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# The importance of model structure in the cost-effectiveness analysis of primary care interventions for the management of hypertension

Abstract

Background: Management of hypertension can lead to significant reductions in blood pressure, thereby reducing the risk of cardiovascular disease (CVD). Modelling the course of CVD is not without complications, and uncertainty surrounding the structure of a model will almost always arise once a choice of a model structure is defined.

Objective: To provide a practical illustration of the impact, on results of cost-effectiveness, of changing or adapting model structures in a previously published cost utility analysis of a primary care intervention for the management of hypertension (TASMIN-SR).

Methods: Case study assessing structural uncertainty arising from model structure and from the exclusion of secondary events. Four alternative model structures were implemented. Long-term cost-effectiveness was estimated and the results compared to those from the TASMIN-SR model.

Results: The main cost-effectiveness results obtained in the TASMIN-SR study did not change with the implementation of alternative model structures. Choice of model type was limited to a cohort Markov model and, due to lack of epidemiological data, only Model 4 captured structural uncertainty arising from the exclusion of secondary events in the case study model.

Conclusion: The results of this study indicate that main conclusions drawn from the TASMIN-SR model of cost-effectiveness were robust to changes in model structure and the inclusion of secondary events. Even though one of the models produced results that were different to those of TASMIN-SR, the fact that the main conclusions were identical suggests that a more parsimonious model may have sufficed.

Words: 242

## Introduction

High blood pressure (hypertension, defined as blood pressure (BP) persistently (140/90mmHg) is one of the most important but preventable causes of premature morbidity and mortality in the UK and worldwide.(1-3) Hypertension is a major risk factor for ischaemic and haemorrhagic stroke, myocardial infarction (MI), heart failure (HF), chronic kidney disease (CKD), cognitive decline and premature death. It has been estimated that in England, a 2 mmHg reduction in average systolic BP for 40-69 year olds could save 1,500-2,000 lives per year.(4) One of the most common interventions in primary care is the management of hypertension. Self-management of hypertension, in which individuals monitor their own BP and adjust their own medication, has been shown to lead to significantly lower BP in hypertension, including individuals with higher cardiovascular risk.(5-7)

Economic evaluations can be undertaken alongside randomised controlled trials (RCTs) where costs and health outcomes are measured. The primary outcome of RCTs in hypertension is often a change in BP. However, a change in BP corresponds to an intermediate outcome, and the final outcome of interest, in this case, is the risk of CVD. As RCT rarely follow patients over the long-term. decision-analytic modelling (DAM) provides a vehicle to extrapolate the impact of a change in BP on the risk of CVD events in the long-term. Modelling the course of CVD can be challenging requiring CVD risk factors (smoking, cholesterol, and diabetes), interactions among the risk factors, adverse events and the resulting health states (e.g. stroke sequelae and angina) to be considered.

Structural uncertainty will almost always arise once a choice of model structure or choice of relationships between inputs and outputs is defined within the model development process.(8)

The TASMIN-SR (6) trial aimed to determine the effect of self-monitoring with self-titration (self-management) of antihypertensive medication on systolic BP among hypertensive patients with suboptimal BP control and pre-existing CVD, diabetes mellitus and CKD compared to usual care. An economic evaluation was undertaken to assess the cost-effectiveness of the self-management intervention compared with usual care.(7) The main results indicated that self-management of BP in high risk patients with poorly controlled hypertension not only reduced BP compared to usual care, but also represented a cost-effective use of healthcare resources.

The aim of this study is to assess structural uncertainty in the TASMIN-SR model-based cost-effectiveness analysis(7) and to provide practical illustration of the impact, on results of cost-effectiveness, of changing or adapting model structures in a model-based economic evaluation on the primary prevention of CVD.
We consider structural uncertainty as uncertainty associated with all aspects of model structure, i.e., health states and relationships between health states. This is in contrast to parameter uncertainty, which is very much focused on the parameters used in a model and their uncertainty. Structural uncertainty reflects the extent to which a given model differs from the real system it is intended to reflect.(12, 30) Differences in model structure are dependent on the importance given to various aspects of the process being modelled, allowing in some instances for model simplifications. In some cases, these originate when data are not available, although their inclusion could potentially still be relevant for the analysis.

## Structural uncertainty

The nature of models being a simplification of reality causes that many assumptions need to be adopted during the building process such that the distance between a model and reality will always be unknown, or whether other plausible models could be a better alternative.(8-10) This can potentially lead to a wide variation in model predictions with potential impact on funding decisions.(11)

Various alternative statistical methods have been proposed to address the impact of structural uncertainty on the results of cost-effectiveness (8, 11-22) whilst some other authors have provided examples on how to implement some of these methods in different clinical areas.(23-25) However, it has been recognised that methods for quantifying structural uncertainty are less well described if compared to methods for characterising parametric or methodological uncertainty. (8, 11, 12, 15) A main challenge in addressing structural uncertainty is posed by the many issues that have been identified as ‘structural uncertainty’ making it a complex task (which may not even be cost-effective) to address properly(26).
Previous studies(15, 27-29) indicate that even though elements pertaining to structural uncertainty are occasionally considered, the assessment of structural uncertainty is not common practice and most modelling tends to omit testing for structural uncertainty. However, it is essential to assess the extent to which model predictions are influenced by such choices made within the model development process.(27)

Challenges posed by the assessment of structural uncertainty might be overcome if additional research is undertaken on an experimental basis. Case studies aimed at measuring the impact of changing or adapting chosen model structures on previous results of cost-effectiveness could provide insightful evidence of how much results would be altered when alternative model structures are implemented. This would also provide evidence of what other elements, besides model structure, may be critical in affecting results of cost-effectivenessMethods

Taking the TASMIN-SR model as the case study, the following research methods are outlined as follows: i) description of the TASMIN-SR model; ii) systematic review to identify plausible alternative model structures to TASMIN-SR; iii) definition and implementation of changes to the structure of the TASMIN-SR model; iv) inclusion of secondary events in the TASMIN-SR model; v) identification of alternative model inputs; and vi) results.

i) TASMIN-SR model structure

A detailed description of the original Markov model can be found elsewhere.(7) Briefly, the economic evaluation consisted of a model-based cost-utility analysis to assess the long-term cost-effectiveness of the self-management intervention in a 'high risk' patient population compared with usual care, using a Markov model to extrapolate the results of the TASMIN-SR trial(6) given in terms of BP to the long-term risk of cardiovascular endpoints. The study considered a cohort of 70 year old patients (39% female) with sub-optimal hypertension (BP>= 130/80 mmHg at baseline), combined with a history of stroke, diabetes, CHD, and CKD. The model was run over a lifetime time horizon using a six-month time cycle, with results presented from a UK National Health Service (NHS) and Personal Social Services (PSS) perspective.

The structure of the TASMIN-SR model is shown in Figure 1. Patients start in an initial 'HR' or high risk health state representing individuals with hypertension and a history of stroke, CHD, diabetes and CKD. The model simulates the lifetime of these patients until any of three possible events occur (stroke, myocardial infarction (MI) and unstable angina (UA)) or the patient dies from other causes. Individuals that survive an acute phase in any of the health states progress into a post event or chronic phase for that condition until death, with no

recurrences of cardiovascular events being possible. A lower quality of life was permanently applied until death in all chronic health states.

The CVD history of patients entering the model was informed by the TASMIN-SR(6) trial data. Transition probabilities of suffering a stroke, MI, or UA were obtained from the literature for each of the high risk conditions. Age-related risk reductions from treatment for MI, UA, and stroke were estimated using trial based systolic BP reductions at 6 and 12 months (Appendix 2 Table 1). Resource use and costs were obtained from trial data and published studies (Appendix 2 Table 2).

ii) Alternative model structures

Structural uncertainty is addressed by assessing issues such as the adequacy of the type of model used (Markov), the structure of the model (health states and transition probabilities) that translates into plausible alternative model structures, and data availability to inform input parameters, for example the risk of secondary events.

A systematic review was used to inform plausible alternative model structures.(29) The review identified model-based studies of interventions aimed at lowering the BP of patients with hypertension and at risk of CVD, where the management of hypertension was part of a primary prevention strategy.(29) The aim of the review was to assess compliance of model-based economic evaluations to DAM guidelines.(29) The review identified 13 model-based economic evaluations from the literature that were used to inform the changes implemented to the TASMIN-SR model.(29)Information on the inclusion or exclusion of potentially relevant comparators, type of model used, health states included, recurrence of events, choice of covariate effects used in the transition probabilities, and the inclusion or exclusion of any other assumption(s) pertaining to structural uncertainty were extracted (Appendix 2 Table 3).

All 13 included studies used Markov models but only two justified their use. Kourlaba(31) justified the use of a Markov study in their own study by saying that it is ‘a conventional model that describes restricted transition probabilities between important health states’ (p.87).Kaambwa(5) indicated that ‘the Markov model overcame limitations associated with within-trial analyses’ (p.1527). In the TASMIN-SR(7) study, it was stated that ‘arguably, a more complex model such as individual patient level simulation could be more appropriate’ (p.9) by incorporating patients' histories more efficiently. The use of Markov models can overcome limitations associated with within-trial analyses, specifically by allowing the modelling of effects and costs of long-term

events and the assessment of the long term cost-effectiveness beyond the trial period.(32) Even though individual patient level simulation models have long been praised for their flexibility and ability to record patient attributes,(33) because cardiovascular diseases are chronic with recurring events and often result in health states with persistently reduced quality of life, the use of a Markov model is often preferred as a more parsimonious approach.(34, 35)

The complexity of the model structures used varied, and this was due to the different approaches to the inclusion of the acute or post-event health states modelled. Model structures were most frequently a reflection of the course and history of CVD events or disease progression. The most common initial state was disease-free and the most common acute states modelled were stroke and MI followed by angina, heart failure and CVD. Few studies modelled only a single health state to describe an acute cardiovascular event (36-38). Some studies modelled additional states such as congestive HF,(39) coronary artery disease,(40) renal failure(41) or peripheral artery disease.(42) Absorbing states consisted of death and non-CVD death. Some authors acknowledged they had excluded states (40, 41) or combinations of health states (HF and stroke)(43) due to data limitations. Compared to the TASMIN-SR model, the review identified a variety of model structures ranging from a simplistic (single CVD morbidity) (37, 38, 44) to more complex approaches (four states including stroke, MI, HF, angina).(39, 42, 43)

The risk of secondary events was modelled in seven (36-40, 42, 43) of the studies reviewed. It could be argued that some of these studies adopted assumptions which would add extra uncertainty to the results. These included assuming that the risk of secondary events was equal to the risk of a first non-fatal event,(38) assuming that the patient with a second event will be in a health state worse than the state prior to the event,(43) or using expert opinion to inform risks of secondary events.(37) Lack of epidemiological data was acknowledged as the main reason for the exclusion of secondary events by some authors.(5, 44) The TASMIN-SR model assumed no recurrence of CV events due to the unavailability of data describing secondary events for a high risk population. The choice of modelling approach should be considered as part of the investigation into the impact of structural uncertainty. However in this study, only the Markov model structure is considered as informed by the results of this review.

iii) Implementation of model structures

Alternative Markov model structures were primarily identified based on the finding of the systematic review. Validation of the adequacy of this type of model over competing structures such as decision trees, DES or individual sampling model were check using a framework to select an appropriate model type.(34) The validation check indicated that Markov was just the right type of model, considering that estimating interactions between individuals was not necessary whilst modelling health states was important (patient pathways would not be adequately represented by probability trees) and we did not required an excessive number of states (excluding the option of individual sampling model).

. Alternative model structures were labelled Model 1 through Model 3 and were developed by varying the number of the health states used from a simplistic structure to one of increased complexity (Figure 2).

Model 1 uses a simplified approximation of the TASMIN-SR model structure. It was informed by the study of Stevanovic(38) and consists of a single CVD state with progression to a chronic state (Figure 2). Following NICE Statin guidelines(45) it was assumed that CVD is a combined state consisting of CHD (MI and UA) and stroke. Assumptions were adopted to estimate transition probabilities, utilities and costs due to lack of data in the literature to inform a single CVD health state (Table 1). Parameters for the CVD state correspond to a weighted average of input parameters used in the case study model for the states stroke, MI and UA (Table 1).

Model 2 applied the assumption that if the costs and utilities for two health states are the same, then it may not be necessary to distinguish between those two states to estimate lifetime costs and effectiveness (Figure 2).(19) In the TASMIN-SR model, treatment effects and the long-term costs and utilities for states MI and UA were assumed to be the same due to lack of data on UA (Table 1). Under these circumstances, it may not be necessary to include a state UA. Model 2 reflects a restricted version of the TASMIN-SR model consisting of two health states Stroke and MI. The review identified studies using a model structure consisting of two states, named stroke and a MI(31, 46) or stroke and CHD.(47) We implemented Model 2 consisting of health states stroke and MI with progression to a chronic phase for individuals who survive (Figure 2 and Table 1).

Model 3 adopted an expanded structure that was informed by the structure of the most complex models,(39, 42, 43) using an increased number of health states (Table 1). In Model 3, high risk patients can move to one of a number of primary CVD events, MI, stroke, HF, UA and transient ischemic attack (TIA) or dead from CVD or other causes. Individuals that survive an acute CVD phase naturally progress to a chronic phase where quality of life is lower and where they remain until death.

iv) Inclusion of secondary events in the TASMIN-SR model

TASMIN-SR did not consider recurrence of cardiovascular events due to the unavailability of suitable epidemiological data to reflect the transition of elderly and high risk patients after a primary cardiovascular event. After carefully reviewing sources of data and literature, including relevant NICE guidelines, no additional suitable data were identified. Therefore in this study assumptions based on expert clinical advice were adopted. In Model 4, individuals that survive a primary acute event can either move into a chronic post event phase (asymptomatic) or may experience a recurrent cardiovascular event one year after the first event. In Model 4 we assume that patients will experience only one cardiovascular event per year and following a primary event, patients may experience a second event one year after the first event with the same probability as for the first event. Transitions from a more severe health state (e.g. stroke) to a less severe state (e.g. unstable angina) are omitted from the model because such transitions would imply lower costs and improvements in quality of life that may not reflect clinical reality (Figure 1 and Table 1).(43)

v) Identification of alternative model input parameters and analysis

Information from the literature was sought to populate all input parameters for models 1 to 4 (Table 1) for a UK setting. When information on transition probabilities or age-related relative risks was not readily available, figures were estimated using a weighted average based on the distribution of patients to primary CVD events.(48) Costs were derived from a combination of standard unit costs(49, 50) and previously published literature and models, (48, 50) and were adjusted using the Hospital and Community Health Service index to the price year of 2014/15.(49) The acute and chronic cost of CVD were estimated using a weighted average based on the distribution of patients to primary CVD events.(48) The probabilities of death due to CV events within a year of the event are reported in Table 1 and were applied to the first year after an event (first two cycles in the model). Life tables were used to determine the overall mortality for each model dependent on age and gender.(51) Risks of death following a second event and utility values following a second event used in Model 4 were taken from the literature (Table 1)

A cost-utility analysis was undertaken for all models to calculate the cost per quality-adjusted life year (QALY) gained. Results from each alternative model specification are presented as scenario analyses. Probabilistic

sensitivity analysis (PSA) was conducted to assess parameter uncertainty. The PSA was run with 10,000 Monte Carlo simulations allowing cost-effectiveness planes (CEP) and cost-effectiveness acceptability curves to be constructed to estimate the probability of self-management being cost effective at different willingness-to-pay thresholds.

Additional sensitivity analyses (SA) were conducted to assess uncertainty in the results of each model (TASMIN-SR and Model 1-4). Deterministic sensitivity analysis was undertaken around key parameters and assumptions. All cost variables were increased or decreased simultaneously by 40%. To further explore a wider range of costs, we increased and decreased costs by 200% and 50% respectively. The time horizon for each model was varied from 30 years (lifetime) to 10, 5, 3, 2 and 1 year In addition, the impact of doubling or halving the probabilities of having a second cardiovascular event were tested in Model 4.

We present the impact of structural uncertainty in terms of the impact on the cost-effectiveness results of a model and EVPI. Including different parameters in the model can be expected to alter the extent of uncertainty captured in the EVPI calculation. Because the models have different parameter sets, comparisons of expected value of partial perfect information would not be helpful'

Results

The main cost-effectiveness results obtained in the TASMIN-SR study were found to be robust to changes in model structure (Table 2) and to the inclusion of secondary events. Self-management of BP remained dominant (more effective and cheaper than usual care) for all models.

The highest QALY outcomes for both interventions were found by implementing Model 2 (restricted version). Higher incremental QALYs were found for Models 3 and 4 between self-management and usual care. Differences found between incremental QALYs for TASMIN-SR and Models 2 and 3 were marginal (0.0001 and 0.0002 respectively) (Table 2).

The CEP (Figure 2) shows the results from the Monte Carlo simulation for 10,000 replications. All the results were in the north-east and south-east quadrants indicating that self-management was always more effective but may be more or less costly. The cost-effectiveness acceptability curves (CEAC) shown in Figure 3 were derived from the joint density of incremental costs and incremental QALYs for the self-management of BP. Each CEAC presents the probability that the self-management intervention is cost-effective for the different model structures. For a willingness to pay of £20,000 per QALY, the proportion of model replications that were cost-

effective was higher than 99% for all model structures (Figure 3). For Models 3 and 4, the proportion of model replications that were cost-effective was 100%.

All sensitivity analyses undertaken appear to indicate that individual results for the various models remained aligned after increasing or decreasing total costs (Appendix 1 Table 4 and 5), varying the length of time horizons (Appendix 1 Table 6), and varying transition probabilities to secondary events (Appendix 1 Table 7). Self-management in Models 1-4 was found to be dominant if the time horizon was two years or more (Appendix 1 Table 6). Lifetime EVPI for alternative model structures compared to TASMIN-SR was reduced substantially for Model 1 at all willingness to pay thresholds. For all other model structures, there was a smaller decrease, again observed at all thresholds (see Figure 4).

## Discussion

DAM represents an organised way to synthesise evidence currently available on the outcomes and costs of alternative health care interventions.(52, 53) The results derived from a DAM will depend on how the model structure has been defined and the data used to populate the model. The analysis of uncertainty in DAM have mainly focused on parameter uncertainty, taking account of any uncertainties in the data inputs.(8, 11, 12, 15, 29) Such analyses are usually based on the premise that the model has been correctly specified. However, an inappropriate model structure can potentially invalidate estimates of cost-effectiveness and therefore, is also of little value to a decision maker.(11, 12, 15) Although limitations in model structure are usually acknowledged, there is a lack of clarity about methods to evaluate structural uncertainty.(11, 12, 15)

This study identified competing and credible model structures in the assessment of the cost-effectiveness of primary care interventions for the management of hypertension in patients at risk of or with established CVD. The results of each alternative model specification, including EVPI were presented and compared.

Main cost-effectiveness results obtained in the TASMIN-SR study did not change when alternative model structures (Model 1 to 3) were implemented or after adjusting TASMIN-SR model for the effect of secondary events (Model 4), suggesting that structural uncertainty was not important in this model

The illustration of various scenarios representing structural uncertainty offers the decision maker the opportunity to decide on which model structure or assumption(s) he/she believes and make policy decisions on that basis. However, it does not provide any explicit framework for quantifying the uncertainty or offer any guidance to

decision makers that have no clear preferences over alternative model assumptions. This case study showed similar results for EVPI across the range of model structures, except for Model 1, where the restricted parameter set meant that a large part of the decision uncertainty was not apparent in the model.

The assessment of structural uncertainty shown in published studies in the area of primary prevention of CVD has mainly focused on assessing parameter uncertainty and there have been relatively few studies that have attempted to examine structural uncertainty in the extend that this study has done. Studies that considered the assessment of structural uncertainty varied in scope (5, 37-39) however none attempted to show the effect of different model structures on the cost-effectiveness of anti-hypertension treatments

Our findings in terms of highest QALY outcomes found by implementing Model 2 may be explained by the fact that when compared with TASMIN-SR, the population entering Model 2 was exposed to an overall reduced risk of CVD due to the exclusion of the angina state, thus leading to increased QALYs. The lowest QALY gained for both interventions and higher self-management costs from Model 3 (expanded model) can be explained by the additional burden of mortality for patients presenting HF and TIA. Model 1 (single CVD state) produced lower QALYs compared to TASMIN-SR and this can be explained by the increased overall risk of CVD due to the added individual risks of stroke, MI and UA used to estimate the risk of CVD. The results of Model 4 show self-management to be even more cost-effective than usual care when compared with results from the case study and alternative Models 1-3. This can be explained by the increased overall risk of CVD due to the occurrence of additional events, and therefore more scope for preventing these events.

The main conclusions drawn from the cost-effectiveness analyses were not altered when alternative model structures were implemented or in the presence of secondary events. This result may lead to the conclusion that a simple model will suffice when examining the potential impact of anti-hypertensive strategies on the primary care prevention of CVD.

This study may well be a reflection of the average level of complexities faced by current practice when undertaking an assessment of structural uncertainty. Currently, guidance regarding the assessment of structural uncertainty in DAM by bodies such as ISPOR or NICE in the UK go as far as recommending to parameterize uncertainties(18) and if this is not possible then the use of sensitivity analysis.(18, 54)

The wide variation in the model structures that were identified by our review supports the need for improved guidance to handle the implications of potential sources of structural uncertainty and, most importantly, the need for a disease-specific or generic model to examine the CEA of self-management of hypertension in patients with

established CVD. Challenges across different disease areas are so varied that it may well be the case that only studies such as this can shed any light on the importance of model uncertainty in different settings.

Current practice seems bound by data availability whilst methods proposed to assess structural uncertainty have been borrowed from other disciplines oblivious to the needs in a health care setting where patient level data is most of the time not readily available.

The main recommendations arising from this study are:

1. The assessment of structural uncertainty should not be ignored as it is an integral part of good practice DAM
2. The reasons why an assessment of structural uncertainty is not possible or not needed should be always stated in the limitations section
3. Data limitations to undertake an assessment of structural uncertainty should be clearly stated and discussed
4. If there is a reason to believe that structural uncertainty is an issue that may have affected the results of CE, then an assessment of structural uncertainty should be included
5. Ideally, sound statistical methods should be used in the assessment of structural uncertainty (discrepancy approach, model averaging, parameterization, model selection, scenario analysis) but if none of the above is possible due to data limitations, then at least appropriate sensitivity analysis should be routinely conducted, as per current ISPOR-SMDM guidelines

Strengths and limitations

The assessment of structural uncertainty shown in published studies in the area of primary prevention of CVD has mainly focused on assessing parameter uncertainty and there have been relatively few studies that have attempted to examine structural uncertainty in the extend that this study has done, showing the effect of different model structures on the cost-effectiveness of anti-hypertension treatments and implementing extensive sensitivity analyses and EVPI

A weakness of our approach to assess structural uncertainty is that there are no establish methods to formally assess the plausibility of alternative models and it is not clear which type of, or how many scenarios should be considered.

Our choice of model type was limited to a cohort Markov model. Some may argue that a microsimulation or Discrete Event Simulation (DES) may offer some advantages such as flexibility in incorporating individual heterogeneity and tracking individual event history. However, our review indicated that all economic evaluations in this disease area had utilized Markov models, presumably based on the trade-off between model flexibility and analytical input.(35) Furthermore, chronic and recurring diseases are often reflected by using Markov models in which individuals move between clinical states of interest in discrete time periods, and each state is associated with a cost and utility.(32) Due to a lack of epidemiological data, Models 1 to 3 did not capture structural uncertainty arising from the exclusion of secondary events of CVD for high risk patients. However, using assumptions based on expert opinion, we assessed the risk of secondary events in Model 4. The exclusion of secondary events in Models 1 to 3 was a conservative assumption, as a reduction in BP was expected to reduce the risk of these events in addition to the primary events already considered, making self-management even more cost-effective as demonstrated in Model 4.

In this study we could not implement more sophisticated methods, for example, model selection, model averaging, or discrepancy approach) to select the best model on the basis of how well the model's output match observed data (commonly judged by the likelihood-based information criteria). This was because we only had single point estimates for key parameters (transition probabilities) taken from the literature which do not allow the estimation of the maximum likelihood of parameters for which, actual patient level data is required. Furthermore, results of previous research seem to indicate that standard likelihood-based approaches to choose between may be unsuitable when underlying datasets are different.(25) Renal failure and peripheral artery disease were not considered in this study as additional health states as they are part of the broader set of diseases that indirectly may lead to CVD and data to populate input parameters for these sates was not available. Finally, the results of cost-effectiveness for self-management of blood pressure in the case study, TASMIN-SR model, were of dominance. It may be that if the results were near the £20,000 threshold, changes in model structure could have led different results of cost-effectiveness and possible EVPI.

Conclusions

The results of this study indicate that the main conclusions from the TASMIN-SR model of cost-effectiveness are robust to changes in model structure. The cost-effectiveness results and the EVPI were not sensitive to model structure specification.

Even though the results from Model 1 were not similar to those of TASMIN-SR, the fact that the main conclusions are the same raises the question whether, in this particular case study, a more parsimonious model would have sufficed. Currently there are no available guidelines indicating how structural uncertainty arising from the structure of a model, should be identified, assessed, and reported. Therefore, further research should focus on the development of general agreed guidelines on how to address issues pertaining to structural uncertainty and, more specifically, how to deal with challenges across different disease areas, perhaps incentivising the development of more studies such as the present study, focusing on disease specific areas.

## Reference List

1. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002;360(9349):1903-13.
2. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2010;380(9859):2095-128.
3. NICE. Hypertension: clinical management of primary hypertension in adults. NICE clinical guideline 127. London: National Institute for Health and Clinical Excellence; 2011.
4. NHS England. Factsheet: Improved detection and management of hypertension 2014 [Available from: https://www.england.nhs.uk/ourwork/futurenhs/deliver-forward-view/sop/red-prem-mort/php/.
5. Kaambwa B, Bryan S, Jowett S, Mant J, Bray EP, Hobbs FDR, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): A cost-effectiveness analysis. European Journal of Preventive Cardiology. 2014;21(12):1517-30.
6. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. Jama. 2014;312(8):799-808.
7. Penaloza-Ramos MC, Jowett S, Mant J, Schwartz C, Bray EP, Sayeed Haque M, et al. Cost-effectiveness of self-management of blood pressure in hypertensive patients over 70 years with suboptimal control and established cardiovascular disease or additional cardiovascular risk diseases (TASMIN-SR). Eur J Prev Cardiol. 2015.
8. Strong M, Pilgrim H, Oakley J, Chilcott J. Structural uncertainty in health economic decision models. ScHARR Occasional Paper2009.
9. Manning WG, Fryback DG, Weinstein MC. Reflecting uncertainty in cost-effectiveness analysis. In: Gold MR SJ, Russell LB, et al, editor. Cost-effectiveness in health and medicine. New York (NY): Oxford University Press; 1996. p. 247-75.

10. Mentz RJ, Bakris GL, Waeber B, McMurray JJV, Gheorghiade M, Ruilope LM, et al. The past, present and future of renin-angiotensin aldosterone system inhibition. International Journal of Cardiology. 2013;167(5):1677-87.
11. Jackson CH, Bojke L, Thompson SG, Claxton K, Sharples LD. A framework for addressing structural uncertainty in decision models. Medical Decision Making. 2011;31(4):662-74.
12. Afzali HH, Karnon J. Exploring structural uncertainty in model-based economic evaluations. Pharmacoeconomics. 2015;33(5):435-43.
13. Bilcke J, Beutels P, Brisson M, Jit M. Accounting for methodological, structural, and parameter uncertainty in decision-analytic models: a practical guide. Medical Decision Making. 2011;31(4):675-92.
14. Bilcke J, Chapman R, Atchison C, Cromer D, Johnson H, Willem L, et al. Quantifying Parameter and Structural Uncertainty of Dynamic Disease Transmission Models Using MCMC: An Application to Rotavirus Vaccination in England and Wales. Medical Decision Making.35(5):633-47.
15. Bojke L, Claxton K, Sculpher M, Palmer S. Characterizing structural uncertainty in decision analytic models: A review and application of methods. Value in Health. 2009;12(5):July/August.
16. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17(5):479-500.
17. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technology Assessment. 1999;3(2):1999.
18. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD. Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6. Value in Health. 2012;15(6):835-42.
19. Jackson CH, Sharples LD, Thompson SG. Structural and parameter uncertainty in Bayesian cost-effectiveness models. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2010;59(2):233-53.
20. Jackson CH, Thompson SG, Sharples LD. Accounting for uncertainty in health economic decision models by using model averaging. Journal of the Royal Statistical Society Series A, (Statistics in Society). 2009;172(2):383-404.
21. Price MJ, Welton NJ, Briggs AH, Ades AE. Model averaging in the presence of structural uncertainty about treatment effects: influence on treatment decision and expected value of information. Value Health. 2011;14(2):205-18.
22. Strong M, Oakley JE, Chilcott J. Managing structural uncertainty in health economic decision models: a discrepancy approach. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2012;61(1):25-45.
23. Brisson M, Edmunds WJ. Impact of model, methodological, and parameter uncertainty in the economic analysis of vaccination programs. Medical decision making : an international journal of the Society for Medical Decision Making. 2006;26(5):434-46.
24. Frederix GW, van Hasselt JG, Schellens JH, Hovels AM, Raaijmakers JA, Huitema AD, et al. The impact of structural uncertainty on cost-effectiveness models for adjuvant endocrine breast cancer treatments: the need for disease-specific model standardization and improved guidance. Pharmacoeconomics. 2014;32(1):47-61.
25. Thom HH, Jackson CH, Commenges D, Sharples LD. State selection in Markov models for panel data with application to psoriatic arthritis. Stat Med. 2015;34(16):2456-75.
26. Caro JJ, Moller J. Decision-analytic models: current methodological challenges. Pharmacoeconomics. 2014;32(10):943-50.
27. Afzali HH, Karnon J, Merlin T. Improving the accuracy and comparability of model-based economic evaluations of health technologies for reimbursement decisions: a methodological framework for the development of reference models. Medical decision making : an international journal of the Society for Medical Decision Making. 2013;33(3):325-32.

28. Peñaloza Ramos MC, Barton P, Jowett S, Sutton AJ. A Systematic Review of Research Guidelines in Decision-Analytic Modeling. Value in Health. 2015;18(4):512-29.
29. Peñaloza-Ramos MC, Barton P, Jowett S, Sutton AJ. Do economic evaluations in primary prevention of cardiovascular disease conform to good practice guidelines? A systematic review. (In Press) MDM Policy & Practice. 2016.
30. Stevenson M, Tappenden P, Squires H. Methods for handling uncertainty within pharmaceutical funding decisions. International Journal of Systems Science. 2014;45(1):60-8.
31. Kourlaba G, Fragoulakis V, Theodoratou D, Maniadakis N. Economic evaluation of telmisartan, valsartan and losartan in combination with hydrochlorothiazide for treatment of mild-to-moderate hypertension in Greece: A cost-utility analysis. Journal of Pharmaceutical Health Services Research. 2013;4(2):81-8.
32. Briggs AH, Claxton K, Sculpher MJ. Decision Modelling for Health Economic Evaluation: Oxford, University Press; 2006.
33. Jowett S. Using Decision Analytical Modelling Techniques in Health Economics: An Application to Screening for and Treatment of Atrial Fibrillation. PhD Thesis: University of Birmingham; 2007.
34. Barton P, Bryan S, Robinson S. Modelling in the economic evaluation of health care: Selecting the appropriate approach. Journal of Health Services Research and Policy. 2004;9(2):April.
35. Karnon J. Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. Health Economics. 2003;12(10):01.
36. Montgomery AA, Fahey T, Ben-Shlomo Y, Harding J. The influence of absolute cardiovascular risk, patient utilities, and costs on the decision to treat hypertension: A Markov decision analysis. Journal of Hypertension. 2003;21(9):1753-9.
37. Perman G, Rossi E, Waisman GD, Aguero C, Gonzalez CD, Pallordet CL, et al. Cost-effectiveness of a hypertension management programme in an elderly population: A Markov model. Cost Effectiveness and Resource Allocation. 2011;9(4).
38. Stevanovic J, O'Prinsen AC, Verheggen BG, Schuiling-Veninga N, Postma MJ, Pechlivanoglou P. Economic evaluation of primary prevention of cardiovascular diseases in mild hypertension: A scenario analysis for the Netherlands. Clinical Therapeutics. 2014;36(3):368-84.e5.
39. Ekman M, Bienfait-Beuzon C, Jackson J. Cost-effectiveness of irbesartan/hydrochlorothiazide in patients with hypertension: An economic evaluation for Sweden. Journal of Human Hypertension. 2008;22(12):845-55.
40. Nordmann AJ, Krahn M, Logan AG, Naglie G, Detsky AS. The cost effectiveness of ACE inhibitors as first-line antihypertensive therapy. PharmacoEconomics. 2003;21(8):573-85.
41. Gandjour A, Stock S. A national hypertension treatment program in Germany and its estimated impact on costs, life expectancy, and cost-effectiveness. Health Policy. 2007;83(2-3):257-67.
42. Granstrom O, Levin L, Henriksson M. Cost-effectiveness of candesartan versus losartan in the primary preventive treatment of hypertension. ClinicoEconomics and Outcomes Research. 2012;4(1):313-22.
43. Wisloff T, Selmer RM, Halvorsen S, Fretheim A, Norheim OF, Kristiansen IS. Choice of generic antihypertensive drugs for the primary prevention of cardiovascular disease - A cost-effectiveness analysis. BMC Cardiovascular Disorders. 2012;12(26).
44. Baker TM, Goh J, Johnston A, Falvey H, Brede Y, Brown RE. Cost-effectiveness analysis of valsartan versus losartan and the effect of switching. Journal of medical economics. 2012;15(2):253-60.
45. Ward S, Jones ML, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technology Assessment. 2007;11(14):iii-160.

46. Wu Y, Zhou Q, Xuan J, Li M, Zelt S, Huang Y, et al. A cost-effectiveness analysis between amlodipine and angiotensin ii receptor blockers in stroke and myocardial infarction prevention among hypertension patients in China. Value in Health Regional Issues. 2013;2(1):75-80.
47. Ekwunife OI, Okafor CE, Ezenduka CC, Udeogaranya PO. Cost-utility analysis of antihypertensive medications in Nigeria: A decision analysis. Cost Effectiveness and Resource Allocation. 2013;11(1).
48. NICE. Statins for the prevention of cardiovascular events. NICE guideline TA94. London: National Institute for Health and Clinical Excellence; 2006 2006.
49. Curtis L, Burns A. Unit Costs of Health & Social Care. Kent: Personal Social Services Research Unit; 2015.
50. Department of Health. NHS Reference Costs Schedule 2013-14. London; 2013 2013.
51. Office for National Statistics. Interim Life Tables for England [Available from: http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2012-2014/indexhtml.2014

52. Brennan A, Chick SE, Davies R. A taxonomy of model structures for economic evaluation of health technologies. Health Economics. 2006;15(12):December.
53. Raiffa H. Decision analysis: introductory lectures on choices under uncertainty. 1968. MD computing : computers in medical practice. 1993;10(5):312-28.
54. NICE. Guide to the methods of technology appraisal 2013. Process and methods guides. London: National Institue for Health and Care Excellence; 2013.