PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Development of an Economic Model to Assess the Cost-Effectiveness of Hawthorn Extract as an Adjunct Treatment for Heart Failure in Australia
AUTHORS	Ford, Emily ; Adams, Jon; Graves, Nicholas

VERSION 1 - REVIEW

REVIEWER	Thomas Ostermann, PhD, MSc Professor for Research Methodology and Information System in Complementary Medicine Center of Integrative Medicine Faculty of Health Witten/Herdecke University GERMANY Statement of competing interests: -I do not have any competing interests-
REVIEW RETURNED	02-Apr-2012

THE STUDY	- The abstract does not reflect the content of the full text. While the objective is rather short the methods directly go into details which have not been introduced. Instead the markov states are extensively mentioned (without mentioning Monte Carlo Simulation), i.e. “Within the decision tree some patients have been admitted to hospital and some have not, some will then die, and some will survive”. This is completely confusing the reader as he has no idea what it’s all about. - The results state something about the “new treatment”, and it’s completely unclear what is meant, while in the conclusion the authors report on “Hawthorn extract”. Introduction: - While epidemiological data on heart failure is fairly well described, the path to the economic modelling has not covered the recent advances both from the viewpoint of conventional nor from the point of complementary therapies. Apart from the fact that several systematic reviews have covered the topic of health economic studies and CAM, several models have been worked out and introduced to describe potential cost effectiveness of CAM therapies from different modelling perspectives and I would be happy to read more about it. At the same time conventional medicine has brought up already several economic modelling papers on heart failure which are also not mentioned. - Instead some general remarks (“Economic evaluation is a structured method for examining the costs and consequences

	involved with alternative methods of treatments and/or programs, in order to inform which is the best alternative from a particular viewpoint…) are presented, which perhaps might be better placed in the methods section or ommitted. Methods: - The methods section is a bit unorganized. While the markov model is described very short, details are provided on the transistion probabilities. In particular, table two lists the transistion probabilities in one row of two pages (which is rather uncommon and includes several rows with no data) instead of using a transition matrix, which nevertheless is given in the appendix. I would additionally prefer a more clearcut description of the model (i.e. see Yao et al. 2007, Eur Heart J) and it's parameters (no of simulation, what kind of software,…). - The authors do not clearly draw how transistion probabilities were found. They only mention that "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" without telling more about it. - In addition the markov chain assumptions (i.e. constant markov chain, time dependency, distribution properties) are not given. If I assume correctly from table 2 there are assumption on the distribution with respect to hospitalisation and to death. However this is not explicated in the text.
RESULTS & CONCLUSIONS	Results: - Again the authors switch their terminology and talk about the "new treatment". It seems that a more formal biometrical report has just been pasted into the manuscript, which is difficult to read. This impression continues throughout the complete results section. - I'm a bit puzzled why the Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model is only provided in the appendix and not further explained as in my opinion it is one of the essential results of the simulation. Discussion: - Although the authors state that 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" the study of Habs mentioned in the introduction is not further discussed. In addition the study of Koller et al. (2005) on "Crataegus Special Extract WS® 1442 in the treatment of early stages of CHD-associated heart failure. Results of a prospective cohort study investigating economics and the impact on quality of life" is also not mentioned. - The authors also state that only "very few studies that examine final outcomes such as hospitalisation and mortality". This is not supported by any reference nor does it reflect the situation of published studies. - The authors discuss that "if such evidence was available this would change the costs and benefits of hawthorn extract, and potentially change the cost effectiveness of hawthorn extract as an adjunct to standard pharmacological treatment. But isn't that the idea of health economic modelling to come to assumptions by simulations if there is not such data. This really does not add to a health economic discussion and the authors should concentrate more on the modelling aspect.

REVIEWER	Gary Asher, MD, MPH Assistant Professor University of North Carolina Chapel Hill, USA I have no competing interests to declare.
REVIEW RETURNED	24-Apr-2012

THE STUDY	Methods Why did patients start off with NYHA II instead of NYHA I, especially considering that less sick patients (based on EF) appeared to do better than sicker patients, at least in SPICE? How were Emergency Department visits and care factored into the model? How was outpatient care factored into the model? What pathology costs are associated with heart failure care? Why was there no inclusion of clinical laboratory evaluation costs? What about surgical costs: HF patients with low EF often have defibrillators placed. What was the estimate of cost for hawthorn and how was it derived? How were the standard treatment costs derived? Were the hospital admissions HF-specific? It is probably incorrect to assume LOS was the same for all NYHA classes: what happens to the model when LOS increases by NYHA class, as we would expect? Please tell us more about the thorough literature searches performed: databases, search strategy, inclusion/exclusion criteria, etc. Rather than state you did not identify data that hawthorn altered disease progression, why not state that you did find data that suggested there was no difference for disease progression (citation 22)? Why was meta-analysis considered inappropriate for SPICE and HERB-CHF? (I think you may have incorrectly reported the number of randomized participants in SPICE by about 15%). How would small changes in the mortality estimates associated with hawthorn alter the CE analysis? This would be a nice place to include a sensitivity analysis. It is fine to create a model that assumes 100% adherence; how does the model change when that assumption is broken? Which model parameters were considered key that were included in the probabilistic sensitivity analysis?
RESULTS & CONCLUSIONS	Discussion Are there cost-effectiveness analyses for any of the aspects of standard heart failure care? It would be a nice addition to the discussion to see how these aspects stacked up. When discussing the study limitations, it would be helpful to include how the limitation might actually affect the study results (ie. direction, magnitude).

	Given the paucity of data for hawthorn on important outcomes for HF, it may be overreaching to conclude that hawthorn is not cost effective. Perhaps the model is not yet fully developed to accurately predict cost-effectiveness for hawthorn. Sensitivity analyses might offer some sense of how effective hawthorn would need to be for certain outcomes in order for it to be cost-effective.
GENERAL COMMENTS	This is a cost-effectiveness analysis comparing standard treatment for heart failure and standard treatment plus hawthorn extract. Although the data are mixed concerning hawthorn's efficacy in heart failure, the Cochrane meta-analysis by Guo et. al. suggests some benefit. Therefore, the cost-effectiveness of the extract is important to consider. In general, the manuscript is nicely written, especially concerning important aspects of their modeling technique that may be unfamiliar to many readers. Addition of certain details in the methods would make the study more transparent. Furthermore, given the paucity of data on hawthorn and other important factors to the analysis, inclusion of some sensitivity analyses would be helpful. Introduction With the paucity of data available in Australia, why not conduct the entire analysis based on data from another country (European or US), then attempt to translate those findings to Australia?

VERSION 1 – AUTHOR RESPONSE

Reviewer:
Thomas Ostermann, PhD, MSc Professor for Research Methodology and Information System in Complementary Medicine Center of Integrative Medicine Faculty of Health Witten/Herdecke University GERMANY Statement of competing interests: -I do not have any competing interests-

- The abstract does not reflect the content of the full text. While the objective is rather short the methods directly go into details which have not been introduced. Instead the markov states are extensively mentioned (without mentioning Monte Carlo Simulation), i.e. "Within the decision tree some patients have been admitted to hospital and some have not, some will then die, and some will survive". This is completely confusing the reader as he has no idea what it's all about.

In the abstract we have summarised the paper so a reader can see if it is relevant to them, at this point in the manuscript we don't feel an explanation of the concepts are required. We have changed the abstract to make it reflect the contents of the paper and make it easier to follow (see Page 2).

- The results state something about the "new treatment", and it's completely unclear what is meant, while in the conclusion the authors report on "Hawthorn extract".

The terminology in the results have been changed to match the conclusion. Instead of 'new treatment', 'hawthorn extract' has been used in the results (see page 2).

Introduction:
- While epidemiological data on heart failure is fairly well described, the path to the economic

modelling has not covered the recent advances both from the viewpoint of conventional nor from the point of complementary therapies.
Apart from the fact that several systematic reviews have covered the topic of health economic studies and CAM, several models have been worked out and introduced to describe potential cost effectiveness of CAM therapies from different modelling perspectives and I would be happy to read more about it.

Information regarding the current state of literature for economic evaluation and CAM has been added to the introduction (see page 5-6).

At the same time conventional medicine has brought up already several economic modelling papers on heart failure which are also not mentioned.

Information regarding the state of current economic modeling and conventional medicine in heart failure has been added to the introduction (see page 4-5).

- Instead some general remarks ("Economic evaluation is a structured method for examining the costs and consequences involved with alternative methods of treatments and/or programs, in order to inform which is the best alternative from a particular viewpoint…) are presented, which perhaps might be better placed in the methods section or ommitted.

We feel the general remarks provide a valuable explanation for someone who doesn't know a lot about economic evaluation, they should either be deleted if not considered valuable or left in place, they are not appropriate for the methods.

Methods:
- The methods section is a bit unorganized. While the markov model is described very short, details are provided on the transistion probabilities. In particular, table two lists the transistion probabilities in one row of two pages (which is rather uncommon and includes several rows with no data) instead of using a transition matrix, which nevertheless is given in the appendix.

We have added the transition probability matrix (See Table 2, page 12).

We have changed the table to make it easier to read (see Table 3, page 12-13). We stayed with the journal convention to use 4 tables and 4 figures, we can make further changes to the table or make it several tables if the editor prefers.

I would additionally prefer a more clearcut description of the model (i.e. see Yao et al. 2007, Eur Heart J) and it's parameters (no of simulation, what kind of software,…).

The number of simulations was 1000 and is mentioned in the section titled 'Probabilistic Sensitivity Analysis' in the Methods (See page 13).
The kind of software used was Microsoft Excel and has been described in the Model Description (See page 6).

- The authors do not clearly draw how transistion probabilities were found. They only mention that "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" without telling more about it.

The literature search details have been added to the manuscript (see page 8).

- In addition the markov chain assumptions (i.e. constant markov chain, time dependency, distribution properties) are not given. If I assume correctly from table 2 there are assumption on the distribution with respect to hospitalisation and to death. However this is not explicated in the text.

The model assumptions are discussed for each parameter, we have added some information for

transition probabilities (see page 8-12).
We have also changed the table to make it easier to read (see Page 12-13).

For example we have described that mortality is dependent on whether a patient has been hospitalised or not, and that mortality is made up of baseline mortality and excess mortality.

Results:
- Again the authors switch their terminology and talk about the “new treatment”. It seems that a more formal biometrical report has just been pasted into the manuscript, which is difficult to read. This impression continues throughout the complete results section.

The term ‘new treatment’ has been replaced with ‘standard treatment with hawthorn as an adjunct’ or the treatment with hawthorn extract’ (See page 15).

- I’m a bit puzzled why the Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model is only provided in the appendix and not further explained as in my opinion it is one of the essential results of the simulation.

The cost-effectiveness plane provides valuable information, however, we consider it the starting point for analysis, not the basis for a definitive decision, so we thought it was not essential to include in the actual manuscript, but needed to be included somewhere.
The journal convention was to include 4 figures and 4 tables, and we considered the other figures were important to include. The EVPI analysis is unique and important to include both figures.
We are happy to include in the main manuscript if the editor prefers.

Discussion: - Although the authors state that 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” the study of Habs mentioned in the introduction is not further discussed. In addition the study of Koller et al. (2005) on “Crataegus Special Extract WS® 1442 in the treatment of early stages of CHD-associated heart failure. Results of a prospective cohort study investigating economics and the impact on quality of life” is also not mentioned.

We have added Habs et al and Koller et al to the discussion (see page 17).

- The authors also state that only “very few studies that examine final outcomes such as hospitalisation and mortality”. This is not supported by any reference nor does it reflect the situation of published studies.

There are very few studies of hawthorn extract which examine final outcomes. This was the result of the literature reviews conducted to inform the parameters used in the model. There are numerous studies that examine the intermediate outcomes of using hawthorn extract, such as physical symptoms, but only two known studies that have examined hospitalisation and mortality.

We have added the references to the sentence for the SPICE trial and the HERB trial and the Cochrane Review (see Page 18).

- The authors discuss that “if such evidence was available this would change the costs and benefits of hawthorn extract, and potentially change the cost effectiveness of hawthorn extract as an adjunct to standard pharmacological treatment. But isn’t that the idea of health economic modelling to come to assumptions by simulations if there is not such data. This really does not add to a health economic discussion and the authors should concentrate more on the modelling aspect.

The role of economic modeling is to utilise the best available information and published evidence. The quality of this will vary and in some cases expert opinion is the best source. We have built a model and made conclusions based on the currently available best evidence, and crucially we have included the effects of uncertainty in the modeling. The value of information analysis completed reveals how research funding should be allocated to reduce uncertainty in the future.

Reviewer: Gary Asher, MD, MPH Assistant Professor University of North Carolina Chapel Hill, USA I have no competing interests to declare.

Methods
Why did patients start off with NYHA II instead of NYHA I, especially considering that less sick patients (based on EF) appeared to do better than sicker patients, at least in SPICE?

NYHA class II was considered the target population as most of the evidence incorporated into the model applied to NYHA class II. SPICE enrolled NYHA class II and III, HERB-CHF enrolled NYHA class II and III. Another consideration was that hawthorn extract is approved for use in Germany for NYHA class II patients.

How were Emergency Department visits and care factored into the model?

Only hospital admission costs were considered. Many of the papers we have used for the study used hospitalisation costs only. We realize this is an omission but modeling studies are inevitably a trade-off between simplifying a complex story and describing the key economic drivers.

How was outpatient care factored into the model?

We have changed the manuscript to include frequency and cost data (see Page 11.

What pathology costs are associated with heart failure care?

It was assumed that patients have pathology every 3 months (urea, creatinine, electrolytes).
This data comes from a 2005 Australian paper written for the Australian Family Physician detailing the general practice care for chronic heart failure.

Cost of pathology:
The fee for pathology (urea, electrolytes and creatinine, item number 66512 under the Medicare Benefits Schedule) is $17.80.

We have added the pathology (urea, electrolytes and creatinine) to the manuscript (see page 11).

Why was there no inclusion of clinical laboratory evaluation costs?

This was included in the calculation of costs, and it has been noted on page 11 that pathology was included in the calculation of outpatient care costs.

What about surgical costs: HF patients with low EF often have defibrillators placed.

This would tend to apply to patients with more severe heart failure. This was not estimated. This would be the same for both cohorts.

What was the estimate of cost for hawthorn and how was it derived?

This has been described in the manuscript, we have added the cost (see page 12).

How were the standard treatment costs derived?

Deriving the costs was a complex process involving estimates of hospital admissions and resource use, this has been outlined in the costs section (see page 11-12).

Were the hospital admissions HF-specific?

Where possible the data used has been for hospital admissions for worsening heart failure. The estimate of the number of hospital admissions per NYHA class is based on all hospital admissions as we were unable to find appropriate estimates for worsening heart failure or cardiovascular admission

alone. This may overestimate the number of admissions.

It is probably incorrect to assume LOS was the same for all NYHA classes: what happens to the model when LOS increases by NYHA class, as we would expect?

Whilst the average length of stay in hospital does not vary by NYHA class, the costs in the model increase with each NYHA class. This is a combination of an increase in the medications and an increased probability of hospitalisation and the number of hospitalisations (see Table 3, Page 12-13).

Please tell us more about the thorough literature searches performed: databases, search strategy, inclusion/exclusion criteria, etc.

This information has been added to the manuscript.

For transition probabilities see page 8.

For mortality see page 9.

For hawthorn extract see page 9-10.

Rather than state you did not identify data that hawthorn altered disease progression, why not state that you did find data that suggested there was no difference for disease progression (citation 22)?

We have changed the sentence to read ‘reliable’ instead of ‘any’. There was an economic evaluation conducted in Germany which suggested that progression was slowed, however, it was not considered a reliable study to include.

‘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. We have incorporated a difference in mortality’ (see page 8).

Why was meta-analysis considered inappropriate for SPICE and HERB-CHF? (I think you may have incorrectly reported the number of randomized participants in SPICE by about 15%).

Meta-anlaysis was considered inappropriate due to the small sample size of the HERB-CHF trial (120 patients), compared to the large scale SPICE trial, and adding 120 patients to the large trial would not impact the conclusion.
The number of randomised patients was 2681, this has been changed in the manuscript (see page 10).

How would small changes in the mortality estimates associated with hawthorn alter the CE analysis? This would be a nice place to include a sensitivity analysis.

Uncertainty with regard to the mortality statistics has been assessed using Probabilistic Sensitivity Analysis. In addition, the results of the EVPI and partial EVPI analysis identify target parameters for potential research in the future.

It is fine to create a model that assumes 100% adherence; how does the model change when that assumption is broken?

These scenarios can be considered in future work.

Which model parameters were considered key that were included in the probabilistic sensitivity analysis?

This is outlined in the table of parameters (see Table 2 and 3), the key probabilistic parameters are identified (see page 12-13).
The probabilistic parameters included transition probabilities, excess mortality, average length of stay in hospital, utilities, relative risk of hawthorn extract and the relative risk of hospitalisation.

Discussion
Are there cost-effectiveness analyses for any of the aspects of standard heart failure care? It would be a nice addition to the discussion to see how these aspects stacked up.

These have been added to the Introduction (see Page 4-5).

When discussing the study limitations, it would be helpful to include how the limitation might actually affect the study results (ie. direction, magnitude).

This has been added (see page 18).

Given the paucity of data for hawthorn on important outcomes for HF, it may be overreaching to conclude that hawthorn is not cost effective. Perhaps the model is not yet fully developed to accurately predict cost-effectiveness for hawthorn.

A lack of evidence is not necessarily a reason to defer a decision regarding cost-effectiveness. As the evidence was limited, we knew the value of perfect information analysis would be helpful in determining whether further research would be of benefit.

Sensitivity analyses might offer some sense of how effective hawthorn would need to be for certain outcomes in order for it to be cost-effective. This is a cost-effectiveness analysis comparing standard treatment for heart failure and standard treatment plus hawthorn extract. Although the data are mixed concerning hawthorn's efficacy in heart failure, the Cochrane meta-analysis by Guo et. al. suggests some benefit. Therefore, the cost-effectiveness of the extract is important to consider. In general, the manuscript is nicely written, especially concerning important aspects of their modeling technique that may be unfamiliar to many readers. Addition of certain details in the methods would make the study more transparent. Furthermore, given the paucity of data on hawthorn and other important factors to the analysis, inclusion of some sensitivity analyses would be helpful.

Uncertainty has been addressed in the model using probabilistic sensitivity analysis. Parameter uncertainties have been included appropriately, 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 generated a joint density of cost and QALY outcomes that summarized the uncertainty in all model parameters.

Additionally, EVPI analysis and partial EVPI analysis shows where future research should be targeted.

Introduction With the paucity of data available in Australia, why not conduct the entire analysis based on data from another country (European or US), then attempt to translate those findings to Australia?

We have used a hierarchy of evidence published by Cooper et al and evidence from the country of origin ranks more highly than evidence derived from another country even if similar. The goal was to obtain as much Australian evidence as possible to make it as applicable as possible. This has been difficult, but we think the use of Australian data remains valuable.

We are aware we have now exceeded the word limit of 4000 words, it was difficult not to exceed this limit as we attempted to include as much of the reviewer feedback as possible.

Yours sincerely

Emily Ford

VERSION 2 – REVIEW

REVIEWER	Thomas Ostermann, PhD, Msc, Professor for Reearch Methodology and Information Systems in Complementary Medicine, Witten/Herdecke University, GERMANY
REVIEW RETURNED	05-Jul-2012

THE STUDY	With respect to the “Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model” I also would ask the editors if it is possible to include this Figure in the main body instead of the appendix.
GENERAL COMMENTS	The authors have adressed all the points in an adaequate manner. There are only some minor points in the introduction which should be addresses to improve the reading of the manuscript: - The section “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 outcomes” might be better placed in the discussion section. - The same holds for the section “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.“ Some of the information give can be place in the following sentence: “There were a number of therapies (i.e. acupuncture for migraine, manual therapy for neck pain) that were… .” - Also the Alexander technique example is described very extensively and might be shortened. - The next example leads the way to the current study. However one sentence in between …acupuncture plus usual care was more cost•effective than usual

	care for these patients 27.“ and “The aim of this study was…” might help the reader to understand why this example is given in the introductory part. After these minor introductory revisions I would be happy to read the full paper in BMJOpen.

REVIEWER	Gary Asher, MD, MPH Assistant Professor University of North Carolina at Chapel Hill USA
REVIEW RETURNED	04-Jun-2012

GENERAL COMMENTS	Thank you for the responses to the original reviews. The responses were thoughtful and thorough in most aspects save for 1 or 2 important points. The baseline assumptions in the models were made based on estimates derived from the medical literature. Therefore, it’s important to be transparent about the literature search. Thank you for including the names of the databases and search terms used. Missing, still, are the inclusive dates of the searches and the number of studies identified with the search strategy. Concerning the search terms, although I have not gone to check all of the terms, a very quick check on the term ‘Markov model’ in pubmed shows that you will miss about 20-25% of the possible citations by using this text term alone without the proper MESH term (Markov chains). Why did you search the term ‘class’? In any event, this search strategy does not exactly appear ‘thorough’. Furthermore, and perhaps more importantly, the search on Hawthorn does not include EMBASE. Many, perhaps most, studies of hawthorn have been done in Europe, and not all of them have been catalogued in Medline. A quick search on the terms ‘Hawthorn or Crataegus’ in pubmed reveals 1438 citations while the same search in EMBASE yields 5038 citations. Concerning the databases themselves, pubmed, medline, and CAM on Pubmed are essentially the same thing: Medline is the actual database that you searched, Pubmed is the search engine to access Medline, and CAM on Pubmed is simply a search filter for pubmed (eg. the same search for ‘hawthorn or crataegus’ yields 573 citations with the CAM filter). The bottom line here is that if you wish to conclude you’ve done a ‘thorough search’, and have ‘identified the existing research for the use of hawthorn’, please do a more convincing job of describing the search strategy and results. Alternately, you could more thoroughly describe the limitations to your search strategy in the Discussion section. It was a nice touch to have looked at the Australian and WHO

	clinical trial registries, but curious that the European (EudraCT) and U.S. (Clinicaltrials.gov) were overlooked since both are freely accessible by the public. Finally, it was encouraging to see the actual costs used in the model for each of the parameters mentioned. However, the price for hawthorn is still confusing. Is this the cost that was used in the model? What does A$25.95 represent, a month supply? The cost listed, at least by a current online search, is approximately equal to 30 tablets of the 450mg dose, or a 15 day supply. I will encourage the editors to allow the manuscript to go beyond the 4000 word limit, since much of the added information will be of value to readers. I would, however, suggest removing the 2 new paragraphs on page 6 that discuss economic evaluations generally (or perhaps summarize them more briefly within the preceding paragraph (end page 5).

VERSION 2 – AUTHOR RESPONSE

Reviewer: Thomas Ostermann, PhD, Msc,
Professor for Reearch Methodology and Information Systems in Complementary Medicine,
Witten/Herdecke University, GERMANY

With respect to the “Cost-Effectiveness Plane Showing Cost and QALY Outcomes for Markov Model” I also would ask the editors if it is possible to include this Figure in the main body instead of the appendix.

We have moved this to the main body instead of the appendix.

The authors have adressed all the points in an adaequate manner.

There are only some minor points in the introduction which should be addresses to improve the reading of the manuscript:

- The section “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 outcomes” might be better placed in the discussion section.

This has been placed in the discussion (see page 17).

- The same holds for the section “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.“

Some of the information give can be place in the following sentence:

“There were a number of therapies (i.e. acupuncture for migraine, manual therapy for neck pain) that were… .”

We have removed some sections of this paragraph to make it less repetitive and shorter, and to make it easier to read (see page 5).

- Also the Alexander technique example is described very extensively and might be shortened.

As per the previous reviewer, we have shortened the two new paragraphs that were on page 6. They have been merged together and now appear at the bottom of page 5 and top of page 6.

- The next example leads the way to the current study. However one sentence in between

…acupuncture plus usual care was more cost•effective than usual care for
these patients 27.“ and “The aim of this study was…”

might help the reader to understand why this example is given in the introductory part.

We have added a sentence to link the research described with the aim of our study (see page 6).

‘This highlights the need for full economic evaluations in many areas of CAM’.

After these minor introductory revisions I would be happy to read the full paper in BMJOpen.

Reviewer: Gary Asher, MD, MPH
Assistant Professor
University of North Carolina at Chapel Hill
USA

Thank you for the responses to the original reviews. The responses were thoughtful and thorough in most aspects save for 1 or 2 important points.
The baseline assumptions in the models were made based on estimates derived from the medical literature. Therefore, it’s important to be transparent about the literature search. Thank you for including the names of the databases and search terms used. Missing, still, are the inclusive dates of the searches and the number of studies identified with the search strategy.

The inclusive dates of the searches have been included (January 2004 until December 2009). The search for transition probabilities identified 17 papers (see page 7/8). The same has been done for the mortality data (see page 8).

Concerning the search terms, although I have not gone to check all of the terms, a very quick check on the term ‘Markov model’ in pubmed shows that you will miss about 20-25% of the possible citations by using this text term alone without the proper MESH term (Markov chains).

We acknowledge that ‘Markov Chains’ would have been a useful additional search term. In order to assess the effect of this on our study, we have redone the searches including this term and have found that although in some cases it resulted in an increased number of papers identified, these were either identified through other means or were not useful.

For the transition probabilities search, the Medline search yielded 17 papers, including Markov chain increased this to 25. Two of the extra papers were identified in other databases and the remainder were not relevant (for example, used children only, looked at defibrillators, cardiac resynchronisation and advanced heart failure only).

For the mortality search Medline yielded 83 papers for our search terms and 91 including 'Markov chains', CINAHL yielded the same number of papers and Cochrane yielded the same number. A quick search of the extra papers found that the extra papers would not have been used in the study.

Why did you search the term 'class'?

A good point, searching for NYHA and NYHA class probably already covered finding papers addressing NYHA class in heart failure, it was searched in an attempt to be thorough, but probably was not necessary.

In any event, this search strategy does not exactly appear 'thorough'.

The search was not intended to be as rigorous as required for the purposes of systematic review. We used the term thorough to indicate that the search was comprehensive.

We are happy to include as a limitation that the search was detailed but not to the standard of a systematic review and this may have missed some research, however, our search was not reliant on databases alone and we feel that we have identified much of what was possible to find (see page 17).

In addition to this we have also added the common finding that the CAM keywords are often not uniform, making searching databases more challenging.

Furthermore, and perhaps more importantly, the search on Hawthorn does not include EMBASE. Many, perhaps most, studies of hawthorn have been done in Europe, and not all of them have been catalogued in Medline. A quick search on the terms 'Hawthorn or Crataegus' in pubmed reveals 1438 citations while the same search in EMBASE yields 5038 citations.

It would have been very useful to use Embase to search for information regarding hawthorn extract, however, this study was conducted as part of post graduate work through the University of Queensland and Embase was not available at the time of the search for information. It is now available.

We have gone beyond a simple Medline search, we have searched AMED, which covers mainly European journals, and covers CAM as one of its specialties.

We have conducted a search of Embase and it provided 2 papers, neither of which were relevant. We have removed the database 'Dynamed' as UQ no longer offers it as a search option and we cannot verify the original search.

Correspondence with authors and pharmaceutical companies identified an additional paper not identified through the literature review. Also, the reference lists of the studies identified through the search and from the Cochrane review were searched and we believe this has identified as much literature as possible.

Our searches were not restricted to the English language, the services of a translator enabled us to assess and utilise the identified German research.

Our main interest for the effectiveness of hawthorn extract was studies that had examined the final outcomes of morbidity (in terms of hospitalisation) and mortality, and we know without a doubt that the two studies mentioned are the only two that have been conducted.

Concerning the databases themselves, pubmed, medline, and CAM on Pubmed are essentially the same thing: Medline is the actual database that you searched, Pubmed is the search engine to access Medline, and CAM on Pubmed is simply a search filter for pubmed (eg. the same search for 'hawthorn or crataegus' yields 573 citations with the CAM filter).

We have deleted Pubmed and CAM on Pubmed from the text (see page 9).

The bottom line here is that if you wish to conclude you've done a 'thorough search', and have 'identified the existing research for the use of hawthorn', please do a more convincing job of describing the search strategy and results. Alternately, you could more thoroughly describe the limitations to your search strategy in the Discussion section.

We have added to the discussion as per the previous point.

It was a nice touch to have looked at the Australian and WHO clinical trial registries, but curious that the European (EudraCT) and U.S. (Clinicaltrials.gov) were overlooked since both are freely accessible by the public.

The WHO Clinical Trials Search Portal provides access to a central database containing multiple trial registration data sets, which enables free access to a great range of registered trials.
These are:
Updated every week:
• Australian New Zealand Clinical Trials Registry
• ClinicalTrials.gov
• EU Clinical Trials Register (EU-CTR)
• ISRCTN
Updated every 4 weeks:
• Brazilian Clinical Trials Registry (ReBec)
• Chinese Clinical Trial Registry
• Clinical Trials Registry
• Clinical Research Information Service
• Cuban Public Registry of Clinical Trials
• German Clinical Trials Register
• Iranian Registry of Clinical Trials
• Japan Primary Registries Network
• Pan African Clinical Trial Registry
• Sri Lanka Clinical Trials Registry
• The Netherlands National Trial Register

Finally, it was encouraging to see the actual costs used in the model for each of the parameters mentioned. However, the price for hawthorn is still confusing. Is this the cost that was used in the model? What does A$25.95 represent, a month supply? The cost listed, at least by a current online search, is approximately equal to 30 tablets of the 450mg dose, or a 15 day supply.

A one month supply of hawthorn extract was considered to be two packets (of 30 x 450mg tablets). We have added this to the manuscript (see page 12).

‘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)’

I will encourage the editors to allow the manuscript to go beyond the 4000 word limit, since much of the added information will be of value to readers. I would, however, suggest removing the 2 new paragraphs on page 6 that discuss economic evaluations generally (or perhaps summarize them more briefly within the preceding paragraph (end page 5).

The two paragraphs have been summarised more briefly and merged together (see page 5/6).

Yours sincerely

Emily Ford