THE ECONOMIC EVALUATIONS OF INTERVENTIONS FOR HEART DISEASES

By

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ABSTRACT

The primary aim of the thesis was to report new cost-effectiveness evidence in the clinical area of heart disease. Following a review of published empirical work, this was achieved by undertaking three new cost-effectiveness studies: one in nurse-led secondary prevention clinics for coronary heart disease in primary care, one on cardiac resynchronisation therapy with or without an implantable cardioverter defibrillator in chronic heart failure, and the final one on a new drug therapy, nebivolol, compared with standard treatment in elderly patients with heart failure. Nurse-led clinics in primary care are highly cost-effective. Nebivolol is a cost-effective treatment to an elderly population with chronic heart failure. Cardiac resynchronisation therapy (CRT-P) is a cost-effective treatment option compared with medical therapy (MT) alone. However, adding an implantable cardioverter-defibrillator to CRT appears to be beyond the traditional willingness-to-pay threshold of £20,000 per QALY gained and might not be a cost-effective option.

The second aim of the thesis concerned the application of modelling methodology, with the intent being the provision of general recommendations in using Markov modelling approaches in economic evaluation conducted in the heart disease area. The focus was on extrapolation of cost-effectiveness of an intervention beyond a trial both in terms of the time horizon of the analysis and in relation to the population involved. Fundamental issues in parametric distribution functions and Markov modelling approaches have been revisited, with detailed consideration of which parametric distribution functions should be employed when extrapolating beyond a trial and how they could be adopted into model-based analyses. The need for further methodology investigations in this area is discussed in conclusion.

DEDICATION

This thesis is dedicated to my daughter Aimee who has brought me such joy and pride, and has motivated and inspired me to complete this work.

ACKNOWLEDGMENT

I would like to thank my supervisors Stirling Bryan and Pelham Barton for their encouragement, understanding and patience. I would especially like to thank Stirling Bryan for his excellent knowledge and outstanding supervision in leading me through the whole research process. I am touched by his commitment to seeing me through to completion of this thesis.

A special thanks to James Raftery for his support and encouragement. Many of the original ideas originated from discussions with him. I would like to thank Nick Freemantle for his comments and advice on several chapters and for being coauthor on three published related papers.

Finally, I would like to mention several individuals who have helped in different aspects of completing the thesis. Thanks to Ann Pope for helping to proof-read the thesis. Thanks to Alec Miners and Sue Jowett for sharing their theses with me, and to my colleagues and friends during the PhD process thanks for their company to name a few, Sonal, Charmaine, Clare, Helen, Katie, and Tom.

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SPECIFIC CONTRIBUTION TO THE RESEARCH

The thesis refers to work that has appeared in four publications, including three main case studies in chapter 3, chapter 6 and chapter 7, and examples used in chapter 4. All those publications involved large multidisciplinary teams. The following sections describe the contributions from each individual and my specific contribution to each chapter in the thesis.

Chapter 3

This chapter is based upon a paper published in British Medical Journal (Raftery *et al.*, 2005). In the thesis different analytic methods were applied. The contributions to the original paper were as follows:

Guiqing Yao conducted data management, data coding and costing data. She led on statistical analysis and contributed the drafting of the manuscript.

James P Raftery originated the idea and initialised the research and supervision of the research.

Peter Murchie provided the data.

Neil C Campbell provided clinical expertise and supervised the study.

Lewis D Ritchie provided clinical expertise in the field.

Chapter 4

This chapter draws on a paper published in the European Heart Journal (Calvert *et al.,* 2005). The specific contributions to the published paper as below:

Guiqing Yao contributed to extrapolating beyond the trial and conducted parametric survival analysis in choosing the best-fitting curves.

Melanie J. Calvert led on data analysis and drafted the paper.

Nick Freemantle supervised on the project and contributed to the discussion and analysis.

John G.F. Cleland provided clinical expertise in this field.

Cindy Billingham contributed advice on analysing quality of life.

Jean-Claude Daubert provided clinical expertise.

Stirling Bryan provided supervision in health economic aspects and contributed methods and comments on manuscripts.

Chapter 6

This chapter is based on a paper also published in the European Heart Journal (Yao *et al.,* 2007). It presented model-based analysis and the seeking of longer-term cost-effectiveness of

interventions. This paper continued the development of the case study presented in chapter 4, seeking to answer a few clinical and policy related questions.

Guiqing Yao conceived the idea and developed the model, re-analysed individual trial data and estimated the clinical input from individual trial data. She drafted the paper.
Nick Freemantle supervised the work and supported the drafting of the paper.

Melanie J. Calvert contributed by providing original SAS program code and reviewing the manuscript.

Stirling Bryan supervised part of the work and provided feedback on the manuscript.

Jean-Claude Daubert provided clinical expertise in the field.

John G.F. Cleland provided clinical expertise and comments at different stage of the model outcomes.

Chapter 7

This chapter is based on a paper published in Pharmacoeconomics (Yao *et al.*, 2008). The chapter reports a model-based study where input data were populated from a trial.

Guiqing Yao led on the analysis and developed the model and drafted the manuscript.

Nick Freemantle provided supervision of the project, and gave comments on the paper.

Marcus Flather provided clinical expertise in the project and contributed comments on the draft manuscript.

Andrew Coats provided clinical expertise in the project and comments on the draft manuscript.

Philip Poole-Wilson provided clinical expertise and contributed comments on the draft manuscript.

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ABBREVIATIONS

AF	Atrial fibrillation
AIC	Akaike's Information Criterion
BHF	British Heart Foundation
BNF	British National Formulary
CABG	Coronary artery bypass grafting
CARE-HF	CArdiac REsychronisation in Heart Failure trial
CCU	Cardiac care unit
CEAC	cost-effectiveness acceptability curves
CHD	Coronary heart disease
CHF	Chronic heart failure
CI	Confidence interval
CRT	Cardiac resynchronization therapy
CRT-ICD	CRT with an implantable cardioverter–defibrillator
CRT-P	cardiac resynchronization therapy without ICD
CUA	Cost utility analysis
CV	Cardiovascular
CVD	Cardiovascular disease
DOH	Department of Health
GP	General practice
HF	Heart failure
HTA	Health technology assessment
ICD	Implantable Cardioverter-Defibrillator

ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
ITT	Intention to treat
MeSH	Medical Subject Headings
MI	Myocardial infarction
MT	Medical therapy
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NYHA	New York Heart Association functional class
PDF	Probability density function
PSA	Probability sensitivity analysis
PTCA	Percutaneous Transluminal coronary angioplasty
QALYs	Quality-adjusted life years
RCT	Randomised control trial
SENIORS	Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure
CUA	Cost utility analysis

CHAPTER 1 INTRODUCTION

1.1 Background on the epidemiology of heart disease

Heart disease or cardiovascular disease (CVD) is a range of conditions which includes coronary heart disease (CHD), cerebrovascular disease, hypertension, peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure (WHO, 2008).

CHD is the most common form of CVD. It is also known as coronary artery disease which refers to disease characterised by narrowing of the blood vessels supplying the heart muscle (BHF, 2007). The condition can cause angina and heart attack. Angina is most often felt as chest pain. Heart attack, also called myocardial infarction (MI), happens when an artery to the muscles of the heart is suddenly and completely blocked. Heart failure is also known as congestive heart failure which causes the heart to become less effective and not to supply enough oxygen containing blood to the needs of the body. It results from coronary heart disease in most cases but it can be caused by high blood pressure. Most often it is a chronic condition that worsens over time in the absence of treatment.

Other common forms of CVD include stroke, aneurysm, and cardiac arrhythmia cardiomyopathy, all of which are related to dysfunction in different parts of the heart or blood vessels.

CVD is the most common cause of death globally. WHO estimated that 17.5 million people died from cardiovascular disease in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks and 5.7 million due to stroke. In the UK, according to British Heart Foundation statistics (BHF, 2007), more than 208,000 deaths a year (36% of all deaths in the UK) are accounted for by CVD. Nearly 48% of all deaths from CVD (approximately 101,000 deaths a year in the UK) are due to CHD. Heart attack is the major cause of death from CHD. About 260,000 people in the UK suffer a heart attack each year, with about 30% of the heart attacks leading to death before the patient reaches hospital (BHF, 2005). Other forms of heart disease cause around 32,000 deaths a year. In 2005 heart disease was responsible for around 133,000 deaths.

In 2003 the estimated prevalence of CHD in England was 7.4% in men and 4.5% in women based on the Health Survey of England (DOH, 2003). Prevalence increased with age with around 25% in men and 20% in women aged 75 and over living with CHD. Figures based on British Heart Foundation statistics (BHF, 2007) indicate that there are over 1.5 million men and 1.1 million women living in the UK suffering from CHD, either as angina or heart attack.

Treatments for heart disease depend on the type of disease and severity of the condition. Most people with coronary heart disease can be managed or controlled on medications. However, acute or worsening conditions, such as a heart attack, require urgent medical or surgical interventions. The UK National Health Service (NHS) National Service Framework for CHD, announced in March 2000, set national standards for the prevention, diagnosis and treatment for CHD in England (DOH, 2007).

The economic costs of CHD are very high. It is estimated to have cost the publicly financed health care system in the UK around £15 billion in 2003, of which care for those patients in hospital accounted for about 76% and medications and dispensing expenses accounting for a further 18% (BHF, 2007).

1.2 Economic evaluation in health care

The increasing demand for health care, as seen in the case of CHD, places ever growing pressure on limited health care budgets. It is therefore important for decision-makers, when deciding whether to cover or reimburse a particular technology, to consider not only safety and efficacy but also efficiency. Economic evaluation provides information on efficiency by estimating the cost and effectiveness of two or more health care alternatives and comparing the relative difference in the outcomes (Drummond *et al.*, 2005). It provides decision-makers with a means for setting priorities in allocating resources.

In recent years, economic evaluations alongside randomised controlled clinical trials have become increasingly popular as a route for generating evidence to allow the evaluation of health care programs. A recent study by Sculpher and his colleagues indicates that nearly 30% of published economic evaluations since 1994, recorded on the NHS Economic Evaluation Database are based on data from a single randomised control trial (RCT) (Sculpher *et al*., 2006).

The growing popularity of trial-based economic evaluation has called for a further advance and methodological development in the analytic approaches for conducting economic

evaluation alongside clinical trials. As will be shown in the next chapter, most analytic methods in economic evaluation running alongside clinical trials rest upon traditional statistical analysis methods. Traditional statistical methods in analyzing cost and quality-adjusted life years (QALYs) face several challenges in economic evaluation at the level of individual data (Barber & Thompson, 1998). For example, missing data is common in clinical trials; and it tends to be a more severe problem when the collection of resource usage data is also considered. In addition, cost data are often characterized by highly skewed distributions with a few patients incurring a very large cost (Barber & Thompson, 2000). This challenges the normality assumption in traditional statistical methods for estimating the difference in means.

Clinical trials are usually designed for specific clinical outcomes. In most cases, they focus on clinical endpoints. In addition, the follow up periods in most trials tend to be relatively short. It is most likely that the impact of an intervention on costs and effectiveness are not reflected within a trial period. Furthermore, trial populations may not commonly be representative of general patient groups (Buxton *et al.*, 1997). Therefore, methods for extrapolating beyond a trial are often sought in order to explore the potential implication in cost-effectiveness over a longer period and when applying the results to more general settings.

However, literature reveals inconsistency on different analytic approaches in conducting economic evaluation (Barber & Thompson, 1998; Richardson & Manca, 2004). Different methods might lead to different conclusions about the same intervention. Therefore, it is necessary to improve the quality and consistency of the methodology applied in conducting

analyses in economic evaluation. Such a development would enhance the usefulness and reliability of economic evaluation to decision-makers.

1.3 Aims of the thesis

The thesis has two primary aims, one empirical and the other methodological. On the empirical side, the primary focus of this thesis is to provide new economic evaluation evidence relating to selected interventions in cardiovascular heart disease. It focuses on the situation where economic evaluation was conducted alongside a randomised clinical trial. The cost and effectiveness of three interventions in cardiovascular disease are investigated:

1. Nurse led clinics in secondary prevention care;
2. Cardiac resynchronization therapy (CRT) with and without the addition of an Implantable Cardioverter-Defibrillator (ICD);
3. Nebiviolol treatment in an elderly patient group with chronic heart failure.

The second aim of the thesis, relating to methodological work, is to provide practical illustrations on the application of methodological aspects when conducting economic evaluation based on individual data from a trial. The thesis illustrates how to extrapolate cost and survival data beyond a trial period and how to conduct model-based analysis when input data are populated from a trial.

1.4 Outline of the thesis

Chapter 2 contains the literature review in economic evaluation conducted in the area of heart disease. It focuses on full economic evaluation conducted within cardiovascular disease excluding stroke. The review also includes an extensive discussion of modeling approaches used in the literature and provides a critique of their application.

Chapter 3 documents an empirical study of cost-effectiveness analysis of nurse led clinics in secondary prevention in primary care for cardiac patients. The study was a within trial analysis and details of statistical methods are illustrated. This chapter was based on a published paper in the British Medical Journal (Raftery *et al*., 2005) and was further developed specifically for the thesis using a different analytic approach. In the published paper, only t-tests are presented in the analysis cost and quality of life data, whereas in the thesis, bootstrapping methods were used for all analyses.

Chapter 4 discusses statistical properties of different distribution functions and their use in extrapolating survival curves from a trial to beyond a trial period. One of the clinical case studies of the thesis, the CARE-HF study, was used as an illustration of the approach. The focus of this analysis was on methods for dealing with the different time perspectives for cost and QALYs within a trial period, in which a large cost occurred with the implementation of the intervention and where, by the end of trial, benefit was still accruing. Methods employed in extrapolating beyond the trial, based on a parametric survival analytic approach, are presented. The case study in this chapter was published in European Heart Journal (Calvert *et al.*, 2005)

Chapter 5 discusses methods based on a modeling approach in extrapolating beyond a trial. An individual simulation model based on a Markov modeling framework is reviewed and details on how to overcome the limitations of the Markov model are discussed. The focus is on step-wise approaches to estimate transition probabilities from individual data, including Matrix algebra in converting different lengths of cycles, and how to estimate hazard ratios. An example used for illustration throughout the chapter is based on a renal transplantation model (Yao *et al.*, 2006).

Chapter 6 contains a case study using a model to go beyond a trial and draws also on the CARE HF study. This chapter focuses on modeling approaches in extrapolating beyond a trial. Details of the modeling approach and model validation is illustrated. This study was published in European Heart Journal (Yao *et al.*, 2007).

Chapter 7 is a case study using the SENIORS trial. This chapter focuses on one approach covering both within and beyond trial analyses. Further, the analyses extrapolated beyond the end of the trial, but I also extended the approach to extrapolate into different populations. This study was published in Pharmacoeconomics (Yao *et al.*, 2008).

Chapter 8 contains a general discussion of all the issues and final remarks on economic evaluation conducted in heart disease. The overall conclusions of the thesis and the implications for future research are discussed.

CHAPTER 2 LITERATURE REVIEW OF ECONOMIC EVALUATION IN HEART DISEASE

2.1 Introduction

The previous chapter gave an overview and outline of the thesis. The aim of this chapter is to present an overview of methods used in economic evaluations based on individual data conducted in the area of heart disease. It focuses on the analytic methods adopted by other researchers in this disease area. Emphasis was placed on how costs and outcomes were collected and estimated, how cost-effectiveness was analysed and presented, modelling methods used in extrapolating beyond a trial period and assumptions made on treatment effects and methods in estimation on survival or time-to-event curves beyond a trial period.

The first part of the chapter considers how the papers to be reviewed were identified and methods used in data extraction from each study. This is followed by a broad critical review of the identified papers using an established review framework, namely the Drummond checklist. In the second part of the chapter (from section 2.6), it focuses on critical review of the modelling methods used in those papers, where modelling was undertaken. The literature on methodological issues related to modelling approaches was discussed.

2.2 Search strategy

To identify published economic evaluation studies based on individual data from randomised clinical trials for cardiovascular disease, a search was undertaken through the MEDLINE database. The search used the terms “heart”, “cost” or “economic” and “clinical trials” in the title and abstract or “heart disease” in MeSH heading. Full details of the search strategy for this review are presented in Appendix 1.

The database search was conducted on October 1st 2007, covering the period from January 2005 to August 2007, the most up-to-date literature available at the time of search. The literature search has been conducted in a thorough and rigorous manner but is not ‘systematic’ in a formal sense. The reason for this is that it was not intended to identify treatment effects but to provide a broad view on the current approaches to conducting economic evaluation based on clinical trials in the clinical area of heart disease.

The narrow time frame was selected because the aim of the search was to report current practice at the time the research was carried out. MEDLINE was chosen as it is recognized as having excellent coverage of English Language papers and is well indexed, making it the first choice database for searching by most reviews. Since the work was not resourced to look at non-English articles, and since it was not conducting a review of a specific treatment effect (but instead a methodological review), the return from the substantial additional work required to extend to EMBASE (the second choice database) was judged unlikely to be worthwhile.

2.3 Inclusion and exclusion criteria

Two broad categories of studies were considered for inclusion in the review: economic evaluations conducted alongside clinical trials, and modelling based studies in which model inputs were populated by individual data from a trial. The disease area was defined as including all cardiovascular disease but excluding stroke. The types of economic evaluations include cost-minimisation, cost-effectiveness, cost-utility, and cost-benefit, which means only full economic evaluations (Drummond *et al.*, 2005) were included in the review. Studies that compared treatment effects and concluded no significant difference between comparators, which is cost-minimisation studies, were included. Studies that did not compare both costs and effectiveness of alternatives were excluded as were studies in which the authors did not access individual patient data from a trial.

2.4 Data extraction strategy

To review the included studies, information was extracted from each paper into four categories:

1. The overview of the studies including study population (disease area), interventions, comparators, results on clinical outcome and costs and setting of economic evaluation.

2. The economic evaluation methods used in each study, including type of economic evaluation, study perspective, outcome measurements, whether a within trial analysis or extrapolating beyond a trial and whether model based analysis were used.

3. Statistical analytic methods used within a trial analysis, including costing analysis, cost- effectiveness analysis, the use of statistical inference on the point estimates and statistical methods in conducting analysis.

4. When extrapolating beyond a trial was conducted, the review explored whether a model-based analysis was conducted, how the input data were populated and how the model was defined and assumptions relating to the model.

At the end of the section, a critical review of modelling work was undertaken. It focused on critical review of the modelling methods used in those papers, where a decision analytic model was used. Literature on methodological issues related to modelling approaches was also discussed.

2.5 Results

The literature search identified 220 studies. Details of the paper selection process are illustrated in the flow diagram (Figure 2.1). Screening on the titles and types of publications led to 77 papers being excluded because the studies were review articles.

On further review of the titles and abstracts of the remaining papers, an additional 90 papers were excluded because the study focus was trial design, they were not relevant to heart disease or heart disease was not the main area of study focus, or only a partial economic analysis with no comparison of two or more interventions in terms of cost and outcome was carried out. The full text of the remaining 54 potentially relevant studies was obtained. Of these, 29 randomised clinical trial based studies met the inclusion criteria for review. A list of excluded studies from the review can be found in Appendix 2.

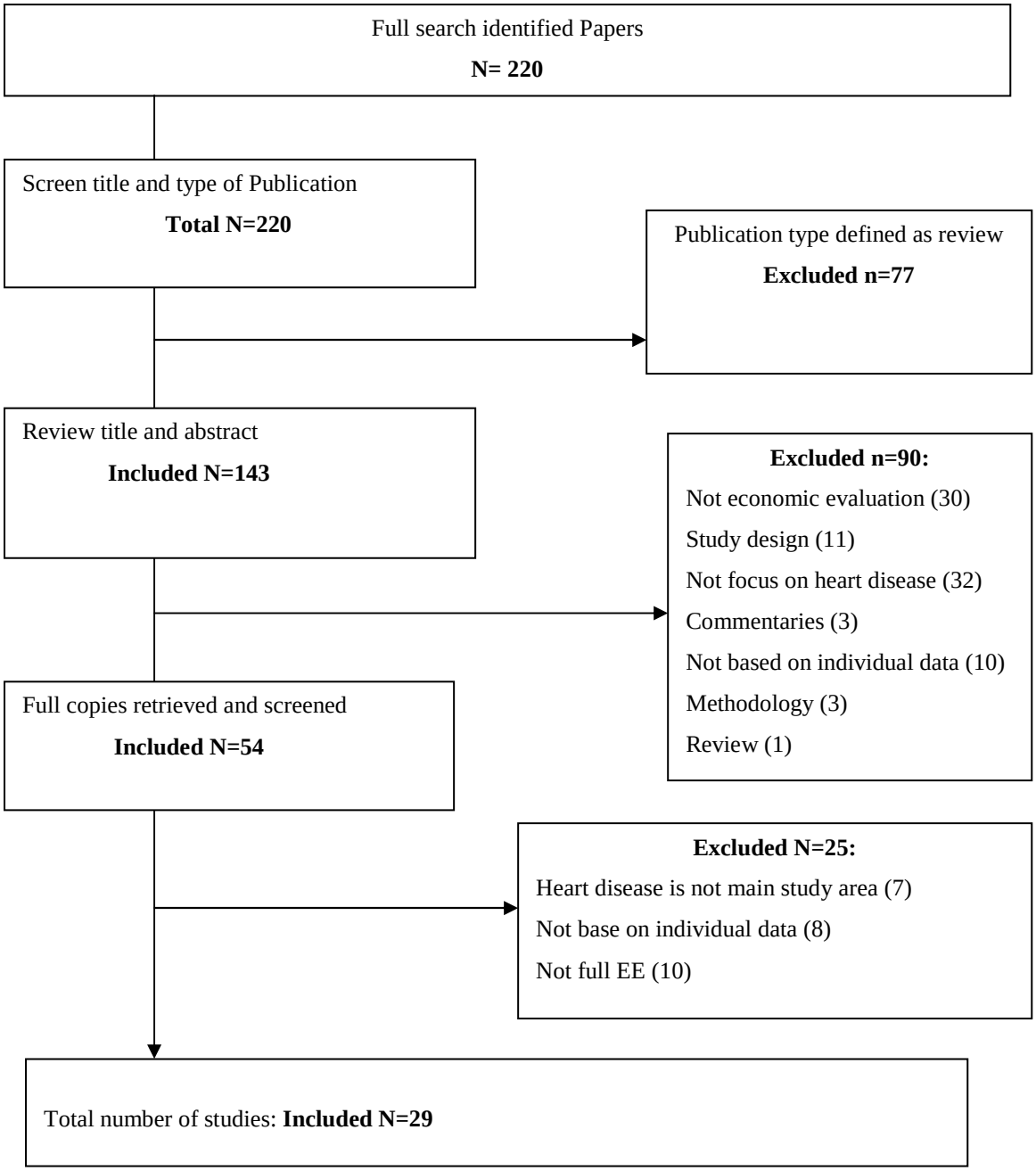

Figure 2.1 Flow diagram of selecting studies in the review

2.5.1 Overview of the included studies

Table 2.1 outlines the general information of the included studies in the review. Among the included 29 studies, 17 concerned chronic heart failure (HF), 3 in atrial fibrillation (AF), 3 in myocardial infarction (MI), 5 in coronary heart disease and 1 in other heart diseases.

Among the 29 studies, 17 focused on drug interventions, 5 were for device interventions, 4 were for care management interventions and 3 were for diagnostic tests. All of the included studies have their original clinical trials designed to compare interventions with placebo or current standard care. Table 2.1 reported the overall view of information which were reported on all included studies.

Ten of the economic evaluations were conducted in the US, 11 in the UK and eight in other countries. Reed and colleagues (2005) conducted an economic evaluation based on a multinational clinical trial setting and used country specific costing, while McMurray and colleagues (2006) conducted their economic evaluations in France, Germany and the UK.

Seventeen of the studies stated that the result of their corresponding clinical trials demonstrated positive intervention benefits and the objective was to examine the cost-effectiveness implications of the interventions. Ten of the studies did not demonstrate a significant benefit of the intervention from the clinical trial, 2 of those aimed to

investigate the cost implications of the interventions, and the others investigated the cost-effectiveness result.

Table 2.1 Overview of all included studies

Study	Population	Intervention	Comparator	Clinical result	Cost result	Setting
Angus 2005	HF	Isosorbide dinitrate /hydralazine	Standard care	Effective	Cost more	USA
Beinart 2005	CHD	Clopidogrel	Placebo	Effective	Cost more	U.S and Canada
***Bond 2007**	CHD	Pharmacy-led medicines	Standard care	NS	Cost saving	UK
Briffa 2005	MI /angina	Rehabilitation	Standard care	Effective	Cost more	Austria
Briggs 2007	CHD	Perindopril	Placebo	Effective	Cost more	European[1]
Calvert 2005	HF	CRT-P	Medical therapy	Effective	Cost more	European[1]
Caro 2006	HF	Metoprolol succinate	Standard care	Effective	Cost more	US
Di 2005	HF	Bisoprolol	Placebo	Effective	cost saving	18 Countries-
Feldman 2005	HF	CRT-P or CRT-D	Medical therapy	Effective	Cost more	US
Inglis 2006	HF	Home-based intervention	Usual post	Inglis 2006	HF	Home-based intervention

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Table 2.1 Overview of all included studies (continued)

Study	Population	Intervention	Comparator	Clinical result	Cost result	Setting
Mark 2006	HF	Amiodarone	Medical therapy	NS	Cost more	US, Canada & New Zealand[4]
McMurray 2006	HF	Candesartan	Placebo	Effective	Cost more	26 countries[2]
Mihaylova 2005	CHD	simvastatin	Placebo	Effective	Cost more	UK
Mueller 2006	HF	B-Type Natriuretic Peptide	Conventional strategy	NS but reduced mortality	Cost saving	Swiss
O'Brien 2005	HF	Physiologic pacemaker	Ventricular pacemaker	Effective	Cost less	Canada
Pietrasik 2007	AF	Rate control	Rhythm control	NS	Cost saving	Polish
Radeva, 2005	Heart transplantation	Everolimus	Azathioprin	Effective	Cost more	Multinational
Raftery 2005	CHD	Nurse led	Standard care	Effective	Cost more	Scotland
Reed 2005	HF	Valsartan	Captopril	NS	Cost more	24 countries[6]
Rinfret 2005	HF	Valsartan	Captopril or both	Not effective	Cost more	US

Table 2.1 Overview of all included studies (continued)

Study	Population	Intervention	Comparator	Clinical result	Cost result	Setting
Scuffman & Kosa2006	PCI	Fluvastatin	Control	Effective	Cost more	Europe, Canada and Brazil[5]
Scuffham & Chaplin 2005	PCI	Fluvastatin	Control	Effective	Cost more	Europe, Canada and Brazil[1]
Szucs 2006	HF	Eplerenone	Placebo	Effective	Cost more	Switzerland
Taylor 2005	MI	Home-based rehabilitation	Hospital-based rehabilitation	NS	Cost same	UK
Walker 2006	CHD-angina	Nicorandil	Standard care	NS but reduced events	Cost more	UK
Weintraub 2005a	Angina or MI	Clopidogrel	Placebo	Effective	Cost more	28 countries EE: US
Weintraub 2005b	HF	Eplerenone	Placebo	Effective	Cost more	37 countries EE: US
Van. Hulst 2005	Valve surgery	Lucodepleted erythrocytes	Buffy-coat-depleted packed cells	Effective	Cost saving	Netherland
Yao 2006	HF	CRT-P or CRT-D	Medical therapy	Effective	Cost more	European EE: UK

NS: Not significant.

The economic evaluation was conducted: 1, UK; 2, France, Germany and the UK; 3, Italy; 4, USA; 5, Hungary; 6,country specific cost

2.5.2 Economic evaluation

When economic evaluation is conducted alongside a clinical trial, the "piggyback" method is usually used to prospectively collect resource data (Gold *et al.,* 1996). This simply refers to the collection of resource use and/or quality of life data within an otherwise typical clinical trial. This might be achieved through the use of interviews, questionnaires, case record forms, hospital notes or patient recorded diary.

The study perspective defines which resource items should be collected. For example, if the UK National Health Service (NHS) perspective was taken, the cost burden to the NHS only should be considered. If the perspective was from societal point of view, then further resources used should be considered such as the cost of traveling, out of pocket expense, family or relative care and loss of productivity.

Clinical trials are usually designed for clinical end points. In cardiovascular disease, the primary outcome of a study is usually on clinical interests, such as the number of cardiovascular events avoided, or time of first unplanned cardiovascular hospitalisations. Decision-makers are interested in assessing the marginal benefit of additional cost of a technology for difference patients groups. This required measuring additional cost per quality-adjusted life-year (QALY) gained or per life-year gained. QALYs are the recommended outcome in economic evaluation (Pearson & Rawlins 2005). The Public Health Services Panel on Cost-effectiveness in Medicine (Gold *et al*., 1996) and the NICE health technology assessment (HTA) process in the UK have recommended using QALYs in its guideline for economic evaluation (NICE, 2007). Those are two most influence bodies which had on the conduct of cost-effectiveness analysis generally. The US panel recommendations form the

basis of the standard US textbook on cost-effectiveness analysis. While the NICE setting the standards are increasingly being adopted in other UK-based analysis.

QALYs are the summary measurement of each life-year weighted by its corresponding utility values, which are usually measured as preference based utility scores. The commonly used for such measurement is EuroQol EQ-5D (EuroQol Group, 1990). The EQ- 5D index has a scale where 0 is equivalent to death and 1 full health. A negative value represents a state of ‘‘worse than death’’ (Drummond *et al*., 2005). Other measurements of preference based quality of life include SF-6D (Brazier *et al*., 2002), and the Health Utility Index (HUI2) and the Health Utility Index 3 (HUI3) (Feeny *et al*, 2002).

In this section, the Drummond definitions on the type of economic evaluation were adopted (Drummond *et al*., 2005). Similarly, all studies were classified into health sector, societal, hospital and health sector plus private perspectives.

Table 2.2 gives a summarisation of information on economic evaluation employed on the papers. Among the 29 studies, 27 conducted a cost-effectiveness analysis, in which 12 incorporated cost-utility analyses, and 2 were cost-minimisation analysis in which the authors had provided no significant treatment effects.

Of the 29 studies, 26 adopted a health care sector perspective, in which 4 of the studies claimed to take the societal point of view. However, three of the 4 studies, which claimed to be from a society point of view, did not collect any cost data related to non-health care or productivity loss. Raftery and colleagues (2005) included direct NHS health care costs and

private hospital visit costs and justified excluding productivity costs as the majority of patients were over 64 years.

Among the 29 studies, 12 used quality-adjusted life-years (QALYs) as the outcome measure, 27 used a life-year or mean survival time, among those 5 studies used the trial's primary end point as the measure of effectiveness in the economic evaluation. Among the 12 cost-utility analyses, 8 collected preference-based utility measures as part of the trial, 2 were based on published utility values and 2 were taken from publicly available survey data.

Twenty-three studies conducted economic evaluation alongside the clinical trial, in which 6 conducted within-trial period analysis and investigated the longer-term cost-effectiveness results by extrapolating beyond the trial without actually using a decision model. Six studies conducted a model-based analysis to investigate the long-term economic implications.

Table 2.2 Summarised information on economic evaluation

Study	Type of EE	Perspective	Outcome measure	Trial follow-up (month)	Extrapolating beyond a trial	Analytic type
Angus 2005	CEA	Societal	Life years	12.8	Yes	Statistical analysis
Beinart 2005	CEA	Health care sector	Life years	12	Yes	Statistical analysis
***Bond 2007**	CMA	Health care sector	QALYs Life years	12	No	Statistical analysis
Briffa 2005	CEA &CUA	Health care sector	QALYs	12	No	Statistical analysis
Briggs 2007	CEA &CUA	Health care sector	QALYs Life years	50	Yes	Model based analysis
Calvert 2005	CEA &CUA	Health care sector	QALYs Life years	29.4	Yes	Statistical analysis
Caro 2006	CEA	Health care sector	Life years	12	Yes	Model based analysis
Di 2005	CEA	Health care sector	Clinical outcome	15	No	Statistical analysis
Feldman 2005	CEA&CUA	Health care sector	QALYs Life years	11.5 to 16.2 (median)	Yes	Model-based analysis
Inglis 2006	CEA	Not stated	Life years	48 (median)	Yes	Statistical analysis

CMA, Cost-minimisation analysis; CEA, cost-effectiveness analysis; CUA, cost utility analysis; EE, Economic evaluation.

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Table 2.2 Summarised information on economic evaluation (Continued)

Study	Type of EE	Perspective	Outcome measure	Trial follow up (month)	Extrapolating beyond a trial	Analytic type
Mark 2006	CEA&CUA	Societal perspective	QALYs Life years	45.5 (median)	Yes	Statistical analysis
McMurray 2006	CEA	Health care sector	Clinical outcomes	38 (median)	No	Statistical analysis
Mihaylova 2005	CEA	Health care sector	Clinical outcomes	60	No	Statistical analysis
Mueller 2006	CEA	Health care sector	Mortality	6	No	Statistical analysis
O'Brien 2005	CEA	Health care sector	Life years	62	No	Statistical analysis
Pietrasik 2007	CMA	Health care sector	Clinical outcomes	12	No	Statistical analysis
Radeva 2005	CEA	Health care sector (Societal)	Clinical outcomes	12	No	Statistical analysis
Raftery 2005	CEA &CUA	Health care sector (Societal)	QALYs Life years	53	No	Statistical analysis
Reed 2005	CEA &CUA	Health care sector	QALYs	24	No	Statistical analysis
Rinfret 2005	CEA &CUA	Health care sector (Societal)	QALYs Life years	33 (median)	Yes	Model-based analysis

CMA, Cost-minimisation analysis; CEA, cost-effectiveness analysis; CUA, cost utility analysis; EE, Economic evaluation,

Table 2.2 Summarised information on economic evaluation (Continued)

Study	Type of EE	Perspective	Outcome measure	Trial follow up (month)	Extrapolating beyond a trial	Analytic type
Scuffman & Kosa2006	CEA &CUA	Health care sector	QALYs Life years	48	Yes	Model-based analysis
Scuffham & Chaplin 2005	CEA &CUA	Health care sector	QALYs Life years	48	Yes	Model-based analysis
Szucs 2006	CEA &CUA	Health care sector	QALYs Life years	16	Yes	Statistical analysis
Taylor 2005	CEA	Health care sector	QALYs		Yes	Health care sector
Van 2005	CEA	Health care sector	Life years	3	No	Statistical analysis
Walker 2006	CEA	Health care sector	Clinical outcomes	18	No	Statistical analysis
Weintraub 2005a	CEA	Heath care sector (Societal)	Life years	12	Yes	Statistical analysis
Weintraub 2005b	CEA	Health care sector (Societal)	Life years	16	Yes	Statistical analysis
Yao 2006	CEA &CUA	Health care sector	QALYs Life years	29.4	Yes	Model-based analysis

CMA, Cost-minimisation analysis; CEA, cost-effectiveness analysis; CUA, cost utility analysis; EE, Economic evaluation,

2.5.3 Statistical methods in analysing cost and cost-effectiveness

One of objectives in economic evaluation is to compare the difference in mean cost per person between treatment groups. The arithmetic mean of the cost is an appropriate focus for decision-making (Drummond et al., 2005). Cost data are often characterised by highly skewed distributions with a few patients having large costs (Barber & Thompson, 2000). This challenges the normality assumption in traditional statistical methods for estimating difference in means. To deal with this problem, bootstrap methods, which are highly attractive methods in conducting cost analysis (Barber & Thompson 2000), do not need the assumption of normality. Recent studies have explored the use of generalised linear models and generalised linear mixed models in dealing with heavily skewed data in cost analysis (Nixon & Thompson, 2004).

Cost-effectiveness analysis seeks to estimate the difference in mean costs between treatments divided by the difference in effectiveness, such as QALYs or life years. The ratio is termed as an incremental cost-effectiveness ratio (ICER), and in cost-utility analysis it refers to incremental cost per QALY gained.

Inference of the point estimate of the ICER has brought a further challenge for analysis, in which the variance of the ratio has no obvious functional form. There are four methods in producing confidence intervals: the box method, the Taylor series method, non-parametric bootstrapping methods and Fieller methods (Polsky *et al.*, 1997). The box method calculates the confidence intervals (CI) by dividing the lower CI in costs by the upper confidence limit for effects to produce the lower limit of the confidence interval for the ratio and the upper limit of the CI by

dividing the upper limit for costs by the lower limit for effects. This can lead to an inappropriately wide confidence interval for the ICER (Wakker *et al.,* 1995). The Taylor series method involves estimating the standard error of the cost–effectiveness ratio itself by a Taylor series approximation (O'Brien *et al*., 1994). This method assumes that both cost and effectiveness and ICER estimate are normally distributed, which is it not always the case. The Fieller theorem method is a parametric method for computing the confidence intervals of a ratio. It is based on the assumption that the costs and effectiveness of the ratio follow a bivariate normal distribution (Willan & O'Brien, 1996).

The bootstrap approach is a nonparametric method that makes no distributional assumptions concerning the statistic in question. It employs the original data in a resampling exercise in order to give an empirical estimate of the sampling distribution of that estimate. The use of nonparametric bootstrapping methods to produce confidence intervals around the estimates of the ICER has been advocated by many authors (Chaudhary *et al.,* 1996; Briggs *et al*., 1997; Briggs *et al*., 1999 & Lord, *et al*., 1999).

There are 25 studies that were undertaken within a trial or within and beyond a trial with statistical analysis conducted using individual data of these. Table 2.3 provides a summarised information on statistical analysis used on those papers. Seventeen studies recognised the skewed nature of the costing data and used bootstrap methods for estimation and made inference on the point estimates. Four of the studies only reported summarised cost and point estimates without any inference on the point estimates, and two employed generalised linear models.

Among the 18 studies that conducted cost-effectiveness or cost-utility analysis, 10 used bootstrapping methods and made inference about the point estimates for the incremental cost-effectiveness ratios, and 14 produced cost-effectiveness acceptability curves (CEAC) in illustrating the probability of intervention being cost-effective at given level of willingness to pay per QALY or per life year gained.

Table 2.3 Summarised information on statistical analysis

Study	Cost difference	Inference	Incremental cost effectiveness (ICER)	Inference on ICER	Assumptions beyond the trial
Angus 2005	Bootstrap	CI and P-value	Bootstrap	CI and P -value	No
Beinart 2005	Bootstrap	CI	Bootstrap	CI	External source
Bond 2007	Point estimates	Inter Quartile	Regression	No	No
Briffa 2005	Point estimates	None	Point estimate	None	No
Calvert 2005	Bootstrap	CI	Bootstrap	CI and CEAC	Parametric survival function
Di 2005	Point estimates	None	No	No	No
Inglis 2006	Point estimates	none	Point estimates	None	No
Mark 2006	Bootstrap	P-value	Bootstrap	CEAC	Parametric survival function
McMurray 2006	Bootstrap	CI and P-value	Bootstrapping	CI	No
Mihaylova 2005	Bootstrap	Standard error	Bootstrap	CI	NO
Mueller 2006	Bootstrap	Standard error	Bootstrap	CI	NO
O'Brien 2005	Bootstrap	CI	Bootstrap	CI	NO

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Table 2.3 Summarised information on statistical analysis (Continued)

Study	Cost difference	Inference	Incremental cost effectiveness (ICER)	Inference on ICER	Assumptions beyond the trial
Pietrasik 2007	Bootstrap	P-value	N/A	N/A	N/A
Radeva 2005	Bootstrap	CIs	Bootstrap	CI	No
Raftery 2005	Bootstrap and T-test	P-value	Point estimate	CEAC	None
Reed 2005	Bootstrap	CI	Bootstrap	scatter plots	No
Rinfret 2005	Kaplan-Meirer	CI	Point estimate	No	Random
Szucs 2006	point estimates	No	Bootstrap	No	Observational data
Taylor 2005	Bootstrap	CI	Bootstrap	N/A	Mean
Van Hulst 2005	Bootstrap	CI	Bootstrap	Not defined	No
Walker 2006	Bootstrap	Point estimate	Mean	Point estimate	No
Weintraub 2005a	Bootstrap	CI	Bootstrapping	CEAC and scatter plot	Constant hazard and used observational data
Weintraub 2005b	Bootstrap	CI	Bootstrapping	CEAC and scatter plot	Used on observational data

2.5.4 Extrapolating beyond a trial

The choice of time horizon is an important consideration in economic evaluations (Drummond et al 2005) and it should be long enough to capture the major health and economic consequences. It is common for an economic evaluation, when conducted alongside a clinical trial, to estimate the cost-effectiveness result at the end of a follow-up period. However, clinical trials are designed to investigate a treatment effect on clinical outcomes. Certain treatments or interventions involve a large initial cost, such as surgery or implantation of a medical device. However, their treatment benefit may last much longer than a trial period. The cost-effectiveness result estimated at the end of a trial period may be substantially different if the treatment effects over a longer-term were considered. Therefore, economic evaluation often requires projection of treatment effects and costs over a longer time.

Extrapolating beyond a trial using a modelling approach is a common method in conducting economic evaluation. In the review, 7 studies have conducted beyond trial analysis by employing a model. Table 2.4 reported the summarised result of those model-based analyses. Among the 7 studies, 2 were based on cohort simulation while 5 were are based on individual simulation, of which 1 was based on a discrete event simulation approach and 4 employed a Markov modelling framework by allowing individuals to carry history and baseline characteristics in adjusting time-varying risks for different events.

For extrapolating beyond the trial, all the studies assumed constant hazard ratios for the intervention benefit beyond the trial; One of the studies assumed a declining rate of treatment

benefit; Three of the studies investigated the baseline function by employing parametric survival functions.

Four of the studies used probabilistic sensitivity analysis (PSA) to investigate second order uncertainty on the cost-effectiveness result and produced incremental cost-effectiveness acceptability curves (CEAC).

In the following sections, a more detailed critique of the modelling approaches used in the modelling papers is presented. It starts by developing an appropriate checklist for such a review, followed by the review of the modelling methods and approaches.

Table 2.4 Summarised information on model based analysis

Study	Type of model	Analysis approach	Transition probability fixed or varying?	Assumptions on baseline survival beyond a trial	Uncertainty
Briggs 2007	Markov	Individual sampling	Time and individual based dependence	Exponential survival function	PSA and CEAC
Caro 2006	Discrete event simulation	Individual sampling	N/A	Trial property	PSA
Feldman 2005	Markov	Individual sampling	Time and individual based dependence	Trial property	PSA
Rinfret 2005	Markov	Individual sampling	Time and Individual based dependence	Trial property	PSA
Scuffman & Kosa2006	Markov	Cohort simulation	Fixed	Exponential	One way sensitivity analysis
Scuffham & Chaplin 2004	Markov	Individual sampling	Fixed	Exponential	One way sensitivity analysis
Yao 2006	Markov	Individual sampling	Time and Individual based dependence	Weibull survival function	PSA and CEAC

2.6 Critique of modelling studies

2.6.1 Introduction to modelling review

The literature review presented thus far provides an overview of methods used in economic evaluation conducted alongside randomised clinical trial data in the area of heart disease. In the last section, all included papers were critically reviewed. In the following sections, the focus of the review changes to a critique of modelling quality for those studies where a model approach is used.

To critique the quality of the models, it is helpful to use a checklist. There are several papers in the literature that provide guidelines for good practice of decision models (Halpern *et al*., 1998, Chilcott *et al*., 2003, Weinstein *et al*., 2003, Sculpher *et al*., 2000 & Philips *et al*., 2004 & 2006). In this section, the items list was largely adopted from the 'Philips and colleagues' checklist' (Philips *et al*., 2006). The checklist was recommended to inform critical appraisal of methodological quality of economic modelling studies in the Cochrane handbook.

In Philips and colleagues' checklist, three general themes were suggested. Those were "Structure", "Data" and "Consistency". The same headings were adopted in this critique and in the following sections I will discuss the three themes in turn.

2.6.2 Structure

In Philips and colleagues' checklist, the structure theme focuses on more general principles. This review aims to critique the suitability of model types and simulation methods, particularly the comparison of using cohort simulation versus individual simulation. Therefore, a broader and

more detailed review is sought. The model types are classified by Barton and colleagues (2004), and enhanced by Brennan and colleagues (2006), Briggs and colleagues (1998) and Sonnenberg and colleagues (1983). The reason for reviewing model types and simulation methods explicitly was to critique the relevant merits in using cohort versus individual simulation methods. While certain types of models are deemed to be individual simulation methods, e.g. the discrete event simulation model, for Markov model and decision trees, the analytic methods are cohort based or individual patient level based simulation. To judge whether the choice of certain types of models are appropriate for the characteristics of the studied disease area, the Barton *et al*., 2004 and Brennan et al., 2006 classifications were adopted.

The structure was reviewed first on type of models and whether the selection of models is appropriate for the clinical questions in study. Secondly, simulation methods and the appropriateness of the methods chosen were reviewed. The following section details these criteria.

2.6.2.1 Classification of types of models

In Barton's paper, selecting a model type was firstly based on the judgment on whether individuals in the model were independent or whether there was interaction between individuals. If it was independent, the most common types of model used in health economic evaluation would be decision trees, Markov models and individual sampling methods. However, for certain kinds of diseases, e.g. infectious disease, individuals are not independent. In the case of interaction, discrete event simulation models had to be sought to account for the dependency among subjects.

Decision Trees

The decision tree has a simple and clear structure in which all possible patient pathways can be illustrated explicitly in a tree structure. Probabilities and outcome measures can be attached to each branch of the tree.

Markov models

Markov models are generally used to represent stochastic processes, which evolve over time. The disease in question is divided into mutually excluded health states. Transition probabilities from current state moving to another state in the next cycle are applied over a fixed time period (Briggs *et al.*, 1998 and Sonnenberg *et al.*, 1993).

For a Markov chain transition probabilities are constant. This means that the transition probability moving from one health state to another does not depend either on the time a patient has spent in a given state or the patient's previous history before entering that state. Markov models thus assume that patients in a given state can be treated as homogeneous groups and the Markov chain does not have any memory for a patient's past disease history. These homogeneity and non-memory assumptions are inherent in a classical Markov chain model.

The simulation methods of a typical Markov model are classified by two types. Briggs classified them as the cohort simulation and individual simulation methods. Cohort simulation refers to a homogenous cohort of patients distributed in an initial disease state at the start of the model. At the end of each cycle, patients will be distributed into different health states by applying appropriate transition probabilities. Hence the numbers of patients in each health state at a given cycle can be estimated. Individual simulation method in a Markov model is also referred to as Monte Carlo simulation (Briggs *et al.*, 1990). This refers to a situation where a large number of patients are generated at the beginning of the model and each patient is followed through the

model over time, individually. The difference between these two methods is that although individual patients are subjected to the same probabilities of transition as the cohort of patients, each individual will go through different disease progression pathways depending on random variation at a particular time. Following the patient through the model allows an overall profile of costs and outcomes to be generated for that patient according to the path that they follow through the model.

Individual sampling models

In more general forms, a Markov process may allow the probabilities to vary with time and the relaxing of homogeneity assumptions. In Barton's paper, one of approaches was to use a Monte Carlo simulation. Individual patient simulation using Monte Carlo methods can provide a vehicle to relax the traditional non-memory and homogeneity assumptions in a Markov chain model. This may be achieved by allowing individuals to carry baseline characteristics and the individual disease process can be recorded. When simulated individuals have attributes attached, such as age or gender, the transition probabilities can be adjusted or updated based on those profiles. Thus, the transition probabilities can be changed according to individual characteristics or time on treatment. Furthermore, attributes can be updated while the model is running.

However, the definitions of modelling types are not always consistent, especially in the case of a Markov model with a Monte Carlo simulation. Barton and colleagues state that it is common to use the terms of discrete event simulation model or state-transitional models to refers the same thing (Barton *et al.,* 2004). Barton proposed that a model that has the ability to track individuals is an essential part of the model structure but in which only one individual is modelled at a time is should be called an "individual sampling model". Individual sampling models can also be based on Markovian states but it can be based on non-Markovian states (Brennan *et al.,* 2006).

When individual level simulation is applied in a Markov modelling framework, the model should be classified as an individual sampling model.

Discrete event simulation model

In Barton's paper, when individual patients in a model are not independent, two circumstances are considered. First, in the case of infectious diseases, the risk of an individual catching the disease depends on how many other people already have it. Individuals are not independent on the risk of the disease. Second, in the case when there are limited resources, individual patients are competing for the available resources. Discrete event simulation (DES) and system dynamics models (SD) are appropriate in those circumstances. A DES model is an individual level simulation, which allows full representation of each individual's history and the interaction between individuals. SD models which are modelling on aggregated levels are not of interest in this review.

Table 2.5 lists the criteria in the assessment of model quality. There are five types of model classification: decision trees, Markov models, individual simulation models, discrete event simulation and system dynamics model. The individual sampling model is sub-grouped as based on a Markov model state or non-Markov states. The judgment for an appropriate model is based on the following paragraph.

2.6.2.2 The choice of an appropriate model type

A decision tree model is simple and straightforward to illustrate a decision problem. Barton suggests that if the time frame is short and if the mortality of patients does not differ across strategies, a simple decision tree is usually appropriate. Briggs and colleagues recommended that Markov models were particularly suited to modelling the progression of chronic diseases.

Barton agreed that the main benefit of a Markov model was the easy with which recurrent events could be represented. When a disease is considered to experience recurrent events, such as in the case of chronic diseases, a Markov model is appropriate.

Barton and colleagues study provided the choice of an appropriate model. A simple diagram has been reproduced here for illustration of the steps in selecting an appropriate modeling type (Figure 2.2). As indicated in diagram (2.1), the selection of the appropriate model type for a particular health care intervention should be made on the key initial consideration of whether the individuals in the model may be regarded as independent. Where interaction is not thought to be an important issue then the choice is between decision trees, Markov models or individual sampling models. Where interaction is a significant issue in modelling, methods such as DES and SD are required.

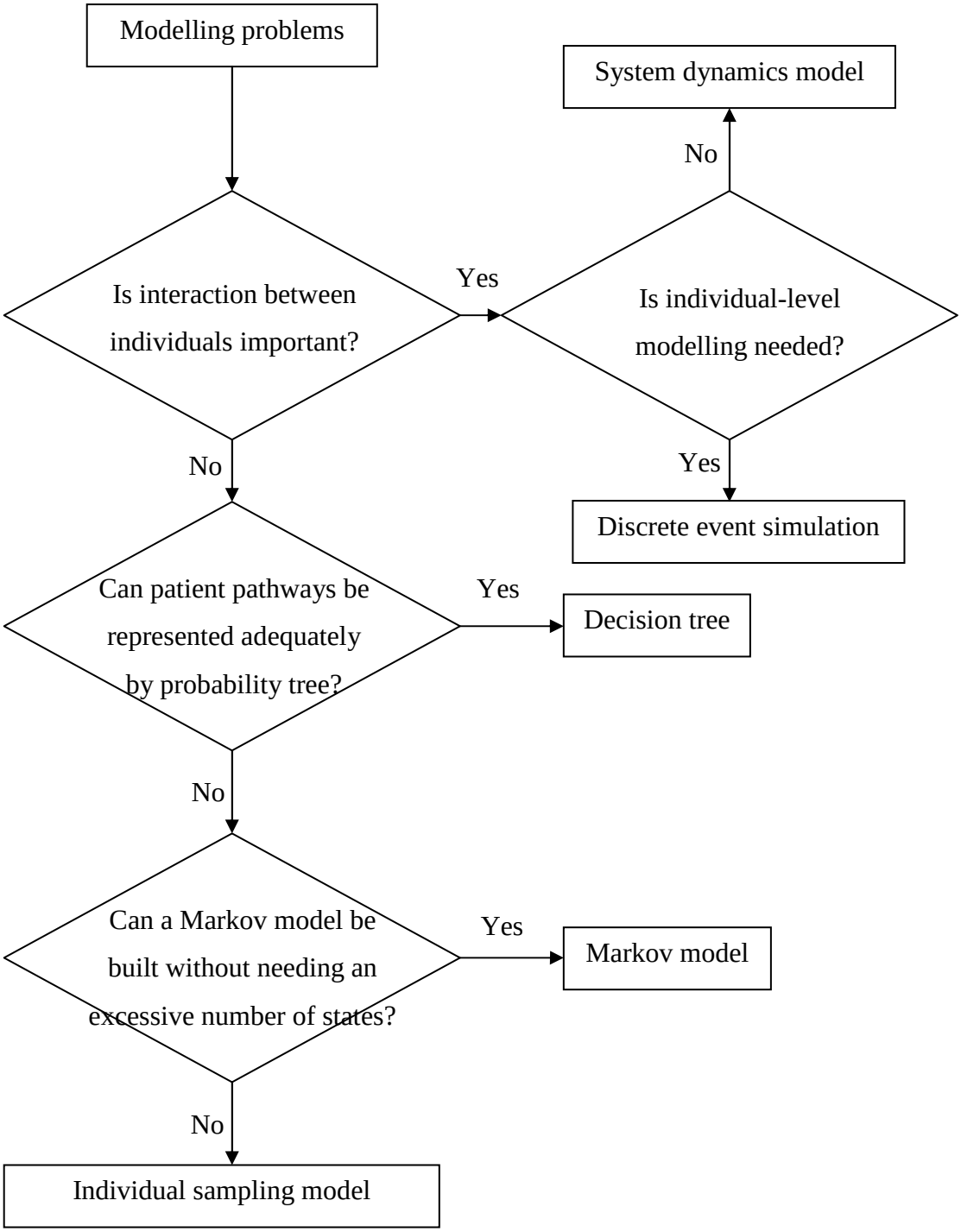

Figure 2.2 Selecting an appropriate model type

**Adapted from Barton (2004): Figure 8*

2.6.2.3 Cohort simulation versus individual patient simulation

The taxonomy of model structure is classified into two broad categories: cohort models and individual level models (Brennan *et al*., 2006). Cohort models, also referred to as aggregate models, are used to examine the proportion of the population experiencing different events. The key assumption in cohort models is homogeneity within health states. Therefore the same costs and utilities are attached to each event to all patients. Individual level models are used to sample individuals with specific attributes and follow their disease progression individually. Therefore, each individual may have different costs and utilities based on their actual experience of events and clinical disease stages.

Brennan and colleagues (2006) reasoned that the cohort model is simple and transparent, but that the homogeneity assumption may produce inaccurate and inadequate solutions. Although cohort models can account for different attributes by increasing the number of states, they become unmanageable when the number of dimensions rises substantially. Individual level simulation models overcome this problem. They are more flexible in simulating a real world situation.

Barton and colleagues argue that the appropriate use of cohort or individual simulation methods should consider the questions of computational feasibility. Individual level simulation models such as DES and individual sampling methods usually demand more time to develop and run than cohort models. However, when individual histories or attributes need to be considered in a model, those based on individual level simulations can provide flexible ways to account for patient pathways.

Table 2.5 lists all the items and questions to ask about simulation methods in this review. The judgment of cohort or individual level simulation is based on whether a decision tree or Markov

model can represent the clinical problem without the excessive number of states, in addition to whether individual level attributes or histories are needed to inform the disease progression in the model. If a large number of states are needed or individual level attributes are important, an individual sampling model is appropriate.

Table 2.5 Assessment of quality of model structure

Quality criteria	**Question for critical appraisal**
Type of models	What type of model is used?
	Is the chosen model appropriate for the clinical problem?
Simulation methods	Is it cohort or individual level simulation?
	Is the simulation method appropriate?

2.6.3 Data

To critique the data component in a model, a short form of the checklist from Philips' paper was used. The rationale to make use of particular items from the checklist in this review was based on the judgment on whether they related to models developed alongside a randomised clinical trial.

The Philips checklist was specially developed for NICE assessment, where input data are mostly gathered from systematic reviews. The papers reviewed in the current chapter are all economic evaluations conducted alongside a single clinical trial. Thus, the Philips check-list refers to a data source based on systematic review or meta-analysis, which is omitted from the checklist adopted here.

The data component of the Philips checklist is divided into four sections as follows:

Section D1: identification methods;

Section D2: pre-model data analysis;

Section D3: incorporation of data;

Section D4: assessment of uncertainty.

Section D1 was related to data identification methods and hence not relevant to the assessment in this thesis, therefore it was not in the checklist used.

Section D2 concerns methods of data synthesis, analysis of trial data, the incorporation of relative risks and the accurate calculation of transition probabilities. While data synthesis methods were omitted from the current checklist, the other three items are included in this review.

Table 2.6 lists the items in the D2 section. While most of the checklist items were straightforward yes or no answer, the final column in the table gives a detailed explanation when judgments on appropriate methods are needed. Table 2.7 and 2.8 lists the items in D3 and D4 section respective. All items in Philips checklist on those sections are included, respectively.

Table 2.6 List of items in Section D2 from Philips' checklist

Quality Criteria Data (D)	Question(s) for critical appraisal	Judgment for appropriate when applied
D2: Pre-model data analysis	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	
D2a: baseline data	Is the choice of baseline data described	Yes/No
	Is the choice of the baseline data justified?	Baseline probabilities may be based on natural history data derived from epidemiological/observational studies or relate to the control group of an experimental study. If a half cycle correction has not been used on all transitions in a state transition model (costs and outcomes), this should be justified
	Are transition probabilities calculated appropriately?	Rates and interval probabilities should be transformed into transition probabilities appropriately. If there is evidence that time is an important factor in the calculation of transition probabilities in state transition models, this should be incorporated.
D2b: treatment effects	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Not relevant, omitted from this review
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	The methods and assumptions that are used to extrapolate short-term results to final outcomes should be documented and justified. This should include justification of the choice of survival Function.
	Have alternative extrapolation assumptions been explored through sensitivity analysis?	
	Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	Assumptions regarding the continuing effect of treatment once treatment is complete should be documented and justified.
	Have alternative assumptions been explored through sensitivity analysis?	Yes/No If evidence regarding the long-term effect of treatment is lacking, alternative assumptions should be explored through sensitivity analysis

**Philips et al 2006, section consistency from table II. Page 364-365*

Table 2.7 Assessment of data incorporation

Quality Criteria (Data: D)	Question(s) for critical appraisal	Judgment for appropriate when applied
D3: Data incorporation	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes / No All data incorporated into the model should be described and the sources of all data should be given and reported in sufficient detail to allow the reader to be aware of the type of data that have been incorporated
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Not relevant, omitted from the review
	Is the process of data incorporation transparent?	Yes / No The process of data incorporation should be Transparent. It should be clear whether data are incorporated as a point estimate or as a Distribution.
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	If data have been incorporated as distributions as part of a probabilistic analysis, the choice of distribution and its parameters should be described and justified
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes / No If data have been incorporated as distributions as part of a probabilistic analysis, the choice of distribution and its parameters should be described and justified

**Philips et al 2006, section consistency from table II. Page 365*

Table 2.8 Assessment of uncertainty

Quality Criteria (Data: D)	**Criteria Question(s) for critical appraisal**	**Judgement for appropriate when applied**
Assessment of uncertainty	Have the four principal types of uncertainty been addressed?	Yes / No
	If not, has the omission of particular forms of Uncertainty been justified?	
D4a: methodological	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Yes/No Methodological uncertainty relates to whether particular analytic steps taken in the analysis are the most appropriate (for example, discount rate used)o
D4b: structural	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes/No There should be evidence that structural uncertainties have been evaluated using sensitivity analysis
D4c: heterogeneity	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Yes/No It is important to distinguish between uncertainty resulting from the process of sampling from a population and variability due to heterogeneity (that is, systematic differences between patient sub-groups)
D4d: parameter	Are the methods of assessment of parameter uncertainty appropriate?	Probabilistic analysis is the most appropriate method of handling parameter uncertainty because it facilitates assessment of the joint effect of uncertainty over all parameters
	Are the methods of assessment of parameter uncertainty appropriate?	Where data have been incorporated into the model as point estimates, the ranges used for sensitivity analysis should be stated and justified. Probabilistic analysis is the most appropriate method of handling parameter uncertainty because it facilitates assessment of the joint effect of uncertainty over all parameters
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	

**Philips et al 2006, section consistency from table II. Page 365*

2.6.4 Consistency

The consistency theme focuses on two categories: internal consistency (C1) and external consistency (C2). Table 2.9 lists the questions to ask in assessment of the review. Again, the last column explained in detail when judgment for appropriateness is applied.

Table 2.9 Assessment of consistency

Quality Criteria Consistency (C)	**Question(s) for critical appraisal**	**Judgement for appropriateness when applied**
C1: Internal consistency	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Yes/No There should be evidence that the internal consistency of the model in terms of its mathematical logic has been evaluated
C2: External consistency	Are the conclusions valid given the data presented?	Yes/No The results of a model should be explicable.
	Are any counter intuitive results from the model explained?	Yes/No Results should either make intuitive sense or counterintuitive results should be fully explained
	Are any counter intuitive results from the model justified?	All relevant data available should be incorporated into a model. Data should not be withheld for purposes of assessing external consistency
	If the model has been calibrated against independent data, have any differences been explained?	Yes/No
	If the model has been calibrated against independent data, have any differences been justified?	Yes / No
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes/No The results of a model should be compared with those of previous models and any differences should be explained.

**Philips et al 2006, section consistency from table II. Page 366*

2.6.5 Critique the modelling papers

Structure

As shown in Table 2.10 and 2.11, five of the studies used Markov modelling approaches but different terms were used. Briggs used the name "state transition Markov model", Yao used "Individual simulation using Markov modelling framework" while Feldman simply stated that a model was used without giving a clear statement of the model type. The rest just said "Markov model". Caro used the term "discrete event simulation model". In fact it was an individual sampling model based on the Barton classification. From the recommendation, all of these studies can be classified as individual sampling methods but none had adopted the term.

Two of the studies were based on cohort simulation and the rest of papers were based on individual level simulations. None of the papers reported computer running times, and only three of the five studies conducted PSA to explore the second order uncertainty.

Data

For pre-data analysis, all studies populated their model based on the corresponding clinical trial. Six of those studies were based on Kaplan Meier analysis for observed survival data and Cox models were used to estimate treatment effects. Briggs presented regression analysis results to estimate the risk profile on different events and adjusted patient baseline characteristics. Rinfret reported using a Kaplan Meier survival function and bootstrapping in analysing cost and utility data.

Referring to the estimated baseline function for extrapolating beyond the trial period, only two papers reported that selecting candidate function were based on the best fitting curves. Yao used

AIC to check the best fitting model; Scuffham (2005) graphically checked the fitting without a formal test.

All studies assumed constant hazard ratios applied to the intervention effect over trial periods, but Briggs explored the assumption using reduced hazard by sensitivity analysis.

None of these studies explored the full uncertainty of the four principal types of uncertainty as suggested by Philips and colleagues. One way sensitivity analyses were conducted in all the studies. Four of those studies explored second order uncertainty through probabilistic sensitivity analysis.

Consistency

For model consistency, none of those studies was calibrated against an independent data source. Instead, three of the studies investigated the model consistency by validating the result from the model against the trial observed events. Yao presented the validation by model estimate survival compared with trial observed survival which was estimated by Kaplan Meier methods from the CARE-HF trial. Rinfret (2005) validated their model by estimating the rate from the model to trial observed event.

Table 2.10 Assessment of quality of model structure

Quality Criteria (Structure)	Question for critical appraisal	Briggs 2007	Caro 2006	Rinfret 2005	Yao 2007
Type of models	What type of model is used? (based on Barton definition)	Individual sampling methods	Individual sampling methods	A Markov model	Individual sampling methods
	What type of model is used? (as stated by author)	A Markov state transition model	Discrete event simulation	A Markov model	Markov modelling framework based on individual simulation
	Is the chosen model appropriate for the clinical problem?	Yes , it reflected the natural history of the disease with recurrent events	Yes, it provided a flexibility to allow the risk of events to depend on individual patient history	Yes, it reflected the recurrent events	Yes. It is suitable to natural history of the disease which is recurrent and chronicle
Simulation methods	Is it cohort or individual level simulation?	Individual level simulation	Individual level simulation	Individual level simulation	Individual level simulation
	Is the simulation method appropriate?	Yes. Individual clinical and characteristics are important on risk of different events	Yes. It simulated trial population.	Individual risk profiles are important"	Yes, it mirrored the trial and individual disease history is important

Table 2.10 Assessment of quality of model structure (continued)

Quality Criteria (Data2)	Question for critical appraisal	Briggs 2007	Caro 2006	Rinfret 2005	Yao 2007
D2	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Yes, reported details of modelling information	No	Yes, used Kaplan-Meier and bootstrapping methods	Based on AIC to select best fit distributions
D2a	Is the choice of baseline data described	Yes	Reported	Not clear	Yes
	Is the choice of the baseline data justified?	Based on risk equations derived from EUROPA data	Based on the risk of events	Based on bootstrapping methods	Based on the curve best fitted to the trial data
	Are transition probabilities calculated appropriately?	Yes, based on risk equation	Not applicable	Details not given	Yes, estimated from the trial
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Not applicable. Based on a single trial	Not conducted	Not applicable. Based on single trial	Not applicable. Based on single trial
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes. It mirrors the trial risk profile	Yes, based on individual simulation and adjusted risk events	Survival function fitted and used to extrapolate beyond the trial	Probability function best fitted to the trial

Table 2.10 Assessment of quality of model structure (continued)

Quality Criteria (Data 3)	Question for critical appraisal	Briggs 2007	Caro 2006	Rinfret 2005	Yao 2007
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes, details reported in tables	Yes, details reported in a diagram and table	Yes, details reported in tables	Yes, details reported in tables
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Not applicable	Not discussed	Not applicable	Not applicable
	Is the process of data incorporation transparent?	Reasonable and supported by a separate reference	Yes	Reasonable	Yes
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Runs PSA and choice of distributions reported separately	Details not given	Not discussed	Reasons for choice not given, but reported in tables
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes, second order uncertainty was addressed by PSA	Second order was not addressed	Not discussed	Yes, second order uncertainty was addressed by PSA

Table 2.10 Assessment of quality of model structure (continued)

Quality Criteria (Data4)	Criteria Question(s) for critical appraisal	Briggs 2007	Caro 2006	Rinfret 2005	Yao 2007
D4	Have the four principal types of uncertainty been addressed?	Yes	Not fully	No, only one way sensitivity analysis	Yes
	If not, has the omission of particular forms of Uncertainty been justified?	Not applicable	Second order uncertainty should conducted	Second order uncertainty should conducted	Not applicable
	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	No	No	No	No
	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes	Yes	Yes	Yes
	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Yes	No	No	Yes
	Are the methods of assessment of parameter uncertainty appropriate?	Yes	No, second order uncertainty not investigated	One way sensitivity analysis performed	Yes
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Not applicable	Yes	Yes	Not applicable

Table 2.10 Assessment of quality of model structure (continued)

Quality Criteria (Consistency)	Question for critical appraisal	(Briggs 2007)	(Caro 2005)	(Rinfret 2005)	(Yao 2007)
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Yes	No	Yes	Yes
C2	Are the conclusions valid given the data presented?	Yes/No	Yes	Yes	Yes
	Are any counter intuitive results from the model explained?	No	No	No	No
	Are any counter intuitive results from the model justified?	Not applicable	Not applicable	Not applicable	Not applicable
	If the model has been calibrated against independent data, have any differences been explained?	Not applicable	Not applicable	Only used internal validation, validate from the trial	Interval validation and external validation
	If the model has been calibrated against independent data, have any differences been justified?	Yes	Not done	Not done	Yes and explained
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes	Yes	Yes	Yes

Table 2. 11 Assessment of quality of model structure

Quality Criteria (Structure)	Question for critical appraisal	Feldman 2005	Scuffham & Chaplin 2005	Scuffman & Kosa2006
Type of models	What type of model is used? (based on Barton definition)	Markov model	Markov model	Markov model
	What type of model is used? (based on author stated)	Not clear	Markov model	Markov model
	Is the chosen model appropriate for the clinical problem?	Yes, based on the events rate over time	Yes, the events are recurrent over a longer time period	Yes the events are recurrent over a longer time period
Simulation methods	Is it cohort or individual level simulation?	Cohort simulation	Cohort simulation	Cohort simulation
	Is the simulation method appropriate?	It only reflected second order uncertainty. But between individual variation can be substantial	Only second order uncertainty reflected	Only second order uncertainty reflected

Table 2.11 Assessment of quality of model structure (continued)

Quality Criteria (Data2)	Question for critical appraisal	Feldman 2005	Scuffham & Chaplin 2005	Scuffman & Kosa2006
D2	Is the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	Details not givens	Details not given	Not given in details
D2a	Is the choice of baseline data described	Exponential fitted to survival data from the trial	Yes	**Not given**
	Is the choice of the baseline data justified?	Can not judge as authors did not provide the rational for the choice	Yes	Not available
	Are transition probabilities calculated appropriately?	Yes. Based on exponential survival function	Yes	Yes, rate translated to propabilities
D2b	If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	Not applicable	Not applicable	*Not applicable*
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Yes. Based on exponential survival function and rate of events were applied to it	Yes	Yes

Table 2.11 Assessment of quality of model structure (continued)

Quality Criteria (Data 3)	Question for critical appraisal	Feldman 2005	Scuffham & Chaplin 2005	Scuffman & Kosa2006
D3	Have all data incorporated into the model been described and referenced in sufficient detail?	Yes, reported details in tables	Yes, reported in table	Yes reported in table
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	Not mentioned	Not applicable	Not applicable
	Is the process of data incorporation transparent?	Yes	Yes	Yes
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	Yes	Yes	Not applicable, determinate analysis
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	Yes, PSA preformed	Not	Not

Table 2.11 Assessment of quality of model structure (continued)

Quality Criteria (Data4)	Criteria Question(s) for critical appraisal	Feldman 2005	Scuffham & Chaplin 2005	Scuffman & Kosa2006
D4	Have the four principal types of uncertainty been addressed?	Only addressed the parameters uncertainty	Some of those detailed as below	Some of those as detailed below
	If not, has the omission of particular forms of Uncertainty been justified?			PSA should conducted
	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	Not	Not	No
	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	Yes, sensitivity conducted on the length of the benefit over two years	Yes sensitivity analysis on discount rate	Yes
	Has heterogeneity been dealt with by running the model separately for different sub-groups?	Not performed	Yes	Yes
	Are the methods of assessment of parameter uncertainty appropriate?	Yes	Yes	No
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	Not addressed	Yes	Yes

Table 2.11 Assessment of quality of model structure (continued)

Quality Criteria (Consistency)	Question for critical appraisal	Feldman 2005	Scuffham & Chaplin 2005	Scuffman & Kosa2006
C1	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	Not done	Yes	Yes
C2	Are the conclusions valid given the data presented?	Yes	Yes	Yes
	Are any counter intuitive results from the model explained?	Not stated	Not stated	Yes
	Are any counter intuitive results from the model justified?	Cannot judge as it did not provide	Cannot judge as it did not provide	Yes
	If the model has been calibrated against independent data, have any differences been explained?	Not	Not	No
	If the model has been calibrated against independent data, have any differences been justified?	N/A	N/A	No
	Have the results of the model been compared with those of previous models and any differences in results explained?	Yes	Yes	No

2.7 Discussion

The aim of this chapter was to review recent studies in which economic evaluation was conducted in cardiovascular disease. It focused on studies where economic evaluations had been conducted alongside clinical trials and modelling based studies in which model inputs were populated by individual data from a trial. Only full economic evaluations were included in the review.

The results were presented in separated categories, including an overview of the included studies: summarised economic evaluation methods used, statistical analytic methods used within a trial analysis and model based approaches when extrapolating beyond a trial. The results show that most of the studies in the review covered the clinical areas of chronic heart failure, atrial fibrillation, myocardial infarction and coronary heart disease. When most of the clinical studies were based on multinational trials, economic evaluation was usually conducted in one country setting. Only one study used country specific cost.

The most commonly used outcome measures in the studies were life years; only half of the studies employed QALYs. Reviewing statistical methods in economic evaluation within trials has demonstrated that most of the studies have addressed the uncertainty around point estimations by using bootstrapping. However, many studies lacked details on how costs data were collected and how aggregated costs were estimated.

Nearly one quarter of the included studies have employed model based analysis to investigate long term economic implications beyond a trial. Using a Markov model was the most common approach in the majority of studies. However, there was a lack of consistency in defining the

type of models, simulation methods and pre-data analysis. From the studies selected, it remains generally unclear how a model was developed, or how assumptions beyond a trial and assumptions on baseline survival beyond a trial were addressed.

CHAPTER 3 SECONDARY PREVENTION CLINICS

3.1 Introduction

The last chapter reviewed methods in economic evaluation conducted alongside a clinical trial and model-based studies, where the input data were populated from a trial data in the area of heart disease. In this chapter an empirical study of an economic evaluation conducted alongside the secondary prevention clinical trial in coronary heart disease (Raftery *et al.*, 2005) is presented, with the aim of illustrating common methods which may be used to conduct an economic evaluation alongside a clinical trial. This includes how cost and utility values were collected, how cumulated cost and QALYs over the trial period were calculated and how the cost-effectiveness of the interventions compared were estimated and presented. This chapter was based on a published paper in the British Medical Journal (Raftery *et al.*, 2005) and was further developed specifically for the thesis using a different analytic approach. In the published paper, only t-tests are presented in the analysis cost and quality of life data, whereas in the thesis, bootstrapping methods were used for all analyses.

3.2 Clinical background

People with mild coronary heart disease are at particularly high risk of coronary events and death. Implementation of secondary coronary prevention in primary care can reduce this risk and this is widely advocated (Scottish Intercollegiate Guideline Network, 2000). Effective secondary prevention, such as medical interventions and lifestyle measures, eg. smoking cessation, regular exercise, and healthy diets, can reduce the risk of coronary events and death in patients with coronary disease (Murchie *et al.*, 2003). Most people with coronary disease are cared for in

primary care, and general practitioners have been encouraged to target them for secondary prevention. In the United Kingdom, general practitioners are rewarded financially for achieving target standards (BMA NHS Confederation, 2004). Several mechanisms to improve secondary prevention have been evaluated, of which the most successful to date have been nurse-led secondary prevention clinics (McAlister *et al.*, 2001; Moher *et al.*, 2001; Murchie *et al.*, 2003). Several randomised trials demonstrated that nurse-led secondary prevention clinics for CHD can improve the uptake of secondary prevention in primary care (Campbell *et al.*, 1998; Moher *et al.*, 2001; Khunti *et al.*, 2007).

3.3 Overview of the nurse-led secondary prevention clinics trial

Full details of the trial design have been reported previously (Campbell *et al.*,1998). In brief, a randomised controlled trial of nurse-led clinics for the secondary prevention of coronary heart disease was conducted in north-east Scotland between 1994 and 1995. The trial was undertaken in a 19 randomly selected general practices. Participants were a random sample of patients with coronary heart disease but without terminal illness or dementia and not housebound.

The nurse-led clinics in primary care were designed to promote medical and lifestyle aspects of secondary prevention and provide regular follow up. Patients in the intervention group were invited to attend nurse-led secondary prevention clinics at their general practice. For each visit, their symptoms and treatment were reviewed, including blood pressure and lipid management, the use of aspirin promoted and lifestyle factors reviewed and assessed. In addition, their behaviour changes were advised. In the control group, patients received the usual care from their general practitioners (GPs).

The principal aim of the trial was to evaluate at four years the effects of nurse-led secondary prevention clinics for coronary heart disease on the use and uptake of components of secondary prevention and to assess their impact on health and mortality. A secondary aim was to estimate the cost-effectiveness of the interventions compared to usual care.

The trial recruited a total of 1343 patients, of which 673 patients were randomised into the intervention group and 670 into the control group. All patients recruited to the study were less than 80 years old. Mean follow up was for 4.7 years. Intervention and control groups were well matched for age, sex and practice characteristics at baseline.

The clinical study reported that all components except smoking, were significantly different at one year (Murchie *et al.,* 2003), but by four years the performance of the control group had improved and the differences were no longer significant. A longer period of clinic attendance was associated with better uptake of secondary prevention. At four years the intervention group had fewer role limitations attributable to physical problems. There were fewer coronary events in the intervention group with 100 out of 673 (14.9%) compared with 125 out of 670 (18.7%) in the control group (p= 0.062), demonstrating that there had been significantly fewer deaths in the intervention group with 100 (14.9%) compared with 128 (19.1%) in the control group (p=0.038).

Running clinics, however, uses resources in primary care, especially nurses' time, and the clinics incur further costs from increased prescribing. The cost-effectiveness of the intervention is uncertain. In the next sections, a detailed cost and cost-effectiveness analysis is presented with the aim of determining whether the intervention was good value for money.

3.4 Methods

3.4.1 Costing

The economic evaluation was undertaken from a societal perspective, including both public and private health service costs. As most participants were older than working age, the effects related to production costs were excluded.

Resource use information was extracted from general practice case notes at baseline, one year and four years. For each patient data were collected on use of cardiovascular drugs, blood pressure and lipid management, number of attendances at secondary prevention clinics, hospitalisation for cardiovascular events, eg. myocardial infarction, and procedures such as coronary artery bypass grafting and coronary angioplasty and use of private health care. Data on deaths, hospital admissions and outpatient attendances were obtained from the Scottish Morbidity Records, linked anonymously.

The cost of admissions to NHS hospitals was calculated by assigning the appropriate unit cost per case based on specialty in hospital. Outpatient costs were based on the number of attendances multiplied by the relevant hospital unit cost. Costing admissions to private hospitals was done using NHS unit cost by specialty.

Costs to primary care of running the CHD clinics during the four years of the study were calculated. The yearly and total attendances at clinics were calculated for each group. It was assumed that each attendance lasted one hour. The costs of clinic materials and training were included at year one. At years two, three and four it was assumed that the only cost incurred in running the clinics was nurse time and this was estimated at £20.00 per hour, based on Unit costs of health and social care (Netten & Curtis, 2000). The total cost and annual costs of

cardiovascular drug prescriptions were calculated based upon the Scottish Drugs Tariff (Scottish Drug Tariff, 1998).

The costs of the secondary prevention clinic interventions were based on the best estimate of whether patients attended that year or not (earlier). Based on an audit of nurse time in year one and interviews with the practices about the subsequent years, a number of assumptions were made. Firstly, not all patients attended their clinics for a baseline assessment. Secondly, patients who attended their clinics for the first year did so twice and patients who attended in any of the subsequent years did so only once. These assumptions were applied to both intervention and control groups. The nurse-led clinics were only accessible to the control group after the second year.

Nearly all medication usage data was collected for all patients who were followed up to the end of the study. Data on all patients admitted to NHS hospitals were collected during those periods. Missing outpatient data were imputed on the basis of the average ratio of outpatient attendances per admission for cardiovascular diseases for surviving patients.

3.4.2 Utility scores

Health-related quality of life data were obtained by postal questionnaire using the SF-36 form at baseline, year 1 and year 4. SF-36 scores were used to calculate SF-6D utility scores for each patient in those three years, based on a previously published algorithm (Brazier *et al.*, 1998). A utility score of zero was assigned at the time of a patient's death and for patients who were lost to follow-up.

Utility scores of SF-6D were derived from the SF-36 at three time points: baseline, year 1 and year 4. Missing values of the SF-6D scores at baseline, year 1 and year 4 were imputed by group mean imputation adjusted for age and gender and treatment groups.

For values for cost and utility scores in years 2 and 3, which were not collected during the study, a linear interpolation based on the closest two point values were used. If a patient died or was lost to follow-up during these periods, the last value to either the time of death or lost to follow-up (Billingham *et al.*, 1999) was used.

3.4.3 Estimating cost

The total cost for each patient was derived by summing the itemised cost at each year and discounting at 3.5% annually. The total cost per patient was calculated using the following formula:

$$\text{Cost}_{ij} = \sum_{year=0}^{4} (\text{Cost}_{i,j,year} \big/ (1+r)^{year})$$

Where *i* denoted patients, *j* denoted treatment group and *r* the annual discounting rate.

3.4.4 Estimating life years and QALYs

Effectiveness was defined in terms of life years and QALYs gained associated with intervention during the trial.

Life years were estimated for each patient within the trial, defined by the survival length from randomisation to death. Each year was discounted at 3.5% annually for years beyond the first year.

$$\text{Lifeyears}_{ij} = \sum_{year=0}^{4} (\text{Length of survival in years}_{i,jyear}) \Big/ (1+r)^{year})$$

The total QALYs for each patient were derived by weighting survival time by the corresponding utility score from the SF-6D data. QALYs were also discounted at 3.5% annually for years beyond the first year.

$$\text{QALY}_{ij} = \sum_{year=0}^{4} (U_{i,j,year} (\text{Length of survival in years}_{ijyear}) \Big/ (1+r)^{year})$$

3.4.5 Analytic methods

Analyses were conducted according to the intention-to-treat principle. Kaplan-Meier methods were employed to estimate the survival and the log rank test was used for testing the difference in overall mortality. Bootstrap methods were employed for estimating difference in mean cost, life years and QALYs between treatment groups (Barber & Thompson, 2000). The incremental cost per life-year gained and incremental cost per QALY was estimated for each replicate. A bootstrap method based on 1000 replicates was used to estimate 95% confidence intervals (CI) for the incremental cost-effectiveness ratios and to produce cost effectiveness acceptability curves at different willingness-to-pay values. All analyses were conducted using SAS software (version 9.12, SAS Institute).

3.5 Results

Table 3.1 reported the analysis results. In the following section, each of those results is presented separately.

3.5.1 Survival and QALYs

Survival status was known for all patients at the end of study. There were 28 fewer deaths in the intervention group: 100 out of 673 (cumulative death rate 14.5%) compared with 128 out of 670 (19.1%) in the control group (P = 0.038). When a 3.5% discount rate was applied, the mean life years' score was 4.35 (95% CI 4.29 to 4.41) for the control group compared with 4.39 (95% CI 4.32 to 4.45) years for the intervention group. The QALYs were 3.01 (95% CI 2.94 to 3.07) in the control group compared with 3.11 (3.04 to 3.18) in the intervention group.

Table 3.1 Cost-effectiveness result by intervention and control

	Control (N=670)	**Intervention (N=673)**	**Difference**
Deaths	128	100	28 (P = 0.038)
Mean of life Years	4.35	4.39	0.04
(95% CI)	(4.29 - 4.41)	(4.32 - 4.45)	(-0.05 to 0.13)
Mean of QALYs	3.01	3.11	0.11
(95% CI)	(2.94 - 3.07)	(3.04 - 3.18)	(0.02 to 0.20)
Total costs (£)	879	1,015	136
(95% CI)	(824 - 934)	(956 to 1,074)	(58 to 214)
Incremental Cost (£) per QALY			1,261
(95% CI)			(913 to 23,516).

3.5.2 Costs to primary care and overall costs to society

Hospital admissions were lower in the intervention group, but part of this difference was accounted for by admissions for non-cardiovascular diseases. For this reason we considered alternative estimates of overall costs to society, one including all types of admissions, the other confined to cardiovascular admissions. Although both estimates were lower in the intervention group, neither difference was statistically significant. When the costs to primary care of the intervention itself were combined with hospital costs, the higher cost to primary care was offset by the lower hospital costs in the intervention group, such that the differences between

intervention and control groups were insignificant. Therefore, costs related to primary care and cardiovascular hospitalisation are discussed.

As shown in table 3.1, the mean cost per patient for the control group within the trial periods was £879 (95% CI 824 to 934) compared with £1015 (95% CI 956 to 1074) per patient in the intervention group, £136 (95% CI 58 to 214) higher in the intervention group. The only difference in cost to primary care was the direct cost of the intervention.

3.5.3 Incremental cost effectiveness

Within the trial period, the incremental life years gained estimate was 0.04 (95% CI -0.05 to 0.13) and 0.11 (95% CI 0.02 to 0.20) QALYs gained for intervention group compared with control group. Costs were £136 (95% CI 58 to 214) higher in the intervention group, resulting in an incremental cost per QALY gained of £1261 (95 % 913 to 23516). Figure 3.1 shows a scatter plot of incremental costs vs. incremental QALYs based on 1,000 bootstrapped replicates with 90% confidence ellipis. Figure 3.2 presents the cost effectiveness acceptability curve showing the probability of the intervention being cost-effective compared with control group even at the value of willingness to pay at £2,000. This is well below the accepted £20,000 threshold.

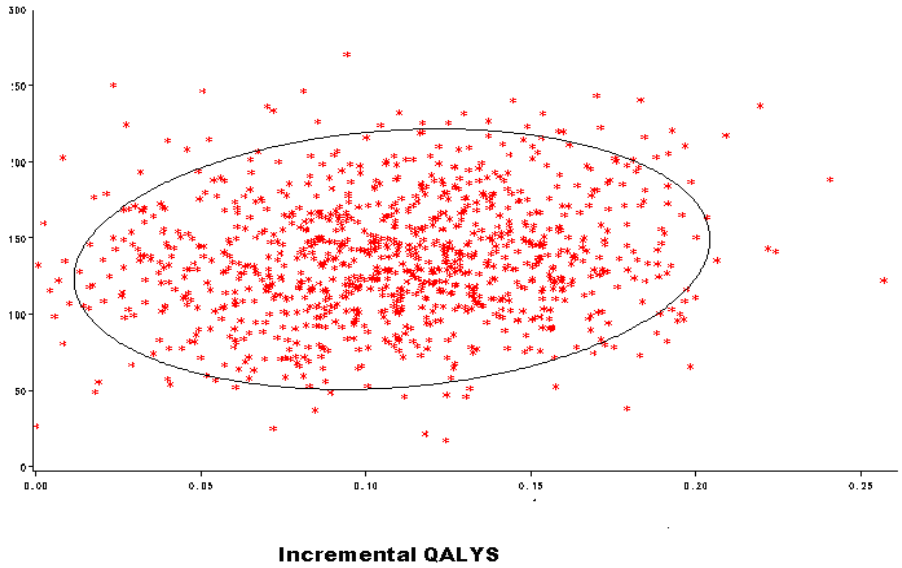

Figure 3.1 Scatter plot with 90% confidence ellipse

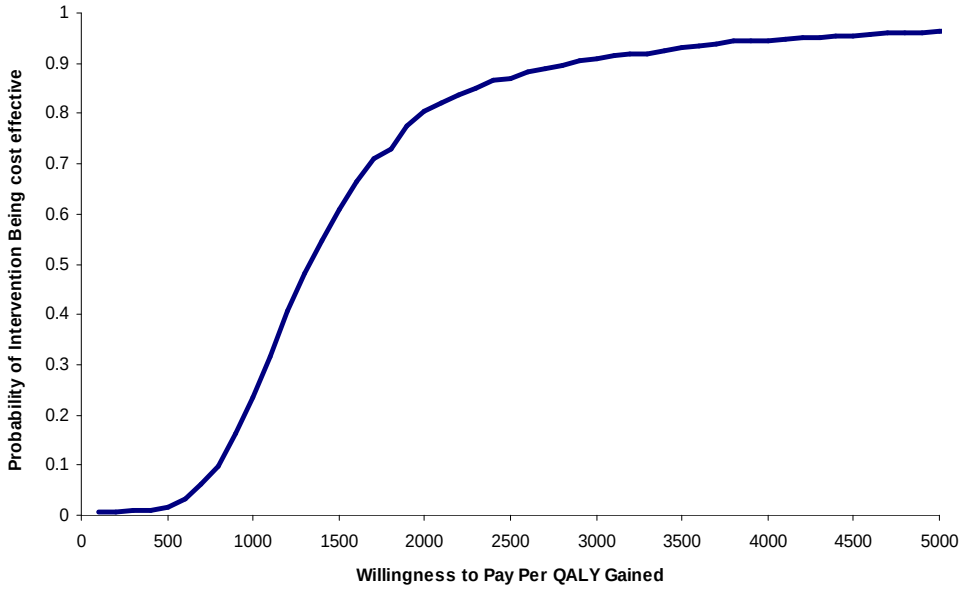

Figure 3.2 Cost-effectiveness acceptability curve

3.6 Discussion

In this chapter, a case study of an economic evaluation conducted within a trial was presented. Cost-effectiveness in this study was calculated on the basis that the trial already had a relatively long follow up period. The initial set-up costs were lower and the effectiveness of the intervention was observed within the trial periods. The initial setting up cost for running nurse-led clinics had been generally balanced within the trial periods.

This study was the first to examine the cost-effectiveness of secondary prevention clinics in primary care. The findings were more consistent with current recommendations and practice on secondary prevention and provide a plausible explanation for the observed reduction in mortality. The cost- effectiveness result by the end of the trial period presented was favourable for nurse-led clinics. Such clinics should be recommended in a general health care setting.

Nurse-led clinics for the secondary prevention of coronary heart disease in primary care are relatively cost-effective compared with the threshold of £20,000 attributed to NICE (Rawlins & Culyer, 2004). The intervention group gained a mean of 0.04 life years and 0.11 QALYs compared with the control group. The incremental cost per QALY gained was £1261. The clinical study demonstrated that improvements in processes of care and prescribing translated into reductions in total mortality. The present study shows that the cost per QALY gained is less than £20,000. The key difference in costs between nurse-led clinics compared with usual care was the increased £136 cost of the intervention to primary care, owing to attendances at the clinics and increased prescribing.

The estimates of cost-effectiveness remain valid, however, as the benefits found will also have been reduced by allowing control group cross-over, allowing patients to attend the nurse-led

clinic after the first year. The increase in both benefits and cost in practice depends on the pre-existing use of cardiovascular drugs, particularly statins, in the control group. Some of the data were incomplete, particularly attendances at hospital outpatients, but these had relatively little effect on overall cost to society. Data on high cost activities and important outcomes, such as mortality, were almost complete. Where assumptions were made, the cost of the intervention tended to be overestimated.

The study was based on a random sample of general practices and patients with good recruitment rates. Therefore, the sample should be representative of general practice at that time, although the changes may have occurred in practice since the study began in 1995. The uptake reported for some secondary preventive drugs, especially statins, was lower than is likely to be in the current climate of national standards and incentives for general practitioners. Nevertheless, it was found that the clinics improved uptake of secondary prevention by similar absolute amounts whatever the baseline levels, even for high uptake of activities at baseline such as blood pressure management and in practices with higher baseline levels of secondary prevention. Newly recommended interventions, such as smoking cessation clinics, may improve secondary prevention further but are unlikely to alter greatly the cost-effectiveness as these changes are likely themselves to be highly cost-effective.

Methodologically, bootstrap methods were used to estimate cost differences, QALY differences and cost-effectiveness ratios and produced confidence intervals around those estimates. The bootstrap method is a convenient way of producing cost-effectiveness acceptability curves, which show the probability of the intervention being cost-effective at different willingness-to-pay values.

The limitations of our study were, firstly, that just over half the control group attended at least one secondary prevention clinic after the initial study year. Rather than compare secondary prevention clinics with usual care, the costs and benefits of having more patients attend secondary prevention clinics for longer were evaluated. The total costs of running clinics to primary care will be higher than the cost difference between control and intervention groups in this study, as an intention to treat analysis, despite many patients in the control arm receiving the intervention in the period after the trial.

The limitation due to the way in which missing values were dealt with is accepted. Multiple imputations have been suggested as a method for replacing missing values, which may produce more accurate estimates of uncertainty around the replaced values (Burton *et al*., 2007). However, a bootstrap method was used for the analysis, and its taking account of repeated sampling around each imputed data set would introduce further uncertainty. In this chapter, standard methods in conducting a within trial analysis was focused on.

In addition, the limitation on the analytic approaches is notable. The data has hierarchical structure with patients nested with practices. Ideally more advanced analytic approaches should be sought, i.e. multilevel modelling approaches (Manca *et al.,* 2005). However, this part of the analysis aimed to present the most conventional methods using in economic evaluation conducted within a trial period. The influence on the potential inference may be theoretically acceptable.

Other studies have evaluated the cost-effectiveness of primary prevention clinics in primary care (Wonderling *et al.,* 1996; Langham *et al.,* 1996; Turner *et al.,* 2008). In Wonderling's and Langham's and colleagues' studies, benefits were measured in terms of risk factors and data on

costs and savings to the health service were incomplete. Turner and colleagues conducted an economic evaluation of a nurse-led disease management programme compared with standard care alongside a cluster randomised control trial. The study was implemented in 20 primary care practices in the United Kingdom and recruited total 1163 patients with coronary heart disease and chronic heart failure, and had a one-year follow up period. They demonstrated that the nurse-led disease management programme was associated with an increase in the QALYs measured of 0.03 per year and an increase in the total NHS costs of £425. The clinics generated additional QALY at an incremental cost of £13,158 per QALY compared to the control group after one year. Although their study had a relatively short follow up period, the results are supportive of the current study and proved that nurse-led clinics were good value for health care resources.

Despite the limitations of other studies, some comparisons can be made with the current study. For example, the running costs for clinics per patient are reasonably consistent across the trials. Running costs for a practice population would, however, be much higher for primary prevention clinics because the target population would be much larger. The estimated cost-effectiveness is much better for secondary prevention (£1236 per life year gained) than for primary prevention (around £20,000 per life year gained).

Compared with the wider range of health interventions, the cost-effectiveness of secondary prevention clinics remains favourable (Raftery, 2001). The incremental cost per QALY is well under £20,000, due to the relatively small increase in cost per patient of £136, in turn due to modest increases in drug use, even the relatively costly statins. This pattern, however, is consistent with other complex health service interventions, where incremental improvements in process outcomes are more likely to be achieved than wholesale changes. Nonetheless, these

relatively low increases in cost were linked to health gains that were considerable in terms of deaths, life years and QALYs.

3.7 Conclusions

This chapter presented a case study for an economic evaluation conducted within a trial period. Cost-effectiveness analysis concluded that the intervention was highly cost-effective. Longer-term cost-effectiveness implications beyond the trial period were not explored. In the next chapter methods of economic evaluation by extrapolating beyond a trial period will be presented.

CHAPTER 4 EXTRAPOLATION USING PARAMETRIC SURVIVAL FUNCTIONS

4.1 Introduction

In the last chapter, a case study of an economic evaluation conducted alongside a clinical trial was presented. Cost-effectiveness analysis concluded that the intervention was highly cost-effective. Longer term cost-effectiveness implications beyond the stated trial period were not explored. Cost-effectiveness was estimated on the basis that the trial already had a relatively long follow-up period. The initial set-up costs were lower and the effectiveness of the intervention was observed within the trial periods.

However, it is not uncommon to see the situation in which significant cost occurred at the beginning of an intervention, although the benefit of the intervention is still accumulated long beyond the end of the trial period (Buxton *et al*., 1997; Hlatky *et al*., 2002). It is ethically not possible to continue a trial beyond the point at which effectiveness has been established, even though the full economic benefit is still not seen fully. The economic evaluations concluded by the end of the trials in those situations more likely underestimate the cost-effectiveness of the interventions. Therefore, alternative approaches are needed to extrapolate cost and effectiveness beyond the trial periods. Survival analysis is often a key approach in projecting outcomes in terms of life year or quality adjusted life year in cost-effectiveness analyses.

Many survival analyses in the current medical literature use non-parametric methods. The Kaplan-Meier method is a simple approach in estimating survival probability for an observed follow-up only (Collett, 1994). Cox proportional hazards models are often employed to estimate

the relative risk of different interventions. Both of these methods are non-parametric, in which either survival distributions or hazard functions need to be specified. In order to project survival time beyond an observed time period, parametric survival functions are frequently used in economic evaluation (Neymark *et al.*, 2002). Whilst exponential and Weibull distributions are frequently used for this purpose, consideration of its appropriateness, given an observed data, has received little attention in the health economics literature. Little work has been done on how best to fit a parametric survival function based on observed data and how to evaluate the appropriateness of a chosen distribution.

In this chapter, five commonly used parametric survival functions are reviewed, stressing the characteristics of their hazard functions, and methods of choosing a best fit parametric survival function based on observed trial data are described. These approaches have been illustrated by using an updated data from CARE-HF study (Cleland et al 2006). The method was adopted from a cost-effectiveness study of cardiac resynchronisation therapy (CRT) based on the CArdiac REsychronisation in Heart Failure (CARE-HF) trial (Calvert *et al*, 2005). The survival analysis methods reviewed in this chapter are based on the book by Collett (1994).

4.2 Probability distribution functions in survival analysis

Standard approaches in survival analysis assume that the time at which events occur follow a random process or a particular distribution (Collett, 1994; Lee & Wang, 2003). There are three different ways to describe a survival probability distribution: probability density function (PDF), survival function and hazard function.

Probability density function is typically used to define probability distributions. It is the probability that if an event occurs at time *t*, the probability of *x* at a given time interval between *a* and *b* is often expressed in terms of an integral as follows

$$F(x) = \int_a^b f(x) d_x = \Pr(a < x < b)$$

Where *f(x)* is the probability density function, *F*(*x*) is the cumulative probability function from time *a* to *b*.

The survival function is the probability that a subject survives longer than *t*.

$$S(t) = 1 - \int_0^t f(u) d_t$$

The hazard function is the instantaneous failure rate at time *t* given its survival to time t. It is expressed as the ratio of the probability density function to the survival function $S(t)$.

$$h(t) = \frac{f(t)}{S(t)} = -\frac{d}{d_t}\{\log(S(t)\}$$

The property of a hazard function may be of particular interest in health economic evaluation, due to many probability distributions corresponding to a specific process, for example, the clinical history of a particular disease. Each of those distributions would have their own unique characteristics in its hazard function. In the following section, parametric distribution functions commonly used in survival analysis literature are reviewed and their corresponding hazard

functions described. The basic concepts and properties of probability distribution functions are based on the book by Larson (1982).

4.2.1 The exponential distribution

An exponentially distributed survival time corresponds to the assumption of a constant hazard. It can be presented as follows

$$h(t) = \lambda$$

The corresponding survival function is

$$S(t) = \exp\{-\int_0^t \lambda d_u\} = \exp(-\lambda t)$$

When survival time is assumed to follow an exponential distribution, the implication is that its hazard function is constant. This means that the probability that an event occurs for the next time period, given survival at the current time, does not depend on the patient's history. As time progresses for a particular disease, the (conditional) probability of death in successive time intervals remains unchanged. This, however, is not plausible in most clinical settings.

4.2.2 The Weibull distribution function

The survival function of a Weibull distribution can be expressed as follows

$$S(t) = \exp(-\lambda t^{\gamma})$$

There are two parameters in a Weibull distribution, the scale parameter λ and the shape parameter γ. A Weibull distribution implies a monotone increase or decrease hazard. The hazard function for a Weibull model is given by

$$h(t) = \lambda\gamma t^{\gamma-1}$$

The hazard function for Weibull survival time could be increasing or decreasing with time depending on the shape parameter γ. If the shape parameter is greater than 1, the hazard rate increases with time. If the shape parameter is less than 1, the hazard decreases with time. If the shape parameter is equal to 1, then the Weibull reduces to the exponential distribution. From the hazard function, we can see that if $\gamma = 1$, the hazard function *h(t)* simplifies to the constant value λ, which is the hazard function for the exponential distribution.

Figure 4.1 shows the hazard plot at different shape parameters (γ). The limitation of a Weibull distribution is that its hazard function is a monotonic function of time. When a hazard rate changes over time, for example, the hazard rate would increase where a patient developed resistance after responding well to initial treatments. In this situation, an alternative distribution is needed to appropriately represent the disease progression process.

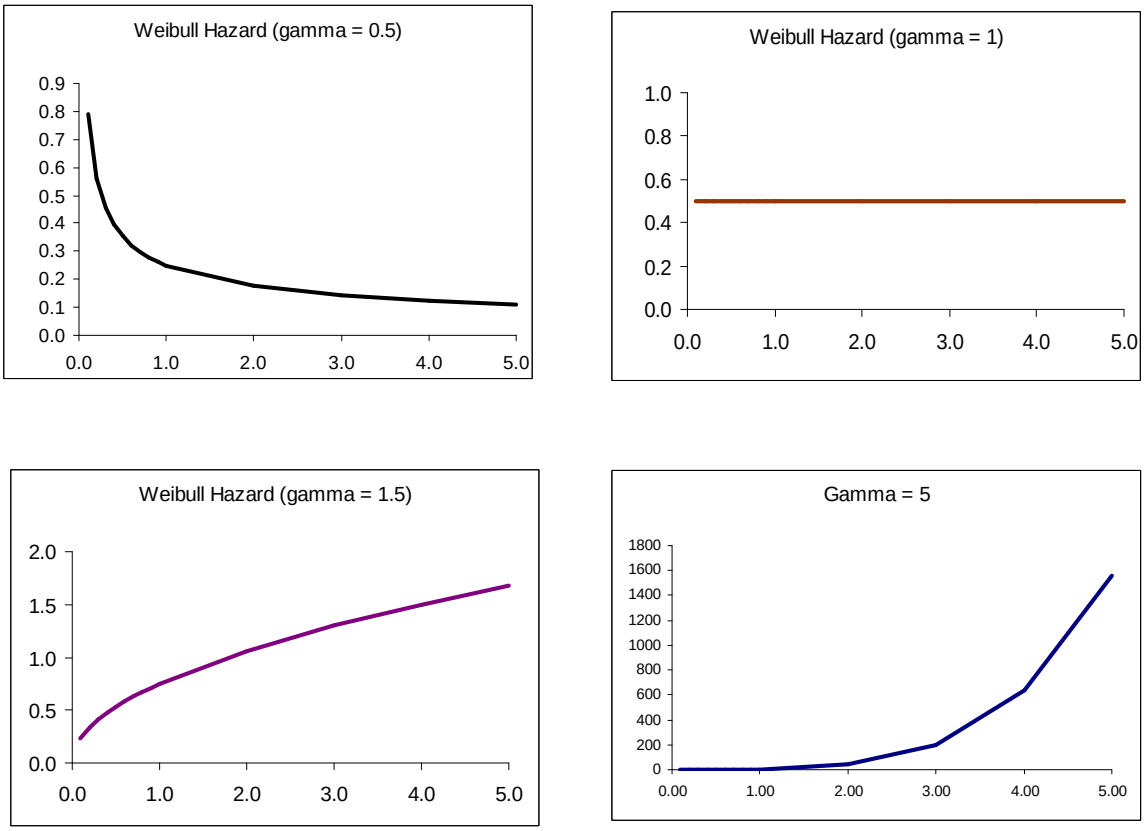

Figure 4.1 The hazard plot at different shape parameters (γ)

4.2.3 The log-logistic distribution

If survival time follows a log-logistic distribution then its logarithm has a logistic distribution. Survival function of log-logistic distribution is represented as

$$S(t) = (1 + \lambda t^{\beta})^{-1}$$

For a log-logistic distribution, its hazard function increases initially; reaches a peak and then decreases. The hazard function of a log-logistic distribution is given by

$$h(t) = \frac{\lambda \beta \, t^{\beta-1}}{1 + \lambda t^{\beta}}$$

A standard log-logistic model has two parameters λ and β. The hazard function decreases monotonically if $\beta \leq 1$, but if β >1, the hazard has a single peak. The hazard function of a log-logistic distribution has a single peak.

The following diagram (Figure 4.2) shows the hazard plot at different values of lambda λ and beta β

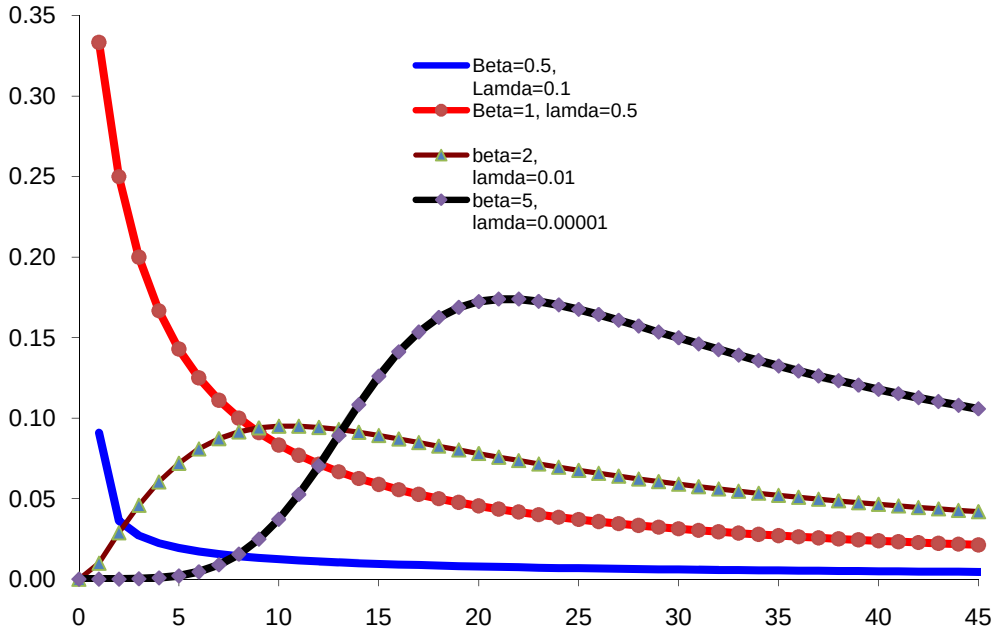

Figure 4.2 The hazard plot at different values of lambda λ and beta β

The advantage of the log-logistic hazard function is that it captures both inverted, U-shaped and monotonically declining rates.

4.2.4 The log-normal distribution

A log-normal distribution has a hazard function as the characteristic in log-logistic distribution. Its hazard functions can increase initially and then decrease over time. The hazard function of a standard lognormal distribution is given as

$$h(t,\sigma) = -\frac{d}{d_t}(\log(s(t)) = \frac{(\frac{1}{t\sigma})\phi(\frac{\ln(t)}{\sigma})}{\Phi(\frac{-\ln(t)}{\sigma})} \quad \sigma > 0;\ t > 0$$

Where ϕ is the probability density function of the normal distribution, and Φ is the cumulative distribution function of the normal distribution.

The hazard functions of log-normal distribution are characterised by inverse U-shape which can increase, reach a peak and then decrease. The following is the hazard plot for a log-normal distribution at different values of σ .

Both log-logistic and log-normal distribution can be used to represent a typical clinical process of a disease. For example, following a renal transplantation a patient faces an increasing hazard of death over the first few months after the transplantation, the hazard then decreases with time as the patient adapts to the new graft.

4.2.5 The Gamma distribution

The formula for the hazard function of a standard gamma distribution, in which the case where location parameter equals to zero and scale parameter equals to 1, can be represented as

$$h(t) = -\frac{d}{d_t}(\log(s(t)) = \frac{x^{\gamma-1}\varepsilon^{-t}}{\Gamma(\gamma) - \Gamma_t(\gamma)} \quad t \geq 0;\ \gamma > 0$$

Where γ is the shape parameter and Γ is the gamma function which has the formula

$$\Gamma(\alpha) = \int_0^\infty t^{\alpha-1}\varepsilon^{-t}d_t = \Pr(a < x < b)$$

The hazard function of a gamma distribution can provide varieties of forms depending on the value of the γ parameter.

4.3 Choosing among survival distributions applied to observed data

When individual data is available from a clinical trial one can fit a parametric survival function into the time-to-event data and use maximum likelihood methods to estimate its parameters. This is a standard method in statistical analysis and most statistical software has the functionality to do so.

When a model is fitted it is important to assess the adequacy of the distribution for the data. One way to perform such verifications is through residual plots. A Cox–Snell residual is widely used to check model fit graphically in the analysis of survival data (Collett, 1994). If a model fitted to an observed data is satisfactory, the estimated survival for an individual at time *t* should be close to the true value of a survival function at time *t*. The theory of the Cox-Snell residuals is that if a random variable *t* is the survival time of an individual and $S(t)$ is the corresponding survival function, the random variable $-\log(S(t))$ has an exponential distribution (Cox & Oakes, 1984).

The goodness-of-fit tests can be performed formally based on likelihood ratio statistics when comparing two nested models. In this case, as the exponential model is a special case of a Weibull model in which the shape parameter is restricted as 1, and log-normal, Weibull and exponential are all nested within a generalised gamma model.

However, when comparing log-logistic or log-normal with Weibull or exponential, they are not nested. In this case a likelihood ratio statistic can not be used for this purpose. The Akaike's Information Criterion (AIC) (Akaike, 1973) or Bayesian information criterion (BIC) (Schwarz, 1978) can be used for model selections when the nesting restriction does not apply. Lindsey and Jones (1998) argued that in the case of analysing clinical trial data, both BIC and AIC will give similar results as the sample sizes are relatively small in clinical trials. Several authors (Clayton & Hills, 1993; Collett, 1994; Lindsey, 1995; Burnham *et al.*, 1995) have recommended the use of the AIC. In this work the AIC was used to select models.

The AIC can be used to compare different parametric models by a statistic that trades off a model's likelihood against its complexity. A lower value of AIC indicates a better model.

$$AIC = -2LL + 2(c + a)$$

Where LL is the log likelihood statistic, c indicates number if parameters in the survival distribution function and a denotes the number of parameters in the model.

In the following section, the trial data from the CARE-HF study was used as an example to illustrate how to fit parametric survival distributions and how to select a best fit model for the data. SAS software was used for all analysis in this section.

4.4 The CARE-HF study

The CArdiac REsynchronisation in Heart Failure (CARE-HF) trial (Cleland *et al.*, 2005) was a multicentre, international, randomised trial. The study compared the effect, on the risk of

complications and death, of standard pharmacologic therapy alone with that of the combination of standard medical therapy (MT) and cardiac resynchronisation therapy (CRT) without a defibrillator in patients with left ventricular systolic dysfunction, cardiac dyssynchrony and symptomatic heart failure. Patients were enrolled at 82 European centres; enrolment began in January 2001 and ended in March 2003.

The primary endpoint was the time to death from any cause or unplanned hospitalisation for a major cardiovascular event. The principal secondary endpoint was death from any cause. The cost-effectiveness analysis was specified *a priori* as a secondary outcome in the protocol and included data from all patients enrolled in the trial. The principal analysis was pre-specified as the incremental cost per QALY gained.

Resource use information was collected at baseline, 1, 3, 6, 9, 12, 18 months, every 6 months thereafter, and at the end-of-study. Patients' quality of life was assessed using the EQ-5D at baseline and 90 days post-randomisation.

A total of 813 patients were randomly assigned to receive medical therapy (MT) alone (404) or with a cardiac resychronisation device therapy (CRT+MT) (409). The mean duration of follow-up was 29.4 months (range 18.0–44.7). By the end of the study, the survival status of all patients was known; 383 patients had reached the primary endpoint, of which 159 patients were in the CRT+MT group, as compared with 224 MT patients (39% vs. 55%; hazard ratio, 0.63; 95% CI, 0.51 to 0.77; P<0.001). There were 384 unplanned hospitalisations for the major cardiovascular events in the MT group and 222 in the CRT group. An extension phase on all-cause mortality was reported in Cleland study with mean follow-up 37.4 months (Cleland et al 2006). There

were 154 deaths (38.1%) in 404 patients assigned to medical therapy and 101 deaths (24.7%) in 409 patients assigned to CRT (hazard ratio 0.60, 95% CI 0.47-0.77, P<0.0001).

4.4.1 Estimation of time to death

Time to death was fitted to the extended phase of the data using exponential, Weibull, log-normal, log-logistic and gamma distributions based on accelerate time failure models. The Cox–Snell residual was used for an initial check of model fitting, Figure 4.3 shows the Cox-Snell residuals from the five candidate models, from which it can be seen that both exponential and Weibull would provide a better fit than log-logistic, log-normal or gamma distributions. A straight line with unit slope and zero intercept indicated the fitted survival model is satisfactory (Collett, 2004).

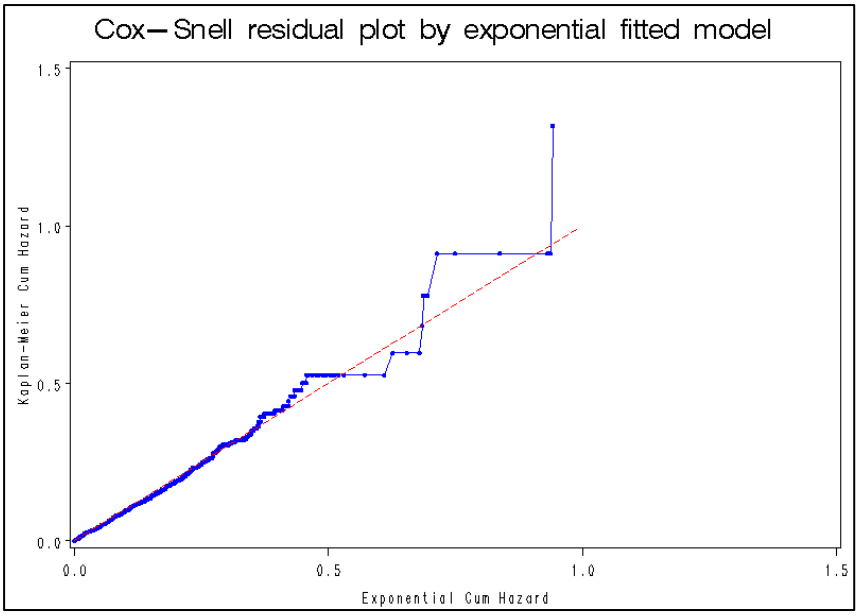

Figure 4.3 Cox-Snell residual plots by different survival functions (a)

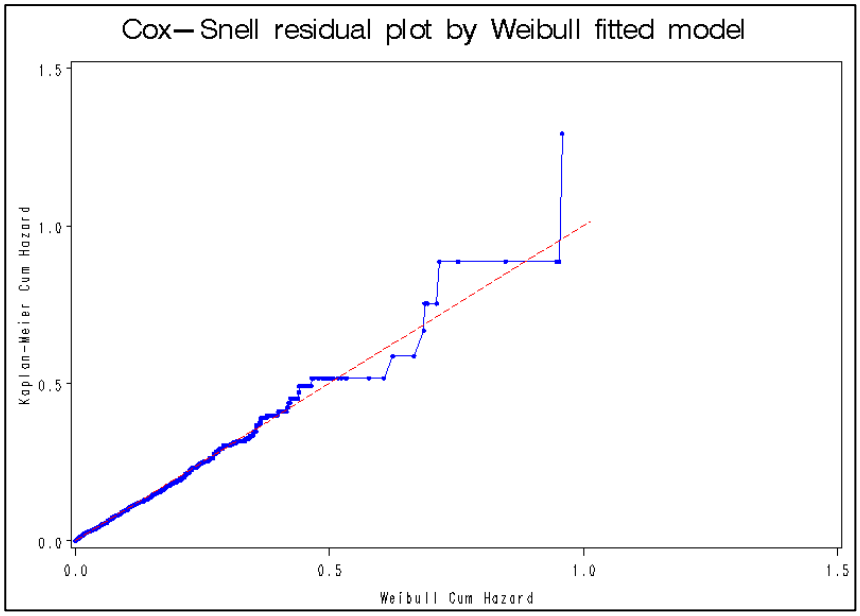

Figure 4.3 Cox-Snell residual plots by different survival functions (b)

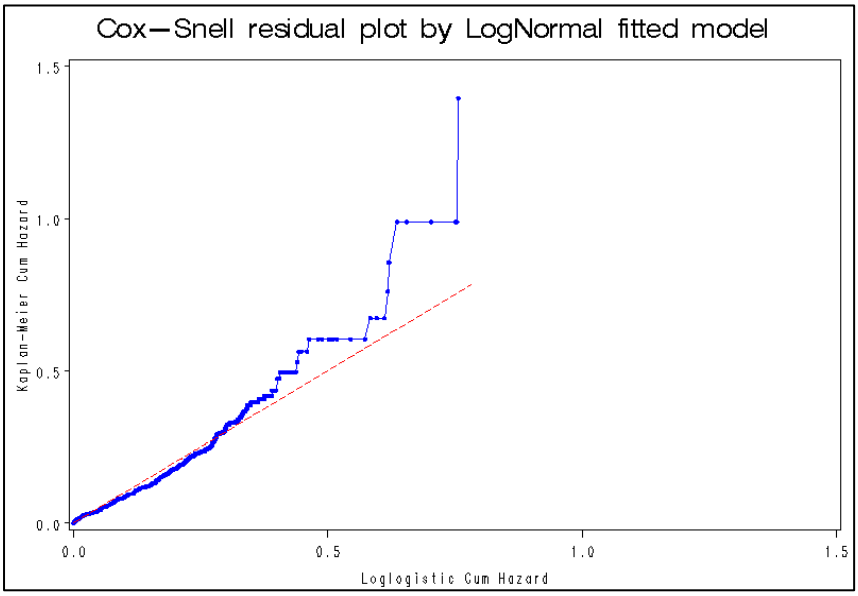

Figure 4.3 Cox-Snell residual plots by different survival functions (c)

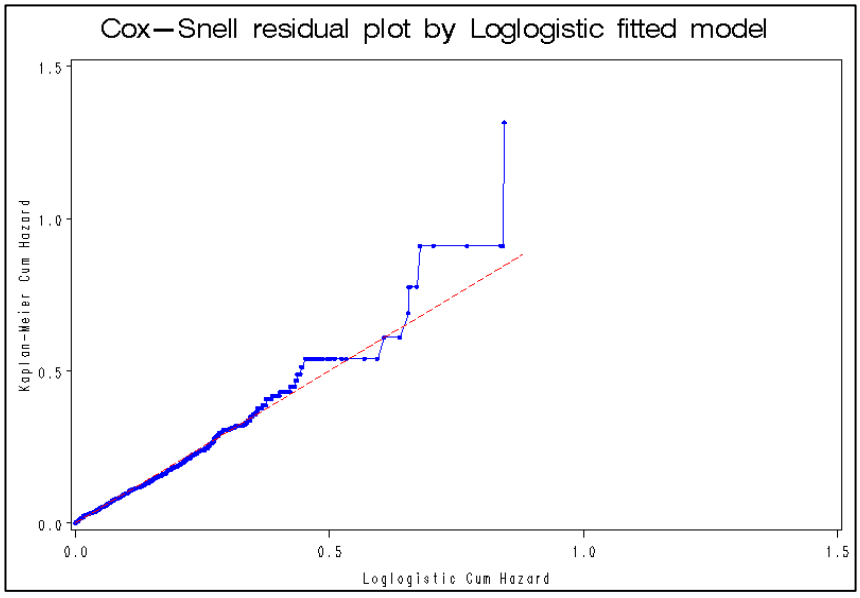

Figure 4.3 Cox-Snell residual plots by different survival functions (d)

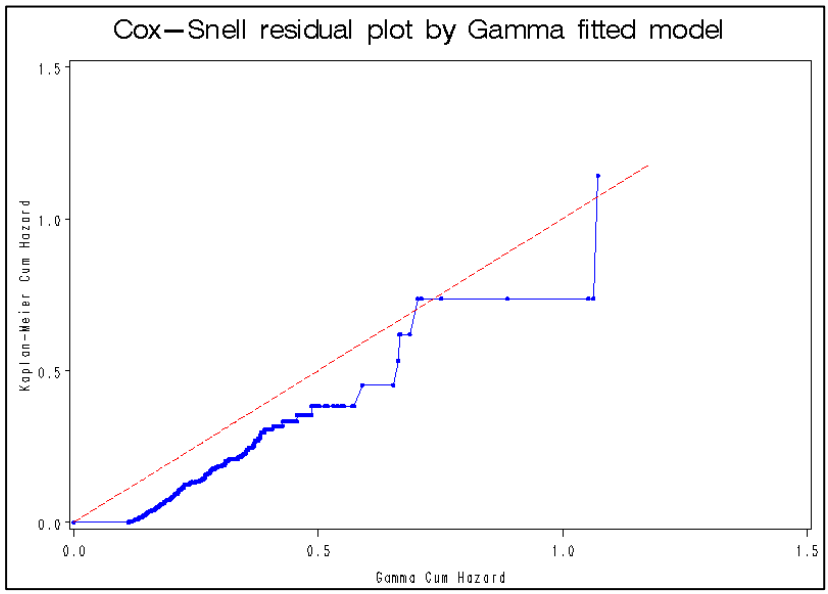

Figure 4.3 Cox-Snell residual plots by different survival functions (e)

Table 4.1 reports negative 2 log likelihood statistics. This statistic is used to compare nested models. The difference between the log likelihood statistics follows the chi-squared distribution. Table 4.1 reported the p-value for different comparisons.

The exponential model was selected as it had the best model fit based on the AIC (Table 4.2). Table 4.3 reports the estimated hazard rate for the MT group and the hazard ratios of CRT+MT compared to MT.

4.4.2 Survival gain in CARE-HF study over lifetime

In the Calvert study is a trial-based analysis and cost-effectiveness result was presented over 29.4 months mean follow-up period (Calvert *et al.*, 2005). A restricted mean survival was estimated for each patient within the trial on the basis of the time from randomisation until death or censorship. The gain in survival associated with CRT was estimated from the difference in mean survival times between treatment groups.

When the exponential was chosen as baseline function and fitted into the extended phase of the data, the estimates of baseline hazard for MT at 0.155 per year, and the survival function of the time to death as

$$S(t) = \exp(-0.155t)$$

The estimated hazard ratio of CRT+MT *vs* MT was 0.604. By applying this ratio to baseline hazard function, the survival over patient lifetime for the CRT+MT treatment group can be calculated. Figure 4.4 shows the estimated survival function and observed survival function.

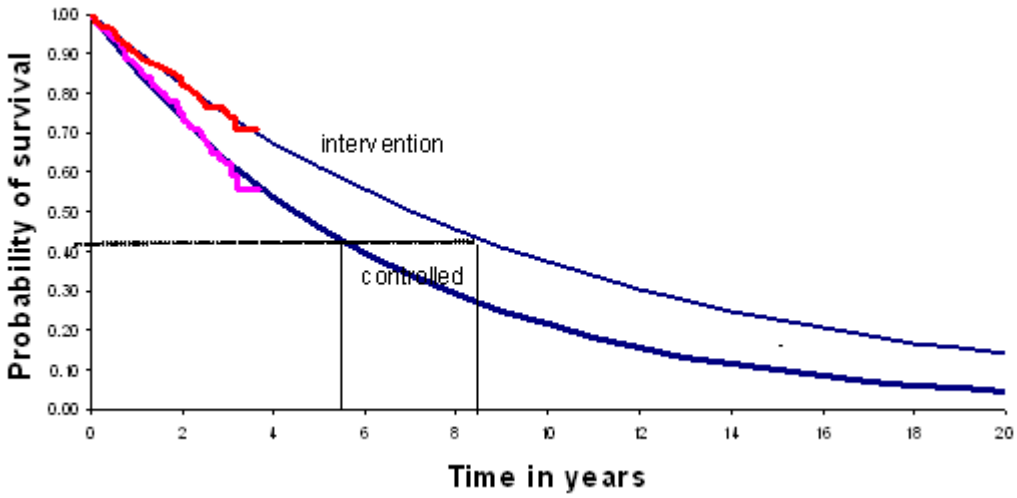

Figure 4.4 Estimated based on fitted curves and observed curves

Based on an area under the curve approach, the life year for CRT+MT and MT and the life year gain over different time points can be estimated. This can be obtained by the different survival time between the treatments. Table 4.4 shows the estimated life year gain at 3 years is 0.19 and 5 years is 0.46 and over 20 years is 2.52.

4.5 Discussion

In this chapter, the most commonly used survival functions in survival analysis were described and characteristics of their corresponding hazard functions compared. Parametric survival analysis was conducted in the CARE-HF trial data for time to death. Methods for selecting the best fitting survival functions for time to death over the observed periods were illustrated and the parameters estimated based on parametric survival analysis methods. Life years gained over different time points after treatments were estimated.

Using survival functions in extrapolating beyond a trial were studied. It is easy to implement and provides the longer-term survival property in economic analysis, but its limitation is that it is concerned with the overall survival property. However, cost and quality of life can be quite different after trial periods and depend on different events in the future. In the case of the CARE-HF trial, further cost is related to whether there was a cardiac hospital event or whether batteries needed to be replaced. In order to catch the further cost-effectiveness implication, it would be more flexible to employ a modelling approach. In the next chapter methodological issues using modelling approaches are presented.

Table 4.1 Likelihood ratio statistic in difference survival functions

Contrast	Likelihood ratio chi-square statistic	Pr > ChiSq
Weibull vs. Exponential	0.36686	0.54472
Gamma vs. Exponential	2.10038	0.3498
Gamma vs. Weibull	1.73352	0.1879
Gamma vs. Log-normal	19.4868	>0.000

Table 4.2 The likelihood statistic and AIC based on different parametric models

Distributions	No. Parameters	AIC	N2loglikelihood
Exponential	1	1309.03	1303.03
Weibull	2	1310.66	1302.66
Gamma	3	1310.93	1300.93
Log-logistic	2	1313.63	1305.63
Log-normal	2	1328.42	1320.42

Table 4.3 Estimated hazard ratio based on exponential model

Treatment class	Hazard yearly	95% CI lower	96% CI Upper	Mean Survival time in years	Life year saved
CRT + MT group	0.155	0.132	0.181	6.6	
Hazard ratio					
CRT+MT vs. MT	0.604	0.470	0.777		
MT group	0.097	0.081	0.116	10.3	3.7

Table 4.4 Projected life years using exponential function

	Life year		Life save in years	Life save in days
Time (year)	**Controlled**	**Intervention**	**Different**	**Days**
3	2.41	2.60	0.19	70
4	2.99	3.31	0.32	115
5	3.49	3.95	0.46	166
10	5.11	6.36	1.25	456
15	5.86	7.83	1.97	720
20	6.21	8.73	2.52	921
life time	6.49	10.15	3.65	1333

CHAPTER 5 EXTRAPOLATION USING A MARKOV MODELING FRAMEWORK

5.1 Introduction

In the last chapter methodological aspects of using parametric survival functions to project longer-term benefits beyond a trial follow-up period were discussed. However, extrapolating costs might present different challenges. For example, it might be the case that for an implanted device, battery replacement is required after a number of years and this is not observed within the limited trial follow-up (as in the CARE-HF study looking at cardiac resynchronisation therapy). To incorporate the long-term events, and to utilize observational study data, it is more flexible to build a model to simulate the longer-term implications for both costs and effectiveness. In addition, a model developed using trial data could provide a means to extrapolate and consider related policy questions in different patient groups and different clinical settings.

In chapter 2 model types were briefly reviewed and classified as decision trees, Markov models or individual sampling models. In this chapter, the focus is on the Markov modeling approaches when applied to economic evaluations. This includes classical Markov chain models and individual sampling models based on a Markov modeling framework. Methods to relax the Markovian limitations are explored. The basic concept and theoretical background of Markov modeling used in this chapter are based on the book by Hillier and Lieberman (1990).

5.2 What is a Markov model?

A Markov model represents a stochastic process which evolves over time, defined by the following five properties (Hillier & Lieberman, 1990):

1. A finite number of states
2. Conditional probabilities
3. A fixed cycle length
4. A set of transition probabilities among Markov states
5. A set of initial probabilities

First, a finite number of states are defined, usually named as health states or Markov Health States. These states should be mutually exclusive and exhaustive. This property indicates that, at a given time, a simulated patient is always in one and only one health state.

Second, the conditional probability refers to the probability that a patient moves from one health state to another, conditional upon his or her current state.

The first two properties lead to the following conclusions: the conditional probability property requires all transition probabilities to be non-negative, and the exhaustive Markov states require that all transition probabilities at a given cycle sum 1.

Third, a fixed cycle length is described as a fixed increment of time in which the stochastic process evolves in a fixed time step over the whole time horizon. The whole length of a Markov model time frame is, therefore, split into equal length Markov cycles.

Fourth, transition probabilities refer to movements among Markov states from the current cycle to the next cycle. The movement between states in the following cycle is called an ‘event’. All events are represented as transitions from one state to another.

Finally, a set of initial probabilities refers to the starting point of all the elements in the stochastic process. In the medical field such elements are usually patients. This property defines the starting state of a person or cohort when the patient enters a Markov model.

5.3 The application of a Markov model in health economics

A Markov model can present a clear structure in demonstrating a patient's disease progression or treatment pathway, and is particularly useful in the health economic field. Cost is usually allocated to a single Markov state across a single cycle and utility scores are associated with health states, usually defined by the severity of a disease. Therefore, cost and utility scores can be attached to each health state in a straight forward way. A patient staying in one state has an associated cost and utility score attached to that state. Therefore, the total cost and utility could be easily summed based on a patient's pathway during treatment periods.

A Markov model is frequently used in health economic evaluation (Sinha & Das, 2000; Stewart *et al.*, 1998; van Hout *et al.*, 1997; Welsing *et al.*, 2006), and especially widely used in the modelling of chronic diseases (Barber *et al*., 2006; Tilden *et al.*, 2007; Wynia *et al.*, 1998; Zhu *et al.*, 2005). Sonnenberg and Beck (1993) provide an introduction to the Markov model approach in the medical field. Briggs and Sculpher (1998) offer further details on the use of Markov modeling when performing economic evaluation. Recently such modelling approaches have emerged in economic evaluation for extrapolating beyond trials (Macario *et al.*, 2006; Rinfret *et al*., 2005; Roze *et al.*, 2006; Scuffham & Chaplin, 2005; Yao *et al.*, 2007).

Many studies have used Markov modelling approaches in economic evaluation, and several studies have addressed the limitations of a Markov model, employing various methods to

overcome them (Caro, 2005; Palmer *et al.*, 2004). However, relatively little work has focused on the methodological aspects of Markov modeling as an approach to extrapolating beyond a trial, especially when individual patient data from a trial are available. This chapter draws on the established foundations of the Markov modelling approach as used in the health economics field. In particular, the limitations of a Markov model are considered and how to overcome such limitations when employing this modeling framework to conduct economic evaluation alongside a clinical trial and extrapolating beyond the trial, are discussed. The aim is to provide details and a comprehensive introduction both on methodological and applied issues. To illustrate the methods, a simplified version of the renal transplantation model developed by Yao and colleagues was used (Miners *et al*., 2007; Woodroffe *et al.*, 2005; Yao *et al*., 2006), examining long term cost and effectiveness of immunosuppressant therapy in renal transplantation. Renal transplantation is obviously not in the area of heart disease but the model has a simple three state structure and is used here as an example to describe the nature of Markov model. The approach illustrated here can be readily projected to other disease areas.

5.4 Renal transplantation model

End stage renal failure occurs when the kidneys no longer function. Patients at this stage of the disease will either require a kidney transplant or dialysis, otherwise they will die. Successful renal transplantation is reliant on the use of immunosuppressant agents. To model the disease progression, Yao and colleagues (2006) employed a Markov modelling approach in assessing the long-term treatment effects of different therapies.

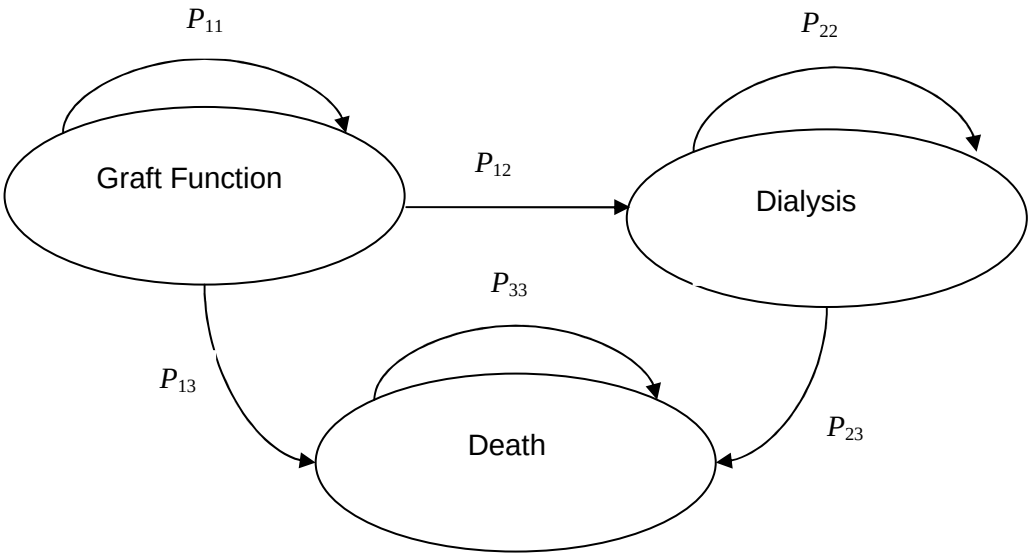

Figure 5.1 Illustrative example of a Markov model in renal transplantation

Figure 5.1 presents a simple version of a Markov chain used to evaluate the cost and effectiveness of immunosuppressant therapies in the treatment of end-stage renal failure. Three health states are defined in the Markov model structure, represented by oval shapes: graft functional state, dialysis and death. The arrows between health states indicate possible transitions between states.

A one year cycle length was chosen in this model. Table 5.1 presents, in table form, the probabilities which need to be estimated in the model: P_{12} refers to the transition probability from graft function to dialysis and P_{13} refers to the transition probability from graft function to death, $P_{11} = (1- P_{12} - P_{13})$ is the probability of a patient in graft function state remaining in a graft function state in the next cycle. P_{23}: the transition probability from dialysis state to death and P_{22} is the probability of a patient in dialysis state remaining so. This equates to $1- P_{23}$. The rest of the probabilities are zero, indicating no possibility of transition directly from one state to another in the following cycle.

Table 5.1 Defining transition probabilities

Transitions From time t to time t+1	Graft function	Dialysis	Death
Graft function	P_{11}(= 1- P_{12} - P_{13})	P_{12}	P_{13}
Dialysis	P_{21} (= 0)	P_{22} (=1 - P_{21} - P_{23})	P_{23}
Death	P_{31} (= 0)	P_{32} (= 0)	P_{33} (= 1)

This information is presented in matrix form below, which illustrates the transition probabilities matrix for the renal transplantation model. A meta-analysis (Miners *et al.*, 2007; Woodroffe *et al*., 2005) based on a systematic review has estimated the transition probabilities among the three health states:

$$\boldsymbol{P}=\left(P_{ij}\right)_{3*3}=\begin{pmatrix} P_{11} & P_{12} & P_{13} \\ P_{21} & P_{22} & P_{23} \\ P_{31} & P_{32} & P_{33} \end{pmatrix} = \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix}$$

Where *Pij* (*i*, *j* = 1, 2, 3) where *i* denotes to state *i* at current cycle and *j* refers to state *j* in the next cycle) refers to the probability that a patient at state *i* in the current cycle will move to state *j* in the next cycle. Please note: all *Pij* are independent from time or any other variables apart from a patient's current state.

5.5 Analysis of a Markov model

The analysis of a Markov model in a health economic evaluation refers to recording a patient's disease progress pathway over time and predicting which health state the patient will occupy at a

given time in the future, based on their starting state. Once a patient's pathway is identified during a period of time, cost or utility scores can be attached to their specific health states at each cycle, which can be the total cost and outcome summarized for the entire time period. Suppose a person in the model starts in health state *I*, which states is he/she going to occupy over the next *j* (*j* =1, 2,…,*n*) cycles?

Before considering methods of analysing a Markov model, a particular form of Markov model, namely the Markov chain, is reviewed. Markov chains are Markov models with one additional restriction, relating to the set of transition probabilities among Markov states from current cycle to the next cycle that do not change over time, it is said to have stationary transition probabilities. A Markov chain is mathematically tractable (Hillier & Lieberman, 1990), which will be discussed in the next section.

There are three main methods to evaluate a Markov chain: matrix algebra, cohort simulation and Monte Carlo simulation. Each of these three methods will be explored in turn, using the renal transplantation model as an example.

5.5.1 Matrix algebra

Suppose all patients started in the graft function state. The initial probability of the Markov model is presented as

$$A_0 = (P_1 \ P_2 \ P_3) = (1 \ 0 \ 0)$$

Where *A t* (*t*=0, 1, 2, …, *n*) denotes the probability that patients will be in cycle *t*. *Pi* (*i* = 1, 2, 3) denotes the probability of a patient in each state at the starting point.

At the end of the first cycle (one year):

$$A_1 = A_0 * P = \begin{pmatrix} 1 & 0 & 0 \end{pmatrix} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix} = \begin{pmatrix} 0.92 & 0.07 & 0.01 \end{pmatrix}$$

At the end of the second cycle (two years):

$$A_2 = A_1 * P = A_0 * P = \begin{pmatrix} 1 & 0 & 0 \end{pmatrix} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix}$$

$$= \begin{pmatrix} 0.92 & 0.07 & 0.01 \end{pmatrix} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix}$$

$$= \begin{pmatrix} 0.92*0.92 & 0.92*0.07 + 0.07*0.75 & 0.92*0.01 + 0.07*0.25 + 0.01*1 \end{pmatrix}$$

$$= \begin{pmatrix} 0.8464 & 0.1169 & 0.0367 \end{pmatrix}$$

And so forth …. The probability of a patient starting at graft function state and being in a different state at the end of the *n*-th cycle is as follows:

$$A_n = A_{n-1} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix} = A_{n-1} * P = A_0 * P^n = \begin{pmatrix} 1 & 0 & 0 \end{pmatrix} * \begin{pmatrix} 0.92 & 0.07 & 0.01 \\ 0 & 0.75 & 0.25 \\ 0 & 0 & 1 \end{pmatrix}^n$$

The limitation of matrix algebra is the relative mathematical knowledge required to fulfill the calculation aspect. Thus, it needs a special program for conducting the algebra, and it is not straightforward for the non-specialist user.

5.5.2 Cohort simulation

Markov cohort simulation refers to a simulation approach assuming a hypothetical and homogenous cohort of patients entered into the model at time zero (Sonnenberg & Beck, 1993). Here the partitioning is based on the initial distribution across health states. In the renal transplantation model we assumed that 1000 patients entered the model at the start of the simulation and all started at the graft functional health state. At each cycle of the model, the transition probability was applied to re-distribute that cohort into a new proportion at different health states. Table 5.2 illustrates the renal transplantation model over a 10 year period (10 cycles). The function at the end of the table provides the formula for calculating the cohort distribution at each cycle.

Table 5.2 Cohort simulation for renal transplantation model

t **(cycle)**	**Health States**			**Total**
	A (Graft Function)	**B (Dialysis)**	**C(Death)**	
0 (start)	1000	0	0	1000
1	920	70	10	1000
2	846	117	37	1000
3	779	147	74	1000
4	716	165	119	1000
5	659	174	167	1000
6	606	176	217	1000
7	558	175	267	1000
8	513	170	317	1000
9	472	164	364	1000
10	434	156	410	1000

At a given cycle t (where t =1, 2, 3, …, 10), the number of patients at each state was calculated using the following formulae:

$$A_t = A_{t-1} * P_{11} + B_{t-1} * P_{21} + C_{t-1} * P_{31}$$

$$B_t = A_{t-1} * P_{12} + B_{t-1} * P_{22} + C_{t-1} * P_{32}$$

$$C_t = A_{t-1} * P_{13} + B_{t-1} * P_{23} + C_{t-1} * P_{33}$$

In fact, a Markov cohort simulation is a graphic presentation of the matrix algebra in evaluation of a Markov model. By pre-multiplying the total number of the cohort into the matrix formula, the exact same result as the cohort simulation will be reached.

However, there are limitations associated with cohort simulations, the most obvious being that it gives fixed proportions of the cohort in different states and therefore has no measure of variability.

5.5.3 Monte Carlo simulation

A Monte Carlo simulation refers to a large number of individuals being followed through the model pathway individually (Sonnenberg & Beck, 1993). In the case of a Markov chain, each individual is subjected to the same transition probabilities, walking through the model pathway defined by probabilities for the next cycle. However, a random process dictates which path of states the individual will follow. The implication for the economic evaluation is that this leads to a different cost and outcome for each individual. Therefore, the result of the estimated cost and outcome is the mean of all individual costs and outcomes, but their variability can be estimated based on the individual cost and outcome (Briggs & Sculpher, 1998).

For example in the renal transplantation model, suppose a patient is in the graft function state at the current cycle; diagram 5.1 illustrates the probability of staying in graft function is 0.92, of graft failure or transfer to dialysis state is 0.07 and the probability of death is 0.01 in the next cycle. In the Monte Carlo simulation, a random number R will be drawn based on uniform distribution and the value will be from 0 to 1. If $R \leq 0.92$, where the patient will stay in graft function state. If $0.92 < R < 0.92 + 0.07 = 0.99$ then the patient will move to dialysis state, and if $0.99 < R \leq 1$, the patient will move to death state. At the start of every cycle, a random number will be drawn for each individual, and based on the same rule as previously indicated, this will define the patient's state in the next cycle. Therefore, simulated patients will have different disease progressions over their treatment time.

The advantage of the Monte Carlo simulation is that variation amongst patients can be measured. Furthermore this simulation approach provides flexibility and allows one to relax a Markov

chain assumption and offer an improvement on a Markov model, especially given modern computer capabilities. This will be discussed in detail in the following sections.

The non-memory property of a Markov model is not applicable in many clinical settings. In many cases in medicine, a patient's progression depends on how long the patient has been in the current health state and the duration of the patient's disease. For example, in the renal transplantation case a patient is more likely to have failure in graft function within the first year of transplantation. After that year, once the body has recognised the new organ, the chance of graft failure is greatly reduced.

One way to overcome the non-memory property of a Markov model is through adding further health states (Barton *et al.*, 2004). However, when a patient's graft failure depends on how long ago a graft was implanted then the Markov model will be difficult to manage. Studies also targeted the limitations of a Markov model in the fixed cycle length, in which case discrete event simulation models can be sought (Caro *et al.*, 2006). However, this is not the focus of this study. In Chapter 2, an overview of different modeling approaches was given, referring to Barton (2004) and Brennan (2006). Both papers review how different terminology is used in modelling techniques and refer to individual sampling approaches where individual patients 'walk through' the model.

In the following section, an individual sampling model based on a Markov framework is presented as a means of overcoming three limitations in traditional Markov models:

1. The non-memory Markov assumption,
2. The fixed transition probability assumption, and

3. The inability to allow temporary events to happen within a health state while keeping the Markov health states and fixed cycle length properties intact.

5.6 Individual sampling simulation

In the previous section, three methods to evaluate a Markov model were discussed. With the use of modern computers, a set of additional variables can easily be employed to take account of the length of time a patient is on treatment when individuals go through the patient's pathway. This could involve an adjustment of the transition probability to be dependent on the duration of treatment. In addition, a separate set of variables could be employed to take account of different temporary events associated with each health state. Therefore, the potential risk factors could be updated accordingly. Furthermore, we can define individual patient characteristics at the start of the simulation or update them as the patient goes through the model. Transition probabilities can be updated at a given cycle, based on individual characteristics and time on treatment or on their current health state.

In the matrix algebra and cohort simulation approaches to evaluation of a Markov model, time components into the evaluation equation could be added. For example, if it is assumed that the transition probabilities are time dependent $P = P(t)$, then in every cycle, different sets of transition probabilities may be employed.

In the renal transplantation example, a transplanted patient has a risk of acute rejection. If a patient experienced acute rejection, the probability of graft failure would be much higher. A variable could be assigned to take account of the risk of acute rejection; therefore, the following transition probability having graft failure will depend on whether a patient has experienced acute

rejection or not. Although the patient is still at the graft function state, if patients do experience acute rejection the cost and utility will be adjusted accordingly. In addition, as the model is running over a patient's lifetime, the risks of death due to other causes will vary depending on age and gender.

This last section takes a closer look at the matrix formula. If the transition matrix is updated in every cycle according to the specific risk at that time period, the non-memory and stationary transition probability can be overcome and the model becomes much more flexible and able to mirror the reality of the clinical situation.

$$\boldsymbol{P}(t,k)=\left(P_{ij}(t,k)\right)_{3*3}=\begin{pmatrix} P_{11}(t,k) & P_{12}(t,k) & P_{13}(t,k) \\ P_{21}(t,k) & P_{22}(t,k) & P_{23}(t,k) \\ P_{31}(t,k) & P_{32}(t,k) & P_{33}(t,k) \end{pmatrix}$$

Where $p(t,k)$ is the probability matrix denoting a probability of moving from one state to another at a given time *t* with characteristics *k*. *t* is the time since starting the model, while *k* is a set of variables attached to each individual.

The Markov model for renal transplantation is represented in a tree diagram as Figure 5.2 below.

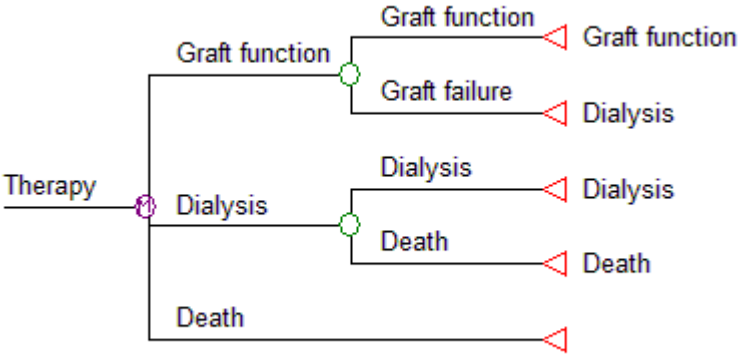

Figure 5.2 A Markov model in renal transplantation in tree diagram

This mirrors the diagram in Figure 5.1 but uses the tree diagram instead of the conventional ways of presenting the Markov model.

The Markov model can be expanded by additional variables (known as tracker variables in the software package TreeAge) attached to each individual. At the start of the simulation, a cohort of individual patients was created, based on their gender and age at the start of transplantation. All patients begin at the graft functional state. A tracker variable *AR (t)* was attached to each individual. This tracker variable records whether patients are having acute rejections or not. If a patient has no acute rejection, then they will follow the same pathway as Figure 5.2. However, if the patient experiences acute rejection, they will follow a different transition probability as shown in Figure 5.3.

In addition, to add the tracker of acute rejection, a set of tracker variables was used to record time on treatment. This variable was defined by patient's age which was updated in every cycle. Death due to other causes was dependent upon a patient's age and gender.

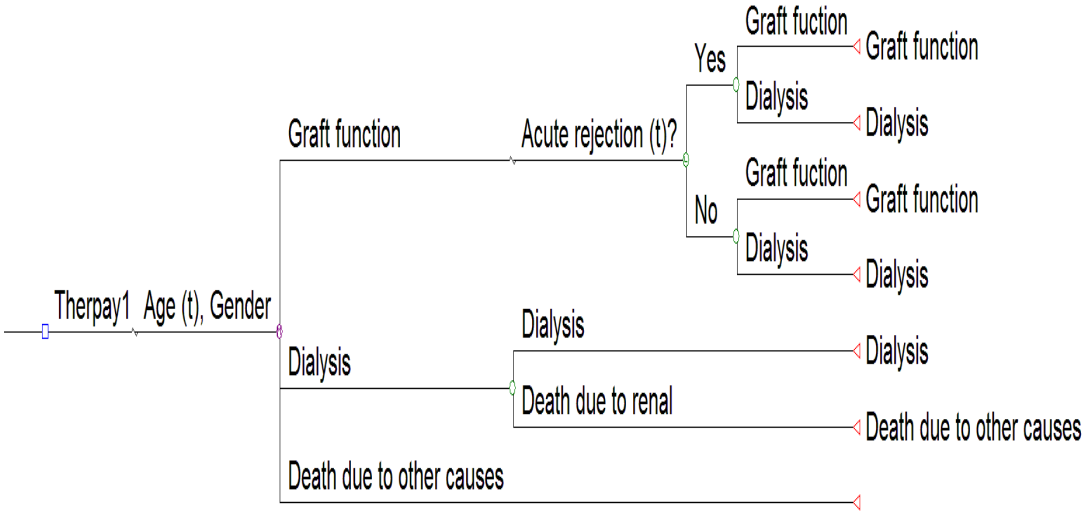

Figure 5.3 Schematic illustration of an individual simulation model in renal transplantation

5.7 Discussion

This chapter reviewed the basic concept of Markov models and their properties were investigated in detail. Specifically discussed were the limitations of the Markovian assumption and stationary transition probability properties. However, those limitations can be easily overcome by modern computer capabilities and by employing tracker variables to account for duration of treatment and risk factors at each health state.

By using tracker variables in the Monte Carlo simulation, time dependent events associated with each health state can be taken into account and their rewards, in terms of costs and QALYs, can be easily summarised.

In a clinical trial patient data are collected at an individual level. Each patient has a baseline profile when they enter the trial. In order to conduct economic evaluation alongside a clinical

trial and to extrapolate beyond the trial based on modeling approaches, it is necessary to model individual pathways at the individual level.

The advantage of individual simulation is that it can closely mirror a clinical trial, and by so doing, the model can be validated by comparing the model-based results and the trial-based results. Once a robust model is created, different cohorts of the population can be generated and entered the model. This can provide research to extrapolate beyond a trial, not only in terms of the extended time-frame but also horizontally to consider the treatment applied to different populations.

In the next chapter, the CARE-HF trial is used to illustrate an individual patient simulation model based on a Markov modeling framework. Detailed methodology and approaches using a real trial are presented and validation of the model-based analysis against a trial-based analysis is undertaken.

CHAPTER 6 CASE STUDY 2 - CARDIAC RESYNCHRONISATION THERAPY

6.1 Introduction

The two previous chapters described the common approaches in extrapolating beyond a trial: parametric survival functions and the Markov modelling method based on individual patient simulation. Chapter 4 presented the theoretical background on parametric survival functions and details of the mathematical properties of different parametric survival distribution functions were reviewed. It focused on how to choose an appropriate survival function based on individual data from a clinical trial. Chapter 5 discussed a Markov modelling approach in economic evaluation and methods in relaxing Markov modelling assumptions were explored. Methodological details were discussed and illustrated by using the renal transplantation model.

This chapter describes a model-based study using the CARE-HF study (CArdiac REsynchronisation in Heart Failure), which was a follow-up to the economic evaluation within the CARE-HF trial (Calvert *et al.*, 2005). A Markov modelling approach based on individual patient simulation was employed. The model provided a practical illustration of model-based analysis in which input data was populated from the trial.

Two survival functions were the time to major cardiovascular events without hospitalisation and time to hospitalisation. The parameters of those survival functions were estimated from individual trial data. The selection of the best fitted parametric survival functions were based on the approaches discussed in Chapter 4, details of which are presented in the later sections. The best fitted survival functions were used to extrapolate those survival times beyond the trial period.

The individual simulation approach was employed to track individual risk profiles and record time on treatments. The trial population was mirrored at the beginning of the model simulation. The risks of time to hospitalisation and cardiovascular events depend upon the patient's baseline characteristics, duration of treatment and type of interventions. This chapter is based on a published study (Yao *et al.,* 2007) but the analysis presented in this thesis is an extension of the original work.

6.2 Clinical background

Heart failure is a common disease and costly in terms of morbidity, mortality and resources consumed (Cazeau *et al.,* 2001; Stewart, 2005).

Randomised controlled trials have demonstrated that cardiac resynchronisation therapy (CRT-P) and CRT with an implantable cardioverter–defibrillator (CRT-ICD) improves symptoms, exercise capacity, ventricular function, quality of life and reduces mortality in patients with heart failure due to cardiac dyssynchrony who have persistent moderate or severe symptoms despite standard pharmacological therapy (Young *et al., 2003;* Bristow *et al*., 2004; Cleland *et al.,* 2005).

A within trial cost-effectiveness analysis based on individual patient data from the CARE-HF trial and UK cost structures showed that CRT-P was associated with increased costs £2,936 (95% CI £903 to £5,092) and increased quality adjusted life years (QALYs) (0.22 95% CI 0.13 to 0.32) (Calvert *et al.,* 2005) compared to medical therapy. The incremental cost-effectiveness ratio was £13,142 per QALY gained. The results were sensitive to the costs of device and

procedure, and indicate that treatment with CRT-P was cost-effective at the notional willingness to pay threshold of £20,000 per QALY gained.

The within trial analysis demonstrated that CRT+MT compared with MT alone was cost-effective, based on observed benefits and costs and when limited to mean 29.4 months follow up. However, there are a few questions that remain unanswered by the within trial analysis. What is the lifetime cost effectiveness of CRT+MT vs. MT? Which population parameters determine cost effectiveness? What is the cost effectiveness implication of adding ICD to CRT?

It is possible that CRT-ICD may appear cost-effective compared to medical therapy but the incremental benefit of ICD in addition to CRT-P might be beyond the threshold of willingness to pay (UK perspective). This could occur if the additional costs associated with the ICD component are high compared to any additional benefits gained (Abraham *et al.,* 2002; Young *et al.,* 2003; Bristow *et al.,* 2004; Cleland *et al.,* 2005). The incremental cost-effectiveness of combined CRT-ICD devices vs. CRT-P alone remains uncertain. The model based analysis aims to answer these questions.

The following section presents an economic model populated with data from CARE-HF (Cleland *et al.,* 2005) to evaluate the long-term incremental cost-effectiveness of CRT-P and medical therapy (MT) compared to MT alone, on incremental cost per QALY and life year gained. In addition, the cost-effectiveness of CRT-ICD+MT vs. MT and the relative cost-effectiveness of CRT-P and CRT-ICD, incorporating estimates of the proportion of sudden deaths that might be prevented with CRT-ICD taken from the results of a landmark trial, the COMPANION (Carson *et al.,* 2005) is evaluated. The incremental cost-effectiveness of CRT-P or CRT-ICD in different patient subgroups is also evaluated.

6.3 Construction of the model

An individual sampling simulation model based on a Markov model framework was constructed using the approaches defined in Chapter 5. Health states were defined by New York Heart Association functional class (NYHA) and death. A monthly cycle was defined in the model. At any given NYHA class, patients face different risks of cardiovascular hospitalisation and death. Mortality was sub-classified by cause, including death due to worsening heart failure, sudden death or death due to all other causes. The risk of these events depended upon the duration of patients' treatment, their NYHA class and the treatments they received.

The model had two components: the short-term, representing changes in health status and the costs and consequences of the process of device implantation, and the long-term effects of the device after successful implantation (Figures 6.1 & 6.2). In the model, MT patients do not receive CRT-P or CRT-ICD during follow up. The CRT-P and CRT-ICD groups received treatment with their assigned therapy in accordance with the successful device implantation rates observed in the CARE-HF trial.

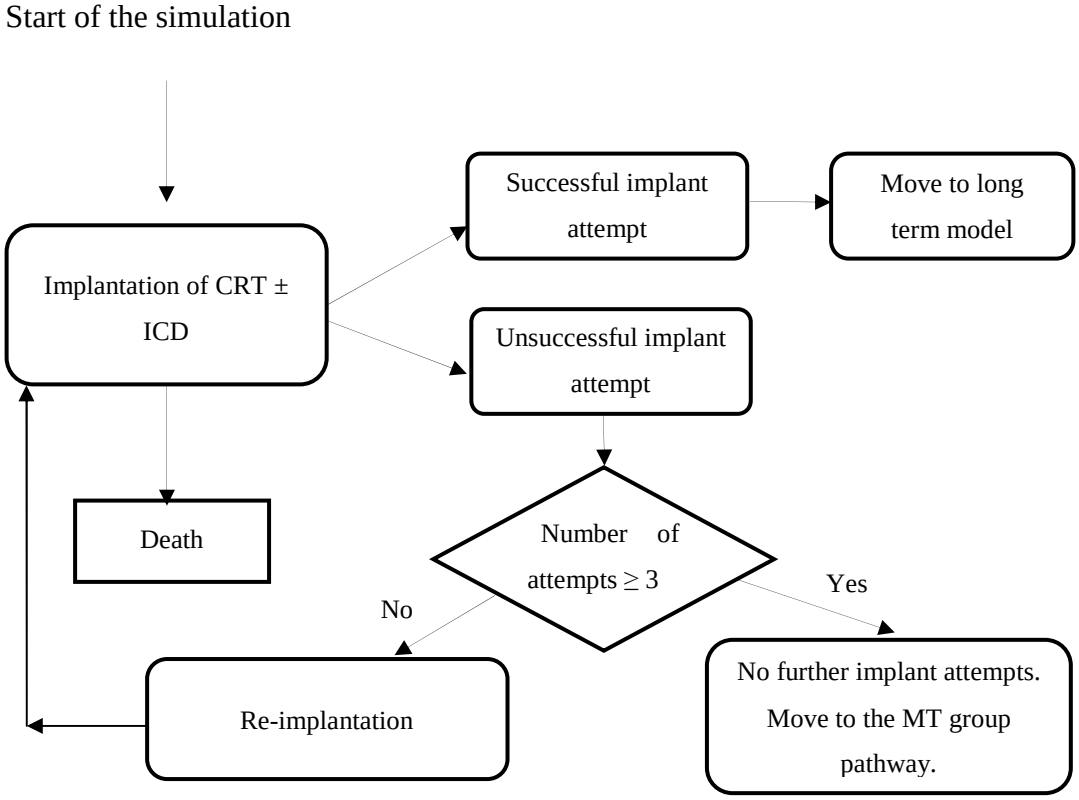

Figure 6.1 Structure of short term model*

**Patients had a maximum of 3 implant attempts. Those patients who received a successful implant moved to the long term model with an NYHA class according to the transition probabilities observed in the CARE-HF trial. Where implants were unsuccessful the patient followed the clinical pathway according to the transition probabilities for the medical therapy group.*

Figure 6.1 illustrates the patient pathway for implantation of CRT-P and CRT-ICD as defined in the short term model. At the start of the simulation a cohort of hypothetical patients is created. Each patient is defined by age, gender and NYHA class. All patients enter the model at the implant phase. The patients face the probability of implantation, successful implantation or failure of implantation or death. If an implantation is successful, the patient moves to the long term model within a NYHA class, according to the transition probabilities observed in the first month in the CARE-HF trial. If the implantation is unsuccessful, the patient will move back to implantation for another attempt. Patients have a maximum of 3 implantation attempts. Where

implants remain unsuccessful, no further attempts will be allowed and patients will follow the clinical pathway, according to the medical therapy alone group.

In the long term phase patients face different risks of major cardiovascular events without hospitalisation, such as sudden death or unplanned hospitalisation. This is dependent on their health state, treatment group and duration of treatment. All patients are at risk of death due to other causes, depending on their age and gender. Figure 6.2 represents the structure of the long term model in NYHA class I, if a patient does not die from other causes. During each cycle of the model, patients could stay in a stable condition state and move among the four NYHA health states, experience major cardiovascular events without hospitalisation or have an unplanned hospitalisation for a major cardiac event. The structure of the model for other NYHA classes was identical but with different transition probabilities and risk of unplanned hospitalisation. Each clone indicates that the patient will follow the pathway indicated at point A on the figure.

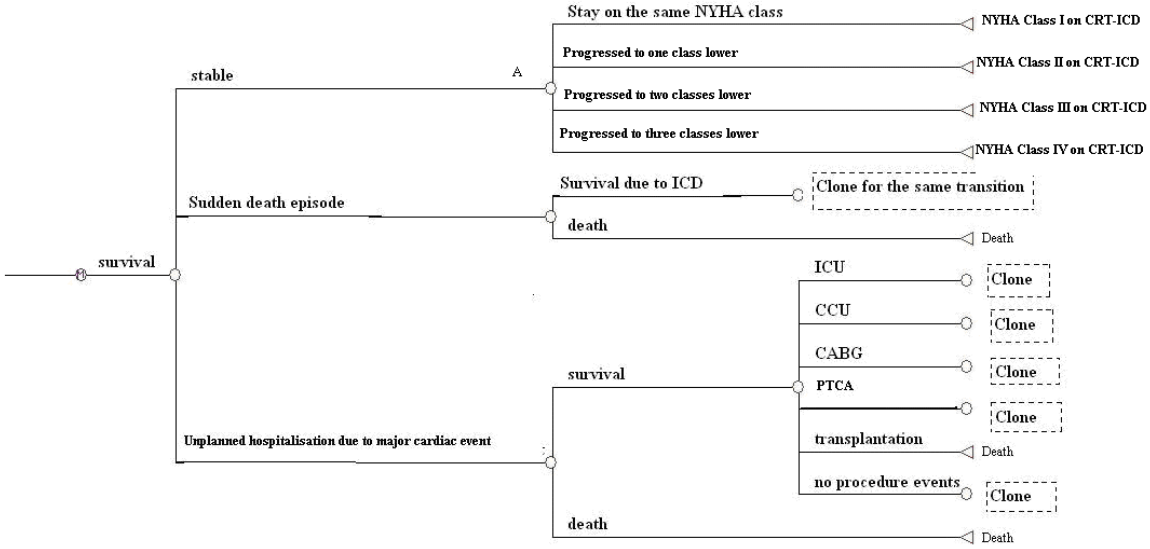

Figure 6.2 Structure of long term model (NYHA class I)

Stable conditions are defined as no major cardiovascular events. If no events occur during a cycle patients follow the stable branch and could move to a different NYHA class according to the transition probabilities at NYHA class and the treatment they receive.

Major cardiovascular events without hospitalisation are defined as acute arrests or a sudden death episode. The proportion of such events can be prevented from the additional component of ICD. However, in the CRD-P group or MT group this means sudden death.

Unplanned hospitalisations were categorised by type: procedure related, non-procedure related and those leading to death due to worsening heart failure. As simulated patients pass through the model cost and utility weighted life years associated with each state they experience are accumulated.

The initial distribution of the NYHA classes, age and gender and subsequent transition probabilities and costs associated with treatment by MT or CRT-P+MT were based on the intention to treat (ITT) analysis of CARE-HF. The additional effect of ICD on sudden death was based on the observed and projected rate in patients assigned to CRT-P in CARE-HF and the proportional reduction in sudden death observed in the COMPANION trial in patients assigned to CRT-ICD compared to CRT-P. Mortality for other causes was derived from the UK population (Government Actuary's Department (GAD), 2006), with variation by age and gender. A set of tracker variables was used to record duration of treatment and patient's ages were updated in every cycle.

6.3.1 Efficacy

Effectiveness is expressed as transition probabilities among the Markov health states. The transition probabilities among NYHA classes differed in the short and long term. In the short term, it was assumed there was an immediate response to the implantation.

Table 6.1a shows the rates of successful device implantation, derived from the total implantation experience inclusive of CRT and Control group in the CARE-HF trial. Table 6.1b shows the estimated transition probabilities among NYHA classes after implantation in the short term based available data derived from 388 (94.1%) and 380 (94.9%) patients in the CARE-HF CRT-P and MT groups, respectively.

The long term treatment effect on NYHA class was assumed to follow constant transition probabilities if patient stayed in stable state (non-events). This is supported by the CARE-HF trial data. In the CARE-HF trial outcomes including NYHA class have been measured at months 1, 6, 9, and 12, and every 6 months thereafter. The monthly transition probabilities from one NYHA class to another for the long term were derived from NYHA classes assessed at months 1 and 6. Monthly transition probabilities were estimated, based on the 5 month data by matrix algebra on the assumption of a constant Markov chain property during this period (Table 6.1c).

6.3.2 Estimating baseline risks

Estimated baseline functions of the time to sudden death and the time to unplanned hospitalisation were based on the parametric survival analysis. Five parametric survival functions were fitted using an accelerated time failure model and conducted using SAS software. Akaike information criterion (AIC) was employed in choosing the most appropriate model. Weibull distribution functions were selected for both of the time-to-events survival time as they had the

best model fit based on the AIC. Further details are given in Appendix 3. All parameters of the Weibull functions were estimated based on the observed data for the MT group in the CARE-HF trial. Table 6.2a shows the estimated parameters in the Weibull functions for those two functions. Table 6.2b presents the hazard ratios of CRT-P compared to MT. It was reported in previous study (Cleland *et al*. 2004; Calvert *et al*., 2005; Yao *et al.,* 2007). They were estimated by adjusting NYHA class for the risk of time to those two events, respectively

6.3.3 Estimating the risk reduction from ICD

The estimated additional benefit of ICD added to CRT in reducing sudden death was based on the observed rate of sudden death in patients assigned to CRT-P in CARE-HF and the difference in sudden death rates in the COMPANION trial between the CRT-P and CRT-ICD groups, based on a median follow up in that trial of 16 months in the device therapy groups (Bristow *et al.*, 2004; Carson *et al.,* 2005). No additional benefit, apart from preventing sudden death attributable to ICD, was assumed. The monthly probability of hospitalisation has been reported to be similar for CRT-P and CRT-ICD in the COMPANION trial (0.098 and 0.097, respectively) (Carson *et al.,* 2005) so no further penalty was applied to CRT-ICD patients for hospitalisation rates due to the presence of the ICD component.

6.3.4 Utility data

The CARE-HF trial provided EQ-5D score estimates at baseline and 90 days (Table 6.3). Utility scores were assumed to be dependent on the NYHA class of a patient, and otherwise independent of treatment. Utility scores measured in the CARE-HF trial were mapped onto NYHA class (Calvert *et al*., 2005). A utility value was assigned to each health state.

6.3.5 Cost Analysis

The economic analysis was conducted from a UK NHS perspective, including device cost of CRT-P and CRT–ICD, implantation procedure cost, cost of hospitalisation (hospital stay during implantation and unplanned hospitalisation), medical care cost, and drug costs. Implantation cost included device cost, procedure cost, intravenous medication, and hospital stay (including ICU and CCU).

Medical care cost included outpatient visits, cardiology or primary care visits, and length of time spent in nursing or residential homes or rehabilitation centres. Cost per patient per day for medical care and drug cost were estimated from CARE-HF (Calvert *et al.*, 2005). The same drug and medical care costs per day for all treatment groups were assumed.

Unplanned hospitalisation for a major cardiac event was characterised by the presence or absence of a procedure cost. Procedure costs included ICU, CCU, CABG, PTCA, and heart transplantation. Procedure costs were based on the frequency and cost of events, and average costs for ICU and CCU.

The unit costs employed have been previously reported (Calvert *et al.*, 2005). In brief, the costs of medications were obtained from the British National Formulary (BNF, 2006). All hospitalisation related costs based on National Health Service reference costs (HRG, 2004). Table 6.4 summarises the cost data by different categories.

6.3.6 Battery life

Based upon product specifications, it was assumed that the batteries were replaced for surviving patients in the CRT-P group every 6 years, and every 7 years in the CRT-ICD group (Medtronic,

2006). In order to examine the influence of battery life on the cost-effectiveness of the CRT-ICD device, which will vary with the device used and the specific programming employed, the cost-effectiveness of CRT-ICD using a device life of 6 years and 8 years were also examined. The cost associated with battery replacement was the device cost plus one cardiac outpatient visit day.

6.3.7 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was conducted across all input values (apart from two fixed parameters, the device and lead costs), together with scenario analysis of the assumptions within the model. Tables 6.1 to 6.4 list all input values and their respective distributions used to examine second order uncertainty (Briggs, 2000). Each set of random input values was drawn based on their specific distributions for every 10,000 patients and the results were iterated 1000 times. Cost-effectiveness acceptability curves were constructed to illustrate the key input parameter uncertainty in the model.

The choices of distributions for particular parameters were based on a general approach by using the distributional form that relates to the estimation of the parameter of interest (Claxton *et al.*, 2005). For utility values, which are bounded to be 0 to 1, the beta distribution was assigned. For costs of all hospital events and procedure costs, log-normal distributions were assigned. For polychotomous transitions, in the case of transition probability among NYHA classes, the Dirichlet distributions were assigned (Briggs *et al.*, 2006).

Similarly, all treatment effects such as hazard ratios which were estimated from a Cox proportional hazard model in the log hazard scale. Therefore, log-normal distributions were assigned to all hazard ratios for unplanned hospitalisation, sudden death and NYHA classes with

relative comparitors. For different events during unplanned hospitalization, a Dirichlet distribution was assigned. The event rates of implantation failures were based on a beta distribution.

There is no clear-cut reference regarding how many runs should be performed for 1st order and 2nd order uncertainty. Here the choice of the number of runs was based on an iterative process. In the case of 1,000 for 2nd order uncertainty, an initial 500 runs were tried in which the result showed a high degree of variability. Then the number was increased to 1,000, at which point reasonably stable results were achieved from different runs. Similarly, the choice of 10,000 on the 1st order uncertainty went through the same trial-and-error approach. The chosen number of runs is consistent with current practice as noted by Andronis and colleagues (2009).

6.3.8 Model validation

The model validation was conducted through replicating exactly the patient cohort observed in the CARE-HF trial. The model predicted survival curves which could be compared with observed survival results from CARE-HF and the published results from COMPANION (Feldman *et al.*, 2005)).

6.4 Results

6.4.1 Survival

For the base case analysis, where all mean input values used were based on 10,000 individual simulations, and patients started at a fixed age of 65 years, the predicted median survival was 7.44, 10.53 and 11.98 years for MT, CRT-P and CRT-ICD respectively and 75% of patients were dead by 11.33, 15.92 and 17.92 years (Table 6.5, Figure 6.3). The undiscounted life gained for CRT-P versus MT was 3.09 years and for CRT-ICD versus CRT-P was 1.45 years.

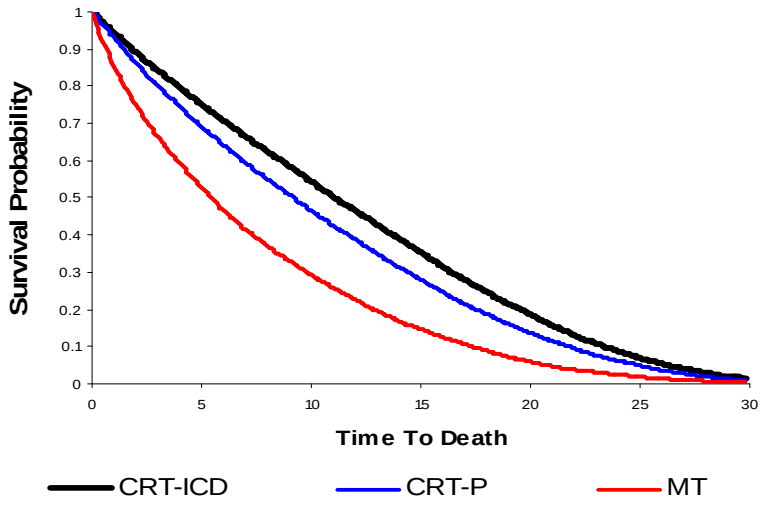

Figure 6.3 Model predicted survival curves for MT, CRT-P and CRT-ICD

6.4.2 Cost-effectiveness results

Table 6.6 and 6.7 shows the difference in costs, life years and QALYs by group. The total cost per patient was £26,572, £36,732 and £59,422 for MT, CRT-P+MT, and CRT-ICD+MT, respectively. The mean life-time QALYs were 4.08, 6.06 and 6.75 and life years were 6.10, 8.23 and 9.16 for MT, CRT-P+MT, and CRT-ICD+MT, respectively.

For the comparison of CRT-P+MT and MT, the probabilistic sensitivity analysis gave an incremental cost of £10,160, QALY score of 1.98 and life year estimate of 2.13. This gave incremental cost-effectiveness ratios (ICERs) of £5,128 (95% CI £3,623 to £8,017) per QALY gained and £4,769 (95% CI £3,637 to £14,704) per life year gained. CRT-ICD+MT versus MT, the incremental cost was £32,850, the QALY was 2.68 and life year gained 3.02. This led to ICERs 13,257 (95% CI £9,864 to £17,055) of per QALY and £10,735 (95% CI £6,254 to £13,421) per life year gained. For CRT-ICD+MT versus CRT-P+MT, the incremental cost was £22,690, the QALY score 0.70 and the life years gained 0.93. The ICER here was £32,529 (95%

CI £24,288 to £54,040) per QALY gained, and £24,397 (95% CI £18,169 to £82,839) per life year gained.

Figures 6.4 and 6.5 present the cost-effectiveness acceptability curves for CRT-P+MT and CRT-ICD+MT versus MT, and CRT-ICD+MT versus CRT-P+MT, respectively. Based on a willingness-to-pay threshold of £30,000 per QALY, CRT-ICD+MT had a probability of 0.40 of being cost-effective compared with CRT-P+MT treatment alone.

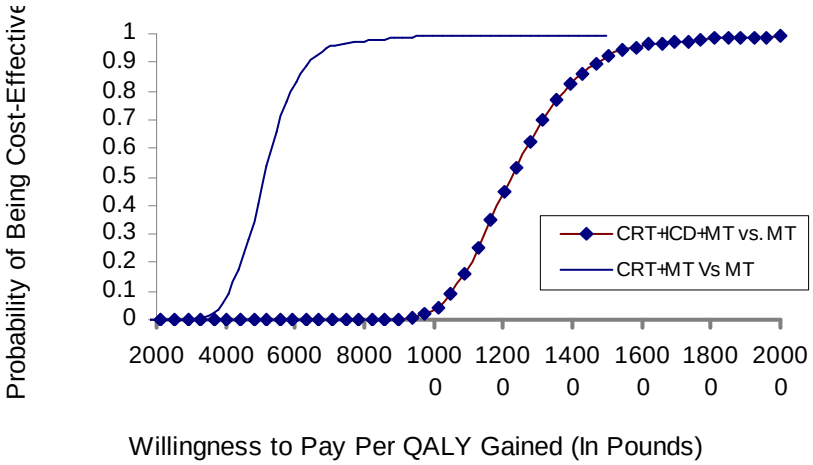

Figure 6.4 Cost-effectiveness acceptability curves of CRT (+/-ICD) vs. Medical Therapy

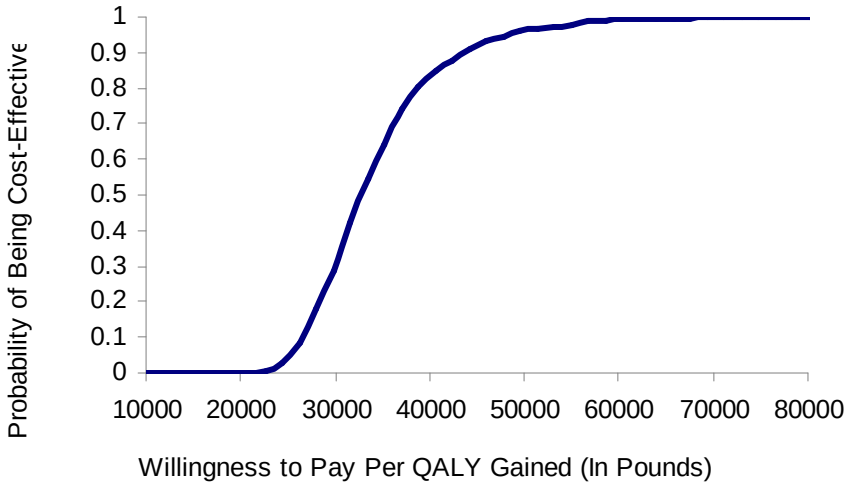

Figure 6.5 Cost-effectiveness acceptability curves of CRT-ICD vs. CRT-P

6.4.3 Analyses by cohort age

Patient groups who started treatment at age 55, 60, 70 and 75 were modelled. The results are shown in Table 6.8 and illustrated in Figure 6.6. If patients received CRT-ICD at age 60, the ICER for the comparison with CRT-P alone decreased from £32,591 to £29,048 per QALY gained, and for patients starting at age 55, the ICER fell to £25,019. For patients starting at age 75, the ICER rose to £37,808. The effect of varying the period of follow-up in the model (Table 6.9) describes the sensitivity of the results for CRT-ICD from the perspective of the analysis.

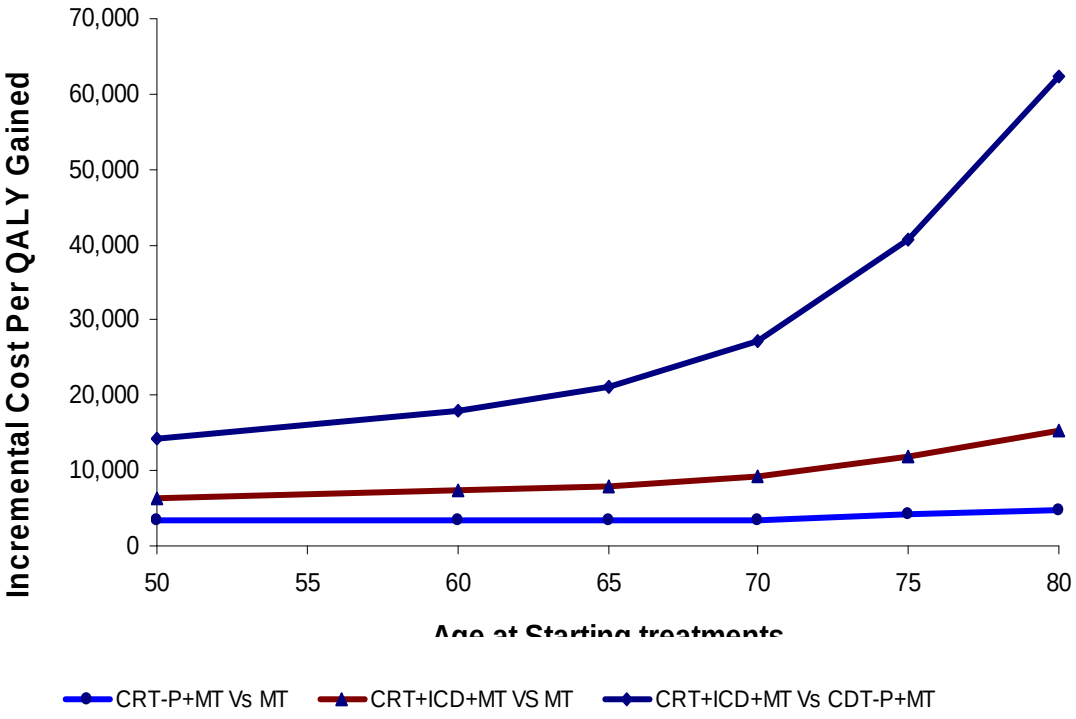

Figure 6.6 Incremental cost per QALY gained by different starting age at treatment

6.4.4 Model validity

In Table 6.9, the internal validity of the model output is reported, by estimating a variety of shorter-term effects to contrast with other models and with the within trial analysis from the CARE-HF trial. When the model was restricted to run over 29 months which was close to the trial mean follow-up periods 29.4 months, the ICER is £13,441 per QALY gained. This is close to the ICER value £13,142 (€1.47 = £1) which was estimated from the trial-based analysis (Calvert *et al.*, 2005). When the model was run over 6 years, before a battery replacement was applicable in the model, the estimated QALY gained for CRT-ICD and CRT-D compared with MT is 0.90 and 0.76 respectively. These results are similar to the estimates from Feldman (2005), which were 0.84 and 0.71 respectively.

When the trial population defined by age, gender and baseline NYHA class was entered into the model, the overall survival predicted by the model compared well with observed survival in the CARE-HF trial, as shown in Figure 6.7.

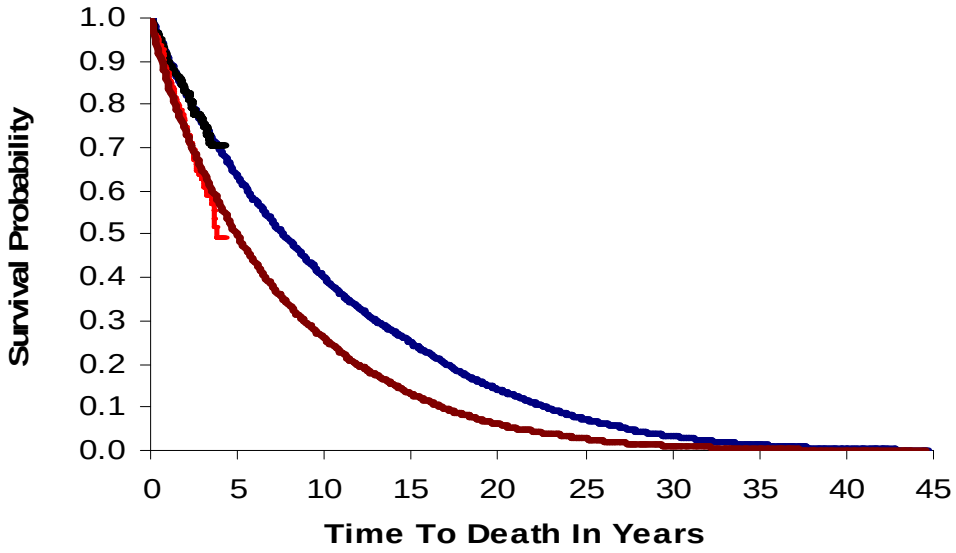

Figure 6.7 Model predicting survival with the CARE HF trial age matched cohort and the trial based Kaplan Meier estimates of survival curves

The effect of different battery life for CRT-ICD on the incremental cost per QALY is described in Table 6.10. Reducing battery life to 4 years, the cost per QALY for CRT-ICD+MT versus CRT-P+MT was increased to £51,769. Conversely, increasing battery life to 8 years reduced the cost per QALY for this to £29,246.

6.5 Discussion

This chapter has presented a full illustration of a case study in model-based analysis with input data populated from a clinical trial (CARE-HF). Parametric survival curves of time to hospitalisation and time to sudden death were adopted in deriving long term baseline survival

functions. The application of adjusting time dependent risk of events in a Markov modelling framework was shown in detail. Death due to other causes was separated, traced and modelled by using UK life table data. The additional benefit of ICD was investigated and different age cohorts at the time of treatment were explored and discussed.

For the base case, CRT-P appears a highly cost-effective addition to medical therapy among eligible patients. CRT-ICD+MT also appears to be cost-effective compared to medical therapy. From a life-time perspective, assuming a reasonable life expectancy when receiving effective treatment for heart failure, CRT-P+MT appeared cost-effective in all age groups. The cost-effectiveness of CRT-P+MT for patients in the 8th decade of life may seem surprising. This gain reflects a substantial benefit on quality of life among survivors, and some increase in longevity. The cost-effectiveness of CRT-ICD+MT is substantially greater in younger subjects, due to the longer potential period when the subject is at risk of sudden death. The cost-effectiveness of CRT-ICD+MT compared to CRT-P+MT was lower in older people partly because these treatments exert similar effects on quality of life and because older patients were more likely to die of other problems if sudden death was prevented. Varying the period of follow up in the model (Table 6.7) indicates the sensitivity of the results for CRT-ICD+MT to the duration of follow-up being considered, effectively the duration of the patients exposure to the risk of sudden death. It also indicates the similarity of the model results to the previously reported within-trial analysis.

This model derived analysis extends the previously published within trial analysis based upon 29.4 months of mean follow up. It also further advances the work described in COMPANION cost-effectiveness analysis which provided estimates of benefit at 7 years (Feldman *et al.*, 2005),

which are similar to those observed in this model at 6 years. In addition, this work examines the incremental cost-effectiveness ratio associated with adding an ICD component to CRT therapy.

The analysis has a number of strengths. The existing clinical trials provide considerable evidence for the long-term effectiveness of both CRT-P and CRT-ICD but most patients were alive and many felt well at the end of the trials. Patients' treatment does not cease at the end of the trial and it is inappropriate to assume that benefits cease at that point. In taking a life-time approach, important issues, such as device replacement, which none of the existing trials have had long enough follow-up periods to address were considered. Economic modelling also enables the inclusion of data and other evidence from a range of sources in order to examine health policy questions (Salkeld *et al.,* 2004).

There are a number of limitations to this analysis. The analysis is based upon simulation rather than the direct observation of event rates achieved in a randomised trial, albeit simulation that has been constructed from a large scale, long term trial in which the additional benefits of CRT-ICD are addressed using individual patient data from the CARE-HF trial to identify potentially preventable sudden deaths, and a further randomised trial of the effects of ICD on sudden death (COMPANION). Thus the current work may be considered a best-evidence synthesis of the likely cost-effectiveness of CRT-P and CRT-ICD, although the strength of that evidence is not as high as direct observation from sufficiently powered and appropriately designed randomised trials.

Furthermore, the analysis was based on patient level simulation while exploring the second order uncertainty using Monte Carlo simulation, which is computationally expensive. In the case of baseline analyses in which the model simulated for every 10,000 patients and the results were

iterated 1000 times, it consumed approximately 9 hours computing time per case. Several studies have developed methods to improve the efficiency of this type of modelling. One of those methods is Gaussian process emulation (Stevenson *et al.*, 2004). The Gaussian process uses results from the patient simulation model which is run at various input values. Then Gaussian process interpolates between these model runs to give sufficiently accurate estimates of the model results that would be obtained from any other set of inputs. O'Hagan and colleagues (2007) developed a method using ANOVA for efficient estimation of mean and variance by reducing the number of inner and outer loops. Their model was based on the algebra of analysis of variance and Bayesian statistics. The methods are simple to apply and will typically reduce substantially the computational burden when conducting Monte Carlo probability sensitivity analysis for patient-level models.

These methods have been shown to reduce the computational demand substantially for suitable models. However, the Stevenson study is based on a Gaussian process emulator which still does not replace the patient simulation model. The O'Hagan study was restricted to two treatments. Both methods are subject to further research before they can be routinely adopted in practical applications.

Several studies in the literature addressed the cost-effectiveness of CRT-P or CRT-ICD compared with medical therapy (Nichol *et al.*, 2005; McAllister *et al.*, 2001; Banz *et al.*, 2005; Feldman *et al.*, 2005; Fattore *et al.*, 2005; Calvert *et al*., 2005; Yao *et al*,. 2007; Fox *et al.*, 2007). Five of these studies were model-based analyses (Nichol *et al.*, 2004; McAllister *et al.*, 2004; Banz *et al.*, 2005; Fattore *et al.*, 2005 ; *Fox et al.* , 2007). Calvert and colleagues (2005) conducted trial-based economic evaluation alongside the CARE-HF trial. Yao and colleagues further developed a model based analysis to extrapolate the cost-effectiveness result beyond the

Care-HF trial and over patient's life time. Feldman and colleagues (2005) carried out trial-based and model-based analyses to extrapolate cost-effectiveness of CRT-P and CRT-ICD compared to medical therapy beyond the COMPANION trial to 7 years.

Previous evaluations have provided varying estimates of the cost-effectiveness of CRT-P and CRT-ICD relative to medical therapy. However, all of those studies evaluated the incremental benefit of CRT_P or CRT-ICD compared with medical therapy. Yao and colleagues published the first paper that directly addressed the cost-effectiveness of CRT-P compared to CRT-ICD. Later that year, Fox and colleagues published their Technology Assessment Report in which a model-based analysis was used to estimate the incremental cost-effectiveness of CRT-P versus CRT-ICD (Fox *et al*., 2007).

Fox and colleagues employed a Markov model to compare CRT-P and CRT-ICD directly with medical therapy and CRT-P compared with CRT-ICD over patient's life time for difference age cohort. They estimated ICER of £16,735 per QALY gained with incremental QALY at 0.70 and costs £11,630 (range £14,630–20,333). For CRT-D versus CRT-P, their result was incremental QALYs gained at 0.29 and cost at £11,689, giving an ICER of £40,160 (range £26,645–59,391) per QALY gained for a mixed age cohort. The QALYs gained are much less and ICERs are higher than the results presented in this chapter. But the differences in cost are similar. This could be explained by the fact that FOX study allowed patients on MT group to switch to ICD treatment.

A strength of the Fox study is that clinical effectiveness parameters (such as hazard ratio of sudden death and hospitalisation among difference treatments) in the model were derived from a systematic review. Resource use and costs associated with CRT and treating heart failure in

based on the published results largely from CARE-HF study (Calvert *et al.*, 2005) and CAMPION study (Feldman *et al.*, 2005).

There were several weaknesses in the Fox study. First, inadequate differentiation between patient groups in their risk of hospitalisation or sudden death; second, their work was based on published, aggregated results rather than individual patient data; final, there were structural limitations that would suggest that patient progression was not sufficiently captured. Thus the Fox paper did not clearly establish a more robust or valid result than the analysis concluded by Yao and colleagues (2007).

6.6 Conclusion

The model concluded that long-term treatment with CRT-P+MT appears cost-effective compared to medical therapy alone. The model provided a flexible way of answering several important questions, including: what is the additional benefit in adding ICD into the CRT?, and what were the implications of battery replacement assumptions at different time points over the patient's life? The model was validated by observed survival in the trial when trial population data was entered into the model.

In the next chapter, a new case study of model-based analysis populated by input trial data will be presented.

Table 6.1 Input value and distributions

Table 6.1a Implantation history (inclusive of CRT and control group in CARE-HF)					
	Expected Rate	**Success**	**Failed**	**Total**	**Distributions**
First attempt	0.87	409	60	469	Beta
Second attempt	0.86	62	10	72	Beta
Third attempt	0.80	8	2	10	Beta

Table 6.1b Transition probability in first month after implant between NYHA Class					
CRT(±ICD)					
	NYHA class I	**NYHA class II**	**NYHA class III**	**NYHA class IV**	**Distributions**
NYHA class III	0.298	0.459	0.227	0.016	Dirichlet (114.96;177.18;87.54;6.33)
NYHA class IV	0.091	0.455	0.409	0.045	Dirichlet (2.34;10.7;9.66;1.3)
Medical Therapy					
NYHA class III	0.103	0.303	0.528	0.067	Dirichlet (38.75;114.15;198.97;25.13)
NYHA class IV	0.000	0.200	0.600	0.200	Dirichlet (0.25;5.65;16.45;5.65)

Table 6.1c Long term monthly transition probability between NYHA Class					
CRT(±ICD)					
NYHA class in current cycle	**NYHA class I**	**NYHA class II**	**NYHA class III**	**NYHA class IV**	**Distributions**
NYHA class I	0.906	0.075	0.016	0.003	Dirichlet (92.44;7.70;1.60;0.26)
NYHA class II	0.067	0.896	0.033	0.004	Dirichlet (92.44;7.70;1.60;0.26)
NYHA class III	0.007	0.121	0.864	0.009	Dirichlet (0.54;9.64;69.13;0.68)
NYHA class IV	0.048	0.048	0.181	0.723	Dirichlet (0.24;0.24;0.90;3.62)
Medical Therapy					
NYHA class I	0.7956	0.1245	0.0738	0.0061	Dirichlet (28.1;4.61;2.83;0.46)
NYHA class II	0.0710	0.8448	0.0765	0.0077	Dirichlet (7.63;88.11;8.21;1.05)
NYHA class III	0.0047	0.0893	0.8845	0.0216	Dirichlet (1.09;16.32;159.46;4.13)
NYHA class IV	0.0000	0.1064	0.1064	0.7872	Dirichlet (0.25;2.8;2.8;19.14)

Table 6.2 Probabilities of events and associated distributions

Table 6.2a Weibull baseline survival functions for Major cardiovascular events without or with hospitalisation				
Without hospitalisation				
	Value	**95% CI Lower**	**95% CI Upper**	**Distribution**
Alpha-scale	0.0058	0.005	0.006	Lognormal
Gamma-shape	0.9206	0.905	0.936	Lognormal
Unplanned Hospitalisation				
Alpha-scale	0.051	0.046	0.061	Lognormal
Gamma-shape	0.77	0.69	0.82	Lognormal

Table 6.2b Hazard ratio for major cardiovascular events without hospitalisation				
	HR	**95% CI Lower**	**95% CI Upper**	**Distribution**
CRT-P vs MT	0.522	0.318	0.858	Lognormal
NYHA Class II vs. I	1.014	0.532	1.931	Lognormal
NYHA Class III vs. I	1.014	0.519	1.978	Lognormal
NYHA Class IV vs. I	0.891	0.249	3.187	Lognormal

Table 6.2c Hazard Ratio for Hospitalisation

	HR	**95% CI Lower**	**95% CI Upper**	**Distribution**
CRT (+/- ICD) vs. MT	0.79	0.613	1.019	Lognormal
NYHA Class II vs. I	1.184	0.818	1.715	Lognormal
NYHA Class III vs. I	1.834	1.265	2.659	Lognormal
NYHA Class IV vs. I	4.991	2.974	8.376	Lognormal

Table 6.2d Death probability given hospitalisation				
	Value	**95% CI Lower**	**95% CI Upper**	**Distribution**
MT Group	0.113	39	345	Beta (39; 345)
CRT (+/-) ICD	0.074	12	162	Beta (12; 162)

Table 6.2e ICD Effect on Probability of Sudden death

hazard ratio of ICD effect	0.367	0.215	0.626	Lognormal

Table 6.2f Conditional probability of 'procedures' given unplanned hospitalisation				
CRT (+/-) ICD	**Expected mean**	**Observed**	**With continuity correction**	**Distribution**
ICU	0.0908	16	16.17	Dirichlet (16.17; 56.17; 0.17; 6.17; 10.17; 89.17)
CCU	0.3155	56	56.17	
CABG	0.0009	0	0.17	
PTCA	0.0346	6	6.17	
Transplantation	0.0571	10	10.17	
No Procedure	0.5009	89	89.17	
Medical therapy group				
ICU	0.0715	25	25.17	Dirichlet (25.17, 90.17, 1.17, 7.17, 9.17, 219.17)
CCU	0.2562	90	90.17	
CABG	0.0033	1	1.17	
PTCA	0.0204	7	7.17	
Transplantation	0.0260	9	9.17	
No Procedure	0.6226	219	219.17	

Table 6.3 Input values of costs and utilities

Utility Scores				
	Mean	**95% CI Lower**	**95% CI Upper**	**Distribution**
NYHA class I	0.815	0.781	0.850	Beta
NYHA class II	0.720	0.693	0.749	Conditional Beta
NYHA class III	0.590	0.551	0.629	Conditional Beta
NYHA class IV	0.508	0.412	0.605	Conditional Beta
Cost				
CRT-P Device and Leads	7,760			Fixed
CRT-ICD Device and Lead	32,625			Fixed
Left ventricular leads	574			Fixed
Drug Cost Per Day	5.84	5.01	6.35	Normal
Days in hospital during implantation - per procedure	3.3	3	3.6	Normal
Days in hospital due to unplanned hospitalisation (per event)	11.80	10.8	12.8	Normal
Days in ICU Per Event CRT(+/-) ICD group	5.7	5.23	6.17	Normal
Days in ICU Per Event MT group	7.6	4.85	10.35	Normal
Days in CCU Per Event CRT(+/-) ICD group	6.8	6.16	7.44	Normal
Days in CCU Per Event MT group	7.8	7.42	8.18	Normal
Days in Planned hospitalisation per event CRT(+/-) ICD group	5.68	4.59	6.76	Normal
Days in Planned hospitalisation per event MT group	7.16	4.73	9.58	Normal
Rate of planned hospitalisation CRT(+/-) ICD group	0.20	81	404	Beta
Rate of planned hospitalisation MT group	0.17	70	409	Beta

Table 6.4 Unit costs of resources use in the CARE-HF trial

Resource costs	Unit	Cost (£)
CRT or CRT-ICD procedure cost	-	1072
Hospital stay (cardiac)	Day	163
ICU stay	Day	1167
CCU stay	Day	310
Cardiac day case	Day	112
Cardiac outpatient visit	Visit	62
Primary care visit (GP)	Visit	28
Residential home (private)	Week	373
Nursing home (private)	Week	527
Rehabilitation centre	Day	179
Heart transplant	-	22 558
CABG	-	5 925
PTCA	-	2 283

**Calvert et al., 2004: Table 1 Unit costs of resources and resource use in the CARE-HF trial*

Table 6.5 Model predicted survival

	Mean life Years	First quartile	Median	Third quartile
MT	7.44	2.00	5.50	11.33
CRT+MT	10.53	4.00	9.25	15.92
CRT+ICD+MT	11.98	5.08	11.08	17.92

Table 6.6 Estimated cost and effectiveness in QALYs and life years

Strategy	Cost (£)	QALYs	Life year	Incremental life years
MT	26,572	4.08	6.10	
CRT-P +MT (vs. MT)	36,732	6.06	8.23	2.13
CRT-ICD +MT (vs. CRT-P +MT)	59,422	6.75	9.16	3.06
CRT-ICD +MT (vs MT)	59,422	6.75	9.16	0.93

Table 6.7 Incremental cost-effectiveness Ratios (per QALY and life year)

Strategy	Incremental			ICER with 95% CI	
	Cost (£)	QALYs	Life Years	£/ per QALYs	£ /per Life Year
CRT-P +MT (vs. MT)	10,160	1.98	2.13	5,128 (3,623 - 8,017)	4,769 (£3,637- 14,704)
CRT-ICD +MT (vs. MT)	32,850	2.67	3.06	13,257 (9,864 - 17,055)	10,735 (6,254 - 13,421)
CRT-ICD +MT (vs CRT-P +MT)	22,690	0.7	0.93	32,591 (24,288 - 54,040)	24,397 (18,169 -82,839)

Table 6.8 Estimated mean incremental cost per QALY for different starting ages

Starting age	Strategy	Cost	Incremental Cost	QALYs	Incremental QALYS	ICER
55	MT	£30,282		4.72		
	CRT-P +MT (vs. MT)	£43,404	£13,122	7.42	2.7	£4,856
	CRT-ICD +MT (vs. MT)	£71,245	£40,963	8.54	3.81	£10,751
	CRT-ICD +MT (vs. CRT-P)	£71,245	£27,841	8.54	1.11	£25,019
60	MT	£28,426		4.39		
	CRT-P +MT (vs. MT)	£40,591	£12,165	6.86	2.47	£4,927
	CRT-ICD +MT (vs. MT)	£65,638	£37,212	7.72	3.33	£11,175
	CRT-ICD +MT (vs. CRT-P)	£65,638	£25,047	7.72	0.86	£29,048
65	MT	£26,572		4.08		
	CRT-P +MT (vs. MT)	£36,732	£10,160	6.06	1.98	£5,128
	CRT-ICD +MT (vs. MT)	£59,422	£32,849	6.75	2.68	£12,257
	CRT-ICD +MT (vs. CRT-P)	£59,422	£22,690	6.75	0.7	£32,591
70	MT	£23,807		3.62		
	CRT-P +MT (vs. MT)	£32,304	£8,497	5.25	1.63	£5,215
	CRT-ICD +MT (vs. MT)	£52,387	£28,580	5.78	2.16	£13,231
	CRT-ICD +MT (vs. CRT-P)	£52,387	£20,083	5.78	0.53	£37,808
75	MT	£21,054		3.16		
	CRT-P +MT (vs. MT)	£27,671	£6,617	4.38	1.22	£5,430
	CRT-ICD +MT (vs. MT)	£44,922	£23,867	4.73	1.56	£15,299
	CRT-ICD +MT (vs. CRT-P)	£44,922	£17,251	4.73	0.35	£49,863

Table 6.9 Estimated mean incremental cost per QALY at different durations of follow up for the base case population

Time Frame	Strategy	Cost	Incremental Cost	QALYs	Incremental QALYS	ICER
Life Time	MT	£26,572		4.08		
	CRT-P +MT (vs. MT)	£36,732	£10,160	6.06	1.98	£5,128
	CRT-ICD +MT (vs. MT)	£59,422	£32,849	6.75	2.68	£12,257
	CRT-ICD +MT (vs. CRT-P)	£59,422	£22,690	6.75	0.7	£32,591
6 Years	MT	£17,066		2.52		
	CRT-P +MT (vs. MT)	£20,897	£3,831	3.28	0.76	£5,051
	CRT-ICD +MT (vs. MT)	£32,723	£15,480	3.42	0.90	£17,200
29 months	MT	£9,359		1.28		
	CRT-P +MT	£12,783	£3,424	1.53	0.25	£13,441

Table 6.10 Estimated mean incremental cost per QALY at different battery life for CRT-ICD device

Battery life in years	Strategy	Cost	Incremental Cost	QALYs	Incremental QALYS	ICER
4	MT	£26,565		4.07		
	CRT-P +MT (vs. MT)	£36,551	£9,987	6.09	2.01	£4,964
	CRT-ICD +MT (vs. MT)	£71,979	£45,414	6.77	2.70	£16,820
	CRT-ICD +MT (vs. CRT-P)	£71,979	£35,427	6.77	0.68	£51,769
5	MT	£26,393		4.05		
	CRT-P +MT (vs. MT)	£36,906	£10,513	6.16	2.10	£4,996
	CRT-ICD +MT (vs. MT)	£66,422	£40,029	6.84	2.79	£14,347
	CRT-ICD +MT (vs. CRT-P)	£66,422	£29,516	6.84	0.68	£43,233
6	MT	£26,634		4.09		
	CRT-P +MT (vs. MT)	£36,620	£9,987	6.07	1.98	£5,043
	CRT-ICD +MT (vs. MT)	£62,099	£35,465	6.77	2.68	£13,233
	CRT-ICD +MT (vs. CRT-P)	£62,099	£25,478	6.77	0.7	£36,232
7*	MT	£26,572		4.08		
	CRT-P +MT (vs. MT)	£36,732	£10,160	6.06	1.98	£5,128
	CRT-ICD +MT (vs. MT)	£59,422	£32,849	6.75	2.68	£12,257
	CRT-ICD +MT (vs. CRT-P)	£59,422	£22,690	6.75	0.7	£32,591
8	MT	£26,646		4.10		
	CRT-P +MT (vs. MT)	£36,562	£9,916	6.10	2.00	£4,958
	CRT-ICD +MT (vs. MT)	£57,153	£30,507	6.80	2.70	£11,299
	CRT-ICD +MT (vs. CRT-P)	£57,153	£20,591	6.80	0.70	£29,246

CHAPTER 7 CASE STUDY 3: NEBIVOLOL TREATMENT

7.1 Introduction

In the previous chapter, an application of a modelling approach of economic evaluation based on the CARE-HF trial was presented and discussed. This chapter describes an economic evaluation of a beta-blocker in chronic heart failure for elderly patients. It seeks to provide further support for the application of modelling based analysis in economic evaluations using clinical trial data.

In Chapter 2 the type of the modelling was classified as decision trees, Markov models and individual sampling methods. It was argued that a Markov model is suitable for modelling chronic disease with recurrent events. When the simulation methods were discussed, it was stated that individual level simulation methods provided more flexibility in reflecting the influence of individual attributes.

A Markov model represents stochastic processes that evolve over time. A cohort of patients is classified by a finite number of states that are mutually exclusive and exhaustive. Patient movement among the Markov states over time is defined by a set of transition probabilities. Chapter 5 addressed the primary limitation of a Markov model of non–memory, whereby the transition probabilities do not depend on how long a patient has been in the current state. With modern computing capabilities, an individual simulation model can be developed based on a Markov modelling framework, in which additional variables can be attached to each patient to record duration of treatment and changes in risk profile, updating transition probabilities where appropriate. Thus, when conducting Monte Carlo simulation to evaluate a Markov model, a set

of tracker variables can be created to carry a patient's baseline characteristics and to monitor duration on treatments. By doing so, each patient may be followed through the model pathway individually and their transition probabilities or risk profiles can be updated at any given time.

This chapter presents a cost-effectiveness analysis of the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Senior population with heart failure (SENIORS). The study aimed to compare the costs and outcomes for nebivolol and standard care in elderly patients with heart failure. An individual simulation model, based on a Markov modelling framework, is presented. The analysis was conducted using the computer program TreeAge Pro 2007 (TreeAge Software, Williamstown, MA). The reason for choosing individual level simulation was to simulate the trial population and project the cost-effectiveness beyond the trial period. This chapter is based on a published study (Yao *et al.*, 2008) but the analysis presented in the thesis is an extension of the original work.

7.2 Background

Heart failure is a common condition with disabling symptoms and a poor prognosis. In Europe, around 1% of persons are affected, with both incidence and prevalence increasing sharply with age (Cowie *et al.*, 2002; Cowie *et al.*,1997; Ho *et al.*, 1993). The condition accounts for about 2% of all health care spending (Stewart *et al.*, 2002).

Several large randomised trials and meta analyses have indicated that beta-blockers reduce the risk of hospital admissions for worsening heart failure and the risk of death in patients with mild to moderate heart failure (Hall *et al.*, 1995; Packer *et al.*, 1996; The CIBIS-II Investigators and

Committees 1999). Shibata and colleagues (2001) conducted a systematic review which identified 22 beta-blocker trials with the mean patient age at baseline for all the studies ranging between 48 and 67 years.

7.3 Overview of SENIORS

SENIORS was a randomised, double-blind, parallel-group, multicentre, international trial comparing nebivolol with standard care in elderly patients with heart failure on standard therapy who were not treated with beta-blockers (Flather *et al.,* 2005). Eligible patients had to be aged 70 years or older, provide written informed consent, and have a clinical history of chronic heart failure with at least one of the following features: documented hospital admission within the previous 12 months with a discharge diagnosis of congestive heart failure or documented left ventricular ejection fraction less than 35% within the previous 6 months. Nebivolol or standard care tablets were provided in identical packaging and tablet appearance. The first patient was enrolled in September 2000, the last patient in December 2002. The date of study end was specified as 15 November 2003 for all patients. A total of 2135 patients were enrolled from 11 countries. A total of 2128 patients, 1067 in the nebivolol group and 1061 in the standard care group, were followed in the trial. Baseline drug usage was recorded within the trial with Ace inhibitors used in 82.1% of subjects at baseline. Angiotensin receptor blockers were used in 6.6% of subjects, and aldesterone antagonists were used in 27.6%.

The clinical study demonstrated the direct health benefits in elderly patients with chronic heart failure (CHF) treated with nebivolol compared with standard care. The primary outcome of death or cardiovascular hospital admission occurred in 332 patients (31.1%) on nebivolol compared

with 375 (35.3%) on placebo [hazard ratio (HR) 0.86, 95% CI 0.74–0.99; P = 0.039]. These benefits included a 14% reduction in the primary outcome – composite of all cause mortality or cardiovascular hospital admission (time to first event).

The aim of this chapter was to evaluate the cost-effectiveness of nebivolol compared with standard care in elderly patients with heart failure. A Markov model based on individual patient simulation was developed, populated with input data from SENIORS. Estimates have been provided for the incremental cost per life year and cost per QALY gained based on the SENIORS study.

7.4 Model description

A Markov model (Sonnenberg, 1993) based on individual simulation was constructed. The model inputs were populated from the clinical data in the SENIORS trial. In the model structure, the treatment effect and age component on mortality are separated. Death is sub-classified by causes of death, including death due to heart failure, sudden death and other mortality. The model serves to extrapolate trial periods to patient's life time. It also extrapolated trial population to different settings – such as a much younger group and enables comparisons with other treatment effects.

Health states were defined by New York Heart Association (NYHA) classification and death. A monthly cycle length is used in the model. Figure 7.1 illustrates the model structure at a given NYHA class and a given cycle. During each cycle patients could die, be hospitalised for cardiovascular disease, or remain stable. Causes of death were sub categorised as: death due to

other causes, sudden death, or cardiovascular (CV) death. The risk for each event depended upon how long a patient was on treatment and their NYHA class at that cycle. Risk for other causes of death depended upon the patient's age and gender.

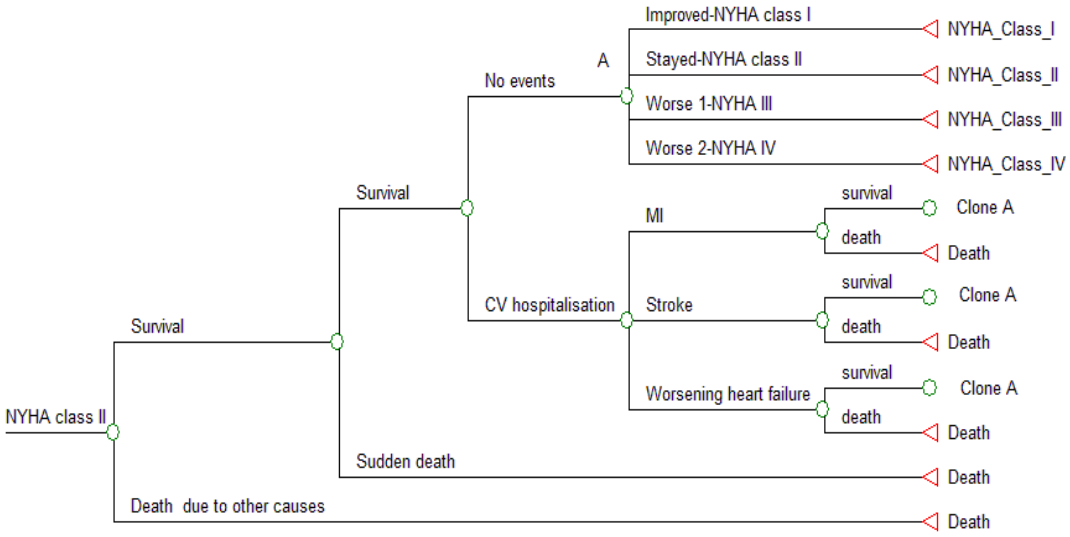

Figure 7.1* Basic schematic diagram of the model structure at a given NYHA class II

**The structure of the model for other NYHA classes was identical but with different transition probabilities and risk of unplanned hospitalisation. Each clone indicates that the patient will follow the pathway indicated at point A on the figure.*

Admissions to hospital due to CV causes were classified into myocardial infarction, stroke or worsening heart failure, in which risk of in-hospital death was assessed. The risk of each event in a given cycle depended upon the patient's baseline characteristics, duration of treatment and NYHA class. If no events occurred (e.g. where no death or hospitalisation event occurred) a patient was classified as being in a stable condition and the patient's NYHA class could improve, remain constant or deteriorate. Transition probabilities among NYHA class were assumed to be fixed over time when a patient was in a stable disease state, but the probability of remaining in a stable disease state reduced over time.

At the start of the simulation, a cohort of 10,000 patients was generated. Each patient was characterised by age, gender and NYHA class. A maximum tolerated beta-blocker dose for each individual was also specified. Patients entered the model for different treatment options in parallel. Patients' baseline characteristics defined their profile of risk of specific events.

7.5 Model assumptions

The SENIORS study (Flather *et al.*, 2005) recruited an elderly heart failure population with a mean age at baseline of 76.1 years. In order to study drug effects on different population cohorts, the cause of death was separated by age, based on the UK general population mortality rate, excluding cardiovascular (type) deaths. The study found that nebivolol treatment reduced cardiovascular (CV) related hospitalisation and CV related death, and had no effect on non-CV events. By identifying the cause of death in this way in the model we can compare directly the effect of nebivolol in different age cohorts.

Any CV death that occurred in hospital involved a hospital stay cost. Sudden death events that happened outside of hospital are assumed to have no additional costs.

7.6 Input data

Tables 7.1-7.6 list all input values used in the model. The following sub-sections provide details on how those input values were derived and estimated.

7.6.1 Estimating the baseline functions and risk

Estimated baseline functions of the time to sudden death and the time to hospitalisation were based on the parametric survival analysis. Five parametric survival functions were fitted to observed time-to-event data using SAS software. Akaike information criterion (AIC) was employed in choosing the most appropriate model. Weibull distribution functions were selected for both of the time-to-events survival time as they had the best model fit based on the Akaike Information Criterion (Appendix 4). The baseline survival function of the time to the first CV hospitalisation in standard care was estimated from SENIORS individual patient data. A Weibull function was fitted for the baseline with a scale parameter of 0.0386 and shape parameter 0.7957 (Table 7.1). Similarly parametric survival analysis was employed to estimate survival property of time to sudden death based on individual data from the trial. AIC indicated that a Weibull function was the best fitted one for the baseline survival function on standard care. It was estimated that a scale parameter of 0.007 and shape parameter 0.8535 for the function.

The hazard ratios for time to sudden death and time to CV hospitalisation were reported previously for nebivolol treatment compared to standard care ((Flather, *et al.*, 2005; Yao *et al*., 2008). Table 7.2 presents the hazard was 0.618 (95%CI 0.420 to 0.910) and 0.8849 (95% CI 0.7464 to 1.0492) for sudden death and hospitalisation respectively for nebivolol compared with standard care. The hazard ratios of NYHA class I/II compared with NYHA class III/IV on sudden death and CV hospitalisation were estimated from SENIORS study data. The hazard ratio for sudden death (NYHA class III/IV as base) was 0.511 (95% CI 0.346 to 0.754) and for CV hospitalisation was 0.5728 (95% CI 0.481 to 0.682). The same hazard ratios of NYHA class were applied to all treatment groups.

7.6.2 Death due to other causes

The model was based on individual simulation. In the base case scenario, all patients started at age 70. Gender and NYHA class profiles were simulated based on SENIORS trial data. Tracker variables were employed to follow patients' ages. Mortality for other causes was derived from the UK population based on age and gender specific mortality excluding cardiac related death.

7.6.3 Estimates of transition probabilities among NYHA class

The SENIORS trial collected individual patient information on NYHA class at baseline and every visit thereafter. It was assumed that the transition between the first visit in the maintenance phase and the following visit was three months. Transition probabilities based on those two data points were estimated. Monthly transition probabilities were derived by assuming constant transition probabilities using matrix algebra (Table 7.3).

7.6.4 Estimates of health utility scores

The SENIORS trial did not identify a difference in the distribution of NYHA classes between the treatment and standard care groups, and provided no evidence of improvement or deterioration in NYHA classes between the two treatment groups. Utility scores were applied on the basis of patients' NYHA class regardless of treatment assignment. Utility scores on each NYHA class (Table 7.4) were based on the reported results of the CARE-HF study (Yao *et al.*, 2007). Life years were weighted by the utility scores to estimate QALYs.

When a patient experienced a CV hospitalisation a disutility of 0.1 was applied for that event. This assumption was based on the difference in utility scores between two consistent NYHA classes.

7.6.5 Estimating costs

The economic analysis was conducted from the National Health Service (NHS) UK perspective, hence only costs relevant to the NHS were included. Costs of CV hospitalization, drug costs and GP visit costs were included. The cost of treatment for severe adverse events was captured in CV hospitalisation. It was assumed that any difference due to nebivolol treatment was captured by the different risks of cardiovascular hospitalisation. Tables 7.5 and 7.6 show the all relevant costs.

Drug costs

The dosage of a patient on nebivolol treatment was based on the maximum dosage, which patients maintained during the treatment periods in the SENIORS study (Table 7.5). The unit costs of nebivolol were taken from the British National Formulary (BNF, 2007). Cost per mg was derived based on the available information on specific dosage.

All patients on both treatments incurred costs for other relevant cardiac medication. The baseline daily cost was estimated from case notes which were collected alongside the SENIORS trial data. Unit costs were based on the British National Formulary (BNF, 2007). Medication costs were based on all available information from the SENIORS trial using individual patient data usage and dosage. Missing doses were imputed using the median value on the specific items. The mean daily cost in pounds was estimated to be £0.493, the median £0.302 and

standard deviation 0.969. The same value was applied for baseline drug cost to both treatment groups. For probability sensitivity analysis, a lognormal distribution was applied to consider the uncertainty related to daily baseline drug costs.

GP visit costs

Monthly GP visits were assumed for nebivolol patients for the first 3 months. Subsequently, patients were assumed to have a GP visit every three months. The cost per GP visit was multiplied by the number of visits. For the standard care group we assumed one GP visit every three months.

CV Hospitalisation costs

Hospitalisation costs included a subgroup of hospitalisations due to stroke, MI and worsening heart failure in which all other CV events and worsening heart failure events were included. Rates of events were derived from the SENIORS trial and the National Schedule of Reference Costs (Department of Health, 2008) was applied. Primary care per visit and out-patient attendance costs, were based on the Unit Costs of Health and Social Care (Curtis, *et al.*, 2006), a standard source.

In the SENIORS trial, no outpatient visit data was available. It was assumed that every CV hospitalisation was followed by two outpatient attendances. The same cost was applied for all treatment groups where a patient was admitted to hospital for a CV cause, regardless of which treatment group they were in. Those costs are presented in Table 7.6.

7.7 Base case

For the base case, the analysis considered a cohort aged 70 and estimated the lifetime cost per life year. This duration was chosen to capture the whole distribution of survival benefits. A variety of treatment group characteristics, for their implication on cost-effectiveness, were investigated. A discount rate of 3.5% annually for costs and benefits was adopted over longer time periods.

7.8 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (Briggs, *et al.*, 1994) across key input values was conducted. The key input values and their respective distributions used to examine second order uncertainty are listed in table 7-6. Each set of random input values was drawn based on their specific distributions for every 10,000 patients and the results were iterated 1,000 times. This provided us with confidence intervals to illustrate uncertainty for cost per life gained and cost per QALY gained.

The choices of distributions for particular parameters were based on a general approach by using the distributional form that relates to the estimation of the parameter of interest (Claxton, *et al.*, 2005). For binormal data, a beta distribution was used for binormal data and Dirichlet distribution function were used for multinormal data. Those are standard and theoretically justified (Briggs, *et al.*, 2006).

All treatment effects such as hazard ratios were estimated from a Cox proportional hazard model in the log hazard scale. Therefore log-normal distributions were assigned to all hazard ratios for unplanned hospitalization, sudden death and NYHA classes. For different events of hospitalisation, a Dirichlet distribution was assigned.

In the case of unit cost of different hospitalisation events, triangle distribution functions were used, due to cost data being positive. Normal distribution would not be appropriate. Lognormal or Gamma distribution may better reflect the potential variability on those items. However, only mean and upper and lower quartile data were available. Defining these distributions would require additional information on the variability. Here the choice of triangular distributions as a convenience

The choice of the number of runs was based on an iterative process. In the case of 1,000 for 2nd order uncertainty, an initial 500 runs were tried in which the result showed a high degree of variability. Then the number was increased to 1,000, at which point reasonably stable results were achieved from different runs. Similarly, the choice of 10,000 on the 1st order uncertainty went through the same trial-and-error approach. The chosen number of runs is consistent with current practice as noted by Andronis and colleagues (2009).

7.9 Result

7.9.1 Base case

Table 7.7 describes the costs, life years and QALYs accrued by treatment groups. For the standard care and nebivolol groups, the total cost per patient was £4,560 and £6,284, mean life-years were 7.547 and 8.378, and QALYs were 5.194 and 5.843 respectively. The probabilistic

sensitivity analysis provided an incremental cost of £1,742, incremental life years were 0.831 and QALYs were 0.649. Thus the incremental cost-effectiveness ratio was £2,074 (95% CI 1,947 to 1,947) per life year, and £2,656 (95% CI 2,814 to 2,814) per QALY.

Figure 7.2 describes the cost-effectiveness acceptability curves. At a given willingness to pay per QALY of £20,000 the probability of treatment of nebivolol being cost effective compared to standard treatment is 100%.

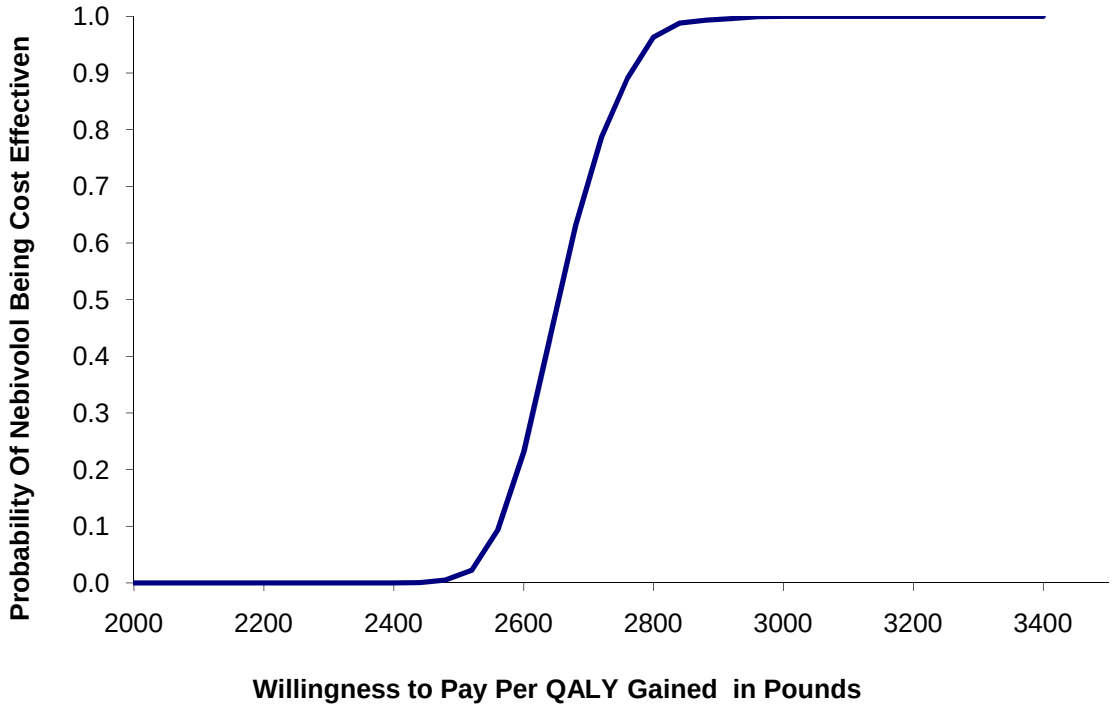

Figure 7.2 Cost-effectiveness acceptability curve of nebivolol compared with standard treatment

7.9.2 Sensitivity analysis

Sensitivity analysis for different starting ages of treatment is described in Table 7.8 and Figure 7.3. The incremental cost-effectiveness ratios for life years and QALYs increase with age. However, they are all well below the UK bench mark of willingness to pay of £20,000 per QALY.

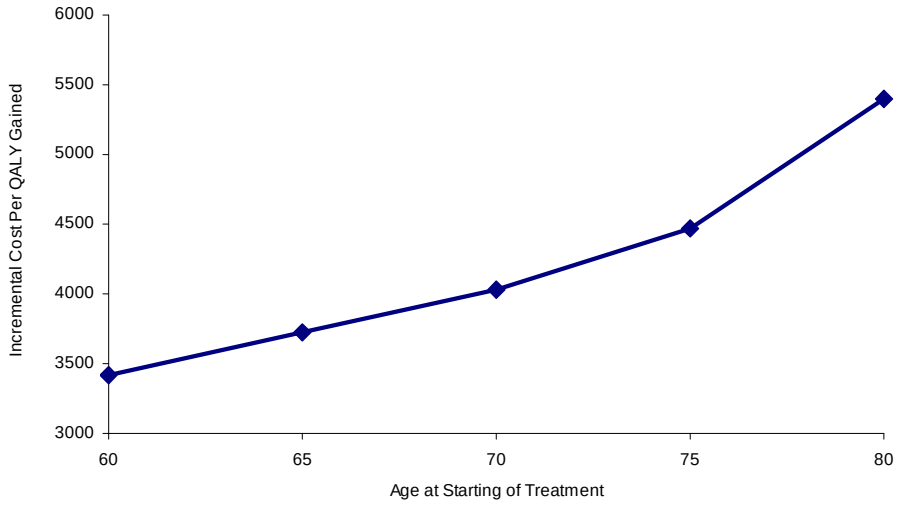

Figure 7.3 Increment cost per QALY at different ages of starting of nebivolol treatment in Pounds

7.9.3 Model Validity

The internal validity of the model output was assessed by estimating the shorter term effects and comparing these with the trial analysis from SENIORS.

Firstly, the model was restricted to 21 months with a mean age at the start of treatment of 76.1 years as per the population profile specified in the SENIORS study. The results of the model-based analysis are presented in Table 7.9. The event rates for all cause mortality and CV

hospitalisation were almost identical to the trial-based analysis. Sudden death was slightly lower than the trial-based analysis (which is itself estimated with uncertainty). This data supported the assumption that sudden death only occurred outside hospital, with any sudden death occurring in hospital included in the CV hospitalisation episodes. Total cardiac related deaths estimated in the model were also confirmed by the trial based results.

Secondly, the model was further validated by running different lengths of treatment by using the SENIORS population. The all cause mortality rate (Figure 7.4) and all clinical events at different time points are presented in Table 7.10. These results reinforced the robustness of the model.

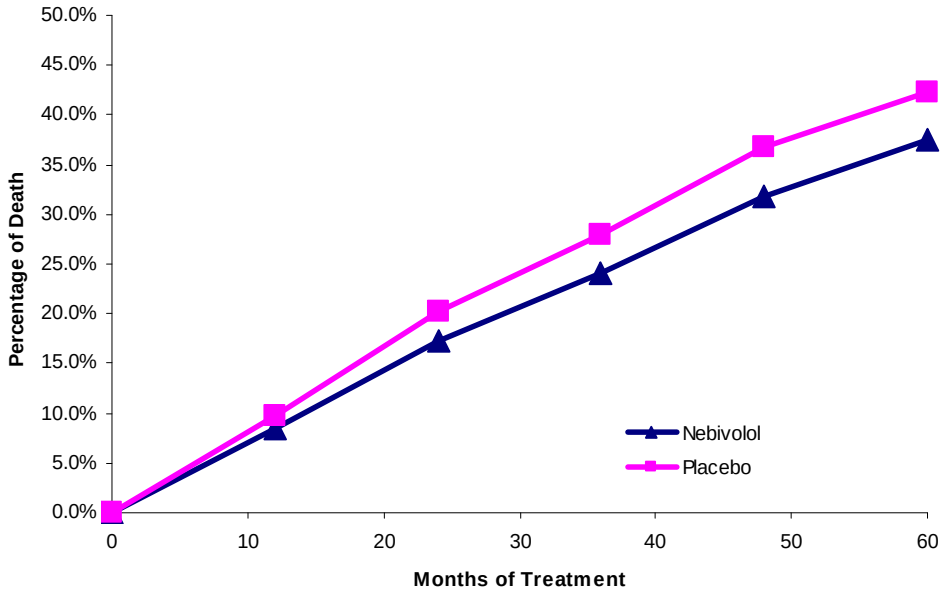

Figure 7.4 Model predicted mortality rate at different length

7.10 Discussion

This chapter described a practical application of using a Markov modelling framework and a parametric survival function in extrapolating beyond a trial. The primary objective of this work was addressed, employing a model-based analysis in which input data was populated from a trial. By employing individual simulation, a trial population can be mirrored and the result can be validated from model based analysis and observed clinical events. The methodology implication proposed in chapters 4 and 5 was revisited and illustrated. The flexibility of using a Markov model to extrapolate cost-effectiveness implications beyond a trial was emphasised.

In this chapter, the cost-effectiveness of nebivolol were estimated in an elderly population with chronic heart failure, with severity and patient characteristics based upon the SENIORS trial. This is the first study which addressed the cost-effectivenss of beta-blocker treatment in elderly patients group. It was found that the routine use of nebivolol in this population would be a cost-effective strategy. The estimated results from the model were validated against the actual observed events from the SENIORS study.

SENIORS enrolled a population of elderly heart failure patients with a wide range of ejection fraction, including about one third with ejection fraction greater than35%. There were about 1300 patients aged 70 or over in the MERIT-HF study (The MERIT-HF Study Group, 1999) which evaluated metoprolol-XL. There was reasonable evidence of efficacy of metoprolol XL in this elderly subgroup, although data was not published separately, and MERIT did not include patients with ejection fraction >40% in contrast to SENIORS. Other trials, including the carvediolol studies and CIBIS-II (The CIBIS-II Investigators and Committees, 1999), do not

have large enough numbers of patients to provide reasonable evidence of efficacy of these beta-blockers in the elderly. Thus SENIORS is the only large heart failure trial to specifically address the role of beta-blockers in the elderly and to provide clear evidence of clinical and cost-effectiveness.

One of the strengths of this analysis was the utilisation of individual patient data from the SENIORS trial in populating the economic model. A further strength is the appropriate sophistication of the model employing tracker variables, which extend the Markov framework to enable the risk of events to be varied with time. In addition, the model was based on individual patient simulation. Each individual was generated with a specific profile at the start of the simulation. This provided considerable flexibility for the model to extrapolate beyond the trial periods both in time horizon and for different patient characteristics.

Several other studies suggest that beta-blockers for heart failure could be cost-effective or even cost saving to society (Caro et al., 2005; Cowper et al., 2004; Levy et al., 2001; Vera-Llonch et al., 2001). Levy and colleagues (2001) demonstrated the incremental cost-effectiveness ratios (ICERs) of $4,140 and $8,394 per life-year gained when carvedilol or metoprolol are used compared to conventional therapy, respectively. for subjects aged 60 years. Cowper and colleagues (2004) estimated that beta-blocker therapy increased survival by 0.3 years per patient and reduced societal costs by $3959 per patient over 5 years. Caro and colleagues (2005) predicted the positive effect of metoprolol succinate on mortality and morbidity, as demonstrated in the MERIT-HF trial leading to substantial savings in patients with a mean age of 63.7 years over 2 years, from a US perspective.

However, no other study has addressed the cost-effectiveness of beta-blocker treatment in elderly patients. Since SENIORS was targeting a population that is not commonly included in clinical trials, the current study reported the potential health economic benefit of a strategy which incorporated routine nebivolol use for elderly patients with heart failure.

A potential limitation of this study is that the comparator for this analysis is standard care and the additional question of the appropriateness of nebivolol or an alternative beta-blocking agent in this population has not been addressed.

Furthermore, the analysis was based on patient level simulation while exploring the second order uncertainty using Monte Carlo simulation, which is computationally expensive. Methods that can be used to improve the efficiency of this type of modelling (O'Hagan *et al.*, 2007 & Stevenson *et al*., 2004).) have not been explored in this study

As discussed above, the only other beta-blocker with reasonable evidence of efficacy in the elderly is metoprolol XL which is not available in the UK. The use of other beta-blockers including carvedilol and bisoprolol in elderly patients is largely based upon evidence in younger patients with a low ejection fraction. Further, no other beta-blocker has been evaluated in a directly similar population to that considered in SENIORS (in particular the age structure) which raises questions about the appropriateness of comparing nebivolol (established therapy in an elderly population) with an alternative therapy without direct evidence supporting its use in that population.

However, such a comparison could be realised by modelling-based analysis. For example, there are no direct head-to-head comparison trials between nebivolol and carvedilol, but individual trials in which both nebivolol and carvedilol have been studied compared with placebo are, respectively, the SENIORS (Flather *et al.*, 2005) and the CAPRICORN (The CAPRICORN Investigators, 2001) trials. The model developed in this chapter could be adopted to assess the cost-effectiveness of nebivolol vs. carvedilol. This thesis focused on economic evaluation based on a randomised clinical trial. Indirect comparison of nebivolol with other beta-blocking agents was beyond the scope of this work.

7.11 Conclusion

In conclusion, this analysis indicates that nebivolol appears cost-effective when compared with standard treatment thresholds (Appleby et al., 2007) and indicates an incremental benefit with the use of nebivolol in this setting. This finding should be interpreted in the context of the available evidence for the efficacy of different agents in different settings. In particular, SENIORS provided large scale evidence on the effectiveness of nebivolol in an elderly population with heart failure with or without evidence of left ventricular systolic dysfunction.

Table 7.1 Baseline survival function of time to first hosiptalisation event and time to sudden Death

	Scale	Shape	Distribution
Weibull Baseline hazard Function of Hospitalisation (monthly)	0.0386	0.7957	Fixed
Weibull Baseline hazard function of sudden death (monthly)	0.007	0.8535	Fixed

Table 7.2 Hazard ratio of hospitalisation and sudden death of Nebivolol vs. standard treatment

	Hazard ratios (Expected Mean)	95% CI Upper	95% CI Lower	Distribution
Time to First Hospitalisation Event	0.8849	0.7464	1.0492	Lognormal
NYHA class I/II vs. NYHA class III/IV	0.5728	0.4810	0.9147	Lognormal
Time to Sudden Death	0.618	0.420	0.910	Lognormal
NYHA class I/II vs. NYHA class III/IV	0.511	0.346	0.754	Lognormal

Table 7.3 Transition probabilities among NYHA class (monthly)

From / to	NYHA Class				Distribution
	I	II	III	IV	
NYHA class I	0.977	0.019	0.004	0.000	Dirichlet (60.25, 1.25,0.25,0.25)
NYHA class II	0.008	0.981	0.010	0.001	Dirichlet (10.25,1169.25,12.25,1.25)
NYHA class III	0.000	0.034	0.959	0.006	Dirichlet (0.25,1.25,5.25,41.25)
NYHAclass IV	0.000	0.000	0.055	0.945	Dirichlet

Table 7.4 Utility scores and initial distribution of NYHA class

	NYHA Class				Distribution
	I	II	III	IV	
Utility Scores	0.815	0.72	0.59	0.508	Conditional Beta
Initial distribution	0.029	0.564	0.387	0.02	Dirichlet (61;1200;824;43)

Table 7.5 Drug dosage and cost

Maintenance dose (mg)	Number People	Percentage	Unit cost (£)/mg	Distribution on Dosage
1.25	69	12.4%	0.0663	Dirichlet (69 73 127 688)
2.5	73	7.2%	0.0663	
5	127	12.5%	0.0663	
10	688	67.9%	0.0663	

Table 7.6 Hospitalisation, outpatient visits and GP visit cost and related distributions

Costs of CV hospitalisation	Mean cost(£)	Lower	Upper	Distribution
Worsening of heart failure	2875	1076	3361	Triangle distribution
Occurrence of stroke	2671	977	4006	Triangle distribution
Occurrence of myocardial infarction	2271	965	3012	Triangle distributions
Outpatient visit – adult	113	93	153	Triangle distributions
Prescription GP visit	34.6			Fixed

Table 7.7 Baseline cost-effectiveness result (age at starting of treatment at 70)

	Cost (£)	LYs	QALYs	Incremental			ICER (95% CI)	
				Cost (£)	LYs	QALYs	£/Life year	£/QALY
Standard care	4560	7.547	5.194					
Nebivolol	6284	8.378	5.843	1724	0.831	0.649	2074 (1947 to 1947)	2656 (2814 to 2814)

Table 7.8 Sensitivity analysis of ICER to age at the beginning of treatment (in QALYs)

Starting Age	Treatments	Cost (£)	Incremental Cost	QALYS	Incremental QALYs	ICER (£/QALY)
60	Standard care	5316		6.208		
	Nebivolol	7568	2252	7.201	0.994	2265
65	Standard care	4889		5.692		
	Nebivolol	6862	1973	6.493	0.801	2463
70	Standard care	4560		5.194		
	Nebivolol	6284	1724	5.843	0.649	2656
75	Standard care	3993		4.439		
	Nebivolol	5424	1431	4.923	0.484	2957
80	Standard care	3463		3.832		
	Nebivolol	4634	1171	4.160	0.327	3580

Table 7.9 Estimated event rates by model based compared with trial based result (SENIORS trial)

Events	Model based		SENIORS Trial result	
	Nebivolol (%) (95% CI)	**Standard care (%) (95% CI)**	**Nebivolol (%) (95% CI)**	**Standard care (%) (95% CI)**
All causes of death	15.5 (14.8 - 16.2)	18.4 (17.6 - 19.2)	15.8 (13.6 - 18.0)	18.0 (15.7 - 20.3)
Non-CV of death	5.5 (5.0 – 5.9)	5.4 (5.0 – 5.9)	5.3 (4.0 - 6.6)	4.4 (3.2 - 5.6)
Sudden death*	3.9 (3.5 – 4.3)	6.3 (5.8 – 6.8)	4.1 (2.9 - 5.3)	6.6 (5.1 - 8.1)
HF death	6.7 (6.2 – 7.2)	7.4 (6.9 – 8.0)	7.4 (5.8 - 9.0)	7.0 (5.5 - 8.5)
Hospitalisation	21.2 (20.4 – 22.0)	23.4 (22.6 – 24.3)	23.9 (21.3 - 26.5)	25.9 (23.3 - 28.5)
CV death	10.6 (9.7 – 11.5)	13.8 (12.7 – 14.8)	11.5 (9.6 - 13.4)	13.6 (11.5 - 15.7)

All patients started treatment at age 76.1 and time frame for the model was 21 months.

Table 7.10 Model predicted events at different time length

Events	Months	Nebivolol	Standard care
Death all	12	8.4%	9.8%
	24	17.3%	20.2%
	36	24.1%	27.9%
	48	31.9%	36.8%
	60	37.5%	42.2%
Non CV death	12	2.7%	2.7%
	24	5.8%	5.8%
	36	9.5%	9.1%
	48	12.7%	12.3%
	60	15.3%	14.7%
HF death	12	4.1%	4.5%
	24	7.5%	8.3%
	36	9.3%	10.4%
	48	12.0%	13.0%
	60	13.2%	14.8%
Sudden death	12	2.4%	3.6%
	24	4.6%	6.8%
	36	5.7%	8.9%
	48	7.7%	12.1%
	60	9.4%	13.2%
CV hospitalisation	12	14.0%	15.6%
	24	23.9%	26.2%
	36	30.3%	32.9%
	48	36.3%	39.0%
	60	39.9%	43.3%

CHAPTER 8 GENERAL DISCUSSION AND CONCLUSIONS

8.1 Introduction

The aim of this chapter is to revisit the objectives proposed at the beginning of the thesis and review how these have been achieved. The chapter then summarises the major findings reported in previous chapters, followed by comparison with similar work reported in the literature. The main contributions of the thesis are highlighted and its limitations and recommendations for further research are also addressed.

The primary aim of the thesis is to report new evidence of cost-effectiveness studies in heart disease. This was realised by three cost-effectiveness studies: one in nurse-led secondary prevention clinics for coronary heart disease in primary care, one on cardiac resynchronisation therapy with or without an implantable cardioverter defibrillator in chronic heart failure, and the final one on a new drug therapy, nebivolol, compared with standard treatment in elderly patients with heart failure.

The second aim of the thesis regarded the application of modelling methodology, with a view to providing general recommendations in using Markov modelling approaches in economic evaluation conducted in the heart disease area. Emphasis was on the provision of practical guidance on how to conduct model-based analysis, in which the primary input data for the model were from a trial. The focus was on extrapolation of cost-effectiveness of an intervention beyond a trial both in terms of the time horizon of the analysis and in relation to the population involved.

The first step of this thesis was to provide a general review of current cost-effectiveness analysis and methodological aspects in economic evaluation conducted in heart disease. The literature search was conducted in a thorough and rigorous manner and provided a broad view of the approaches to conducting economic evaluation based on clinical trials in the clinical area of heart disease.

This was followed by a case study on the nurse-led secondary prevention clinical study, presented in Chapter 3. This was a trial based analysis without seeking long-term cost-effectiveness results over longer periods. The study highlighted potential limitations of within trial period analysis in economic evaluation.

The applications of methodology reported in the thesis were on methods in economic evaluation when extrapolating beyond trials. First, the use of parametric distribution functions in extrapolating survival curves beyond a trial was explored, and second, a Markov modelling framework based on individual patient simulation was discussed.

Two empirical studies were then presented in Chapters 6 and 7, both of which employed model-based analysis. Parametric survival functions were fitted into observed data and the most appropriate distribution functions were adopted to extrapolate survival curves beyond the trial periods. Markov modelling approaches based on individual patient simulation were later presented. The risk of different events over time and beyond the trial periods were estimated from the best fitted distribution functions.

8.2 The contributions of the thesis

The substantive contributions from this thesis research fall under two main areas: contributions from the empirical components, where the focus is the three case studies of the thesis; and the contributions from the application of methodological issues in economic evaluation, focusing on an illustration of applying Markov modelling methods in conducting economic evaluation in situations where extrapolating beyond a trial was needed.

8.2.1 Empirical contribution

The primary contributions of this thesis were on the new evidence on the costs, effects and cost-effectiveness of interventions in heart disease. Each of the three case studies was novel in an empirical sense, representing the first cost-effectiveness study to address the clinical question at hand.

The first case study presented in Chapter 3 reports on the cost-effectiveness of nurse-led secondary prevention clinical study. This study was the first to examine the cost-effectiveness of nurse-led secondary prevention clinics in primary care. The cost-effectiveness analysis by the end of the trial period demonstrated that nurse-led clinics are highly cost-effective when compared with usual care. The findings were more consistent with current recommendations and practice on secondary prevention and provide a plausible explanation for the observed reduction in mortality.

The second case study, presented in Chapter 6, was on the cost-effectiveness analysis of a cardiac resynchronisation device. This study was the first to address directly the cost-effectiveness of CRT-P compared to CRT-ICD. In addition, the study took a life-time approach

and so extrapolated well beyond the trial period, for example with regard to important issues such as device replacement, which none of the existing trials had had long enough follow-up periods to address.

The third case study, presented in Chapter 7, was on the cost-effectiveness of nebivilol in elderly patients. The study was the first paper to address the cost-effectiveness of beta-blocker treatment in an elderly patient group. Since the SENIORS trial targeted a population that was not commonly included in clinical trials, the current study reported the potential health economic benefit of a strategy which incorporated routine nebivolol use for elderly patients with heart failure.

8.2.2 Contribution on application of methodological approaches

The major contribution of this work on the application of methodological approaches was to provide an illustrative guidance on conducting model-based economic evaluation when individual data from a trial is available. It provides real world examples of developing model-based analyses. This was achieved by revisiting fundamental issues in parametric distribution functions and Markov modelling approaches. It adds value to the current health economics literature in heart disease, enriching the literature with its detailed consideration of which parametric distribution functions should be employed when extrapolating survival beyond a trial and how they could be adopted into model-based analyses. Chapter 4 provided detail of the systematic steps that should be followed when choosing a candidate function based on observed data. Chapter 5 provided a stepwise illustration of a Markov modelling property and how to relax the classical assumptions, providing a solid view of different simulation methods, the weakness and strength of which were discussed.

These methods were then applied in Chapters 6 and 7 to provide examples of real case studies of conducting economic evaluation alongside clinical trials, how to fit survival functions based on individual trial data and how to conduct model-based analyses.

8.3 New evidence of cost effectiveness findings in heart disease

8.3.1 Major findings in case study 1

Chapter 3 presented a case study of an economic evaluation conducted within a trial analysis, where the focus was nurse-led secondary care prevention for coronary heart disease. The study revealed that the mean cost per patient for standard care within the trial period was £879 (95% CI 824 to 934) compared with £1015 (95% CI 956 to 1074) per patient in the nurse-led clinics group. Within the trial period, the incremental QALYs gained were 0.11 (95% CI 0.02 to 0.20) and the incremental costs per QALY gained was £1261 (95% CI £913 to £23,516) for the nurse-led clinic compared with the control group. The estimated mean QALY was below the notional willingness-to-pay threshold of £20,000/QALY.

The cost-effectiveness result by the end of the trial period presented favourable cost effectiveness results for nurse-led clinics. The initial set-up cost for running nurse-led clinics was generally balanced within the trial periods. Even if one was to extrapolate beyond the trial, the expected result would be that the intervention could still have a very low incremental cost-effectiveness ratio.

However, what was observed in this clinical study, in terms of such a long follow up in a clinical trial, is very rare. Most clinical trial data aims for a short-term clinical outcome. In most economic evaluations researchers are faced with the need to seek longer-term implications for

cost-effectiveness results. Reliance on measurement of short-term outcomes is justified if the intervention will not also have long-term effects on outcome but most interventions have much longer clinical and economic benefits than those captured in the trial period. Extrapolating beyond a trial is therefore needed in most studies when trial-based economic evaluation is carried out.

8.3.2 Major findings in case study 2

Chapter 6 presented a model based analysis populated with data from CARE-HF to evaluate the long-term incremental cost-effectiveness of cardiac resynchronisation therapy (CRT-P) and medical therapy (MT) compared to MT alone. In addition, the cost-effectiveness of adding an implantable cardioverter-defibrillator (CRT-ICD) plus MT vs. MT and the relative cost-effectiveness of CRT-P and CRT-ICD were also evaluated by incorporating estimates of the proportion of sudden deaths that might be prevented with CRT-ICD from a different trial (COMPANION).

The total cost per patient for CRT-ICD+MT was £59,422 compared with £36,732 and £26,572 for CRT-P+MT and MT, respectively. The mean life-time QALYs were 6.75, 6.06 and 4.08 and life years were 9.16, 8.23 and 6.10 for CRT-ICD+MT, CRT-P+MT and MT, respectively.

The probabilistic sensitivity analysis showed that in comparison with MT, CRT-P+MT gave an incremental cost of £10,160, a QALY score of 1.98 and a life year estimate of 2.13. This gives an incremental cost-effectiveness ratio (ICER) of £5,128 (95% CI £3,623 to £8,017) per QALY gained. The incremental cost-effectiveness of CRT-ICD+MT versus CRT-P+MT, the incremental cost is £22,690, the QALY score is 0.70 and the life years gained was 0.93. The ICER here was £32,591 (95% CI £24,288 to £54,040) per QALY gained.

The study concluded that long-term treatment with CRT-P+MT appeared cost-effective compared to medical therapy alone. When considering the addition of the ICD component, CRT-ICD+MT was beyond a notional threshold at a willingness-to-pay of £20,000 per QALY, in the treatment of patients with moderate to severe heart failure characterised by dyssynchrony, except in those who have a poor life expectancy.

The analysis reported in this thesis is a further development of earlier work on a within trial cost-effectiveness analysis using individual patient data from the CARE-HF trial (Cleland *et al.*, 2005). The result of the within trial analysis showed that CRT-P was associated with increased costs, increased survival and increased quality adjusted life years (QALYs). The within trial analysis suggests that CRT-P might be cost-effective over a patient's lifetime, but this had not been established with trial evidence.

This model-based analysis extends the previously published within trial analysis and also further advances the work described in the COMPANION cost-effectiveness analysis which provided estimates of benefit at 7 years, which were similar to those predicted by the model at 6 years. In addition, the modelling work examined the incremental cost-effectiveness ratio associated with adding an ICD component to CRT therapy.

The existing clinical trials provide considerable evidence for the long-term effectiveness of both CRT-P and CRT-ICD but most patients were alive and many felt well at the end of the trials. Patients' treatment does not cease at the end of the trial and it is inappropriate to assume that benefits cease at that point. In taking a life-time approach, an important issue is device replacement which none of the existing trials had had long enough follow-up in order to address.

The model also enables the inclusion of data and other evidence from a range of sources in order to examine broader health policy questions. The model provides a best-evidence synthesis of the likely cost-effectiveness of CRT-P and CRT-ICD.

8.3.3 Major findings in case study 3

Chapter 7 presented a model based economic evaluation populated from the SENIORS trial. An individual patient based simulation model was developed to evaluate the cost-effectiveness of nebivolol compared with standard care in elderly patients with heart failure. Since SENIORS targeted a population, a group that are not commonly included in clinical trials, it is important to understand the potential health economic impact of a strategy incorporating routine nebivolol use in elderly patients with heart failure. In this model, patient characteristics were estimated, based upon the SENIORS trial and demonstrated that the routine use of nebivolol in this population would be a cost-effective strategy.

The cost-effectiveness result suggested the total cost per patient was £4,560 and £6,284; mean life-years were 7.547 and 8.378; and QALYs were 5.194 and 5.843 for the standard treatment and nebivolol groups, respectively. The probabilistic sensitivity analysis provided an incremental cost of £1,742, incremental life years were 0.831 and QALYs were 0.649. Thus the incremental cost-effectiveness ratio was £2,074 (95% CI 1,947 to 1,947) per life year gained, and £2656 (95% CI 2,814 to 2,814) per QALY gained. The analysis indicates that nebivolol appears cost-effective when compared with standard treatment under notional thresholds of willingness-to-pay per QALY gained were £20,000. It indicates an incremental benefit with the use of nebivolol in this setting.

An important strength of the model-based analysis was the utilisation of individual patient data from the SENIORS trial in populating the economic model. The model was validated against the actual SENIORS results providing excellent concordance.

A further strength was the appropriate sophistication of the model employing tracker variables which extend the Markov framework to enable the risk of events to be varied with time. In addition, the model was based on individual patient simulation. Each individual was generated with a specific profile at the start of the simulation. This provided considerable flexibility for the model to extrapolate beyond the trial periods both in time horizon but also for different patient characteristics.

8.4 Major findings in application of methodology

The methodology focus of the thesis has attempted to serve as an illustration of applying Markov modelling methods in conducting economic evaluation in situations where extrapolating beyond a trial is needed. The methodology aspects in using parametric survival function in exploring the longer-term property of an intervention were presented in Chapter 4. This chapter focused on how to fit parametric survival functions based on observed data, drawing on authoritative and standard sources (Collet, 1994), often used in conducting parametric survival analysis in medical statistics. Methods on how to choose the best fitting survival curves and how to estimate parameters in a chosen distribution function were discussed and illustrated by the CARE-HF trial data.

The research was inspired by the lack of detailed consideration in the current health economics literature on which parametric survival functions should be employed when extrapolating

survival property beyond a trial. In most cases, exponential distribution or Weibull distribution functions were commonly assumed and used without examining the property of the underlying data. Chapter 4 concluded that more systematic steps should be followed and examined before a candidate function is chosen based on observed data.

Parametric survival functions are useful in most cases if one wants to investigate long-term implications for time-to-events or survival. However, to investigate longer-term costs or QALYs, it depends on health states and further events and also potentially other costs. For example, it is difficult to use parametric survival to cope with future events such as battery replacement and further CV related hospitalizations, as was seen in Chapter 6. Given that individuals have different risk profiles based on their age and gender, the choice of most cost-effective options for different age cohorts is of policy and clinical relevance.

In this case, a simulation model would provide a tool to incorporate further events and use evidence from observational studies or the literature. The future costs would more accurately be counted, which would never have been captured within a limited trial period. It is more flexible to build a model to simulate the longer-term implications, both in cost and in QALYs. In addition, a model developed based on the trial data would provide a tool to extrapolate into different patient groups and different clinical settings.

In Chapter 5, an individual patient simulation model based on a Markov modelling framework to extrapolate beyond a trial was presented. A general introduction to a Markov model and the overall methodological aspects of a Markov modelling framework were provided. The basic concept of Markov models and their properties was reviewed and mathematical formulae were presented for the estimation of a Markov chain model. Limitations of the classical Markov

model were discussed, methods for relaxing the assumptions inherited in a classical Markov model were unveiled and mathematical formula for estimating transition probabilities were discussed and enhanced by the support of the methods presented in Chapter 4.

An individual sampling approach was introduced and methods on how to adjust this into a Markov modelling framework proposed. By employing tracker variables for each individual patient in the Monte Carlo simulation to account for time on treatment and risk factors at each health state, time dependent events associated with each health state could be taken into account and their rewards in the terms of cost and QALYs could be easily summarised. The methodology aspects of this approach were supported by a renal transplantation model.

Two completed case studies in applying the methods presented in Chapters 4 and 5 were applied in Chapters 6 and 7. Individual simulation models based on a Markov modelling framework were constructed. Tracker variables were used in recording individual patient's characteristics and risk profiles. Time-to-event survival data were examined using accelerated time-to-failure models and parametric survival analysis was fitted to all time-to-event data. Baseline functions on time-to-event data were fitted by the best selected distribution functions, risk profile beyond the trial periods were estimated and used in model transition probabilities in the Markov models. Model validations were presented. The two cases studied served to illustrate how to conduct model-based analysis when individual data are available.

The application of methods in Chapters 6 and 7 demonstrated that individual patient simulation based on a Markov model framework is a promising and flexible approach in extrapolating beyond a trial period. Trial data provide a realistic way in deriving model parameters and a model framework can cope with different events and associate cost and QALYs. The model can

be extrapolated beyond a trial period and, in addition, it can be used on different population groups by setting different characteristics for different patient populations.

8.5 Comparison with other contributions

Buxton and colleagues (1997) stated that trial-based economic evaluations were necessary although modelling analysis is essential in reality. They argued that clinical trials give high internal validity for comparing different treatments but were often bounded by limited outcome data usually collected during a short follow-up period. Unless the effect of an intervention is believed to stop after the trial period, reliance on measurement of short-term outcomes could not be justified. This was because economic evaluation and policy-making depend upon the effect of longer-term outcomes, in which the interest is to improve future health with limited health care resources. Therefore, economic evaluations based on clinical trials often need to extrapolate beyond the trial.

The studies in this thesis have proved the claims made by Buxton and his colleagues that trial-based economic evaluation were not always the ideal. The advantage of developing model-based analysis methods has been illustrated. This was achieved by the economic evaluation of CRT compared with MT in heart failure patients, through the within trial analysis and model-based analysis for the CARE-HF trials. The difference in the ICERs was compared and the advantage in using model-based analysis was illustrated in Chapter 6. Chapter 7 took further steps in developing the model-based analysis.

Philips and colleagues (2004) undertook a review of modelling in health economics and recommended that methods and assumptions in extrapolating beyond a trial should be

documented and that validation of the methodology should be conducted, for example the choice of survival functions should be justified. Furthermore, they argued that life tables should be based on all cause mortality. Chapters 6 and 7 serve as practical examples in following these guidelines.

Sonnenberg and Beck (1993) provided an introduction to the Markov modelling approach in the medical field. Briggs and Sculpher (1998) offered further details on the use of Markov modelling when performing economic evaluation. However, these two papers focused on methodological issues. In this thesis, I not only reviewed the methodological background of Markov modelling in principle, but further emphasised the flexibility and advantages of Markov modelling used in economic evaluation by relaxing some of the core assumptions and introduced individual patient simulation approaches.

Sculpher and colleagues (2006) stated that clinical trials usually provide a major source of data in economic evaluation but also indicated that there are several limitations in a trial-based analysis. They recommend that a suitable time horizon should be considered. In many situations, an analysis should seek a lifetime time horizon if an intervention impacts on mortality. Costs and benefits of interventions in health care most likely present different outcomes in the short-term. In Chapter 6, I further progressed the within trial-based analysis to develop a Markov model to extrapolate the survival and cost beyond the trial and incorporate further evidence from the COMPANION trial, extending the trial population into different age cohorts. Chapter 7 moved to directly develop a model-based analysis and provide the potential to compare other similar treatment instead of standard or placebo as the trial frame.

8.6 Strengths and limitations of the thesis

One of the major strengths of the thesis is that it is based on a thorough and rigorous literature review on economic evaluation in cardiovascular heart disease. The inconsistencies in methodological approaches and lack of detail on how the analysis was conducted, highlighted from the review, has encouraged the development of a general guideline on how to conduct economic evaluation when individual data is available from a trial.

Another strength of the thesis is that methods derived from other fields, including medical statistics and operational research, that have traditionally been used sparingly in health economic literature, are discussed and applied. Chapter 4 is based on probability theory and survival analysis methodology, and presented the hidden properties of hazard functions which are more intuitive to economic evaluation when cost and effectiveness highly depend on future events. Chapter 5 revisited the Markov modelling property, based on operational research and utilised more computational advantages in developing individual patient simulations based on the Markov modelling framework. While the advantage of individual simulation approaches provided flexibility to mirror a trial population and equally provide a tool to be used on different populations, the clear properties in Markov model framework gives a more straight forward modelling structure.

Furthermore, the thesis employed data from three real world RCTs, as an illustration, on novel and important clinical and policy questions. All of these trials were conducted to the highest research standards, evidenced by their publication in high-ranking clinical journals, and provide real evidence of cost-effectiveness results in heart disease. Chapters 6 and 7 were model based analyses, providing several additional answers beyond the trials, making them more relevant to policy-making, and helped answer several ‘what if’ questions.

Finally, the thesis reviewed the methodological background in time-to-event analysis and adopted a Markov modelling methodology in trial based analysis. It then presented completed illustrations from deriving data inputs from a trial building, model structures and validation of the models.

There are several limitations of the thesis. Firstly, alternative modelling approaches in using trial-based analysis have not been investigated and it did not compare the relative efficiency of using other methods. The foci of the thesis were mainly on the most frequently used Markov modelling approaches and so it provides guidelines in applications with particular focus on these methods.

Furthermore, the thesis focused on a particular disease area – heart disease. Methods discussed in the thesis might limit its use in other disease areas. Different methodology should be explored when economic evaluation is conducted in other different disease areas, especially in the setting of infectious diseases where interaction between individuals is important. Markov models fail to capture such interaction.

Finally, I should emphasise that the thesis is based on application of methods rather than methodological development. In the thesis I focused on individual trials and aimed to provide guidelines for extrapolating beyond a trial. The analysis did not include evidence synthesis for data input as proposed by Sculpher and colleagues (Sculpher *et al*., 2006).

8.7 Recommendations for policy and future research

On a methodological note, when conducting extrapolation of a time-to-event survival beyond a trial, the choice of survival functions should be based, where possible, on observed data from a trial as the best evidence instead of making assumptions. Investigating different alternatives in sensitivity analysis should be encouraged.

There would be great benefit derived from more empirical research to investigate the comparison of alternative methods in extrapolating beyond a trial. This could be achieved by employing longer follow up data from a trial and exploring the potential bias by artificially cutting off the end point earlier and investigating potential bias by employing different approaches.

This thesis has used both within trial analysis and model-based analysis, with a particular focus on three case studies. Further research should be conducted on the relative impact of using different analytic approaches and using more case studies on different disease areas. This would provide more insight and recommendations on best practice of trial-based economic evaluations.

This thesis has revisited the fundamental issues in parametric distribution functions and Markov modelling approaches. The methodology aspects in using parametric survival functions in exploring a longer-term property of a disease profile were presented in Chapter 4. This chapter focused on how to fit parametric survival functions based on observed data. The distribution functions and their hazard functions were discussed. It appears that the hazard function is more intuitive in choosing a candidate model. By investigating the hazard property, a best fitting distribution function can be chosen to represent the underlying risk profile over time. Methods on how to choose the best fitting distribution functions over observed data were illustrated by

real trial data from the CARE-HF study. This is a fundamental step in estimating risk profile beyond a trial period for use in a modelling framework.

Finally, on an empirical note, the three clinical case studies in the thesis indicate their cost-effectiveness results related to policy making. Nurse-led clinics in primary care are highly cost-effective. They should be recommended in a general health care setting. The study of the nebivolol based on SENIORS concluded that nebivolol is a cost-effective treatment to an elderly (mean 76.1 years) population with chronic heart failure. It found that the routine use of nebivolol in this population would be a cost-effective strategy and should be considered by policy makers.

The long-term cost-effectiveness analysis of CARE-HF trial data concluded that cardiac resynchronisation therapy (CRT-P) was a cost-effective treatment option compared with medical therapy (MT) alone. However, adding an implantable cardioverter-defibrillator to CRT appears to be beyond the traditional willingness-to-pay threshold £20,000 per QALY gained and might not be a cost-effective option compared to CRT-P.

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APPENDIX 1 SEARCH STRATEGY IN THE LITERATURE REVIEW

Database: Ovid MEDLINER <2004 to August Week 1 2007>

Search Strategy:

#1 economic$ adj3 evaluation$.mp.

#2 economic adj3 analy$6.mp.

#3 cost$2 adj5 benefit$2.mp.

#4 cost$2 adj5 effect$7.mp.

#5 cost$2 adj5 utilit$4.mp.

#6 #1 or #2 or #3 or #4 or #5

#7 heart$2.ab,ti.

#8 Heart Diseases.mp.

#9 #7 or #8

#10 trial$2.ab,ti.

#11 6 and 9 and 10

All limited to abstracts and english language and yr="2005 - 2007"

mp = title, original title, abstract, name of substance word, subject heading word

ab = abstract

ti = title

APPENDIX 2 DETAILS OF PAPER SELECTION IN THE LITERATURE REVIEW

No.	Study	Scope of the Review	Reasons for Exclusion
1	Ali and Antezano 2006	Title	Review
2	Andriolo 2005	Title	Review
3	Ballok 2005	Title	Review
4	Barnes and Howards 2005	Title	Review
5	Bartlett 2001	Title	Review
6	Bieniarz and Delgado 2007	Title	Review
7	Bjork-Eriksson 2005	Title	Review
8	Boersma 2006	Title	Review
9	Bryant 2005	Title	Review
10	Bryant 2007a	Title	Review
11	Bryant 2007b	Title	Review
12	Burnier 2006	Title	Review
13	Castelnuovo 2001	Title	Review
14	Chattipakorn 2007	Title	Review
15	Chaudhry 2007	Title	Review
16	Cheng 2006	Title	Review
17	Chiappa 2007	Title	Review
18	Chiasson 2006	Title	Review
19	Chircop and Jelinek 2006	Title	Review
20	Clark 2007	Title	Review
21	Clegg 2006	Title	Review
22	Clegg 2007	Title	Review
23	Collins and Gurm, 2007	Title	Review
24	Cooper 2006b	Title	Review
25	Croom and Plosker, 2005	Title	Review
26	Croom 2005b	Title	Review
27	Dauerman 2007	Title	Review

28	Daviglus 2006	Title	Review
29	Ebrahim 2006	Title	Review
30	El-Menyar 2005	Title	Review
31	Ermis and Benditt 2006	Title	Review
32	Feringa 2007	Title	Review
33	Field and Sweeney 2006	Title	Review
34	Franco 2005	Title	Review
35	Garner 2005a	Title	Review
36	Garner 2005b	Title	Review
37	Gendo 2005	Title	Review
38	Gillis and Willems 2005	Title	Review
39	Hadian and Pinksky 2006	Title	Review
40	Hancock 2005	Title	Review
41	Holmes and Wood, 2006	Title	Review
42	Jamieson and Naghavi 2007	Title	Review
43	Jolly 2006	Title	Review
44	Kapur 2007	Title	Review
45	Lazzaroni 2005	Title	Review
46	Lim 2007	Title	Review
47	Lowe 2005	Title	Review
48	Macdonald and Taghian 2007	Title	Review
49	Maclure 2006	Title	Review
50	Mangoush 2007	Title	Review
51	Menasche 2006	Title	Review
52	Menasche 2006a	Title	Review
53	Merchant and Laborde 2005	Title	Review
54	Naccarelli 2005	Title	Review
55	Nielsen 2006	Title	Review
56	Nilsson 2006	Title	Review
57	Novak 2007	Title	Review
58	Papadakis 2005	Title	Review
59	Parry and Fetridge-Durdle 2006	Title	Review

60	Pell 2007	Title	Review
61	Petchetti 2007	Title	Review
62	Psychosocial Outcomes Workgroup of the Nursing and Social Sciences Council of the International Society for Heart and Lung Transplantation 2006	Title	Review
63	Ryan and Rittershaus 2006	Title	Review
64	Sackner-Bernstein 2005	Title	Review
65	Sharples 2006	Title	Review
66	Siddiqui and Scott 2005	Title	Review
67	Solheim 2006	Title	Review
68	Stevenson 2005	Title	Review
69	Taylor 2005	Title	Review
70	Thomas 2006	Title	Review
71	van Geijn 2005	Title	Review
72	Vidaillet, 2005	Title	Review
73	Vidaillet and Greenlee 2005	Title	Review
74	Ward 2007	Title	Review
75	Wyse 2005	Title	Review
76	Yokota 2007	Title	Review
77*		Title	Review
78	Anderson 2005	Title and abstract	Not EE
79	Ashraf 2005	Title and abstract	Not EE
80	Bentkover 2007	Title and abstract	Not EE
81	Danilouchkine 2005	Title and abstract	Not EE
82	Duffy 2005	Title and abstract	Not EE
83	Fischell 2007	Title and abstract	Not EE
84	Fox 2006	Title and abstract	Not EE
85	Hacker 2005	Title and abstract	Not EE
86	Horn 2006	Title and abstract	Not EE
87	Huybrechts *et al*, 2005	Title and abstract	Not EE
88	Ishikawa 2007	Title and abstract	Not EE

89	Kristiansen 2006	Title and abstract	Not EE
90	Miraldi 2007	Title and abstract	Not EE
91*	Non English	Title and abstract	Not EE
92	Newcomb 2005	Title and abstract	Not EE
93*	Non English	Title and abstract	Not EE
94*	Non English	Title and abstract	Not EE
95	Ogah 2006	Title and abstract	Not EE
96	Rashba 2006	Title and abstract	Not EE
97	Richards 2005	Title and abstract	Not EE
98	Seow 2006	Title and abstract	Not EE
99	Shelton 2005	Title and abstract	Not EE
100	Slagboom 2005	Title and abstract	Not EE
101	Smith 2005a	Title and abstract	Not EE
102	Smith 2005b	Title and abstract	Not EE
103	Smith 2005c	Title and abstract	Not EE
104	Stramba-Badiale 2006	Title and abstract	Not EE
105	Vanek 2005	Title and abstract	Not EE
106	Varga 2005	Title and abstract	Not EE
107	Yan 2007	Title and abstract	Not EE
108	Alisky 2007	Title and abstract	comments
109	Speidel and Hilleman 2006	Title and abstract	comments
110*	Non English	Title and abstract	comments
111	Inaguma 2006	Title and abstract	Heart disease is not the main study area
112	Nuijten 2007	Title and abstract	Heart disease is not the main study area
113	Simpson 2007b	Title and abstract	Heart disease is not the main study area
114	Zethraeus 2005	Title and abstract	Heart disease is not the main study area
115*	Non English	Title and abstract	Heart disease is not the main study area
116	Willan 2005	Title and abstract	Methodology

118	Fenwick 2006	Title and abstract	methodology study but based on individual trial
119	Hallstrom 2006	Title and abstract	methodology study not based on individual trial
120	Fintel 2007	Title and abstract	Not base on individual data
121	Gerber 2006	Title and abstract	Not base on individual data
122	Gerhard 2006	Title and abstract	Not base on individual data
123	Hay and Sterling 2005	Title and abstract	Not base on individual data
124	Hirsch 2005	Title and abstract	Not base on individual data
125	Jongerden 2007	Title and abstract	Not base on individual data
126	Martikainen 2007	Title and abstract	Not base on individual data
127	Pignone 2007	Title and abstract	Not base on individual data
128	Sanders 2005	Title and abstract	Not base on individual data
129	Shrive 2005	Title and abstract	Not base on individual data
130	Bampidis 2005	Title and abstract	Not heart disease Hypertension
131	East 2006	Title and abstract	Not heart disease Hypertension
132	Haas 2006	Title and abstract	Not heart disease Hypertension
133	Joffres 2007	Title and abstract	Not heart disease

			Hypertension
134	Love and Benson 2006	Title and abstract	Not heart disease Hypertension
135	Plans-Rubio 2006	Title and abstract	Not heart disease Hypertension
136	Saito 2006	Title and abstract	Not heart disease Hypertension
137	Siddiqui and Scott 2006	Title and abstract	Not heart disease Hypertension
138	Storrow 2005	Title and abstract	Not heart disease
139	Tokatli 2006	Title and abstract	Not heart disease Hypertension
140	Zeeuwe 2006	Title and abstract	Not heart disease Hypertension
141	Ara and Brennan. 2007	Title and abstract	Not heart disease
142	Brennan 2006	Title and abstract	Not heart disease
143	Fernandez and Griffiths 2005	Title and abstract	Not heart disease
144	Gokce 2007	Title and abstract	Not heart disease
145	Kilonzo 2007	Title and abstract	Not heart disease
146	Lester 2007	Title and abstract	Not heart disease
147	Lofdahl 2005	Title and abstract	Not heart disease
148	Lundkvist 2007	Title and abstract	Not heart disease
149	Marcus 2007	Title and abstract	Not heart disease
150	Mason 2005	Title and abstract	Not heart disease
151	Obuchowski and Modic 2006	Title and abstract	Not heart disease
152	Ritzwoller 2006	Title and abstract	Not heart disease
153	Simpson 2007a	Title and abstract	Not heart disease
154	Slichter 2006	Title and abstract	Not heart disease
155	Smith 2006	Title and abstract	Not heart disease
156	Tracy 2006	Title and abstract	Not heart disease
157	Bramkamp 2005	Title and abstract	Review
158	Cooper 2006a	Title and abstract	Study design
159	Hochman 2005	Title and abstract	Study design

160	Jolly 2007	Title and abstract	Study design
161	Kapur 2005	Title and abstract	Study design
162	Krumholz 2005	Title and abstract	Study design
163	Matchar 2005	Title and abstract	Study design
164	McQueen 2005	Title and abstract	Study design
165	Nichol 2005	Title and abstract	Study design
166	Rose 2007	Title and abstract	Study design
167	Rosenman 2006	Title and abstract	Study design
168	Sweeney 2006	Title and abstract	Study design
169	Pietrasik 2007	Full paper	within trial analysis
170	McMurray 2006	Full paper	within trial analysis
171	Inglis 2006	Full paper	within trial based-longer follow up
172	Paez and Allen 2006	Full paper	Not EE
173	Mueller 2006	Full paper	within trial
174	Pearson 2006	Full paper	Not based on individual data
175	Di 2005	Full paper	within trial analysis
176	Briffa 2005	Full paper	within trial analysis
177	Reed 2005	Full paper	within trial analysis
178	van Huslt 2005	Full paper	within trial analysis
179	O'Brien 2005	Full paper	within trial analysis
180	Raftery 2005	Full paper	within trial analysis
181	Radeva 2005	Full paper	within trial analysis
182	Szucs 2006	Full paper	within trial and beyond trial
183	Mark 2006	Full paper	within trial and beyond trial
184	Feldman 2005b	Full paper	within trial and beyond trial
185	Angus 2005	Full paper	within trial and beyond trial

186	Calvert 2005	Full paper	Within trial
187	Beinart 2005	Full paper	Within a trial and beyond a trial
188	Weintraub 2005a	Full paper	within trial and beyond a trial
189	Weintraub 2005b	Full paper	within trial and beyond a trial
190	Briggs 2007	Full paper	yes - model based
191	Yao 2007	Full paper	yes - model based analysis
192	Scuffham and Chaplin 2006	Full paper	yes- model based analysis
193	Cram 2006	Full paper	yes - model based analysis
194	Caro 2006	Full paper	yes- model based analysis
195	Stecher 2006	Full paper	Not based on Individual data
196	Scuffham and Kosa 2006	Full paper	yes - model based
197	Rinfret 2005	Full paper	yes- within trial and model based
198	Mihaylova 2005	Full paper	yes - within trial analysis
199	Bond 2007	Full paper	yes - within trial analysis
200	Taylor 2007	Full paper	yes- within trial analysis
201	Murray 2007	Full paper	yes- within trial analysis
202	Walker 2006	Full paper	yes - cost study
203	Caro 2005	Full paper	Not full EE
204	Dawkins 2006	Full paper	Not full EE
205	Del 2007	Full paper	Not full EE

206	Feldman 2005c	Full paper	Not full EE
207	Giada 2007	Full paper	Not full EE
208	Girling 2007	Full paper	Not full EE
209	Gregory 2006	Full paper	Not full EE
210	Kaul 2005	Full paper	Not full EE
211	Lopez 2006	Full paper	Not full EE
212	Mozaffarian 2007	Full paper	Not based on individual patient data
213	Banz 2005	Full paper	Not based on individual patient data
214	Kohli 2006	Full paper	Heart disease is not the study focus
215	Lindgren 2005	Full paper	Heart disease is not the study focus
216	Miller 2005	Full paper	Heart disease is not the study focus
217	O'Connor 2005	Full paper	Heart disease is not the study focus
218	Olsen 2005	Full paper	Heart disease is not the study focus
219	Hallstrom 2005	Full paper	Not EE
220	Quist-Paulsen 2006	Full paper	Not EE

** No authors listed on Medline*

APPENDIX 3 MODEL FIT INFORMATION FOR CHAPTER 6

Table 1 Model fit information for time to sudden death

Model	Model Akaike information criteria
Weibull	690.4505951
Exponential	726.4328276
LLogistic	727.5760968
Lognormal	733.5597493
Gamma	725.3366251

**The smallest AIC produced the best fit*

Table 2 Model fit information for time to hospitalisation

Model	Model Akaike information criteria
Weibull	1870.338
Exponential	1871.126
Gamma	1881.631
LLogistic	1887.1
Lognormal	1934.674

**The smallest AIC produced the best fit*

APPENDIX 4 MODEL FIT INFORMATION FOR CHAPTER 7

Table 1 Model fit information for time to sudden death

Model	Model Akaike information criteria
Weibull	660.8083
Lognormal	662.4853
Exponential	663.4678
LLogistic	663.8212
Gamma	664.1923

**The smallest AIC produced the best fit*

Table 2 Model fit information for time to hospitalisation

Model	Model Akaike information criteria
Weibull	3692.615
Lognormal	3696.761
LLogistic	3702.224
Gamma	3711.657
Exponential	3738.396

**The smallest AIC produced the best fit*

APPENDIX 5 RECENT PUBLISHED PAPERS ARISING FROM THIS RESEARCH

1. Yao, G., Freemantle, N., Marcus, F., Tharmanathan, P., Coats, A. and Poole-Wilson, P. A. (2008). Long-term cost-effectiveness analysis of nebivolol compared with Placebo in elderly patients with heart failure – an individual patient based simulation model. Pharmacoeconomics, 26(10): 879-889
2. Yao, G., Freemantle, N., Calvert, M. J., Bryan, S., Daubert, J. C. and Cleland, J. G. F. (2007). The Long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. European Heart Journal, 28: 42-51
3. Raftery, J. P., Yao, G. L., Murchie, P., Campbell, N. C. and Ritchie. L. D. (2005). The cost effectiveness of nurse-led secondary prevention clinics for coronary heart disease in primary care: four- year follow up of a randomised trial. British Medical Journal, 330: 707
4. Calvert, M., Freemantle, N., Yao, G., Cleland, J., Billingham, L, Daubert, J., Bryan, S. and on behalf of the CARE-HF Investigators (2005) . Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. European Heart Journal, 26: 2681-2688
5. Miners, A. H., Yao, G., Raftery, J. and Taylor, R. S. (2007). Economic evaluations of calcineurin inhibitors in renal transplantation: a literature review. Pharmacoeconomics, 25(11): 935-47
6. Whitehurst, D. G., Lewis, M., Yao, G. L., Bryan, S., Raftery, J. P., Mullis, R., Hay, E. M. (2007). A brief pain management programme and physical treatments for low back pain: results from an economic analysis alongside a randomised. Arthritis Rheum, 57(3): 466-73.
7. Copas, A. J., Farewell, V., Mercer, C. H. and Yao, G. (2004). The sensitivity of estimates of the change in population behaviour to realistic changes in bias in repeated surveys. Royal Statistical Society Series A, 167 (4): 579-595
8. Yao, G., Albon, E., Adi, Y., Milford, D., Bayliss, S., Ready, A., Raftery, J., Taylor, R. S. (2006). A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. Health Technology Assessment, 10(49)

9. Woodroffe, R., Yao, G. L., Meads, C., Bayliss, S., Ready, A., Raftery, J. and Taylor, R. S. (2005). Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study. Health Technology Assessment, 9(21)
10. Wilson, J., Yao, G. L., Raftery, J., Bohlius, J., Brunskill, S., Sandercock, J., Bayliss, S., Moss, P., Stanworth, S. and Hyde, C. (2007). A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technology Assessment, 11(13)
11. Wilson, J., Connock, M., Song, F., Yao, G., Fry-Smith, A., Raftery, J. and Peake, D.(2005). Cost effectiveness analysis of imatinib mesylate for the treatment of patients with unresectable and/or metastatic gastro-intestinal stromal tumours. Health Technology Assessment, 9 (25)