**Bayesian Models for Cost Effectiveness Analysis   
of a Prognostic Model for Sudden Cardiac Death in Hypertrophic Cardiomyopathy  
  
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Abstract

1. **Introduction**

The research undertaken in this dissertation sought to bring to full realization the seminal work done by (O'Mahony et al., 2014), in developing a predictive model for assessing risk of Sudden Cardiac Death (SCD), among patients with Hypertrophic Cardiomyopathy (HCM). Bringing a predictive model to full realization requires satisfying three conditions, one of which is cost- effectiveness (Moons et al., 2009).

The work done by (O'Mahony et al., 2014) is built on in this dissertation also because of the public health and medical importance of the underlying HCM condition (Gersh et al., 2011, Maron et al., 2003). Hypertrophic Cardiomyopathy (HCM)[[1]](#footnote-1) is an inherited heart muscle disorder that is unlike most heart conditions; it is neither associated with one’s lifestyle nor is it associated with the natural aging process of the human body (Cooper et al., 2017, Gersh et al., 2011, Maron et al., 2003). It affects both young and old people (Gersh et al., 2011, Maron et al., 2003). In the medical literature HCM is described as unexplained hypertrophy (extreme growth), of the middle muscular layer of the heart wall or the myocardium (Cooper et al., 2017). Medical understanding of the immediate, or remote causes of the condition is therefore limited to its observed occurrence in families, hence despite several efforts to find a cure for HCM, a known cure is yet to be reported in the medical literature. Hypertrophic Cardiomyopathy results in several medical complications among which are stroke, and death for most cases (Sanchis-Gomar et al., 2016, Winkel et al., 2017a, Winkel et al., 2013, Wong et al., 2019).

Sudden Cardiac Death (SCD), is the most feared, and highly prevalent medical complication of HCM (Sanchis-Gomar et al., 2016, Winkel et al., 2017a, Winkel et al., 2013, Wong et al., 2019). Sudden Cardiac Death events are associated with extreme emotional pain; deaths are usually sudden and occur in persons otherwise considered healthy (Weissler-Snir et al., 2016, Winkel et al., 2017a). In the general cardiovascular disease population SCD is responsible for about half of all deaths (Sanchis-Gomar et al., 2016, Winkel et al., 2017a, Winkel et al., 2013, Wong et al., 2019). According to (Winkel et al., 2017b, Winkel et al., 2013), this proportion is even higher in the inherited cardiac diseases subpopulation, especially among young adults (). For whom, about 75% of SCD events are attributable to inherited cardiac diseases, that include HCM (Winkel et al., 2017b, Winkel et al., 2013).

The epidemiological literature of SCD is characterized by inconsistencies in definitions, for example while according to (Wong et al., 2019), a SCD is any unexpected death from a cardiovascular disease whether witnessed or not, Elliott et al. (2000) insist such deaths must be witnessed. There is also dispute on how estimates of SCD incidence are to be obtained (Albert et al., 2003, Sanchis-Gomar et al., 2016). For example there is disagreement on methodological issues such as whether or not to include non-autopsied unexplained sudden deaths in estimating SCD incidence, or what autopsy ratios to use (Winkel et al., 2017a). These inconsistencies exist because on one hand, general agreement on what is a SCD does not appear to exist in the SCD research community, while on the other there is disagreement on what methods to use in a SCD investigation (Winkel et al., 2017a).. For purposes of consistency this study follows (O'Mahony et al., 2014), in defining HCM1, and in defining SCD as was done by (Elliott et al., 2000)[[2]](#footnote-2).

Amiss these definitional and methodological challenges, the SCD literature suggest SCD is responsible for between 15% - 20% of deaths in western societies (Albert et al., 2003, Sanchis-Gomar et al., 2016). In the United Kingdom (UK) incidence of SCD among young adults is suggested to be 1.8 per 100,000 person-years, which translates to 8 youth deaths per week (Papadakis et al., 2009, Vaartjes et al., 2009). This rate is higher than that of the Netherlands (1.6) and lower than the rate in Australia (2.8) (Papadakis et al., 2009, Vaartjes et al., 2009).

Risk prediction

Despite the apparent high incidence rates cited above, incidence of SCD in the general HCM population is reported to be between 0.5% to 1% per year (Elliott et al., 2015). While this rate of incidence may appear low, there exist within the HCM population a minority of patients whose risk of SCD is considerably higher than that observed in the general population of HCM patients (Elliott et al., 2015). Identifying this group of patients is the most critical clinical routine of any HCM clinical management strategy (Elliott et al., 2015).

All clinical guidelines on HCM recommend that patients at high risk of SCD undergo a surgical procedure to receive an Implantable Cardioverter Defibrillator (ICD), often as a day case (Cardiology, 2003, Gersh et al., 2011, January et al., 2014, Maron et al., 2003). The guidelines however do not specify what absolute SCD risk justifies an ICD, leaving that to clinical judgement (Gersh et al., 2011). There is however consensus on what parameters should be considered in an SCD risk assessment (O'Mahony et al., 2013).

Clinical guidelines that are currently used in the USA, and Europe recommend that SCD risk assessment methods be based on an agreed set of clinical parameters, that reveal the severity of the growth of the middle muscular layer of the heart wall (Gersh et al., 2011, Maron et al., 2003). The presence or absence of these risk factors in an SCD risk assessment, inform clinical decision on whether or not an ICD implantation is needed for any particular patient (O'Mahony et al., 2013). These SCD risk assessment methods have however, recently been discredited in validation studies, and suggested to be responsible for less than optimal clinical decisions that resulted in inappropriate ICD therapy (O'Mahony et al., 2013).

O’Mahony et.al. (2013) observed in one such study that, despite these methods successfully identifying patients with the greatest risk of SCD in observational studies, they overestimate risk, and mislead clinicians to implant ICD’s in patients who otherwise, have no immediate need for them. Another weakness reported by (O'Mahony et al., 2013), is an inappropriate consideration of one of the risk factors (hypertrophyare) as a binary variable, whereas it is continuous, and registered increasing values with increasing risk of SCD. O’Mahony et.al. (2013), further observe that these methods are unable to specify the size of individual risk factors, making it impossible for clinicians to tell the relative contribution of each risk factor to the overall risk of SCD (O'Mahony et al., 2013). Thus resulting in clinical uncertainty regarding how the SCD risk of patients with solitary risk factors or those without the full complement of risk factors are to be determined (O'Mahony et al., 2013).

The weaknesses discussed above are complicit in research towards more innovative methods of assessing risk of SCD in patients with HCM (O'Mahony et al., 2013). The outcome of one of such efforts is the HCM-SCD risk prediction model (O'Mahony et al., 2014). The HCM- SCD risk prediction model has been shown to perform better in clinical settings at Identifying young adults (16 years) with HCM who need ICD therapy compared to currently recommended SCD risk assessment methods (O'Mahony et al., 2014).

Unlike currently recommended SCD risk assessment methods, the HCM-SCD risk prediction model provides precise estimates of SCD risk by generating for each risk factor, an individual effect size, making it possible to determine each risk factors contribution to overall SCD risk (O'Mahony et al., 2014). Despite the superior performance of the HCM-SCD risk prediction model, evidence that benefits of its use in clinical setting in the UK offset cost favorably, when compared to currently recommended SCD risk assessment methods is not available to inform policy change in SCD risk assessment.

Cost-effectiveness models

Economic evaluation is one of the ways to determine if a health intervention is better than another on the basis that derived benefits offset cost (Neumann, 2004). In the health economics literature it is defined as the formal process of comparatively analyzing alternative interventions with regard to cost and consequences, to aid decision making on resource allocation (Drummond et al., 2015, Morris et al., 2007). For example, deciding whether or not to adopt a new risk assessment strategy by comparing the cost and benefits from its use, to that of existing strategies or to a no strategy scenario, if none exist. These evaluations seek to maximize gains in investments in health technology within monetary constraints (McPake et al., 2013). They therefore form the basis for decisions on health technology investment and resource allocation in general.

A major beneficiary of such evaluations in the United Kingdom is the National Institute for Health and Care Excellence (NICE) (McPake et al., 2013). Bodies such as NICE are described in McPake et al. (2013) as regulators who specify regulations that outline how economic evaluations should be done. Regulations from NICE specify several analytical approaches, of which the most popular is cost-effectiveness analysis(McPake et al., 2013)**.**

Although, also widely cited in the health economics literature, cost-effectiveness analysis is not generally referenced positively, its use as a policy tool has been criticized by many (Asch et al., 2003, Prosser et al., 2000, Ubel, 2001, with critics labelling it as a tool for cost cutting to soar up profits, thus calling into question its true motive (Asch et al., 2003, Prosser et al., 2000, Ubel, 2001). Others have also questioned methods used for the analysis, citing use of incomplete evidence, for example evidence obtained from randomized controlled trials characterized by short follow-ups (Luce et al., 1996, Titlow et al., 2000).

Consequent to these criticisms, particularly those pertaining to use of incomplete evidence, (Karnon and Brown, 1998) has advocated cost-effectiveness modelling[[3]](#footnote-3), with models – abstract representation of reality, defined mathematically or statistically based on understanding of interrelationships among input variables obtained from theory or observation. Cost – effectiveness modelling is unlike standard statistical analysis performed on clinical studies, whereas in the latter the objective is inference making (Claxton 1999). Cost-effectiveness modelling seeks to inform the process of deciding the best policy from competing alternatives (Loomes and McKenzie, 1989).

The process of cost-effectiveness modelling involves defining a model for the covariates of a multivariate outcome variable , consisting of an appropriate measure of clinical benefit , and corresponding cost, induced by each of the competing interventions under consideration, (Loomes and McKenzie, 1989). Most often than not, clinical benefits in the literature is expressed by way of a utility measure (e.g. Quality Adjusted Life Years or QALYs) that value the time spent in a given health state (e.g. perfect health), with a preference measure of the quality of life associated with that health state (Loomes and McKenzie, 1989).

The cost-effectiveness of risk assessment methods has been investigated using several methods as reported in the economic evaluation literature (Field et al., 1995, Finkelstein et al., 2006, Wakker and Klaassen, 1995, Willan and O'Brien, 1996, Wonderling et al., 1996a, Wonderling et al., 1996b), these studies considered risk assessment strategies including prediction models for some cardiovascular diseases and SCD risk assessment in pre-preparation selection of young athletes (Wheeler et al., 2010).

There is little or no evidence of economic evaluations of SCD risk assessment methods including prediction models in patients with HCM. Also, most of the cited evaluations used limited evidence (evidence from: studies with short follow-up, and studies with poor external validity or small sample size) obtained from randomized controlled trials (Field et al., 1995, Mistry et al., 2012, Wonderling et al., 1996a, Wonderling et al., 1996b), observational studies (Aljutaili et al., 2014, Finkelstein et al., 2006, Finkelstein et al., 2002), and hypothetical models (Schuetz et al., 2013, Zomer et al., 2017)***.*** Analytical methods used where generally frequentist with pre-post study designs.

While the approach to cost-effectiveness modelling has historically been frequentist (Field et al., 1995, Finkelstein et al., 2006, Wakker and Klaassen, 1995, Willan and O'Brien, 1996, Wonderling et al., 1996a, Wonderling et al., 1996b), there has been a recent shift in trend, with majority of evaluations increasingly implementing a Bayesian statistical framework with decision-theoretic foundations (Abrams et al., 2011, Baio, 2012, O'Hagan and Stevens, 2001, O'Hagan et al., 2001).

The current study is the first to consider the cost-effectiveness of SCD risk assessment in HCM patients using a risk prediction model, it therefore seeks to extend the field of economic evaluation of risk assessment strategies for cardiovascular diseases to include hypertrophic cardiomyopathies, using a Bayesian decision-theoretic approach. By using the Bayesian approach, it is expected that the study will exploit the full range of evidence (including expert knowledge) available on use of the HCM-SCD risk prediction model in clinical practice settings in the United Kingdom (UK). Consequently, the following research question and Objective will be addressed in the current study:

* 1. **Research Question**

What is the cost-effectiveness of using the HCM–SCD risk prediction model in assessing risk of SCD in patients () with HCM in clinical practice settings in the United Kingdom?

* 1. **Research Objective**

To evaluate the cost-effectiveness of using the HCM–SCD risk prediction model in assessing risk of SCD in patients () with HCM in clinical practice settings in the United Kingdom.

The Bayesian decision-theoretic approach adopted, for the dissertation was implemented by following a concise and comprehensive framework of the processes involved in a standard economic evaluation, such as cost-effectiveness modelling or cost-utility modelling described in (Baio, 2018). even though a similar framework is provided by (Cooper et al., 2004), The current study follows the framework described in (Baio, 2018), because its intuitive, and amenable to different forms of data. the framework described in (Cooper et al., 2004), requires evidence synthesis in the form of meta-analysis, which was not done in this dissertation.

The process of cost-effectiveness modelling in this dissertation procedure from the perspective of the UKs National Health Service (NHS). It begun with specifying a statistical model (Section 4.1), that is used to estimate the relevant parameters from model inputs, which were fed to the economic model (Sections 3.0,4.1a, and 4.5a), where appropriate population averages for cost and benefits for each intervention being compared were generated by combining the estimated parameters. Decision theory was applied to the generated averages in Decision Analysis (Sections 4.5b) to choose the best intervention on the basis of evidence, and expected utility maximization. Undergirding the whole process is Uncertain Analysis (Section 4.2.4, and Section 4.5c), the procedure for assessing the impact of uncertainty surrounding the current model and available evidence on the decision-making process. Techniques adopted in this analysis include the cost-effectiveness acceptability curve, and a measure of expected value of future information to the decision-making process.

The rest of this dissertation is structured as follows: Section 2.0, concludes the discussion on Bayesian cost-effectiveness modelling begun in the introduction with a review of two computational approaches, close form statistical manipulation, and Markov Chain Monte Carlo simulation, specifically Gibbs sampling is discussed. The section ends with a summary of some debates on Bayesian Statistics and Bayesian decision analytic modelling in medical research. Sections 3.0 provides an overview of the design of the study, topics discussed include economic modelling, data sources and study population.

Section 4.0 describes the conceptual framework adopted in this study (as described above), in subsection 4.2, I pull together arguments on Bayesian Cost-effectiveness modelling from section 1.0, and continued in Section 2.0, using Bayes theorem and outline the theoretical framework underlying the analysis described in (Section 4.5). In Sections 5.0, 6.0. and 7.0), I respectively, summarize the findings, provide an evaluation of the findings, and present conclusions representing insights drawn from evaluating the findings.

1. **Bayesian Cost-effectiveness Computation.**

The Bayesian approach is reported as been flexible, allowing the incorporation of information external to that inputted into the model; for example, the expert beliefs about what the UK annualized rate of SCD among HCM patients with Stroke might be. Beliefs such as this are specified in a prior distribution and combined with data (Cooper et al., 2004). The combination under Bayes theorem produces a posterior that is an update of the prior distribution due to the data. The posterior distribution for some simple analysis can be written in standard statistical notation (Cooper et al., 2004).

Unfortunately, according to (Cooper et al., 2004) , it’s not always possible to write the posterior distribution in standard statistical notation. When this happens a Bayesian solution may be arrived at from using simulation methods such as Markov Chain Monte Carlo (MCMC) (Khandker et al., 2000). Of the MCMC simulation methods Gibbs sampling is the most referenced in the applied Bayesian analyses literature (Khandker et al., 2000). The routines needed to complete a computation are freely provided in the software OpenBugs (Surhone et al., 2010), and others like it.

The MCMC sampler reaches convergence when it is sampling from the true conditional posterior distribution. Cowles and Cartlin (1996) suggest verifying that the sampler is sampling from the required conditional posterior to avoid biased estimates (Cowles and Carlin, 1996). They further suggest a number of assessment methods, of which one was applied in this study. This involved starting the MCMC with extreme starting values, they argue that it’s possible to monitor performance of the MCMC sampling with prior knowledge of the data and the model structure (Cowles and Carlin, 1996).

Advocates of the Bayesian approach point to its flexible modelling framework that allows unconventional statistical manipulation to account fully for model uncertainty (Frazier et al., 2000), for instance a common refrain in the applied Bayesian cost-effectiveness literature is its facilitation of probabilistic sensitivity analysis, this happens when input uncertain described by prior distributions in the analysis is passed through Bayes theorem resulting in distributions of cost-effectiveness ratios from an updating simulation process (Briggs and Gray, 1999).

The Bayesian approach to cost-effectiveness modelling of health interventions is not without criticism, as far back as the mid 90’s, critics pointed to slow computations due to a lack of suitable software (Lilford and Braunholtz, 1996). This was despite evidence that fast processing and user-friendly Bayesian software were becoming increasingly available, following developments of faster computer processors that increased computer processing time (Gilks et al., 1994, Kruschke, 2014).

Philosophical debates following early attempts to introduce Bayesian methods into medical research still remain; the loss of objectivity, the definition of subjective probability construed as gambling on different outcomes were considered by many then (and even now by some) as remote from medical research (Lilford and Braunholtz, 1996, Lilford and Braunholtz, 2000)[[4]](#footnote-4). The question of what the posterior represents (What a Bayesian believes, should believe or Would believe) given the prior and the model were raised and are still been raised.

Brophy and Joseph provide an elaborate defense of a Bayesian approach to medical studies (Brophy and Joseph, 1995), one of which, Cooper et al. (2004) reiterates by arguing that a Bayesian analysis does not require the provision of subjective or informative a priori beliefs about the distribution of parameters since distributions containing very little or no information (vague or non-informative priors) compared to the data can be used.

For [[5]](#footnote-5)detailed examples of the Bayesian approach to cost-effectiveness modelling, excellent reads include (Parmigiani et al., 1997, Samsa et al., 1999). While an equally good but gentle introduction to the Bayesian decision analytic approach to modelling medical decision making is provided by (Parmigiani, 2002).

1. **Modeling** **Overview**
   1. **Design**

The study is setup as a simulation from a hypothetical model of the progression of an HCM – ICD implanted virtual patient cohort of 1000, over 10-years. The sample of 1000 was chosen to manage the complexities in modelling, and to predict transitions, costs, and health outcomes. The heterogeneity of people with HCM related ICD implants is captured by data from a real cohort of HCM -ICD implant patients. The model was created in OpenBugs, and RStudio.

### **Population**

The study population was all successively evaluated patients (N= 1593) with HCM, followed-up at the Heart Hospital London in the United Kingdom, one of the participating centers in a retrospective multicenter longitudinal cohort study.

Risk of SCD is assessed for patients using the HCM – SCD risk prediction model and currently recommended SCD risk assessment methods. Risk scores generated from the HCM – SCD risk prediction model were classified under one of three thresholds (Threshold One: > 6%, Threshold Two: 4 – 6%, Threshold Three < 4%).

|  |
| --- |
| A |
| B |
| Figure 1 (A) Decision tree of how those with HCM will be targeted for SCD management. (B) Markov model of possible health states and transitions in the economic model. Where the Healthy state comprises HCM patient’s with ICD implants (having been assessed), who may transition to either a fatal health state (Death All causes, SCD) or non-fatal health state (Stroke HCM Related). Patients in the Stroke HCM Related health state may only transition to a fatal health state (SCD). |

### **Model Structure (Research Design)**

The economic model of baseline patient characteristics includes (1) a Decision tree that describes how HCM patients at risk of SCD over 5-years and eligible for ICD implantation are identified (figure 1A), and (2) a Markov state transition model of 10, one-year cycle (time horizon), where virtual patients after ICD implantation may remain ‘healthy’, have a non-fatal event ‘Stroke HCM Related’, or a fatal event ‘SCD’ or ‘Death All Causes’ (figure 1B). these health states were chosen by clinicians at the Heart Hospital London.

At baseline all patients present with HCM enter the decision tree in the economic model, and one of two described SCD risk algorithms (section 3.2) applied to calculate their 5-year SCD risk score. Depending on their score, an ICD is implanted or not; patient who do not receive an ICD continue to receive usual care. Decisions on ICD implantation on the basis of HCM-SCD risk predicted scores are determined as follows (>6% ICD recommended, 4 – 6% up to the clinician, < 4% ICD not recommended). Virtual patients cycle through the Markov model in one-year cycles beginning from the ‘Healthy’ state, the ‘SCD’ state is occupied by patients with the primary event of interest Sudden Cardiac Death, a fatal event. Patients who die from other causes that may or, may not directly relate to HCM are in the ‘Death All Causes’ state. Patients with risk scores >6% are entered into the Markov model, this is because the European Society of Cardiology (ESC) recommends ICD implants for patients with risk scores >6%.

## **Primary and Secondary Outcome Measures**

### **QALYs**

The quality and quantity of years lived in each state in the Markov model were measured using Quality Adjusted Life Years (QALYs). QALYs are computed by multiplying a utility score (a preferred value of a health state) by the length of time spent occupying that health state. A utility score of 1 represented perfect health, while a score of 0 represented death in the model. All patients entering the model were assigned a utility score 0.637, corresponding to a patient being managed with an ICD implant (Noyes et al., 2007). In any year that a patient had a non-fatal HCM related event, a utility decrement was applied for that year, and all other years following it, until the end of the model or the death of the patient. Utility decrement of 0.1, associated with non-fatal event ‘Stroke HCM Related’ was taken from published literature (Colquitt et al., 2014). Additive?

### **Direct Cost**

In this study direct cost included in the model are defined as the cost of SCD risk algorithm, SCD risk management. Cost of SCD risk algorithm included a value of the time taken to use the HCM- SCD risk prediction model (£20) and also currently recommend risk assessment methods, to review results with the patient. Cost of SCD risk management was considered for only Day case procedures at £4792, as this is the most common procedure (Waight et al., 2019). The cost of non-fatal HCM related events (£22,880) were extracted from published literature by the UK Stroke Association. See appendix for a detailed description of how cost estimated were obtained.

### **Transition Probabilities**

In the Markov model transition probabilities were defined for each pair of health states using data obtained from observational studies of patients moving from one health state to another. So for instance if observational data suggest *y*  out of *n* HCM patients with ICD implants develop stroke, then with a suitable model that describes the number of ICD implant patients developing stroke (*y*) and an appropriate prior distribution for the parameter generating *y* , it’s possible to learn from the posterior distribution the underlying transition probabilities corresponding to the pair of health states (i.e. ‘Healthy’ and ‘Stroke HCM Related’).

Separate models were estimated for each SCD risk assessment strategy, using on each occasion a sample of 1000 virtual patients, while incorporating data from real cohorts of ICD implant patients.

* 1. **Modelling Framework (Conceptual Framework)**
  2. **Markov Model**

From figure (1B), if we define a Markov model consisting of nodes ………., where , for are mutually exclusive and exhaustive health states that a patient with a particular disease may experience. Then the set = (………. represents all the possible clinical pathways that may be experienced by the patient over a time period .

Arrows connecting any two nodes suggest it is possible to move from the node where the originate to the node they terminate. Where connecting arrows do not exist between two nodes, then it is not possible to move either way (to or from), between the two nodes. For instance patients occupying the health state ‘Healthy’ at time , may remain healthy, or move to any one of the health states ‘Stroke HCM Related’, ‘SCD’, or ‘Death All Causes’ at the next time These movements are determined by a corresponding transition probability defined for each pair of states (, by a random variable .

If at time , a set of patients enter the Markov model occupying the different health states of the model at discrete times *j= j+1,*  then we define a dataset  such that at least contains three variables ) that measure respectively well-defined clinical benefits, associated cost and transition probabilities. For each intervention or treatment (where , and ), we can define sub-datasets where the are assumed to be independent and identically distributed (i.e. *i.i.d.).*

The number of patients sojourning in each health state at any given time , may be modelled as , such that for a Markov model with k states. The generic element represents the absolute number of patients in state , at time At any time the absolute number of patients in a state is directly proportional to the number patients in that state at time Hence the absolute number of patients may be defined as

= ……………… 1,

where , a transition matrix, that describes the probability of moving from state to the state at time Equation 1 is written generally for any treatment as

……………….. ………. 2

* + 1. **Cost and Effect Modelling**

The utilities, and the cost associated with each health state are multiplied by the number of patients in each state at any time , to estimate the appropriate economic summaries for the economic evaluation.

Total cost for year in any one of two-intervention group,

………………………………………3

Where ‘DAC’ = Death All Causes, and  is the number of patients in health state multiplied by the cost of applying treatment , to the patients concern in health state in year

While in equations 4 and 5, is the number of patients in health state multiplied by the cost of applying treatment (i.e. using currently recommended methods of SCD risk assessment), to the patients concern in health state in year .

To model the number of QALYs accumulated from occupying the non-fatal health states, we follow (Sonnenberg and Beck, 1993), by multiplying the utility score corresponding to each non-fatal health state by the length of time spent occupying each health state. The computations are specified as follows:

………………………6

Where and , are the number of patients occupying the health states ‘Healthy’, and ‘Stroke HCM Related’ respectively at time , while and, are the utility scores for the respective health states. Equation 7 specifies how the clinical benefits for each treatment are derived.

* 1. **Bayesian Parametric Modelling**

We set out in the paragraph below a concise summary of Bayesian Parametric modelling, and draw on arguments in (sections 1.0 and 2.0), to setup the theoretical basis for the Economic Evaluation (Data Analysis).

Proceeding from section 4.1b, knowledge of the dataset  collected from each cycle of the Markov model for each treatment is imperfect due to limitations in valuing cost or consequences of the interventions and assumptions made about patient movements from one state to another. For instance, the true cost of using the HCM- SCD risk prediction model is unknown, so also is the true utility of a health state. We therefore consider the dataset as a random sample from a reference population (HCM patients with ICD implants) generated by a certain parameter that is random but unobservable, thus the true values of both *D* and are uncertain. The sampling variability in *D* may be described by a probability distribution . Under the Bayesian approach the uncertainty in the parameter may be modelled by relying on subjective knowledge to specify a suitable probability distribution ) (O'Hagan and Stevens, 2001). This leads to the posterior , obtained from Bayes theorem (O'Hagan and Stevens, 2001). The probability distribution is the sampling distribution or likelihood, while is known as the prior distribution (O'Hagan and Stevens, 2001).

* + 1. **Modeling Sample Distribution**

Of the elements of the dataset ), the clinical benefit (), and the associated cost (), from occupying any particular health state of the Markov model are deterministic variables, that is their respective values can be predicted to a greater degree of accuracy, also they are mathematically, functionally dependent on the transition probabilities, as specified in equations (1 - 7). Hence, a prior on the transition probabilities directly induces priors on the measures of clinical benefit and cost. Based on this reasoning we go on to specify a sampling distribution for the transition probabilities as follows.

We observe , as the count of the number of patients moving from health state  to health state in time out of the patients observed to occupy at time .

Then a model describing , may be specified by choosing any suitable probability distribution, in this instance a binomial distribution is considered suitable.

We therefore proceed to model probability of , in the general case as

…………………………8

Where at time, is the number of patients observed to occupy health state , and is the number of patients we observe moving in or out of health state at time for treatment , while is the underlying parameter characterizing the probability of movements in or out of health state , at time for treatment

We define suitable priors on model parameters  to complete the model. The literature suggests this should be done on natural scale parameters (i.e. mean, standard deviation), while noting that for many distributions, priors may have to be defined on scales other than natural ones even though doing so may make it difficult to formalize prior knowledge (Baio, 2012). In the current study we consider a conjugate prior distribution (i.e. a distribution that results in a posterior having the same distributional family as the binomial distribution above) to the model defined above.

* + 1. **Modelling Prior Distribution for Transition Probabilities**
       1. Beta Distribution

A prior distribution is defined for the parameter , as a beta distribution. The choice of beta distribution is appropriate since it conjugates with the binomial distribution defined as the sampling distribution in (section 4.2), to a close form under the Bayesian framework. The full definition of the prior distribution is as follows:

……………………………………. 9

Where for health state , time , and treatment are the shape parameters of the beta distribution. Within the context of the current modelling, represents expert opinion on the number of patients transitioning out of health state , at time , while is opinion on the number of unsuccessful transitions.

* + 1. **Modelling Posterior Distribution**

Having defined models for the sampling distribution (section 4. 2..1), and the prior distribution (section 4.2.2), we proceed on the basis of theory setout in section 4.2 to derive the model for the posterior distribution as follows:

With all variables retaining their meanings, as previously defined.

* + 1. **Sensitivity to Parameter Specification for Transition Probabilities**

As acknowledged by Spiegel halter et al (2004), and others such as (O'Hagan and Stevens, 2001), a thing as the true prior does not exist, there is therefore the potential that priors reflecting alternative assumptions when applied under the Bayesian framework will lead to different results. In this study, the range of values that may be assumed by the variables  and , in the model described in (section 4.2.2.1), express priors that reflect different perspectives about the parameter . The impact of these perspectives on the economic evaluation is explored in a sensitivity analysis using a specified range of values of the variables and .

* 1. **Model Specification**
     1. **Markov Assumptions**

The Markov model described above (section 4.1) is modelled assuming (1) a discrete time sequencing, and (2) that transition probabilities are the same for each time unit (i.e. transition probabilities are time-homogeneous) that patients cycle through the model.

* + 1. **Bayesian Parametric Models**
       1. **Sampling distribution**

* + - 1. **Prior distribution**
      2. **Posterior distribution**

Please note for the sake of making it easy to derive a close form solution for the posterior distribution we assume = =….=

* 1. **Discounting Cost and Effects**

Since the Markov model will be simulated over a 10 – year period in one-year time cycles, a discount rate of 3.5% was applied to all future cost and benefits to bring them to their present value in accordance with NICE requirements using the Net Present Value formula, when considering each intervention (treatment), as follows;

For cost:

For benefits:

Where

* 1. **Economic Evaluation (Data Analysis)**

The specified Bayesian parametric model was then fitted to the observed data for the 1000 patients, upon which summary measures of effectiveness, costs, and transition probabilities are estimated directly from the posterior distribution, for example ), to carry out the health economic evaluation. For instance, it’s possible from these summaries to drive appropriate health economic summaries such as the incremental of the mean effectiveness: and the incremental of the mean cost: *.*

After obtaining from the posterior distribution the summaries, using the Markov Chain Monte Carlo (MCMC) sampling procedure. The outputs were then post-processed using the R package BCEA, and proceeded to perform the economic analysis. Beginning with a description of the joint distribution of (, from a construct of the cost-effectiveness plane. To determine the cost of a unit of effectiveness, the Incremental Cost-Effectiveness Ratio ICER, was computed from: **.**

Expectations of increases in benefits resulting from applying a particular intervention was evaluated by computing the Expected Incremental Benefit (EIB), as follows , where *k* is the willingness to-pay threshold. The EIB a relative measure of cost, essentially is a rescaling of the differential effectiveness with the willingness to-pay threshold to a unit comparable to the differential cost. Applications of different willingness to pay threshold values to computing the EIB made it possible to analyze a decision to choose one intervention instead of an alternative by determining if expected increases in effectiveness from its use always corresponded to expectation of increases in cost saving. An intervention was cost-effective if the EIB was positive.

Probabilistic sensitivity analysis to test the range of willingness to-pay threshold values for which the cost and effectiveness of an intervention is acceptable in preference to another, the Cost-Effectiveness Acceptability Curve (CEAC) was plotted as , a determination of the impact of future information on parameters to the decision making process was also considered by performing an expected value of information analysis.

Structural sensitivity analysis to determine the impact of distributional assumptions were obtained directly from the Bayesian modelling framework adopted in this dissertation.

1. **Results**
2. **Discussion**
3. **Conclusion**
4. **References**

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1. Hypertrophic cardiomyopathy was defined in (O’Mahony et al., 2014) as a maximum left ventricular wall thickness ≥15 mm unexplained by abnormal loading conditions (Elliott et al., 20008 or in accordance with published criteria for the diagnosis of disease in relatives of patients with unequivocal disease (McKenna et al., 1997). Patients with known metabolic diseases (e.g. Anderson-Fabry disease) or syndromic causes of HCM (e.g. Noonan syndrome) were excluded from the study [↑](#footnote-ref-1)
2. Sudden cardiac death was defined as witnessed sudden death with or without documented ventricular fibrillation or death within 1hr of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms. ELLIOTT, P. M., POLONIECKI, J., DICKIE, S., SHARMA, S., MONSERRAT, L., VARNAVA, A., MAHON, N. G. & MCKENNA, W. J. 2000. Sudden death in hypertrophic cardiomyopathy: identification of high risk patients. *J Am Coll Cardiol,* 36**,** 2212-8. [↑](#footnote-ref-2)
3. There is a complex structure of relationships linking costs and benefits; for instance, there may be strong positive correlation, because effective treatments could be associated with higher unit costs, given that they are innovative and result from intensive and lengthy research. Conversely, they may be negatively correlated, as more effective treatments may reduce total care pathway costs, for example, by reducing hospitalizations or side effects. Consequently, an appropriate statistical model for costs and benefits should is needed to formally account for this association [↑](#footnote-ref-3)
4. For an early, intelligent but not particularly pro-Bayesian discussion of the issues see Mainland’s statistical ward round number MAINLAND, D. 1967. Statistical ward rounds--5. *Clin Pharmacol Ther,* 8**,** 738-48.. [↑](#footnote-ref-4)
5. For a much more thorough description of the use of Bayesian methods in Health Technology Assessment (HTA) see Spiegel halter et al. SPIEGELHALTER, D. J., MYLES, J. P., JONES, D. R. & ABRAMS, K. R. 1999. An introduction to Bayesian methods in health technology assessment. *Bmj,* 319**,** 508-512. and references therein. [↑](#footnote-ref-5)