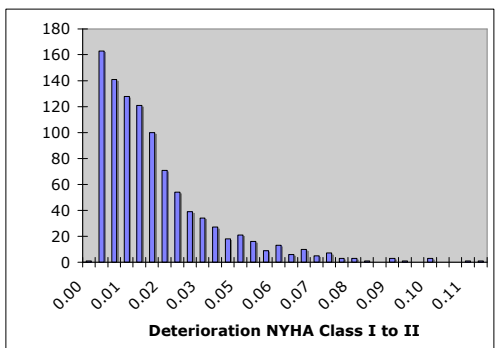
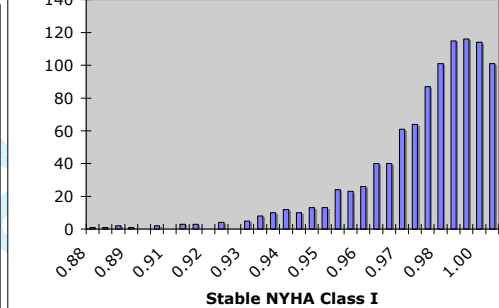
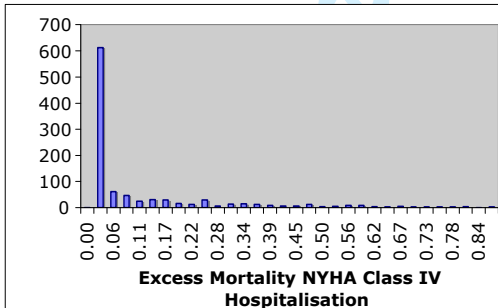
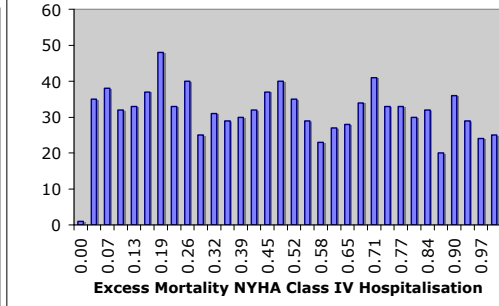
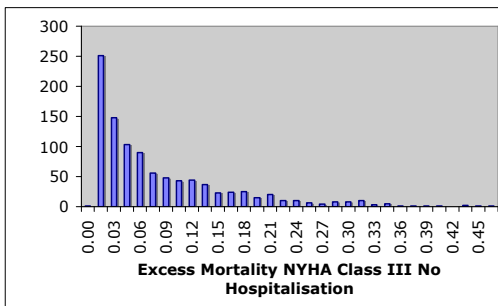
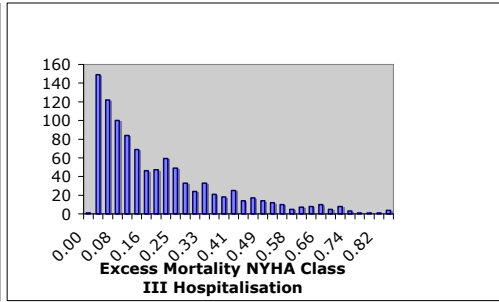
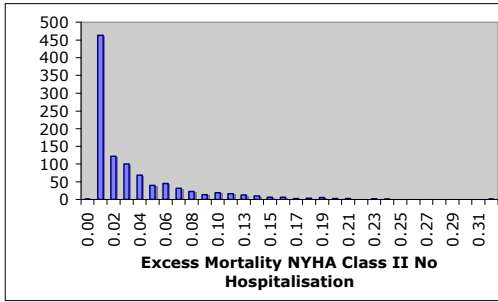
5. Random dirichlet probabilities

	NYHA I	NYHA II	NYHA III	NYHA IV	totals
NYHA I	0.976	0.013	0.010	0	1.00
NYHA II	0.011	0.971	0.017	0.000	1.00
NYHA III	0	0.043	0.951	0.005	1.00
NYHA IV	0	0	0.107	0.893	1.00

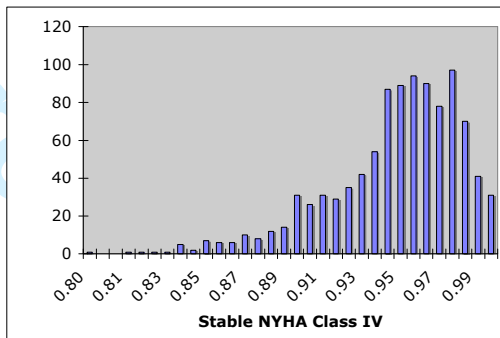
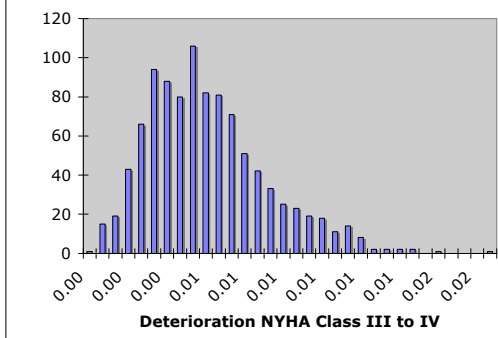
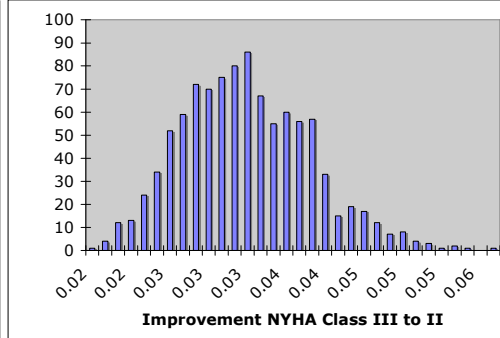
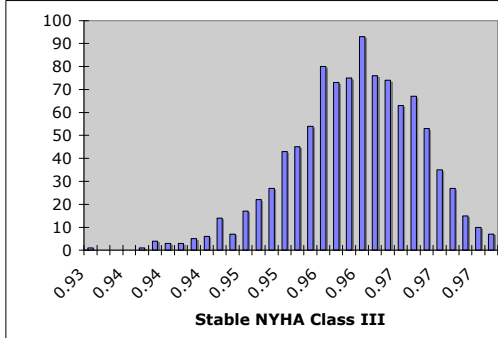
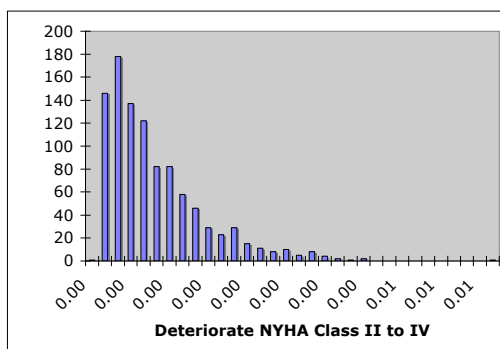
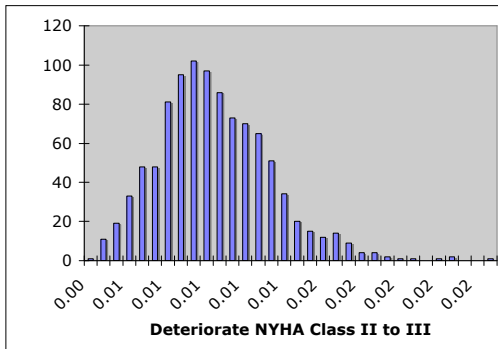
Appendix 3. Histograms of Individual Parameters



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EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	
(2) The economic importance of the research question is stated	Introduction	
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction	
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Introduction	
(5) The alternatives being compared are clearly described	Introduction; Methods	
(6) The form of economic evaluation used is stated	Introduction; Methods	
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Methods; Discussion	
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods	Presented in table form and in written form
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from multiple sources
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	N/A	Meta-analysis was not used
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	
(12) Methods to value health states and other benefits are stated	Methods	
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods	
(17) Methods for the estimation of quantities and unit costs are described	Methods	
(18) Currency and price data are recorded	Methods	
(19) Details of currency of price adjustments for	NA	As the study is

inflation or currency conversion are given		looking for relative cost, then inflation would be comparable between the different treatments
(20) Details of any model used are given	Methods	
(21) The choice of model used and the key parameters on which it is based are justified	Methods	
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods-Model construction; Discussion	Based on current cost estimates
(23) The discount rate(s) is stated	Methods	
(24) The choice of rate(s) is justified	N/A	
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	
(28) The choice of variables for sensitivity analysis is justified	Methods	
(29) The ranges over which the variables are varied are stated	Methods, Table 2	
(30) Relevant alternatives are compared	Methods	
(31) Incremental analysis is reported	Results	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Results	
(33) The answer to the study question is given	Results Discussion; Conclusion	
(34) Conclusions follow from the data reported	Discussion; Conclusion	
(35) Conclusions are accompanied by the appropriate caveats	Discussion; Conclusion	