ECONOMIC EVALUATIONS FOR HEALTH TECHNOLOGIES WITH AN EVOLVING EVIDENCE BASE: A CASE STUDY OF TRANSCATHETER AORTIC VALVE IMPLANTATION

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ABSTRACT

The primary aim of this thesis is to investigate the challenges in conducting economic evaluations for medical devices with evolving evidence bases. While economic evaluations for capital projects and medicines are well established in theory and practice, the same cannot be said for novel medical devices. New medical devices are often expensive and rely on scarce evidence for efficacy and cost. This increases uncertainty surrounding their clinical and cost effectiveness. In addition, as fewer formal procedures exist for evaluating devices relative to medicines, evidence bases are weak and health technology assessment agencies are reluctant to make rapid decisions. To address these issues a continuous iterative framework developed and proposed for economic evaluations of medical devices.

In this thesis, using Transcatheter Aortic Valve Implantation (TAVI) as a case study, an iterative economic evaluation, employing Bayesian techniques, is developed to investigate how the challenges associated with medical devices can be overcome to produce an efficient and informative economic evaluation. This study is the first to investigate these challenges and identify solutions while conducting an economic evaluation early in a device's life cycle, using the proposed continuous iterative framework. The consideration of Access with Evidence Development schemes to overcome these challenges and balance access with evidence generation for expensive and novel medical devices, with evolving evidence, is another important contribution of the thesis.

Transcatheter Aortic Valve Implantation (TAVI) is a novel treatment for severe Aortic Stenosis for operable and inoperable patients. The iterative economic evaluation concludes that TAVI can be considered cost effective for inoperable patients compared to medical management. There is little value in commissioning new research for continued data collection for this group. However, the continued collection of evidence via the UK TAVI registry as indicated in the National Institute of Clinical Excellence (NICE) guidelines will ensure up to date evidence is available to inform future decisions regarding TAVI in this patient group. For operable patients, the iterative model could not conclude that TAVI was cost effective compared to Aortic Valve Replacement (AVR). However, additional evidence of improved outcomes from TAVI should enhance its cost effectiveness for these patients. The Bayesian value of information analysis indicates that further information on short and long term probability, resource and quality of life parameters is most valuable and the optimal research design for collecting such information is a registry.

Using TAVI as a case study affords the opportunity to examine the challenges in undertaking a cost effectiveness analysis for complex medical device technologies in real time. These challenges were identified and overcome by employing flexible Bayesian techniques in the continuous iterative framework. This demonstrates that economic evaluations do not have to be static once-off activities. In fact, owing to the characteristics of medical devices (learning curve, incremental innovations etc.) economic evaluations of this kind should be continuous. Therefore, incorporating evolving evidence into the decision making process to re-estimate cost effectiveness on an iterative basis.

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FREQUENTLY USED TERMS

AED	Access with Evidence Development
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CE	Cost Effectiveness
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CI	Confidence Interval
DAM	Decision Analytical Model
Dist	Distribution
EUnetHTA	European Network for Health Technology Assessment
EuroSCORE	European System for Cardiac Operative Risk Evaluation: A method of calculating predicted operative mortality for patients undergoing cardiac surgery.
EVPI	Expected Value of Perfect Information
EVPPI	Expected Value of Partial Perfect Information
EVSI	Expected Value of Sample Information
HTA	Health Technology Assessment
ICE	Incremental Cost Effectiveness
ICER	Incremental Cost Effectiveness Ratio
ISPOR	International Society For Pharmacoeconomics and Outcomes
LYGs	Life Years Gained
LYs	Life Years
MM	Medical Management
MR	Mortality rate
n	Sample size
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NYHA	New York Heart Association: functionality classification
PARTNER	Placement of AoRTic TraNscathetER Valve Trial
PBRSA	Performance Based Risk Sharing Agreements
PRE	Procedure Related Event
Prob	Probability
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
QOL	Quality of Life
RCT	Randomised Control Trial
SE	Standard Error
SHTG	Scottish Health Technologies Group
TAVI	Transcatheter Aortic Valve Implantation
UK	United Kingdom
US	United States
VOI	Value of Information

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AUTHORS DECLARATION

This dissertation, except where explicit reference is made to the contribution of others, is the result of the authors work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Elements of the research conducted for this dissertation have been presented and submitted as publications, reports and presentations as follows:

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3. Economic Evaluations – Is once enough? Poster presentation at Society for Medical Decision Making, Oslo, Norway. June 2012. ~ *Chapters 5 and 7.*
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5. Cost Effectiveness of Transcatheter Aortic Valve Implantation (TAVI) Compared with AVR for Severe Aortic Stenosis in Operable Patients. Report submitted to NIHR Health Technology Assessment Programme. 31st October 2011. ~ *Early version of Chapters 6/7.*
6. Examining the Cost Effectiveness of Transcatheter Aortic Valve Implantations in the United Kingdom as Evidence Evolves. Poster presentation at International Health Economics Association Congress. Toronto, Canada. July 2011. ~ *Chapter 4 and Chapter 5*
7. Evidence Development Pilot Project: Transcatheter Aortic Valve Implantation in Scotland. Report submitted to Scottish Health Technologies Group. 29th November 2010. ~ *Chapter 4*

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CHAPTER 1 INTRODUCTION

1.1 INTRODUCTION

This thesis develops a framework for conducting economic evaluations of expensive, novel medical device technologies with evolving evidence. While economic evaluation methods and guidelines are well established for capital projects and medicines, the characteristics of medical devices present unique challenges which need to be addressed in conducting evaluations. Using Transcatheter Aortic Valve Implantation (TAVI) as a case study, a framework for a continuous iterative economic evaluation, employing Bayesian techniques, is developed here to investigate how the challenges associated with medical devices can be overcome to produce an efficient and informative economic evaluation.

While the challenges associated with economic evaluations of medical devices have been reported on retrospectively (i.e. after the evaluation) (Sorenson et al., 2011), this study is the first to investigate these challenges and identify solutions while conducting an economic evaluation early in a device's life cycle. The consideration of Access with Evidence Development schemes to overcome these challenges and balance access with evidence generation for expensive and novel medical devices with evolving evidence, is another important contribution of the thesis.

1.2 CONTEXT AND RATIONALE

Health care systems are subject to many challenges: scarce resources, rising expenditures, increased pressures from stakeholders and advancing health technologies. These challenges present infinite demands on already limited resources necessitating choices between competing alternatives. Economic evaluations offer a means of informing these choices, by comparing the costs and benefits of alternative resource uses (Banta, 2003, Drummond et al., 2007), therefore addressing four issues: does the technology work, for whom does it work, at what cost does it work and how does it compare with alternatives (HTA, 2012). It

is recognised that other issues, such as affordability, the budgetary impact of the technology, the financial and fiscal environment, patients' needs and preferences and other matters pertaining to the political and health environment at that time, are considered alongside economic evaluations when decision makers consider technologies. The latter include, the demographics of the population, incentives and motivation amongst clinicians; influence of partisan groups; political stability; emotional ambivalence associated with the condition/disease; availability of the health technology in neighbouring countries and public and industry pressures (Europe, 2008, Scotland, 2012, Sorenson et al., 2008, Garrido et al., 2008, Robert et al., 2009, Gagnon et al., 2006, Gerhardus and Dintsios, 2005). However, this thesis focuses on economic evaluations and cost effectiveness, these other issues are considered to be outside the remit of this thesis.

Employing the results of economic evaluations then, along with budgetary considers, preferences etc. mentioned above, health care decision makers are encouraged to consider two related decisions. These are the adoption and research priority decisions. The adoption decision is related to the granting of coverage for a technology, given current information. That is to say, should the technology be made available to patients and reimbursed or not. The research priority setting decision is concerned with determining if there is value in collecting additional information on that technology and how that additional information should be collected.

Since the application of economic evaluations to health care, methods and policies surrounding adoption and evidence collection have developed (Glick, 2007). The employment of value of information (VOI) analysis for example, provide methods to determine if further information is required, after the adoption decision is made (Griffin et al., 2011). Incorporating VOI analysis into the decision making process provides formal recognition that data collection is not costless (Claxton et al., 2001). Also, decisions are often delayed owing to unsubstantiated needs for further evidence; such behaviour is deterred with VOI as the need for further evidence is formally quantified. Iterative frameworks for employing economic evaluations are also recommended, whereby the adoption and need for further research decisions are re-assessed on an iterative basis as the evidence base develops (Fenwick et al., 2000, Sculpher et al., 1997).

While economic evaluation methods and frameworks for capital projects and medicines are well established in theory and practice, the same cannot be said for novel medical device technologies (Drummond et al., 2008). New medical devices are often expensive, have scarce evidence and subsequently there may be high uncertainty surrounding their clinical and cost effectiveness. Also, as patients are becoming more health literate they, and other stakeholders, can put pressure on health care systems to be early adopters of technologies. In addition, fewer formal procedures exist for evaluating devices relative to medicines. As a result of these challenges, health technology assessment agencies are reluctant to make rapid, definitive decisions on reimbursement and further research of medical devices.

When decision makers are reluctant to make speedy decisions patients are denied access to potentially promising technologies. Emerging policy strategies, such as Access with Evidence Development schemes, aim to overcome such issues while recognising persisting uncertainty surrounding effectiveness and the risk that a technology granted coverage may have to be removed if concerns about its effectiveness and/or cost effectiveness persist or are confirmed. VOI analysis can be employed here also, facilitating an alternative to the conventional "yes/no" adoption decision. Here, by granting conditional coverage to specific sub-group(s) of patients, additional evidence can be collected while offering limited access (Pearson et al., 2006, Tunis and Chalkidou, 2007, Tunis and Pearson, 2006). This evidence can be used when the adoption decision is re-addressed on an iterative basis.

1.2.1 Challenging Characteristics of Medical Device Technologies

While drugs and medical devices are both health care technologies, the latter have unique characteristics which when combined can present challenges in performing economic evaluations. These characteristics are identified and explained below.

Evidence Requirements / Licensing Procedures / Diffusion

Unlike drug technologies, there are no formal requirements to undertake randomised control trials (RCTs) for market approval for medical devices. While RCTs are standard for drug approval, they are far beyond what is required for devices to obtain a CE Mark[1].

[1] The Conformitè Europèene or CE Mark is the requirement for market authorisation in the European Union (Drummond et al. 2009).

Only the demonstration of performance and safety is necessary for market approval (for example, the CE Mark) and generally this is only performed at the point of market entry. As a result, there is rapid clinical uptake of these devices and they often become part of clinical practice as soon as they become available (Drummond et al., 2009).

While this rapid approval process has advantages, in that it can improve competition, which may reduce prices and provide quicker access for patients, it can discourage further research. In fact, the current regulatory process provides incentives for manufacturers to be fast followers rather than inventors, so as to avoid high research costs (Sorenson et al., 2011, Drummond et al., 2009).

Learning Curve

Unlike drugs, there is a learning curve with medical devices owing to the interaction between the operator/clinician and the medical device. This interaction increases the probability of errors and adverse events along a learning curve. This device-clinician learning curve raises issues in clinical trials where the new technology is being compared to standard practice. As clinicians have been performing the standard procedure routinely they are proficient in its delivery, so the probability of errors and procedure related events is significantly reduced. However, it takes time to reach this level of proficiency and competency with a new procedure. This means that in early trials it can be difficult to distinguish between the performance of the device and the clinician, owing to the interaction between them, and their experience with the old and inexperience with the new. Difficulties in isolating this learning curve effect mean the true potential of the device may not be realised in early trials when compared to the standard alternative (Drummond et al., 2009, Sorenson et al., 2011, Taylor and Iglesias, 2009).

Difficulties with Randomised Control Trials (RTCs)

Small, non-randomised studies are common for medical devices, owing to the initial small patient population for devices relative to drug technologies (Sorenson et al., 2011). Also, randomisation can be difficult owing to the device-clinician learning curve. This is because inexperience with the new technology can influence uncertainty concerning the merits of the technologies in each arm of the trial, which impacts clinical equipoise. Consequently, there may be no "gold standard" i.e. randomised evidence, available when conducting an

economic evaluation. In addition, studies with small sample sizes may not be able to detect mortality results as they are often not large enough to demonstrate statistically significant differences. The short term follow up in early studies also makes it difficult to fully realise the value of a new device relative to the standard model of care. This is because the incremental costs mainly represent the initial cost of the new device, whereas the benefits are found in long term efficiency. These benefits are not demonstrated in short term follow up studies. Not being able to detect important differences between standard and new technologies can increase uncertainty in the analysis (Sorenson et al., 2011, Zwanziger et al., 2006).

There is also a tendency for these early studies to focus on higher risk patients, where most benefit can be demonstrated. Such data are used as "generic" and are "genericized" or applied to other patient groups. This practice makes it difficult to consider heterogeneity between sub-groups of patients and tends to ignore the relevance of the evidence for different patient groups (Drummond et al., 2009, Taylor and Iglesias, 2009).

Incremental Innovation

Unlike drugs, where phase III trials are undertaken when clinical results are robust, devices undergo frequent modifications which impact efficiency and end-points overtime. These evolutions are in response to clinical evidence and practice and may result in reduced procedure length, reduction in the number failures etc. Consequently, there is rarely a "steady-state" period where RCTs for devices could be undertaken without being obsolete upon reporting (Drummond et al., 2009, Taylor and Iglesias, 2009).

Genericization and Class Affect

Another challenging characteristic of medical devices is the lack of equalised clinical evidence for all products. With drugs, where assumptions about class effects are common, treating clinical evidence as generic may be suitable. With respect to devices however, while some clinical outcomes between brands are similar, their properties and modes can differ. Thus, assuming evidence is generic for medical devices can be flawed if the assumption is based on inadequate evidence of equivalence. Consequently, extrapolating evidence from one brand to another may be acceptable in the short run but assuming

devices are generic in the long run can be inaccurate and discourages research, which can impact patient safety (Drummond et al., 2009, Sorenson et al., 2011).

Pricing

Also, unlike drugs the price of medical devices can change frequently. This is due to new market entrants, incremental innovations in the device development and more flexible procurement systems for devices compared with drugs. This represents a further challenge as it affects the incremental cost effectiveness ratio (ICER) and subsequently impacts pricing and adoption decisions. Again, short term data collection efforts are insufficiently powered to detect such changes (Drummond et al., 2009, Sorenson et al., 2011).

1.2.2 Case Study

The regulation process, lack of randomised control trials, incremental innovations, the learning curve and other challenging characteristics of expensive medical device technologies (see Section 1.2.1) raises the question of how economic evaluations can be performed to inform adoption and research priority setting decisions in a timely and informative manner. To test the hypothesis that a continuous iterative framework (explained in Chapter 2) for economic evaluations is suitable for these technologies, a case study of an expensive novel technology with an immature evidence base for which demand is great is warranted. The case study chosen for this thesis is Transcatheter Aortic Valve Implantation (TAVI) for the treatment of severe, symptomatic patients with Aortic Stenosis (AS) in the United Kingdom (UK).

AS is a degenerative heart valve disease. It refers to an age-related, progressive build-up of calcium in the aortic valve. Once symptoms develop progression is rapid and if left untreated survival estimates are low at 2-3 years (Legrand et al., 1991, Vahanian et al., 2008). Therefore, managing AS effectively and efficiently is a priority. The traditional treatment for AS was aortic valve replacement (AVR) via open heart surgery. However, this procedure is often considered inappropriate for severe AS patients who have multiple co-morbidities, owing to increased complications post-surgery and mortality. Consequently, approximately one third of patients are considered inoperable and only receive medical management. The latter only offers transient relief. Transcatheter Aortic

Valve Implantation (TAVI) is a less invasive treatment for patients, whereby a bio prosthetic valve is inserted through a catheter and guided to the diseased aortic valve where it is implanted. The less invasive nature of TAVI suggests reduced complications and length of stay for operable patients compared with AVR and offers an alternative to medical management for inoperable patients. Despite its potential, uncertainty surrounding TAVI's effectiveness persists, evidence is evolving and consequently access is limited (Vahanian et al., 2008).

This thesis is the first iterative investigation of the cost effectiveness of TAVI for operable and inoperable patients. Also, as an economic evaluation for a novel expensive medical device technology, with an evolving evidence base, it identifies and addresses the key challenges with using economic evaluations to address coverage and research priority decisions for such technologies. Using TAVI as a case study, this thesis aims to contribute to the discussion about how health technology assessment agencies could deal with such medical technologies.

1.3 AIMS AND OBJECTIVES OF THESIS

The overall objective of this thesis is to investigate the challenges in applying economic evaluation methods, frameworks and policies to novel expensive medical technologies with evolving evidence. In doing so the cost effectiveness of TAVI in treating severe AS amongst operable and inoperable patients and value of collecting further information is investigated for the UK in an iterative manner. As outlined above, TAVI's adoption has become a topical issue in the UK where demand for TAVI amongst patients and clinicians is great but access is restricted owing to scarce evidence. In this context the following research questions will be addressed:

- How could uncertainty surrounding the cost effectiveness of a novel expensive medical device be incorporated into an economic evaluation?
- Could a continuous iterative framework be used to reflect evolving evidence in investigating the cost effectiveness of a novel expensive medical device?
- Can TAVI be considered cost effective for operable and/or inoperable patients with severe AS in the UK?

- Is there value in collecting additional evidence on TAVI?
- How might Access with Evidence Development schemes be used for technologies like TAVI in collecting evidence and reducing uncertainties?
- What are the challenges in determining the cost effectiveness of technologies like TAVI?
- Can the lessons learnt in this economic evaluation of TAVI inform future analyses of similar technologies?

Objective 1: Identify the challenges and recommendations for conducting economic evaluations of uncertain technologies with evolving evidence bases.

This thesis employs TAVI as a case study to identify the challenges presented when attempting to investigate the cost effectiveness of novel technologies with evolving evidence. Recommendations to address these challenges are made.

Objective 2: Investigate the cost effectiveness of TAVI.

To investigate the cost effectiveness of TAVI a decision analytical model, reflecting current understanding of the disease and technology, is constructed in this thesis. This incorporates the uncertainty surrounding the technology from a variety of sources from the evolving evidence base. A probabilistic sensitivity analysis produces estimates of the mean costs and quality adjusted life years (QALYs) to determine the cost effectiveness of TAVI for operable and inoperable. Employing a continuous iterative framework, this is re-examined as the evidence base evolves.

Objective 3: Examine the value of collecting further evidence for TAVI

This thesis examines the value of collecting further evidence on TAVI. To do so the results of the probabilistic sensitivity analysis are employed in a Bayesian Value of Information (VOI) analysis to investigate the following for TAVI: Is there value in collecting additional information? On which parameters is additional information most useful? How should the additional information be collected? These questions are re-examined in an iterative manner as the evidence base evolves.

Objective 4: Consider the Suitability of Access with Evidence Development Schemes

Having determined the cost effectiveness and value of collecting further information for TAVI on an iterative basis, as the evidence evolves, attention in the thesis turns to where now with TAVI. This assessment includes examining the suitability of Access with Evidence Development schemes for novel medical technologies with evolving evidence.

1.4 STRUCTURE OF THESIS

Chapter 2 presents the conceptual framework, theories and methodologies employed to address the research questions and objectives of the thesis. This includes economic decision analytical modelling, VOI analysis and an overview of Performance Based Risk Sharing Agreements, including Access with Evidence Development schemes. A continuous iterative framework, incorporating these methods, to address the challenges associated with medical devices is proposed.

In Chapter 3, the empirical case study is introduced and a detailed description of AS and the treatments for AS (including TAVI) are provided. This includes a review of the epidemiology of the disease and technology and the clinical and cost effectiveness evidence base, which existed at the time the case study commenced.

In Chapter 4, a decision analytical model is described and the results from the cost effectiveness analysis of TAVI are presented. This Chapter includes a description of the model structure and mechanics, the model parameters and the evidence used to populate the model in the first instance. The model is employed for a cost effectiveness analysis and Bayesian VOI analysis of TAVI for operable and inoperable patients.

Following the release of new evidence the cost effectiveness and VOI analyses for inoperable and operable patients are revised and presented in Chapters 5 and 6, respectively. Each chapter includes a detailed description as to why and how the new evidence was incorporated into the model and its effect on the adoption and research decisions. Also, the results from the re-analyses are compared to the original analyses from Chapter 4. This addresses objectives one, two and three.

Chapter 7 investigates what next for TAVI. The effect of further advances in the TAVI evidence base on the cost effectiveness and value of collecting further information on TAVI is considered for operable and inoperable patients. This includes considering the suitability of Access with Evidence Development schemes. This addresses objectives three and four.

Finally, Chapter 8 summarises and discusses the main findings of the thesis, with respect to conducting economic evaluations of expensive novel medical devices with evolving evidence. Here the challenges and recommendations for informing adoption and research priority decisions are discussed. The limitations of the thesis and the scope for future research are also presented.

CHAPTER 2 A METHODOLOGICAL FRAMEWORK FOR APPROACHING ECONOMIC EVALUATIONS

2.1 INTRODUCTION

Health systems globally face many challenges, the largest of which is rising health care expenditures (Banta, 2003). In the United States (U.S.) for example, total health expenditure as a percentage of gross domestic product (GDP) increased from 7.4% in 1972 (Glick, 2007) to 17.9% in 2009 (McKinsey, 2011). While in the United Kingdom (U.K.), health care expenditure increased from 4.6% of GDP in 1972 to 9.8% by 2009 (Qaiser, 2011). Such rising health care expenditures are thought to reflect changes in population demographics and citizens' health needs, increased availability of health technologies, wage and price inflation, changes in service intensity and the quantity of inputs per unit of health care demanded (Banta and Luce, 1993, Thorpe, 2005, Erixon, 2011). Linked to this is the rapid development and pace of change, of health technologies. Health technologies include pharmaceutical products, devices, interventions programmes etc. and refer to some form of applied knowledge which aims to contribute to a healthier population (Banta and Luce, 1993).

These challenges put further pressure on already scarce resources in health care systems. The unlimited demands for scarce resources means choices have to be made between competing health technologies, leading to cost control efforts. To address this at the macro level, risk-sharing between interested parties (patients, payers, providers etc.) and reliance on market-orientated incentives are advocated (Glick, 2007). While at the micro level, choosing between competing health technologies is increasingly based on an assessment of value for money (Glick, 2007). Those assessments are termed economic evaluations and involve the comparison of alternative health technologies in terms of their costs and consequences (Drummond et al., 2007). They address whether the benefits accruable from the technology are worth the cost of implementing the technology (Banta and Luce, 1993). Such assessments are most appropriate when the efficacy, effectiveness and availability of the technology are also determined. Efficacy examines if the technology works and does more good than harm (Drummond et al., 2007). Therefore, determining the extent to which

a technology can bring about the intended effects in ideal circumstances, such as those provided by randomised control trials (Marley, 2000, Bégaud, 2000). Effectiveness assesses if the technology works, its usefulness and considers the efficacy and acceptance of the technology amongst the target audience (Drummond et al., 2007). Thus, determining if a technology works in practice (Marley, 2000, Bégaud, 2000). Availability determines if the technology is accessible to those who need it and who could benefit from it (Drummond et al., 2007).

Economic evaluations provide a means of assessing the costs and benefits of competing health technologies under consideration. This allows for a comparison between them, following which the best (i.e. most cost effective) technology can be recommended for reimbursement (Drummond et al., 2007).

2.1.1 Healthcare Decision Making

In recent years, economic evaluation methods have advanced and are considered capable of informing technology adoption/reimbursement decisions and research and development prioritisation (Chalkidou et al., 2008, Sculpher et al., 2006).

The first decision, the adoption decision, considers if the technology is cost effective compared to its' alternative(s), given current evidence on costs and benefits. This adoption decision is based on what is currently known about costs and benefits of a technology relative to its comparators. Consequently, there is a chance that the decision made may be the wrong decision, i.e. when further information becomes available the decision may change, and this has associated costs (i.e. opportunity costs) (Briggs et al., 2006). If a technology is falsely rejected, patients are denied access to cost effective technologies. Alternatively, if a technology is falsely accepted, patients are exposed to technologies which are not cost effective. Therefore, it is important that adoption decisions are re-examined as evidence evolves, especially if there is uncertainty surrounding the original decision. The cost effectiveness analysis techniques for measuring decision uncertainty are described in this chapter.

The second decision, the research decision, considers if it is worthwhile collecting further evidence. It is recommended that, irrespective of the adoption decision the value of

collecting further information should be considered. Where this research decision is positive, the additional evidence, once collected, can be used in re-considering the adoption and research priority setting decisions (Chalkidou et al., 2008, Sculpher et al., 2006). However, generating additional evidence after a positive adoption decision can be difficult. Research (Griffin et al., 2011) has demonstrated that there is a negative relationship between further evidence generation and adoption; whereby once access to a technology is granted the likelihood of collecting further evidence decreases. An explanation for this lies in the recruitment difficulties and the ethical concerns surrounding randomisation of patients between technologies where the technology under review is widely available outside the study (Chalkidou et al., 2008). In addition, there may be difficulties sourcing finance for further research once a coverage decision has been made (Chalkidou et al., 2008).

2.1.2 Chapter Structure

This Chapter presents a methodological framework for approaching economic evaluations, to consider both the adoption and research priority setting decision. Before describing such a framework, the tools and techniques necessary for addressing the adoption and research priority setting decisions are explained and traditional frameworks are examined. While these techniques and analyses are performed routinely for consideration of medicines, capital projects etc., conducting economic evaluations for medical devices is relatively unexplored. This is owing to the distinctive characteristics (discussed in Section 1.2.1) and the lack of formal requirements for economic evaluations of medical devices, which present unique challenges in conducting evaluations. These challenges contribute to a lack of evidence on long term outcomes, incremental innovations and movements along the learning curve, which result in an evolving evidence base. Therefore, after examining existing frameworks, a methodological framework for novel expensive medical devices with evolving evidence is proposed. This framework incorporates decision analytical modelling, probabilistic sensitivity analyses, Bayesian value of information (VOI) techniques and Performance Based Risk Sharing Agreements (PBRSA) in a continuous iterative manner to address the challenges associated with medical devices.

This chapter therefore is structured as follows:

- Section 2.2 Tools And Techniques for the Adoption Decision

- Section 2.3 Tools And Techniques for the Research Priority Setting Decision
- Section 2.4 Policies For Collecting Additional Information
- Section 2.5 Traditional Frameworks for Conducting Economic Evaluations
- Section 2.6 A Continuous Iterative Framework for Economic Evaluations
- Section 2.7 Conclusion

2.2 TOOLS AND TECHNIQUES FOR THE ADOPTION DECISION

Economic evaluations inform decisions regarding the adoption of new technologies and whether further research should be undertaken using evidence of incremental costs and effects based on current information (Eckermann and Willan, 2008). The process begins with the identification of the decision problem after which the tools and techniques used to address the adoption decision for a technology are explained in this section. This includes decision analytical modelling, probabilistic sensitivity analysis etc. The results of which can be used in presented the cost effectiveness (CE) plane, incremental cost effectiveness ratio (ICER), cost effectiveness acceptability curve (CEAC) and incremental net benefit (INB) to address the adoption decision in a cost effectiveness analysis.

2.2.1 Definition of the Decision Problem

To begin the process of an economic evaluation, a clear statement identifying the decision problem, the objective of the economic evaluation and its scope should be written (Roberts et al., 2012, Caro et al., 2012). This should be in line with the perspective taken and the policy context in which the decision is being considered. The statement should also include a detailed description of the technology, the condition under consideration and the target population and sub-population, including the stage of the disease, co-morbidities and location (Philips et al., 2006). Also, all expected outcomes, health and other, should be defined (Briggs et al., 2006, Caro et al., 2012, Roberts et al., 2012). The health outcomes can be measured as events, deaths, quality-adjusted life-years (QALYs), disability-adjusted life-years etc.

2.2.2 Decision Analytical Modelling

In the last 20 years, the methodology for conducting economic evaluations has developed rapidly (Glick, 2007). For example, 20 years ago economic evaluations were informed by key findings from clinical trials; output parameters were point estimates of incremental costs and effects and uncertainty was only accounted for in a deterministic sensitivity analysis. Since the 1990's however, evidence from clinical trials and various other sources need to be brought together and extrapolated into the future when considering the decision problem, so as to include all relevant comparators (Buxton et al., 1997). Subsequently, the use of decision analytical modelling as a complement to cost effectiveness analysis has evolved. It employs quantitative methods to systematically examine the clinical, epidemiological and economic evidence base of the technology under review. This generates a precise point estimate for a specific outcome, as well as reporting uncertainty surrounding this outcome and the decision under review, which can be used to inform medical decisions and health care resource allocation (Briggs et al., 2012).

Decision analytical modelling is particularly useful when a technology is in the early stages of development, where data is sparse (Buxton et al., 1997). This may be owing to the lack of clinical trials conducted or where the clinical trials did not gather economic data. Here, decision analytical models can be employed to extrapolate beyond the data observed in trial; link intermediate clinical endpoints to final outcomes; generalise outcomes to other settings and synthesise head-to-head comparisons where relevant trials are non-existent thereby offering a means to inform decisions in the absence of mature data (Buxton et al., 1997).

Using mathematical relationships to describe a series of possible consequences which could occur, from a set of alternative technologies under consideration, decision analytical modelling provides a framework for making decisions under conditions of uncertainty (Briggs et al., 2006, Drummond et al., 2007). This framework provides a structure to represent the possible prognoses and treatment pathways arising from the technology. According to the ISPOR-SMDM Modelling Good Research Practices Task Force (Roberts et al., 2012, Caro et al., 2012), current understanding of theory and practice of the condition(s) and treatment pathways should be captured in decision analytical models. However, while the decision model aims to reflect reality in terms of the condition and treatment pathways they can be limited, owing to the constraints of the model type employed. Thus, it may not be possible to include all possible consequences and outcomes

from a disease or following a technology. Modellers therefore need to decide what options, outcomes or pathways will be formally captured in the model to best reflect current understanding (Briggs et al., 2006).

It is also worth noting, that while the availability of data can impact on model boundaries and scope, the model structure itself should reflect the natural history of the disease and treatment pathways and should not be determined by the availability of data (Philips et al., 2006).

Decision analytical modelling can also handle uncertainty and variability across sub-groups and individuals. Uncertainties arise owing to methodological variation between analysis; data requirements; sampling variation; where results need to extrapolated over time or from intermediate to final settings and where results from one study are generalised to another setting (Briggs et al., 2006, Drummond et al., 2007) (see 2.2.4 for full description). Economic evaluations should indicate how such uncertainties translate into decision uncertainty, i.e. indicate the probability that the decision made is the right one. Although, the use of decision analytical modelling in economic evaluations is not universally accepted it is endorsed and recommended by prominent decision makers such as the National Institute of Clinical Effectiveness (NICE) in the UK (Briggs et al., 2006).

Some concern has been raised about the inappropriate use of decision analytical modelling and the transparency and validity associated with models generated (Buxton et al., 1997). These concerns centre around the inappropriate use of clinical data, biases from observation data and the resulting difficulties with extrapolating and verifying results (Buxton et al., 1997). However, despite the short-comings, decision analytical modelling is a useful tool in economic evaluations. While it is true that no amount of modelling can fully offset the gaps in available information, modelling can provide point estimates for cost effectiveness analysis (Buxton et al., 1997). In particular, modelling permits valid statistical analysis of data (Drummond et al., 2007), to inform economic evaluations.

Types of Decision Models

There are many types of decision models such as decision trees, state transition modelling, dynamic transition modelling and discrete event simulation (Sonnenberg and Beck, 1993, Drummond et al., 2007).

Decision trees, the simplest and most common decision model, provide a means of graphically representing the prognosis of alternative interventions using pathways (Sonnenberg and Beck, 1993, Drummond et al., 2007). Their use is recommended for simple models, those with short time horizons or where there are complex value structures (Roberts et al., 2012). The key components of decision trees are the decision and chance nodes, pathways and probabilities. At the beginning of the decision tree there is a square decision node: this indicates a decision point between alternative options representing the decision problem. Circular chance nodes are used where two or more alternative events are possible from the decision node. These are depicted as branches growing out of the decision node. Pathways illustrate the mutually exclusive sequence of events possible, i.e. treatment effects. Finally, probabilities demonstrate the likelihood of a particular event occurring at a chance node. Expected costs and outcomes are derived from the pathway values weighted by the probability associated with that pathway (Briggs et al., 2006). There are however some limitations which hinder their use. These include the undefined nature of time within trees, the inability for repeat treatments or relapses and the cluttered appearance as the number of pathways and nodes increase.

State transition models conceptualise decision problems in terms of a set of states and transitions between those states, for a particular condition. State transition models are useful where time-dependent parameters are required and if time to an event or repeated events are important (Siebert et al., 2012). Also, they are particularly useful for representing events whose rates vary over time or the effect of interventions that span long time frames (Roberts et al., 2012). A common type of state transition model is a Markov model (Siebert et al., 2012). These models represent random processes that occur over time using cycles (Briggs and Sculpher, 1998). Cycles are discrete time periods through which the probability of a patient occupying a given state is assessed. Each state presents a different prognosis associated with alternative health interventions and has an associated cost and outcome (Drummond et al., 2007). States are illustrated as ovals. Movement between states, including direction and speed, are defined by transition probabilities. These are represented by arrows. Probabilities are attached to the Markov model to facilitate the cost and health outcome estimations. Finally, the costs and outcomes are discounted to improve the representation of the model (Briggs and Sculpher, 1998). Markov models offer distinct advantages over decision trees in that they facilitate better handling of disease complexities. Also, they can simultaneously manage costs and outcomes straightforwardly

over the long term, facilitating the calculation of quality adjusted life years (QALYs) (Briggs et al., 2006, Briggs and Sculpher, 1998).

However, a key limitation of Markov models is the "Markov Assumption", which refers to the 'memory-less' feature. Whereby, if a patients moves from one state to another the model has 'no memory' of where the patient has come from or when. This makes it difficult to build history into the model, as the probability of moving out of a state is not dependent on the previous states that the patient experienced before entering that state (Briggs et al., 2006, Briggs and Sculpher, 1998, Drummond et al., 2007). This has implications on future transition probabilities where it is not feasible to assign different transition probabilities to patients categorised by the nature or timing of their condition. However, building time dependent transition probabilities into the model and/or including additional distinctive disease states can control for this limitation (Briggs and Sculpher, 1998).

To overcome the disadvantages of decision trees and Markov models they can be used simultaneously when for example, a decision tree is more suitable for modelling a particular prognosis and the Markov model provides the time element (Drummond et al., 2007).

Cohort Simulation

By summing the costs and outcomes for all possible 'states of the world' (mutually exclusive states that can occur), weighted by the likelihood of that 'state of the world' occurring, the expected costs and outcomes can be estimated. This calculation in a Markov model also needs to take into account the length of time patients spend in each health state. Such a calculation is referred to as cohort simulation. It involves multiplying the proportion of the cohort (e.g. 1,000 patients) ending in one state in a cycle by the relevant transition probability to derive the proportion starting in another state. This is repeated for subsequent cycles and can be set up in a transparent and convenient manner in a spread sheet. Calculating the expected costs involves adding the cost of each state weighted by the proportion of the cohort in the state and adding across the cycles. The costs are discounted as appropriate. Estimating the expected survival involves adding the proportion

of the living cohort(s) for each cycle and adding across the cycles. This is repeated for each intervention, following which the costs and outcomes can be compared.

Other Types of Decision Models

Where more complex modelling is required, first order Markov modelling can be used instead of the cohort modelling described above. Or if more intricate modelling is necessary dynamic transition models or discrete event simulations can be performed.

Dynamic transition models offer a means of modelling the direct and indirect effects of communicable disease control programmes. They assume a risk of infection, which is a function of the number of infectious individuals in the population at any given time. They are appropriate when an intervention impacts on a pathogen's ecology or on disease transmission (Pitman et al., 2012). While these models are useful for modelling interactions, as the characterisation of the problem under analysis becomes more detailed, the interactions required in the model may become large and complex and/or geographical and spatial proximity may become necessary. In these situations discrete event models are more suitable (Roberts et al., 2012).

Discrete event simulation modelling offers a means of simultaneously modelling health events occurring to an individual along with that individual's interactions with others, the health system and general environment. It moves over time and the health events are mutually exclusive (Karnon et al., 2012). These models are useful for complex models representing patient events, when resource constraints are required and when the interaction between groups has a substantial impact on the results (Roberts et al., 2012).

2.2.3 Identifying and Synthesising Evidence

Identifying relevant evidence for a decision analytical model should be done in a systematic way in line with evidence based medicine. Various methods of identifying data are proposed such as starting with the highest quality studies (e.g. randomised trial data) and working down, or only employing high quality studies (Tunis et al., 2003). Where such studies do not exist, for example for novel technologies at the early stage in their lifecycle,

expert opinion can be used as a legitimate data source. According to O'Hagan (1998) and O'Hagan and Luce (2003) when eliciting expert opinion one must realise that they are unlikely to be experts in probability/statistics, therefore it is important that the language used is familiar to the expert. When eliciting expert opinion simple expressions from their knowledge, in the form of median, quartiles etc. can be elicited, to which some sensible distribution can be fitted (O'Hagan and Luce, 2003). This probability distribution should appropriately represent the expert's knowledge and uncertainty about the parameter (O'Hagan et al., 2006). There are different means of eliciting expert opinion. For example, if individual opinions are sought, structured workbooks with closed ended questions can be employed. Alternatively, where group opinion is sought after, a group interview containing five to eight experts is recommended. Here, Delphi, modified Delphi or nominal group techniques can be employed. The Delphi technique involves the anonymous elicitation of expert opinion via a survey/questionnaire, following which a summary of the results is provided to the experts and the sequence is repeated until a stopping point is reached (Normand et al., 1998). A disadvantage of this technique is that is considered to force consensus, which may underestimate true parameter uncertainty (Philips et al., 2006). To avoid forced consensus Philips et al. (2006) recommend the use of modified Delphi panels. For example, a two stage Delphi panel which involves holding face-to-face meetings with the experts and a moderator during which items where disagreement has occurred in the initial survey can be discussed. After which the survey is repeated (Normand et al., 1998). Another alternative is the nominal group technique which facilitates the pooling of experts' knowledge and judgement to arrive at estimates which are a genuine product of the group's dialogue (McDonald et al., 2009). Within each of these techniques the experts chosen should hold credibility in their field, be from a variety of practical settings and geographical locations (Philips et al., 2006). While these methods are useful, they are not flawless and it may be difficult to elicit expert opinion on variables for which there is no existing evidence (Vallejo-Torres et al., 2008). Philips et al. (2006) advocate that regardless of what method is used to identify data for parameter inputs, it should be documented and be transparent and consistent with the objectives of the model. It is often the case that data identified requires mathematical and statistical processing before it can be incorporated into the model. In such cases, it is recommended that the pre-model data be presented along with the transformed data (Philips et al., 2006).

The expanding role for economic evaluations means that evidence from a variety of sources, including other clinical, cost and health-related quality of life evidence, is required

for a number of reasons (Philips et al., 2006, Buxton et al., 1997, Sheldon, 1996). Firstly, it is uncommon that all of these parameters would be informed by a single source. Secondly, economic evaluations need to consider all relevant comparators and it is rare that a single study or trial will include all the alternatives considered relevant in an economic evaluation. Thirdly, economic evaluations require a time horizon sufficient to capture the differences in costs and effects between technologies. A single trial is unlikely to have sufficient follow up to satisfy this criterion, so to bridge the gap between evidence generated in trials and what is expected to happen in the longer term, evidence will have to be extrapolated into the future (Drummond et al., 2007). Thus, it is likely that data from a number of sources, i.e. 'multiplicity', will inform each parameter. Consequently, evidence will have to be synthesised (Spiegelhalter et al., 2004).

In light of this need for evidence synthesis, following evidence identification, Bayesian frameworks are increasingly employed to synthesise evidence for use in decision analytical models (Spiegelhalter et al., 2004, Briggs et al., 2006, Drummond et al., 2007, Sutton, 2001, Ades, 2003). A Bayesian approach refers to the formalisation of the process of learning from experience, which is in line with the incremental nature of health care advances (Spiegelhalter et al., 2004). A formal Bayesian approach, using Bayes' theorem, begins with a probability distribution describing prior beliefs about the parameter arising from external sources *(prior distribution)*. When new information is provided *(likelihood function*) the prior distribution is updated to give a new updated belief about the data *(posterior distribution)* (Welton et al., 2012). Owing to its flexible nature (compared to frequentist or classical statistical approaches) it has many advantages, such as being able to incorporate background information and facilitating sequential updating as new information becomes available (Lau et al., 1992, Prevost et al., 2000, Jones, 1995)

In this study, a fixed-effects meta-analysis is employed to synthesise the available evidence. This type of analysis assumes that all the studies employed are evaluated as having a common treatment effect. That is to say, the true outcome is the same in all the studies and differences observed are owing to randomness or sampling error (Spiegelhalter et al., 2004). The meta-analysis in this study adopts a Bayesian perspective and makes two further assumptions about the information being synthesised. Firstly, it is assumed that the baseline parameters being measured are identical between studies. Assuming identical parameters implies that the parameters are alike, suggesting that the data can be pooled and the individual studies or units can be ignored (Spiegelhalter et al., 2004, Cochrane, 2002).

Secondly, it is assumed that the information is exchangeable between the studies. This is a formal expression of the idea that there is no systematic justification for differentiating between variables from each study. Here then the 'true' treatment effect in each study is considered a random quantity drawn from some population distribution. Under broad conditions, the assumption of exchangeability is mathematically equivalent to assuming the parameters were drawn at random from a population distribution. Thus, under these assumptions the analysis can be considered the same as a traditional random-effects meta-analysis. In a random-effects meta-analysis the true intervention effect is assumed to be randomly observed from a common population distribution, thus the effects from the different studies are not necessarily equal (Spiegelhalter et al., 2004).

By assuming exchangeability, in a fixed-effects meta-analysis, a Bayesian approach to multiplicity can be applied. Here all the outcomes from the different studies can be integrated into a single model, in which it is assumed that the parameters are drawn from some common prior distribution whose parameters are unknown. Box 2.1 presents a hypothetical example of a fixed-effects meta-analysis technique (assuming exchangeability and independent parameters).

Box 2.1 Sample Evidence Synthesis

Assuming the parameter of interest, θ, is the number of deaths occurring following a procedure. Four studies (AB, CD, EF, and GH) report mortality outcomes following this procedure as shown below. Assuming identical parameters and exchangeable information the results from the four studies can be pooled to estimate θ. Letting α denote the number of deaths per study and n the number of patients per study, θ is the sum of α divided by the sum of n: $= \frac{\sum \alpha_{i=4}}{\sum n_{i=4}}$. This is shown below, where the $\sum \alpha = 4$ and $\sum n = 121$ so $\theta = 4/121 = 0.03$.

Study	**α**	**β**	**n**	**θ**
AB	1	19	20	
CD	0	26	26	
EF	2	47	49	
GH	1	25	26	
	4	117	121	**0.03**

2.2.4 Handling Uncertainty - Probabilistic Sensitivity Analysis

In every economic evaluation, and its decision analytical model, uncertainty and heterogeneity occur (Drummond et al., 2007, Briggs et al., 2006). There are various types of uncertainties which can occur. Stochastic or first order uncertainty refers to the fact that individuals faced with the same probabilities and outcomes will experience the disease/technology differently. This is owing to random variability in outcomes between identical patients (Briggs et al., 2012). Structural uncertainty refers to fact that it is uncertain if the structural assumptions in a model actually reflect reality, so is concerned with the assumptions inherent in the model (Briggs et al., 2012). Parameter uncertainty refers to the notion that the probabilities which govern outcomes are uncertain, i.e. the uncertainty in estimating the parameter of interest (Briggs et al., 2012). While heterogeneity relates to the extent to which inter-patient variability can be accounted for by patients' characteristics (Briggs et al., 2012).

Uncertainties are costly and increase the risk of making the incorrect decision regarding the cost effectiveness of a technology and its comparators. Incorrect decisions impose a cost on society, owing to delayed access to beneficial technologies and exposure to technologies later shown to be ineffective. Also, there are costs associated with attempting to reverse incorrect decisions made owing to uncertainty surrounding the results (Briggs et al., 2006, Claxton, 1999b). Thus, the uncertainties defined above need to be handled.

With respect to structural uncertainty, the impact of the model assumptions can be examined using sensitivity analysis. Determining which assumptions to consider for a scenario analysis is based on judgement by the analyst and decision maker (Drummond et al., 2007).

Parameter uncertainty refers to the accuracy with which input parameters are calculated. Imprecision can arise from using limited sample evidence to estimate input parameters such as probabilities, costs, utilities and treatment effects for populations (Briggs et al., 2006, Drummond et al., 2007). For many years, such uncertainty was only handled through deterministic sensitivity analysis (Glick, 2007, Drummond et al., 2007) but this has disadvantages and a thorough assessment of how this uncertainty impacts on the analysis of results is needed. The disadvantages include that it is only suited for a small number of parameters in practice, problems arise when parameters are correlated and it has no suitable summary measure of the implications of the uncertainty (Drummond et al., 2007,

Claxton, 2005b). Probabilistic sensitivity analysis therefore has emerged as an alternative to handle parameter uncertainty.

Probabilistic sensitivity analysis (PSA) provides a means of addressing joint uncertainty in model parameters. Probabilistic models facilitate the incorporation of uncertainty from input parameters and are a means of describing the implications of uncertainty on output parameters (Briggs et al., 2006). There are three elements to conducting a PSA: characterising uncertainty in input parameters; propagating uncertainty through the model and presenting the implications of parameter uncertainty (Section 2.2.5).

The joint implications of parameter uncertainty in a model can result in a distribution of possible cost effectiveness relating to the technologies under consideration. This is another type of uncertainty, decision uncertainty (Briggs et al., 2006), which is discussed in Section 2.2.5.

Characterising Uncertainty in Input Parameters

To characterise uncertainty about the input parameters in a model the first step is to assign probability distributions. This involves replacing the point estimates of probabilities, costs and utilities with specified probability distributions so as to reflect the uncertainty around them (Drummond et al., 2007). This assignment of distributions can be applied to characterise uncertainty in probability, cost and utility/effect parameters. This can be done in three ways.

The first way of characterising uncertainty involves using sample data. This requires fitting a parametric distribution and generating a distribution from bootstrapped samples. The second means of characterising uncertainty is based on the employment of secondary data. Whereby, distributions are assigned to the parameters based on information reported in the literature. With a beta distribution for example, this information includes the number of events which occurred and did not occur. The third way of characterising uncertainty relies on employing experts. Whereby, distributions are assigned using information obtained from experts in the field of study using available elicitation methods.

If characterising uncertainty using secondary data, probability distributions have to be assigned. Common distributions employed are the normal, log-normal, beta and gamma distributions. In selecting a distribution the logical constraints on the parameter, the type of

data and the estimation method employed for the parameter are used. That is to say, one is matching what is known about the model input parameter with the characteristics of the distribution. Thus, the choice of distribution is not arbitrary, it is guided by the form of the data, type of parameter and the estimation process (Claxton, 2005b). Box 2.2 provides descriptions of common probability distributions.

Box 2.2 Common Probability Distributions

Normal Distribution
The normal distribution is continuous in nature and when large numbers of measurements are plotted a bell shaped form is revealed (Bradley, 2007). The curve is symmetrical about the mean (μ), so the area to the left of mean is 0.5 and area to the right of the mean is 0.5. This type of distribution is always considered a candidate distribution to represent uncertainty owing to the central limit theorem.

According to the *Central Limit Theorem*, the sampling distribution of the mean will always be normal, regardless of the distribution of the underlying data, where there is sufficient sample size.

Log Normal Distribution
The log normal distribution ranges from zero to positive infinity and is positively skewed (Vose, 2007). The natural logarithm of its value generates a normal distribution.

Beta Distribution
The Beta distribution is employed to model the proportion of successes (n) in a binomial trial and ranges from zero to one taking a wide range of shapes. Here, the probability of success (p) is a Beta (α, β) random variable (Koop, 2003). These parameters correspond to the number of events occurring (α) and number of non-events (β).

Dirichlet Distribution
The Dirichlet distribution is the multinomial extension of the beta distribution. It is multivariate in nature, with one parameter per category. As its components take values (0, 1) it is considered flexible and computationally convenient for parameters with categories (Koop, 2003).

Gamma Distribution
The Gamma distribution is useful for continuous variables, particularly those considered to be highly skewed. It is constrained on the interval zero to positive infinity (Vose, 2007).

Given that probability parameters can only take values between zero and one and the probabilities of mutually exclusive events must sum to one, suitable distributions here are constrained to those which obey these rules, influenced by their method of estimation. Owing to these constraints on probabilities, often the beta distribution is considered suitable (Briggs et al., 2006). Here α and β represent the number of successes and failures

($\alpha + \beta$ = sample size (n)). Also, as it is the conjugate of the binomial distribution it is easy to update as new information becomes available.

Similar to probability parameters, cost parameters also have rules to take into consideration. Namely they are non-negative, count parameters. Often cost data is made up of counts of resource use weighted by unit costs. The count nature of these parameters suggest a Poisson distribution or its conjugate, the gamma distribution, would be suitable for cost parameters as it is constrained to values between zero and positive infinite. The normal distribution could also be used for cost parameters, appealing to the central limit theorem, as long as the constraints are not violated. Alternatively, the lognormal distribution could be used as both it and the gamma distribution can reflect the skewness often present in cost data (Briggs et al., 2006).

Similarly, the theoretical constraints for utility parameters (negative infinity at the lower end representing the worst possible health state and one at the upper end representing perfect health) influences the distribution employable. Here the beta, gamma, normal or lognormal distributions could be applied (Briggs et al., 2006). Care must be taken with states close to zero (e.g. death) and close to one. Also, as values less than one are possible the properties of some distributions are violated. A transformation of $X = 1 - U$, offers a solution such that X is a utility decrement. Here X is constrained on the interval 0 to positive infinity so can be fitted with a Gamma or log normal distribution (Briggs et al., 2006).

With respect to relative risk parameters, as the confidence limits for such parameters are estimated on the log scale (because they are made up of ratios) the lognormal distribution is considered the most suitable distribution (Briggs et al., 2006). Finally, if the parameter has categories, for example health states, the data is considered multinomial. In this instance, a multivariate generalisation of the beta distribution with parameters corresponding to the number of categories in the multi-nominal distribution can be used, this is the Dirichlet distribution (Briggs et al., 2006).

Propagating Uncertainty through the Model - Probabilistic Sensitivity Analysis

Having assigned probability distributions, the next stage of the probabilistic sensitivity analysis (PSA) is to assess the implications of the uncertainty surrounding all of the input parameters simultaneously on the model results (Drummond et al., 2007). The most

common means of propagating this uncertainty is to employ a Monte Carlo simulation with a large number of iterations e.g. 1,000 (Claxton, 2005b, Drummond et al., 2007). Here each iteration involves a random draw from each input parameter distribution. This gives a large number (e.g. 1,000) of expected costs and effects which reflect the joint parameter uncertainty in the decision model, which can be employed to inform the adoption decision.

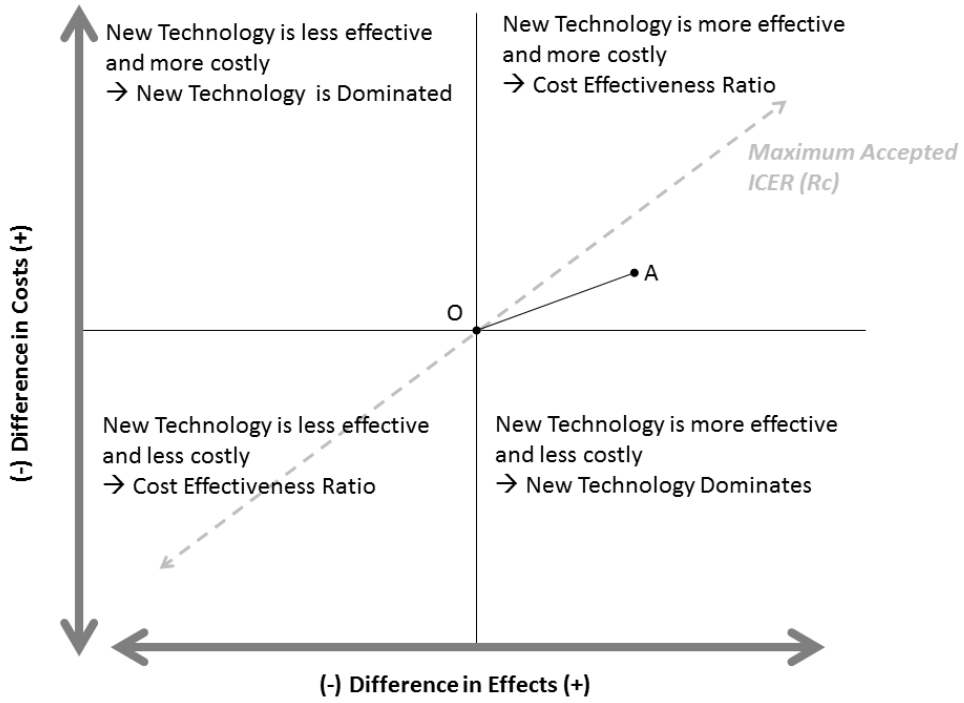
2.2.5 Presenting Cost Effectiveness Results

Cost Effectiveness Plane

A cost effectiveness (CE) plane is a four quadrant diagram which plots the incremental costs and effects (or benefits) of the technology under evaluation compared to the alternative (Black, 1990). The incremental costs are plotted on the vertical axis and effects are plotted on the horizontal axis. On Figure 2.1, Point "A" represents a point estimate for the incremental cost and effect of a hypothetical technology under consideration against a comparator.

If the health technology under consideration is more effective and less costly than the alternative, the impact falls in the South-East quadrant on Figure 2.1. Under these conditions the technology under consideration is said to dominate the alternative and is the recommended technology. There is also dominance where the technology under consideration is more costly and less effective than the comparator. Here the impact falls in the North-Western quadrant on Figure 2.1 and the comparator should be recommended. The decision is more ambiguous however when the technology under consideration is more effective and more expensive (North-Eastern quadrant on Figure 2.1) or less effective and less expensive (South-Western quadrant on Figure 2.1). In these scenarios an external measure is required to choose between alternatives (Morris et al., 2007, Drummond et al., 2007).

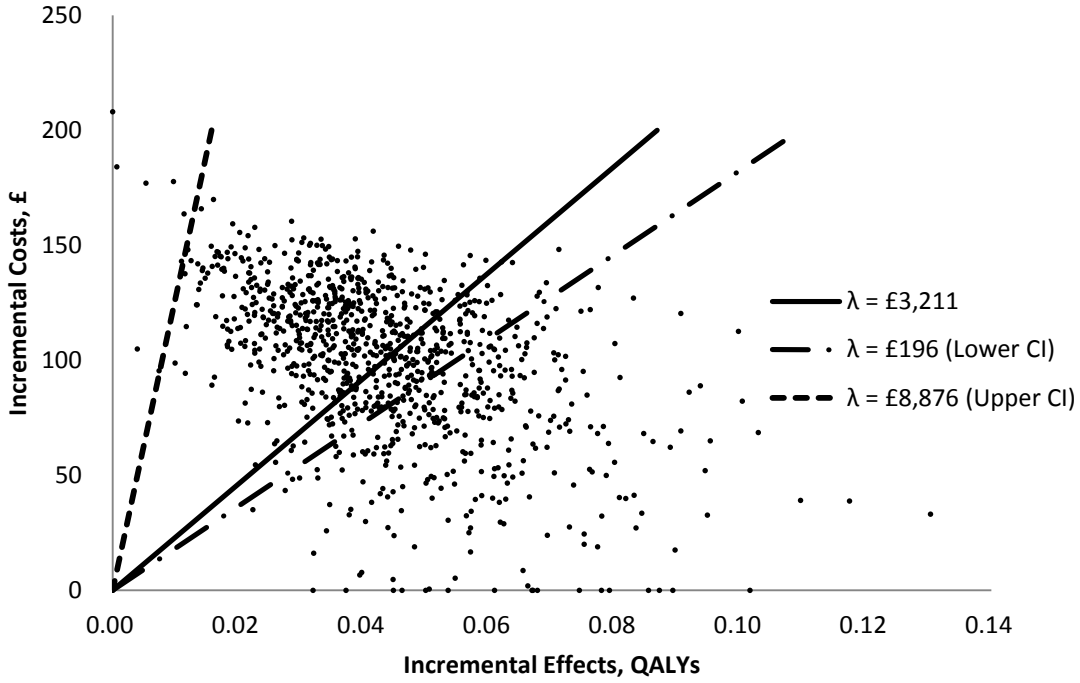
Figure 2.1 Sample Cost Effectiveness Plane



Source: Adapted from Morris et al. (2007) Pp. 254 and Drummond et al. (2007) Pp. 40

As discussed in the previous section, probabilistic models can be executed to handle uncertainty. They provide the distribution of increment cost, incremental effect and the joint effect distribution. The results of the simulation yield a large number of points (corresponding to the simulation e.g. 1,000) which can be plotted in a similar fashion to Figure 2.2. In this sample CE plane all the coordinates from the simulation lie in the north eastern quadrant. Here the vertical plane represents the uncertainty surrounding the costs and the horizontal plane represents the uncertainty in effectiveness. As per the case with one co-ordinate, here in the north-eastern and south-western quadrants an external measure is required to decide between alternatives (Morris et al., 2007, Drummond et al., 2007).

Figure 2.2 Sample Cost Effectiveness Plane from Probabilistic Sensitivity Analysis



Source: Adapted from Briggs et al. (2006) Supplementary material

Incremental Cost Effectiveness Ratio

The Incremental Cost Effectiveness Ratio (ICER) provides a measure of the additional cost per additional unit of health gain produced by one alternative when compared to another (Briggs, 2001). The ICER is calculated as the additional cost of the technology under consideration over the comparator (change in cost, ΔC) divided by the additional health gain from the technology under consideration over the comparator (change in effects, ΔQ) (Stinnett and Paltiel, 1997):

$$ICER = \Delta C / \Delta Q \qquad (2.1)$$

The Monte Carlo simulation for the PSA yields a large number (e.g. 1,000) of expected costs and effects which reflect the joint parameter uncertainty in the decision model. The average of these expected costs and benefits are used to estimate the ICER in a probabilistic model. The ICER can also be presented on the CE plane as the slope of the

line joining the point determined by the average incremental costs and effects of the technology and the origin. On Figure 2.1 this is the slope of the line joining points A and O.

Once calculated, this ICER can be compared to an external threshold value to assess if the technology can be accepted. The threshold value (or ceiling ratio), to which the ICER is compared, represents the maximum that society (or the health care provider) is willing to pay for an additional unit of effect/health gain. This is used to assess if the technology represents an efficient use of resources, considering the opportunity cost of implementing this new intervention (McCabe et al., 2008, Briggs et al., 2006, Drummond et al., 2007). The dashed line passing through the origin on Figure 2.1 represents the acceptable ceiling ratio. If the ICER is less than the ceiling ratio, the intervention is considered to be good value for money and should be implemented (Briggs, 2001). So for example, using point "A" on Figure 2.1 (representing incremental costs and effects) and recalling that the ICER is the slope of the line joining the point determined by the incremental costs and effects of the technology (A) and the origin (O), the slope of OA is less than the ceiling ratio, therefore the technology can be considered cost effective.

In the UK, the threshold value or nationally accepted ceiling ratio is currently considered to range between £20,000 and £30,000 (Rawlins et al., 2009). A range, as opposed to a fixed value, is used as it allows for consideration of the degree of uncertainty around the ICER calculation; the innovative nature of the technology under consideration; the characteristics of the condition and patient population for whom the technology is meant and wider societal costs and benefits (Simon, 1994).

Incremental Net Benefit

The incremental net benefit (INB) is an alternative to the ICER in considering the cost effectiveness of a technology. Recalling that the ICER is the ratio of the change in costs to change in effects (Equation 2.1) and if the ICER is less than the ceiling ratio (R_T) the technology is considered cost effective: $\Delta C/\Delta Q < RT$. (2.2)

Rearranging this, it can be said that the technology is cost effective if the monetary net benefit (incremental net benefit) is greater than zero. Where the monetary net benefit is the change in effects multiplied by the ceiling ratio, representing the amount the decision

maker is willing to pay for each unit of increased effectiveness less the additional costs:

$$RT * \Delta Q - \Delta C > 0. \quad (2.3)$$

That is to say, for net benefit to be positive the monetary benefit must be greater than the incremental cost (Drummond et al., 2007):

$$RT * \Delta E > \Delta C \quad (2.4)$$

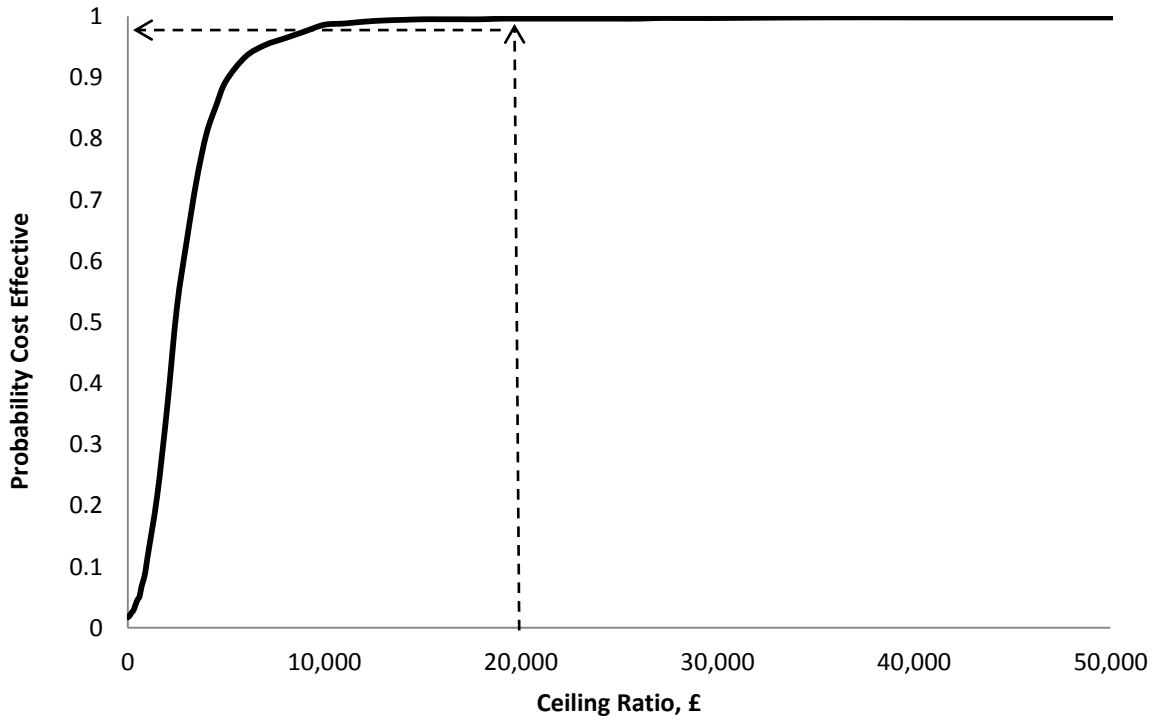
Cost Effectiveness Acceptability Curve

Owing to the issues with ICERs and the lack of cost effectiveness summary measure with the cost effectiveness plane, the cost effectiveness acceptability curves (CEAC) can be used to summarise decision uncertainty. Recall the decision rule which indicates that on the incremental cost effectiveness plane (Figure 2.2) points falling below and to the right of a line with a slope equal to the ceiling ratio indicate the technology is cost effective. Using the results of the Monte Carlo simulation, the probability of the technology being cost effective is estimated as the number of points falling in this region as a proportion of all the points. This can be used to summarise uncertainty as the probability that the technology is cost effective at that ceiling ratio. This can be repeated for all potential values of the ceiling ratio, with lines through the origin representing different willingness to pay thresholds for additional units of effectiveness. The probability of cost effectiveness at each ceiling ratio can be plotted on the CEAC. For example, if on a hypothetical Incremental Cost Effective (ICE) plane, at a ceiling ratio of £5,500/QALY, 65% of the points lie in the cost effectiveness region, so there is a 65% probability that the technology is cost effective at this ceiling ratio.

Repeating this for other ceiling ratio values show that as the ceiling ratio varies, evidence in favour of the intervention being cost effective varies also. The CEAC therefore summarises the evidence supporting the intervention being cost effective for various values of the ceiling ratio (O'Brien and Briggs, 2002), which represents the decision uncertainty in the economic evaluation (Drummond et al., 2007). Figure 2.3 presents an example of a CEAC where the proportion of the points considered cost effective for threshold values ranging from £0 to £100,000 are plotted for a hypothetical technology. The ceiling ratio values are on the x-axis and probability of the intervention being cost effective is on the y-axis.

The dashed arrows on Figure 2.3 illustrate how to read the curve to estimate the probability that the technology is cost effective. Choosing a ceiling ratio of £20,000/QALY, on the horizontal axis, move up along the dashed arrow until the curve is reached. Then move leftward to the vertical axis, to read the probability that the technology is cost effective at the £20,000/QALY ceiling ratio (shown by the vertical dashed arrow). In this example, the probability that the technology is cost effective at the £20,000/QALY ceiling ratio is 99.6%.

Figure 2.3 Sample Cost Effectiveness Acceptability Curve



Source: Adapted from Briggs et al. (2006) Supplementary material

In addition, to overcoming the issues associated with using ratios and confidence intervals CEACs also provide more information on uncertainty than the former. Firstly, where the curve intersects with the y axis this is the p-value (one sided) for the difference in costs, as a ceiling ratio of £0/QALY implies that only costs matter in the cost effectiveness calculation (Drummond et al., 2007, O'Brien and Briggs, 2002). Secondly, the ICER can be plotted as a vertical line on the same figure as the CEAC. However, the ICER will not automatically be at the 50% point. This is because the CEAC corresponds to the median difference in costs and effects, whereas the ICER corresponds to the mean difference in

costs and effects (Fenwick et al., 2001). Thirdly, the shape of the CEAC is determined by the joint uncertainty in the differences in costs and effects (Fenwick et al., 2004).

Multiple Cost Effectiveness Acceptability Curves

Patients are rarely homogeneous which gives rise to patient subgroups. As patient characteristics influence model parameters they also influence cost effectiveness results. So where an intervention can be applied to several patient types the decision to provide that intervention can be made independently on patient characteristics. Economic evaluations therefore should consider and allow for patient sub-groups. This includes producing multiple CEACs, one for each patient group so as to consider different treatment decisions for different patient subgroups (Briggs et al., 2006).

Also, for the same group of patients there can be multiple treatment options. As outlined above, decision models should include all relevant treatment options. When more than two interventions are being compared multiple CEACs can be presented, whereby there is an acceptability curve representing each treatment option. As the interventions are mutually exclusive, the CEACs should vertically sum to a probability of one.

2.3 TOOLS AND TECHNIQUES FOR THE RESEARCH PRIORITY SETTING DECISION - VALUE OF INFORMATION ANALYSIS

As outlined in Section 2.1, economic evaluations can also address research priority setting decisions. Such decisions consider if there is value in collecting additional information on the technology. Value of information (VOI) analysis is the proposed method for estimating this worth of future information.

As economic evaluations performed using the methods discussed in previous section are populated with existing information, the resulting decisions based on expected net benefit (ENB) are subject to uncertainty. This implies that there is a probability that the decision made is the wrong decision. That is to say, the decision is correct given existing

information but once the uncertainties resolve, a different decision might be made. Owing to the costs associated with making the wrong decision, including the opportunity costs of the benefits and resources foregone, this poses a problem. The expected cost of the aforementioned uncertainty is jointly determined by the probability of making the wrong decision based on current information and the associated costs of a wrong decision. These estimates of the expected cost of uncertainty can be used to calculate the value of additional information via Bayesian VOI (Chalkidou et al., 2008, Chilcott, 2003).

VOI analysis (using the results of the PSA) can address four related questions concerning the collection of further evidence (Eckermann et al., 2010): 1) Is further research worthwhile? 2) Is the cost of the proposed research design less than the expected value from the research? 3) What is the optimal design for collecting further evidence? And 4) how can research funding be best prioritised for alternative economic evaluations? To address the value of collecting further information, and the related questions, different levels of VOI analysis can be employed: Expected Value of Perfect Information (EVPI); Expected Value of Perfect Information about specific parameters (EVPPI) and Expected Value of Sample Information (EVSI). Each of these VOI methods is based on the difference in payoffs to the decision with and out information, which is used to value the information.

2.3.1 Expected Value of Perfect Information

The value of eliminating all uncertainty is referred to as Expected Value of Perfect Information (EVPI), as after all having perfect information removes uncertainty and eliminates the probability of making the wrong decision. Given the objective of health care systems to maximise health gains subject to a budget constraint, EVPI can be considered to represent the maximum health care systems are willing to pay for further information to inform the adoption decision in the future. Thus, placing an upper bound on the value of future research (Briggs et al., 2006, Claxton, 1999a, Claxton and Posnett, 1996, Eckermann and Willan, 2007, Willan and Pinto, 2005, Claxton and Sculpher, 2006).

EVPI is estimated using the expected costs, effects and cost effectiveness parameters from a DAM and PSA as follows (Ades et al., 2004, Briggs et al., 2006, Felli and Hazen, 1998, Sculpher and Claxton, 2005): the expected costs (C) and effects (Q) along with the ceiling

ratio (λ) can be used to estimate net benefit (NB) for intervention j (as per equation 2.3), as follows:

$$NB_j = Q_j\lambda - C_j \quad (2.5).$$

Assuming intervention j has unknown parameters (θ) and given current information the adoption decision is made based on the intervention that generates the maximum expected net benefits (ENB) over all iterations of the simulation (whereby, each iteration presents a possible value for θ):

$$max_j \, E_\theta NB(j, \theta) \quad (2.6)$$

If there was perfect information it would be known how the uncertainty resolves in each iteration and therefore the value of θ would be known with certainty. Consequently, the intervention with the maximum NB given the value of θ would be chosen in each iteration:

$$max_j NB(j, \theta) \quad (2.7)$$

Therefore, if the true value of θ was known, the value of the optimal decision at these known values could be obtained by maximising over *j*, max_jNB(j, θ). However, it is not known where the uncertainty around θ will resolve. So the expected value of the decision made with perfect information is estimated by averaging the maximum NB over the joint distribution of θ, given by:

$$E_\theta \, max_j \, NB \, (j, \theta) \quad (2.8)$$

To estimate EVPI the maximum expected net benefits given current information is subtracted from the expected maximum net benefits given perfect information.

$$EVPI = E_\theta \, max_j \, NB \, (j, \theta) - max_j E_\theta \, NB(j, \theta) \quad (2.9)$$

Box 2.3 provides a worked example using just five iterations with two interventions X and Y. Here, given current information the optimal decision would be to choose intervention Y as it has the highest expected net benefit (average of the net benefit over five iterations) of £39. However, if there was perfect information the decision maker could make a different decision for each iteration, choosing the intervention with the maximum net benefit for

each resolution of uncertainty. So in iteration one intervention Y would have been chosen, for the second iteration intervention X would be chosen, for the third iteration intervention Y etc. Nevertheless, it is not known in advance which is correct so the expected net benefit with perfect information is calculated as the expectation of the maximum net benefit, which here is £41.40. The EVPI then is the difference between the expected net benefit with perfect information and the expected net benefit with current information (£41.40 - £39 = £2.40). As shown in the last column this is equivalent to the opportunity loss which was estimated as the expected difference between the optimal choice and choice under perfect information per iteration (£2.40).

Box 2.3 Illustration of Expected Value of Perfect Information Calculation

Iteration #	ENB/Treatment		Optimal Choice	Maximum NB	Opportunity Loss
	X	Y			
1	27	36	Y	36	0
2	36	30	X	36	6
3	42	60	Y	60	0
4	33	30	X	33	3
5	42	39	X	42	3
Expectation	**36**	**39**		**41.40**	**2.40**

Source: Adapted from (Briggs et al., 2006)

Population Expected Value of Perfect Information

Given the public good characteristics of information, including non-rivalry, once information is produced for one patient it can be used to inform treatment decisions for all patients at no additional cost (Claxton et al., 2001, Culyer, 1999, Samuelson, 1954, Sculpher et al., 2006, Briggs et al., 2006, Claxton, 1999a, Claxton and Posnett, 1996). Therefore, the population EVPI (pEVPI) can be estimated. This is the maximum benefit more information could yield, as well as estimating the maximum return from research efforts in an area. Thus, it is a useful method when setting research priorities, identifying decision problems where the costs of uncertainty are high and where further information would be most valuable (Claxton and Posnett, 1996). The pEVPI is calculated using estimates of current and future patient numbers (I), over the lifetime of the new

intervention (T) in each time period (t) discounted at a discount rate (r) as follows (Briggs et al., 2006, Claxton et al., 2001):

$$pEVPI = EVPI \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \quad (2.10)$$

Determining the estimates of current and future patient numbers (I) and the lifetime of the new intervention (T) can be complicated to assess. It should consider far enough into the future so as to reflect important differences between alternative technologies, the duration of treatment and duration of treatment effects (Philips et al., 2006).

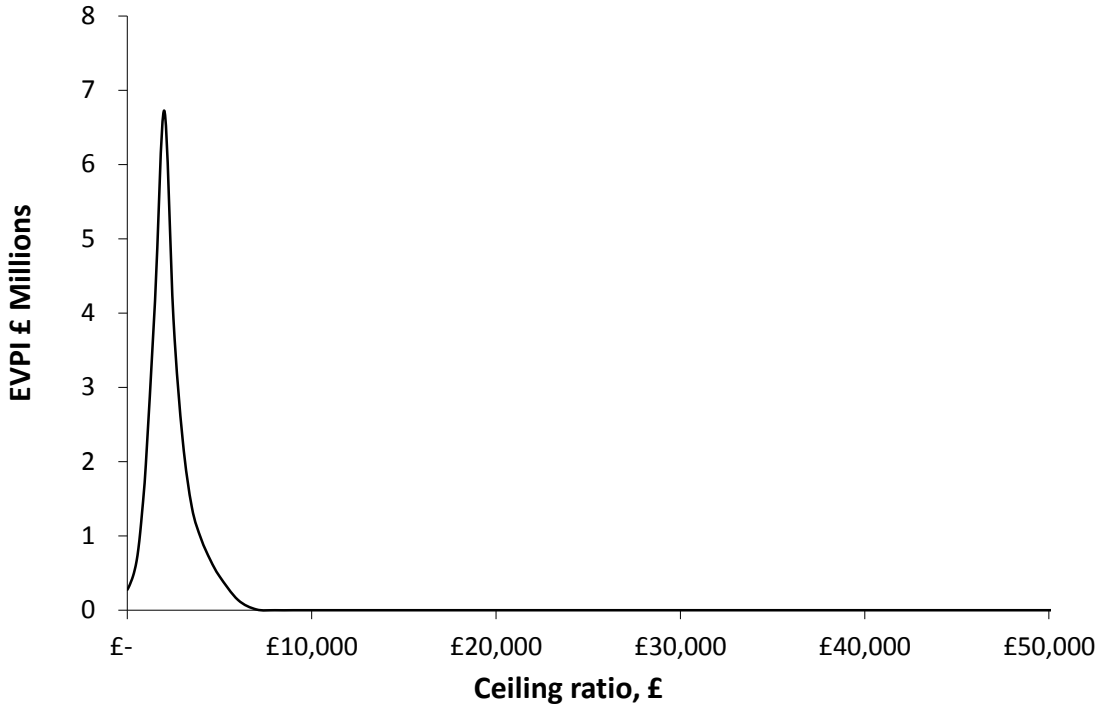
Expected Value of Perfect Information and the Ceiling Ratio

Recalling that expected net benefit is estimated using the ceiling ratio, ($NB = Q\lambda - C$), the EVPI can be estimated for different values of the ceiling ratio and plotted as a curve. The EVPI reaches a point of inflection where the ceiling ratio equals the ICER. At this point the incremental NB is zero (if only two technologies under consideration): it is the point of most uncertainty between the technologies. Figure 2.4 presents an example. Here the pEVPI reaches its point of inflection (£6.7 million) at a ceiling ratio of £2,500/QALY. Where there are two technologies under consideration this point of inflection is also the maximum pEVPI. Owing to the reliance on the ceiling ratio when estimating net benefit, there can be different EVPI estimates for different technologies for different patient populations, as well as different estimates the same technology can employed for different indications, patients and health care systems with different nationally accepted ceiling ratios (Briggs et al., 2006).

The EVPI is low when the ceiling ratio is less than the ICER and the intervention is not expected to be cost effective. Here additional information will have little effect in changing the adoption decision. In these circumstances, current evidence may be sufficient to reject the technology. However, if a higher ceiling ratio was chosen, the EVPI would increase. This is because the probability of error (decision uncertainty) increases and the consequences of making the wrong decision are valued more highly. Alternatively, if the ceiling ratio is greater than the ICER and the intervention is expected to be cost effective, generating additional information as the ceiling ratio increases is unlikely to change the decision. This is explained by the reduction in decision uncertainty as the technology appears increasingly more cost effective. Thus, as the ceiling ratio increases the probability

associated with making the wrong decision decreases which tends to reduce the EVPI. However, more value is placed on the consequences associated with making the incorrect decision which tends to increase the EVPI (Briggs et al., 2006). What happens in this trade-off between making the wrong decision and the consequences of a wrong decision depends on the elements in the decision.

Figure 2.4 Sample Population Expected Value of Perfect Information Curve



Source: Adapted from Briggs et al. (2006) Supplementary material

Using Expected Value of Perfect Information

Estimating the value of conducting future research using EVPI therefore is dependent on the uncertainty surrounding estimates of costs and effects, the expected cost effectiveness of the technology, existing evidence and size of the patient population who can potentially benefit from the additional research. It is suggested that as EVPI represents the maximum potential worth of future research it can be used in addressing the first question associated with collecting further information: Is further research worthwhile? However, as perfect information is not achievable, EVPI alone is not sufficient to determine the potential for conducting future research. It must be compared to the costs of undertaking the research,

which are dependent on the type and size of the research project. Whereby, if the EVPI is greater than the costs, **it is potentially cost effective** to conduct research to gather more information (Briggs et al., 2006, Eckermann et al., 2010). Thereby, attempting to address the second question associated with collecting further information: Is the cost of the proposed research design less than the expected value from the research? (Eckermann and Willan, 2007).

2.3.2 Expected Value of Perfect Information for Parameters

Having investigated if further research is worthwhile using EVPI, attention turns to assessing what is the optimal design for collecting further evidence? (Question 3, (Eckermann and Willan, 2007)). One consideration here is to establish on which parameters further information will be most valuable, i.e. for which parameters will a reduction in uncertainty most likely influence the decision. This can include identifying suitable end points or better estimates of existing parameter points to be included when collecting further evidence (Briggs et al., 2006, Claxton et al., 2001). The value of reducing uncertainty surrounding individual or groups of parameters in a decision analytical model can be estimated using similar methods to EVPI. Whereby, the EVPI for a parameter (EVPPI) is estimated as the difference between the ENB with perfect information, about the parameter of interest, and the ENB with current information (Ades et al., 2004, Briggs et al., 2006, Brennan et al., 2007).

In a decision analytical model with uncertain parameters θ, the value of perfect information about the parameter/subgroup of parameters (φ) are of interest. If there was perfect information it would be known how φ resolves, then the alternative with the maximum ENB could be chosen by averaging the ENB over the remaining uncertain parameters (ψ), where $\varphi \cup \psi = \theta$. That is to say, with a value for φ the ENB over the remaining uncertainties (ψ) is estimated and the alternative with the maximum ENB (j) is selected:

$$max_j E_{\psi|\varphi}\, NB(j, \phi, \psi) \qquad (2.11)$$

However, the true value(s) of φ are unknown so the expected value of the decision with perfect information is found by averaging the maximum ENBs over the distribution of φ:

$$E_{\varphi} max_j E_{\psi|\phi} NB(j, \varphi, \psi) \quad (2.12)$$

As for the expected value of the decision made with current information, as per EVPI (Equation 2.6), the optimal decision is made based on the intervention that generates the maximum ENB over all iterations of the simulation, as $\varphi \cup \psi = \theta$.

The EVPPI for the parameter/sub group of parameters (φ) is the difference between the expected value of the decision made with perfection information on φ and the decision made with current information:

$$EVPPI_{\varphi} = E_{\varphi} max_j E_{\psi|\phi} nB(j, \varphi, \psi) - max_j E_{\theta} NB(j, \theta) \quad (2.13)$$

Similar to estimating the EVPI, the results from the decision analytical model and PSA are used here to calculate the EVPPI. The simulation needs to be run for the parameters ψ with each value for φ. Values for φ are selected using an outer loop. The simulation is then run for each value of φ to generate the expected cost and effect which are used to estimate the ENB (this is the inner loop). These steps are repeated until there is sufficient sampling from the distribution of φ. Owing to the requirement for an inner and outer loop, estimating EVPPI is more computationally intensive than the EVPI estimation. The number of iterations in each loop is arbitrary but should reflect the number of parameters in φ and ψ. For example, if there is only one parameter in φ and ten in ψ, then the inner loops should have more iterations than the outer loop. However, if there are an equal number of parameters in φ and ψ then an equal number of iterations in both loops are reasonable. These steps are described in further detail in Box 2.4.

Box 2.4 Monte-Carlo Algorithm for Calculation of Expected Value of Perfect Parameter Information

Preliminary Steps ~ Adoption Decision

1. Set up a decision model comparing different strategies and set up a decision rule, for example, ICER $\leq \lambda$.
2. Characterise the uncertain parameters with probability distributions.
3. Simulate L iterations (e.g. l = 10, 000) sample sets of uncertain parameter values (Monte Carlo).
4. Work out the baseline adoption decision given current information, that is, the strategy giving the highest estimated ENB, from the average of l simulations.

Partial EVPI for a Parameter Subset of Interest

5. Obtain a sample value for the parameter of interest (φ) from its prior distribution, given by φ_k. For example, φ_k ~ Beta $(\alpha_\varphi, \beta_\varphi)$. This step corresponds to the outer-level simulation. Note these parameters of interest are a subset of the entire set of parameters ($\varphi \cup \psi = \theta$).
6. Run the Monte Carlo simulation which was set up in the preliminary steps to estimate the expected net benefit of the technology given this perfect information on φ, which is fixed at the sample value φ_k obtained in the outer loop.
   In running this simulation all remaining uncertain parameters (ψ) are simulated over l iterations (e.g. l = 10,000 times) varying according to their probability distribution conditional on φ_k . This corresponds to the inner-level simulation.
7. Calculate the expected net benefit of each strategy given the perfect information about the parameter of interest (φ). The technology chosen is the one with the highest estimated expected net benefit for the sampled value of φ.
8. Repeat steps 5-7 j times (e.g. j = 10,000 times) and calculated the average net benefit of the revised decisions given perfect information on φ.
9. Calculate and record the average net benefit of each strategy across all the inner loop iterations and then calculate the maximum of those average net benefits.
10. Across all l outer loop iterations, calculate the average of the average net benefit for each strategy and the average of the maximum net benefits.
11. To estimate the EVPPI then across the two strategies get the difference between the average maximum net benefit and the maximum average net benefit of each strategy calculated in step 7.

Source: Adapted from Brennan et al. (2007)

Selecting Parameters or Groups of Parameters

Additional parameter information is only valuable for those parameters for which additional information would change the decisions. Generally, parameters with more uncertainty, which are more closely related to the differences in NB, will have higher VOI attached to them.

As NB is a function of many parameters, often resolving uncertainty about single parameters will have little impact on NB and subsequently will have little impact on changing the decision. Consequently, considering groups of parameters, so that the joint uncertainty is resolving, is more meaningful and closer to what would be collected in a study. This process is also the first step to estimating EVSI (Section 2.3.3) and setting research priorities. A good strategy is to conduct EVPPI on small groups of parameters. This may mean grouping parameters according to the baseline risk/ natural history of the disease; based on vulnerability to selection bias; quality of life etc. Parameters with little effect on NB will have smaller VOI. It is important to note that the EVPI for groups of parameters is not equal to the sum of all the individual parameter EVPIs (Claxton et al., 2001).

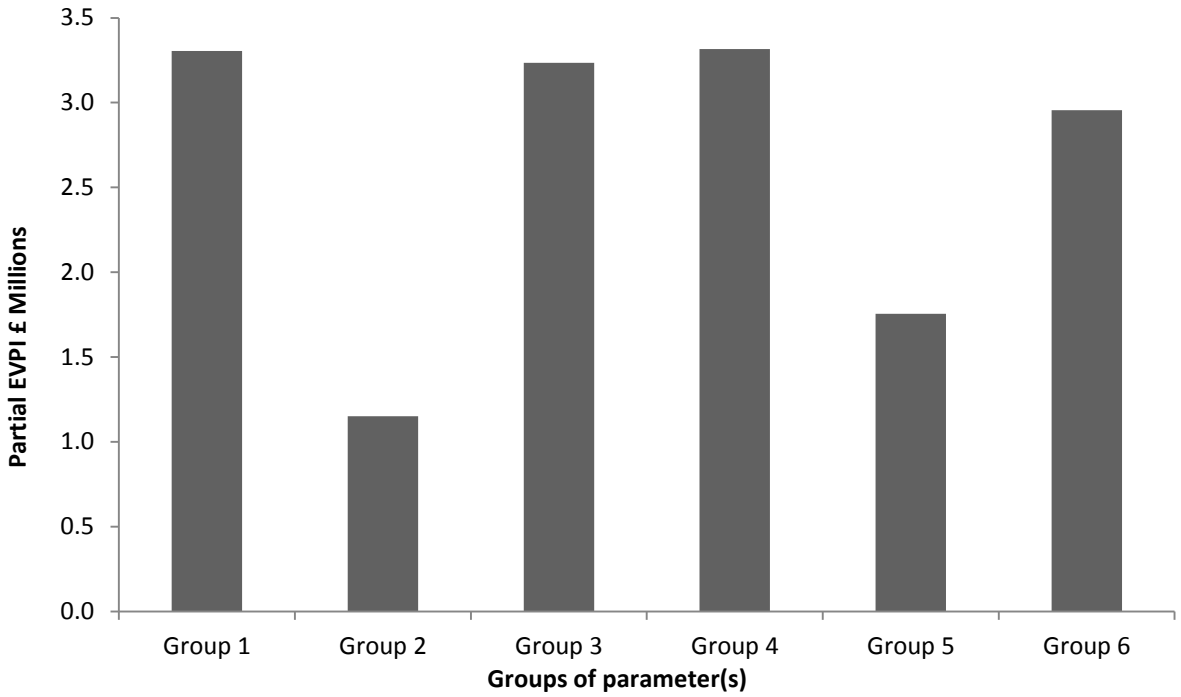
Also, parameter specific and device specific characteristics should be considered when selecting parameters and estimating EVPPI. These characteristics can mean that different parameters may be applicable for different time frames, for different populations etc. Thus, when estimating EVPPI, especially at the population level, there should be an appropriate match between the parameters included, the time frame selected and the population estimates employed.

Figure 2.5 presents sample EVPPI results, showing the EVPPI for six groups of parameters estimated using a ceiling ratio of £2,200. Alternatively EVPPI could be plotted against a range of ceiling ratios as per the EVPI (shown on Figure 2.4).

Advantages of Expected Value of Perfect Information for Parameters

EVPPI measures the sensitivity of the decision problem to uncertainty in particular parameters. This has several advantages over traditional sensitivity analyses. Firstly, a linear relationship between the parameters and NB is not required for estimating EVPPI. Secondly, as EVPPI is driven by uncertainty surrounding the decision it examines the impact of parameters on this uncertainty. Finally, the VOI estimates are consistent with the general health system objective of maximising health care subject to a budget constraint. This implies that the VOI can be compared to the costs of conducting research as well as contributing to the research design by identifying on which parameters should additional information be collected on (Briggs et al., 2006).

Figure 2.5 Sample Expected Value of Perfect Information for Parameters



Source: Adapted from Briggs et al. (2006) supplementary material.

2.3.3 Expected Value of Sample Information

As indicated above, EVPI and EVPPI can be used to begin addressing the questions surrounding the collection of further evidence. However, EVPI and EVPPI do not fully answer questions one to three outlined at the outset (1) Is further research worthwhile for this economic evaluation? 2) Is the cost of the proposed research design less than the expected value from the research? 3) What is the optimal design for collecting further evidence?). Eckermann et al. (2010) and others (Briggs et al., 2006, Claxton, 1999a) suggest that while having the EVPI greater than the cost of additional research is necessary, it is not sufficient to determine if further research should be collected. To fully address those three questions and the fourth question (How can research funding be best prioritised for alternative economic evaluations?) the VOI framework should be extended to analyse the value of sample information for a particular sample size (n) and particular research design. Thus, the marginal benefits of sampling for a patient population and the marginal costs of sampling must be examined. The Expected Value of Sample Information (EVSI) assesses the value of the trial (generation sample information) representing the amount by which the expected opportunity cost of making a decision is reduced (Willan

and Pinto, 2005). It is estimated by predicting possible sample results to form a number of possible predicted posterior means as follows (Ades et al., 2004, Briggs et al., 2006).

To estimate EVSI a process similar to that used to estimate EVPI and EVPPI is employed. However, in estimating EVSI a sample is drawn rather than assuming perfect information about parameters. Thus, the reduction in uncertainty resulting from sample information is captured; uncertainty is not eliminated. Here, the approach described in the previous sub-sections is extended, where there is more than one uncertain parameter and the value of sample information about a parameter, or subset of parameters φ, can be estimated over the remaining parameters (θ - φ = ψ).

If φ and ψ are independent then a sample of n on φ provides the sample result D. If D were known the ENB could be averaged over the prior distribution of ψ and the posterior distribution of φ given D:

$$max_j E_{\psi,\theta|D} NB(j, \varphi, \psi) \qquad (2.14)$$

However, D is unknown so the expectation of the maximum ENB over the predictive distribution of D, conditional on φ, is taken and averaged over the prior distribution of φ:

$$E_D max_j E_{\psi,\theta|D} NB(j, \varphi, \psi) \qquad (2.15)$$

As above, the EVSI is the difference between the expected value of the decision made with sample information and that with current information:

$$EVSI = E_D max_j E_{\psi,\theta|D} NB(j, \varphi, \psi) - max_j E_{\theta} NB(j, \theta) \qquad (2.16)$$

So when estimating EVSI, the predicted sample results need to be combined with prior information regarding parameters and predicted posteriors. To do this with conjugate priors is computationally intensive and inner and outer loops are required as a sample value for D from the predictive distribution conditional on θ is required. Following which a sample from the prior of ψ is needed and the posterior distribution of φ given D. Another sample of D is taken from the predictive distribution of D conditional on the revised φ. Following this the inner loop is run again. This process is repeated until a sufficient sample is drawn from the distribution of φ (corresponding to the outer loop) (Briggs et al., 2006). Note this

can also be done without conjugate priors, which is more computationally intensive, using Markov Chain Monte Carlo methods using specific software such as WinBUGS.

With respect to the sample size, the greater n is, the more possible sample results there are. Consequently, the predicted posteriors are some distance from the prior. As n increases, there is more uncertainty about the posterior distribution and it becomes more likely that the sample information will change the decision. When the mean ENB over the predicted posteriors are estimated they are greater than those with current information. Therefore, the EVSI is positive and increases as n increases. In addition, the predicted posteriors can resolve anywhere across the prior distribution so the variance of the predicted posterior tends towards the prior variance and concurrently the EVSI tends towards the EVPPI. Thus, the EVSI for a given n approaches the EVPI as n approaches infinity (Briggs et al., 2006, Claxton and Posnett, 1996). This corresponds with the consideration of EVPI as the maximum benefit possible from sample information (Claxton and Posnett, 1996). For a worked example of EVSI see Box 2.5.

Population Expected Value of Sample Information

As for the estimates of EVPI, population EVSI can also be estimated. This indicates the benefits of sample information for current and future patients. It is calculated using estimates of current and future patient numbers (I), over the lifetime of the new intervention (T) in each time period (t) discounted at a discount rate (r) as follows (Claxton and Posnett, 1996, Eckermann et al., 2010)

$$pEVSI = EVSI \sum_{t=1}^{T} \frac{I_t}{(1+r)^t} \qquad (2.17)$$

Box 2.5 Example of Expected Value of Sample Information

Preliminary Steps ~ Adoption Decision

1. Set up a decision model, with parameters θ ($\varphi \cup \psi = \theta$), comparing different strategies and set up a decision rule, for example, ICER ≤ λ.
2. Characterise the uncertain parameters with probability distributions.
3. Simulate *l* iterations (e.g. *l* = 4) sample sets of uncertain parameter values (Monte Carlo).
4. Work out the baseline adoption decision given current information, that is, the strategy giving the highest estimated ENB, from the average of *l* simulations.

Estimating EVSI

The algorithm has 2 nested loops.

5. As per step 3 above generate *l* outputs corresponding to the parameters not of interest (ψ) by sampling from their prior distributions.
    a. Suppose the set parameters not of interest, ψ, contains three parameters i.e. $\psi = (\theta_1, \theta_2, \theta_3)$.
    b. Sample values for each parameter are drawn from their prior distributions in each iteration.
        For example, if θ_1 had a beta distribution a sample value of θ_1 is drawn from the prior distribution in each simulation: $\theta_1 \sim Beta\ (\alpha_1, \beta_1)$.
        This is repeated for θ_2 and θ_3.
6. Suppose a trial with sample size n_s and follow-up period t_f collects information on the parameters of interest $(\varphi = (\theta_4, \theta_5))$. To model this, an outer loop is used in which samples for these parameters of interest are drawn from their prior distribution.
    a. For example, if θ_4 has a Gamma distribution, $\widetilde{\theta_4} \sim Gamma\ (\alpha_4, \beta_4)$ and if θ_5 has a beta distribution, $\widetilde{\theta_5} \sim Beta\ (\alpha_5, \beta_5)$.
    b. This sample information from the hypothetical trial can be used to update the α and β values for the parameters of interest (θ_4, θ_5), given the posteriors ($\tilde{\alpha}$ and $\tilde{\beta}$).
        So for θ_2: $\tilde{\alpha}_4 \sim \alpha_4 + Poisson\ (n_s * t_f * \tilde{\theta}_4)$ and $\tilde{\beta}_4 = (n_s * t_f) + \beta_4)$.
        For θ_5: $\tilde{\alpha}_5 \sim \alpha_5 + Binomal\ (n_s, \tilde{\theta}_2)$ and $\tilde{\beta}_5 = (\alpha_5 + \beta_5) + (n_s - \tilde{\alpha}_5)$.
    c. An inner loop then runs *j* times to generate an output for the parameter of interest corresponding to its posterior distribution..
        For example, $\hat{\theta}_4 \sim Gamma\ (\tilde{\alpha}_4, \tilde{\beta}_4)$ and $\hat{\theta}_5 \sim Beta\ (\tilde{\alpha}_5, \tilde{\beta}_5)$.
    d. The Monte Carlo simulation (step 3) is then run using the sample estimates for the parameters of interest and the simulated values of the parameters not of interest and the expected net benefits for each strategy is estimated (this can be done for multiple ceiling ratios).
7. The average net benefit of each strategy across all *j* inner loop iterations then can be calculated. Following which the maximum of those average net benefits can be estimated.
8. Then across all the outer loop iterations the average of the average net benefit for each strategy can be calculated and average of the maximum net benefits is estimated.
9. The EVSI can then be estimated be getting the difference between the average maximum net benefit and the maximum average net benefit of each strategy (calculated in step 8).

Source: Adapted from Ades et al. (2004) and Brennan et al. (2007)

Determining Optimal Sample Size – Expected Net Benefit of Sampling

By comparing the EVSI with the expected costs of sampling, the optimal sample size can be defined. The costs of sampling are defined in terms of financial resource costs (fixed and variable costs) and the opportunity costs. The latter include the foregone benefit for patients who are in the study (the population who stand to benefit from the research results are "used up"); the ENB foregone by those patients being treated with the inferior treatment in the trial and those who are not enrolled in the trial who receive the standard treatment while the trial is under way, therefore foregoing the future ENB (Cinto, 2008, Claxton and Posnett, 1996, Willan and Pinto, 2005, Ades et al., 2004). The difference between the EVSI and the expected costs of sampling is the Expected Net Benefit of Sampling (ENBS). The ENBS reaches a maximum at the optimal sample size. If the maximum ENBS is greater than the fixed costs of conducting the additional research then demands for additional evidence are efficient and justified (Claxton, 1999a, Claxton and Posnett, 1996, Eckermann and Willan, 2007).

Expected Value of Sample Information and Ceiling Ratio

EVSI also depends on the ceiling ratio, so different ENBS and different optimal sample sizes will be estimated at different ceiling ratios. Given the definition of ENBS above, it is apparent that it reflects a similar relationship to that between EVPI and the ceiling ratio and EVSI and the ceiling ratio. Ceiling ratios are central in determining the value of research and optimal samples sizes and ultimately research design decisions (Briggs et al., 2006, Cinto, 2008).

2.3.4 Prioritising Research

Value of information (VOI) analysis provide a formal means for decision makers to decide if there is value in collecting further evidence to inform future adoption decisions. These techniques offer a means of determining what additional evidence is needed and the type of additional evidence that would be most valuable. Efficient research design therefore is determined by characteristics of the decision problem, prior information and the monetary value of health outcomes (i.e. ceiling ratio). Determining the optimum research design is not a binary decision about whether the research should be collected, nor is it only about

determining optimal sample size. A wider consideration of research design dimensions need to be considered, such as how to allocate patients between arms, the range of combination of types of studies that could be conducted to inform uncertain parameters etc. (Cinto, 2008). The following issues also require consideration: can the evidence be provided once approval has been granted for the technology, what type of research is feasible and who should pay for the collection of that data. In light of these issues and those arising from the characteristics of medical devices, such as the device-clinician learning curve, incremental innovations etc., in assessing cost effectiveness, the challenge to develop methods which address these issues is presented (Taylor and Iglesias, 2009).

Policy developments, including Access with Evidence Development schemes, have emerged as a means of reducing uncertainty and increasing value for money, while balancing evidence generation and patient access. Such schemes track performance and link it to reimbursement; these are explained in further detail in the next section.

2.4 POLICIES FOR COLLECTING ADDITIONAL INFORMATION

2.4.1 Performance Based Risk Sharing Agreements

As discussed in Section 2.1, there are two related decisions to be made concerning adoption (Is the technology cost effective?) and collecting further research (Is there value in collecting further evidence?). As outlined in Section 2.3, Bayesian VOI techniques can be used to inform the latter, by determining if there is value in generating further evidence. After all, evidence collection is an expensive and lengthy process, during which time patients who could benefit from the technologies later proven to be cost effective are losing out.

So determining the cost effectiveness of a technology compared to its alternative(s) informs decision makers when deciding to grant access/coverage of a technology. Traditionally, this is a dichotomous decision: yes or no, whereby a suitable technology is granted coverage and unsuitable ones are not (Miller and Pearson, 2008). However, in

practice there are ambiguities, unique technologies etc. and dichotomous decisions are not always appropriate (Kamerow, 2007).

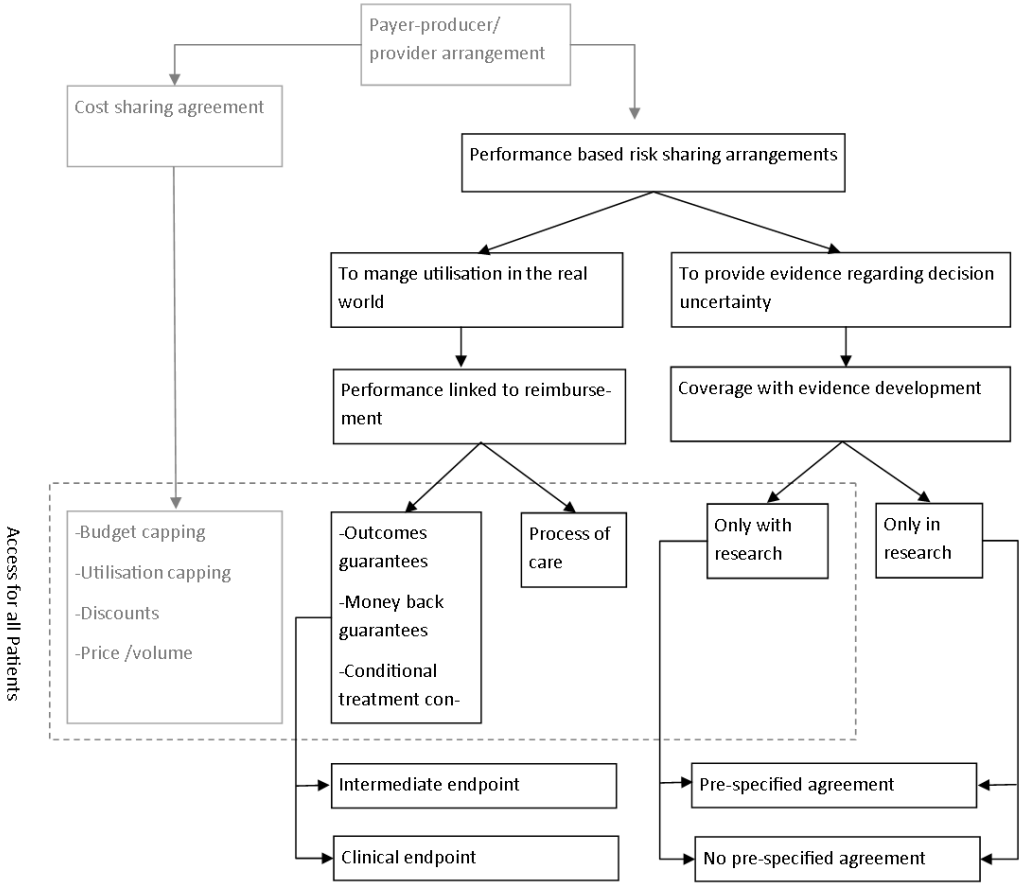
In addition to uncertainty about the decision and scarce evidence, decision makers are coming under increased pressures to become "early adopters" of new technologies. Tensions result between payers who grant coverage and patients who want access to new technologies (Mortimer et al., 2011, Booth et al., 2007, Tunis and Pearson, 2006, Chalkidou et al., 2008). Also, generating further evidence following adoption of a technology is difficult. If a technology is widely available people are less unlikely to enrol in a trial where there would randomisation between the standard and new treatments etc.

A proposed means to overcome these difficulties, which goes beyond tradition dichotomous coverage decision and coordinates and structures additional data collection, while employing economic evaluation methods, are Performance Based Risk Sharing Agreements. Such schemes track technology performance in a specified group, which can be used to influence reimbursement levels. Interest in performance tracking of technologies is increasing owing to desires amongst payers and producers to increase certainty and achieve value for money (Garrison et al., 2012).

Garrison et al. (2012) propose the term "Performance Based Risk Sharing Agreements" (PBRSA) to collectively describe the various types of schemes which exist. Under their definition, PBRSAs have five characteristics. Firstly, it is a programme for data collection which is agreed upon between the manufacturer and the payer. Secondly, the programme is initiated following regulatory approval, but prior to full diffusion of the technology. Thirdly, price and reimbursement of the technology are linked to the programme outcomes, either explicitly or implicitly. Fourthly, the primary aim of the programme is to reduce uncertainty about expected health outcomes; efficacy in a heterogeneous population; long-term endpoints; size and value of cost offsets; response rates amongst patient population etc. Fifthly, the programme provides a different distribution of risk between the payer and manufacturer than usual evidence generation methods.

Based on those criteria, Garrison et al. (2012) propose a taxonomy of the various schemes available, presented in Figure 2.6. Here PBRSAs are categorised PBRSAs into three types: Cost sharing agreements, those which aim to provide coverage while the evidence base develops and those which aim to manage utilisation and control the cost effectiveness of a new technology in the real world, where performance is linked to reimbursement.

Figure 2.6 A Taxonomy of Performance Based Risk Sharing Arrangements



Source: Garrison et al. (2012)

The first type of scheme, cost sharing agreements between the payer and the provider, refer to when access to the technology is available for all patients but budgets or utilisation is capped or discounts (perhaps based on volume) are applied.

The second are those which aim to manage utilisation and control the cost effectiveness of a new technology in the real world, where performance is linked to reimbursement, for example outcome guarantee schemes. Here performance at patient level can be linked to reimbursement for a new technology in two ways. Payment can be linked to the process of care, whereby reimbursement is specified ex-ante to depend on the clinical decision making process. Or alternatively, the focus can be on ex-post reimbursement, whereby intermediate or clinical endpoints can be measured. For example, with "outcomes guarantees" payment is received for responders only. While with "conditional treatment continuation" continuous payment is dependent on intermediate endpoints.

The third type of scheme is those which aim to provide coverage while the evidence base develops. In contrast, with these types of schemes, for example Coverage with Evidence Development schemes (also known as Access with Evidence Development), there may not be a pre-specified agreement as to how the results will impact price, revenues etc. Here all patients might receive the new technology ("only with research") or only those patients included in a trial or registry receive the new technology ("only in research").

To determine the suitability and viability of any PBRSA, the potential value of the additional evidence that it is expected to generate needs to be assessed. In addition, the expected value of that information should be greater than the expected costs of generating the evidence (Garrison et al., 2012). Thus, to assess if a proposed PBRSA meets these requirements, results from a decision analytical model and VOI analysis should be used to estimate the expected net benefit of sampling (ENBS) (This examines the difference in the expected net benefit from the scheme (EVSI) and the expected costs, described in Section 2.3). If ENBS is positive, the potential value of the additional evidence expected from the PBRSA is greater than its expected costs and the PBRSA is considered cost effective.

As indicated at the outset of this thesis, one aim is to examine the suitability and feasibility of employing PBRSAs for novel medical technologies with evolving evidence. Access with Evidence Development (AED) schemes, as a form of PBRSA, have received considerable attention in recent years and are used internationally as a means of handling the need for further evidence, monitoring performance and granting coverage. While acknowledging that there are many types of PBRSAs, the focus in thesis will primarily be on AED schemes which are discussed in further detail in the following sub-sections.

2.4.2 Introduction to Access with Evidence Development Schemes

AED schemes offer an alternative to an outright rejection for promising technologies, where current evidence is insufficient to demonstrate effectiveness/cost effectiveness (Chalkidou et al., 2008). Here restricted coverage is granted to patients for a specific period during which time additional evidence on risks, costs and effectives can be collected. This temporary coverage provides a way of generating additional evidence without widespread diffusion, the latter of which has significant costs if coverage has to be

discontinued (Lindsay et al., 2007, Turner et al., 2010, Pearson et al., 2006, Tunis and Pearson, 2006, Trueman et al., 2010, Tunis and Chalkidou, 2007). As discussed in Section 2.1, there are ethical issues surrounding the randomisation of patients between technologies when the technology under review is widely available outside the scheme. Also, there can be logistical issues surrounding how and who to recruit, as well as difficulties sourcing funding for such schemes.

AED schemes also address concerns regarding the generation of further evidence post adoption, discussed in Section 2.1. Unsurprisingly research has shown (Griffin et al., 2011) that there is a negative relationship between further evidence generation and adoption, whereby once coverage for a technology is granted, the likelihood of collecting further evidence decreases. However, a technology which is considered cost effective can have persisting uncertainties and evolving evidence. AED schemes can be useful here where further evidence is required as it offers an alternative to the affirmative "yes" in a dichotomous coverage decision, to ensure evidence is collected without delaying patients' access to the promising but unproven technology. Whereby, evidence generation and funding is linked to the recommendation by the national HTA agency, e.g. NICE in the UK (Chalkidou et al., 2007)

2.4.3 Types of Access with Evidence Development Schemes

Different forms of AED schemes have been implemented in various ways over the past 15 years across Australia, Canada, France, Italy, The Netherlands, United Kingdom and the United States, for pharmaceutical and medical device technologies (Stafinski et al., 2010). In the US, for example through the Centres for Medicare and Medicaid, AED is implemented by enrolling patients in a clinical trial to gain access to a technology while evidence is gathered (Mortimer et al., 2011, Tunis and Pearson, 2006). Examples of this include colorectal cancer drugs (Carino et al., 2006) and Positron Emission Tomography (PET) (Lindsay et al.). In Australia, the Medical Services Advisory Committee uses temporary listings on the Medical Benefits Schedule to collect additional information for promising technologies (Mortimer et al., 2011). While in the UK, NICE can issue an "only in research" recommendation rather than just "yes" or "no". This enables additional evidence collection while partial coverage is granted for the purposes of research (Mortimer et al., 2011, Neumann et al., 2011, Briggs et al., 2010).

Only in Research (OIR) refers to a situation where coverage for a technology is only available to patients who are involved in research, for example, enrolled in a trial or registry. Here the purchaser may be paying for the research or the purchaser may have rejected the technology and requested further information where the obligation and responsibility for generating this additional information lies with the manufacturer (Walker et al., 2012).

Alternatively, Only with Research (OWR) refers to a situation where a positive coverage decisions is conditional on additional evidence being generated which will influence the decision to continue, expand or withdraw with technology (Carlson et al., 2010). Here reimbursement is granted for the technology but further research is mandatory, which may be funded by the purchaser, manufacturer or other (Walker et al., 2012).

2.4.4 Advantages of Access with Evidence Development Schemes

Reviews by Stafinski et al. (2010) and others (Briggs et al., 2010, Hutton et al., 2007, Neumann et al., 2011) have identified the advantages of AED schemes for patients, providers, decision makers/payers and industry manufactures. The chief purpose of AED schemes is to generate further information, while granting conditional coverage. As information displays the two necessary characteristics of public goods, non-rivalry and non-excludability (Stiglitz, 1999), additional evidence should resolve the uncertainties surrounding the parameters and decision for all patients. Non-rivalrous consumption means that consumption of a good by one individual does not detract from another. Non-excludability suggests it is impossible to exclude anyone from consuming a good, again for information this would mean it cannot be provided privately (Stiglitz, 1999).

For patients, the main advantage is the access to promising medical technologies earlier in the technologies' life cycle, which will improve health outcomes. Such new technologies may not be made available in a tradition dichotomous decision making environment. Thus, these schemes can result in greater treatment options for patients (Stafinski et al., 2010, THETA, 2009, U.S., 2009b, U.S., 2009a, Briggs et al., 2010, Hutton et al., 2007, Committee, 2006).

For providers, AED schemes also provide access to technologies earlier in their lifecycle that without AED may not be available, thus increasing options available for their patients. The schemes also provide a means of linking research and data collection to decision making. This contributes to ensuring an appropriate quality of care is being provided (Stafinski et al., 2010, U.S., 2009b, U.S., 2009a, Committee, 2006, THETA, 2009) (Network, 2006, Carapinha, 2008, Hutton et al., 2007).

AED schemes also offer a means of managing and supporting decision-making under uncertainty for decision makers, including payers. This can include supporting reimbursement decisions by ensuring "value for money" and affordability. Employing scarce resources more efficiently should improve equality of access to promising technologies and reduce biases against promising technologies which ultimately can improve population health. Controlling evidence generation directly links research and decision making. This collaboration between industry and decision makers promotes good clinical practice while reducing uncertainty through evidence generation (2010) (U.S., 2009b, U.S., 2009a, Committee, 2006, THETA, 2009, Network, 2006, NHS, 2008c, Tonks, 1994, OHTAC, 2006, PATH, 2009, Carino et al., 2004, Médicale, 2004, Briggs et al., 2010, Hutton et al., 2007, Neumann et al., 2011).

With respect to industry stakeholders and manufactures, AED schemes can improve the return on research and development investments and incentivise future innovations. This is achieved by protecting prices and securing patient access to novel technologies with immature evidence bases, which may have been rejected in a traditional dichotomous setting. Indeed it provides faster, more flexible and more secure market access for technologies. This can provide manufacturers with the opportunity to differentiate their products early in the product lifecycle and avoid biases towards promising technologies. Linking research and decision making offers industry and decision makers the opportunity to work together, promoting good clinical practice and evidence generation (Stafinski et al., 2010, Hutton et al., 2007, Neumann et al., 2011, Médicale, 2004, Network, 2006, Carino et al., 2004, Tonks, 1994, THETA, 2009, U.S., 2009c).

2.4.5 Disadvantages of Access with Evidence Development Schemes

Despite the attractiveness of AED schemes and potential benefits for patients, industry, providers and decision makers, there are some outstanding concerns and disadvantages of AED schemes. While access to promising technologies is attractive, AED schemes by their nature only grant partial access. Thus, some patients or subgroups can be denied access if they do not meet scheme criteria which some (Wadman, 2005, Groeneveld, 2006) argue is inequitable owing to coercion, whereby access is limited to only those who enrol in the trial. However, others (Miller and Pearson, 2008, Kamerow, 2007, Pearson et al., 2006) have indicated that these arguments are unfounded where the available evidence does not provide adequate confidence in the technology under review and without the schemes there would not be access to that technology. Having access conditional on study participation may also be considered a drawback. The main disadvantage however, lies in the fact that these are promising technologies. The additional evidence collected may indicate they are unsafe and/or ineffective and coverage needs to cease. Removing access can be difficult, owing to patient resistance and risk exposure. For example, if withdrawal is owing to safety concerns there may have been a health risk for patients. This may have litigation implications for providers, payers and industry who had raised expectations (Hutton et al., 2007, Stafinski et al., 2010, Staginnus, 2009, Chapman et al., 2003, Carino et al., 2004).

While there are obvious benefits for manufactures for their products to be included in such schemes in terms of market access, AED schemes can reduce the incentive for extensive/sufficient evidence generation prior to the initial evaluation. There is a worry that AED schemes may even become an 'opt-out' for earlier, costly data collection efforts e.g. clinical trials. This may make trial recruitment difficult and randomisation unethical, all which further reduce the size and quality of initial evidence bases (NHS, 2008c, Tonks, 1994, Hutton et al., 2007, U.S., 2009b). As outlined in the Chapter 1, such concerns are already real for medical devices where there are no formal evidence collection requirements for market access and there are disincentives for research.

There is also a heavy administration, reporting, monitoring and financial burden with AED schemes and physicians must be willing to participate (Stafinski et al., 2010, Carapinha, 2008, NHS, 2008c, U.S., 2009a, Hutton et al., 2007). Setting up such schemes is also complex, requiring consensus on a range of issues such as data collection parameters,

administration arrangements, what constitutes sufficient evidence of a benefit etc. (Levin et al., 2007) (Carapinha, 2008, NHS, 2008c).

It also can be difficult to secure funding for such schemes owing to the high risks involved (Network, 2006, Carino et al., 2004). This includes financial risks. For example, an investment may have been made in a technology which is later shown not to be cost effective. Profits may also be impacted if the AED scheme delays access to the full market where for example, in a traditional dichotomous setting full coverage would have been granted at the outset (U.S., 2009b, Hutton et al., 2007, U.S., 2006). As mentioned earlier, there may be a risk of litigation if the technology is found to be unsafe or ineffective. Also, withdrawing access owing to cost effectiveness is exposing decision makers to risk (U.S., 2009b, Hutton et al., 2007). Finally, there is the risk that the scheme does not actually resolve the uncertainty or address an appropriate decision (Carino et al., 2004).

2.4.6 Future for Access with Evidence Development Schemes

In light of these disadvantages there are several challenges which need to be addressed for using AED schemes (Tunis and Pearson, 2006). Firstly, standards of evidence for the optimal scenario (whereby unconditional coverage would be granted) and the worse-case scenario (where uncertainty is considered too great for any coverage) need to be defined. For the technology to be considered for an AED scheme their evidence base should lie between the two extremes. Secondly, robust criteria should be established to rank technologies by priority based on the quality of existing evidence when considering them for an AED. Thirdly, AED schemes need to improve the quality of evidence rather than generate new uncertainties. Different stakeholders can have different views on what additional information is required, so a clear focus should be maintained when designing AED schemes. With respect to how the evidence should be collected, registries and clinical trials are both considered suitable (Miller and Pearson, 2008). Fourthly, ethical concerns must be addressed concerning patient enrolment etc. A final major challenge is ensuring there is appropriate management and sustainable funding of AED projects in the long term (Tunis and Pearson, 2006).

Experience and commentary on AED schemes conducted to date reveal consensus amongst stakeholders on the potential for AED schemes to reduce uncertainty but challenges and

concerns relating to design and implementation persist (Stafinski et al., 2010, Hutton et al., 2007, Briggs et al., 2010, Neumann et al., 2011, Tunis and Pearson, 2006). Trueman et al. (2010) propose criteria indicating where AED schemes are deemed to be suitable. Here it is recommended that AED schemes be employed for technologies which are theoretically valid but evidence is insufficient. AED schemes are also most useful where persisting uncertainty is owing to clinical or cost effectiveness outcomes, which are expected to improve, rather than financial or budgetary impacts. Here it is expected that data collection will resolve the uncertainty and traditional coverage tools are not appropriate. Lastly, for AED schemes to be successful there should be stakeholder agreement on how the additional evidence can be collected and in a reasonable timeframe.

While AED schemes are not new and still face challenges (e.g. transaction costs; outcome measurement and information technology infrastructure (Neumann et al., 2011)) they do provide a means of improving evidence bases in an ethical manner (Pearson et al., 2006). It is recognised that their full potential and appropriateness along with "best practice" guidelines for implementation are yet to be realised and they should be considered as a developing experimental policy (Miller and Pearson, 2008). In light of this, case studies are needed to examine how best AED schemes could provide input into decision making processes in real time. Such case studies need to consider the likelihood that further research will reduce the uncertainty; value of money of the additional research; implications of a positive recommendation on the evidence bases; current data collect initiatives; feasibility of new initiatives and patient access issues (Chalkidou et al., 2007).

This thesis presents such a case study by examining the cost effectiveness and value of collecting further information, for Transcatheter Aortic Valve Implantation (TAVI) in the UK in treating severe Aortic Stenosis (AS). The UK is a suitable location as the health care decision making processes here are considered one of the most unequivocal internationally. Meanwhile, TAVI was chosen as it is a novel technology which has received considerable attention internationally as one of the key medical advances in the last decade and is considered the future of cardiology.

The next section considers suitable frameworks for using the tools and techniques described in Section 2.2-2.4, for conducting the economic evaluation of the case study being considered in this thesis.

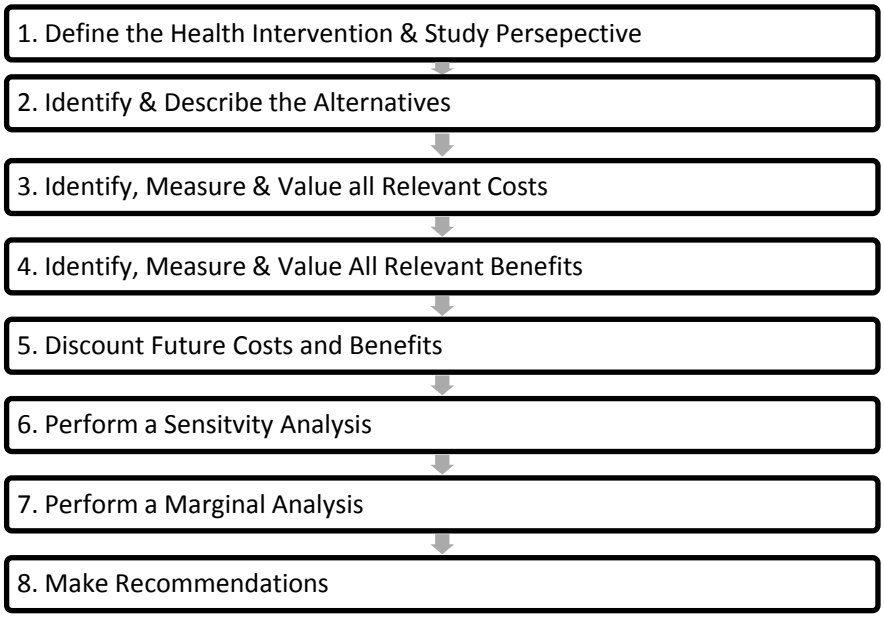
2.5 TRADITIONAL FRAMEWORKS FOR CONDUCTING ECONOMIC EVALUATIONS

Given the tools and techniques for conducting economic evaluations, described in previous sections, attention turns to how they can be used in conducting economic evaluations of novel expensive medical devices with evolving evidence. Here the suitability of three frameworks is considered.

2.5.1 A Framework for Conducting Economic Evaluations

An eight step framework for conducting economic evaluations, illustrated in Figure 2.7., has been proposed by Drummond et al. (1987) (2007). While, this eight step framework is commendable for its simplicity and transparency, it can give a false impression that economic evaluations just involve completing and summarising a balance sheet using a cost and effect for each technology (Morris et al., 2007).

Figure 2.7 Drummond's Framework for Economic Evaluation



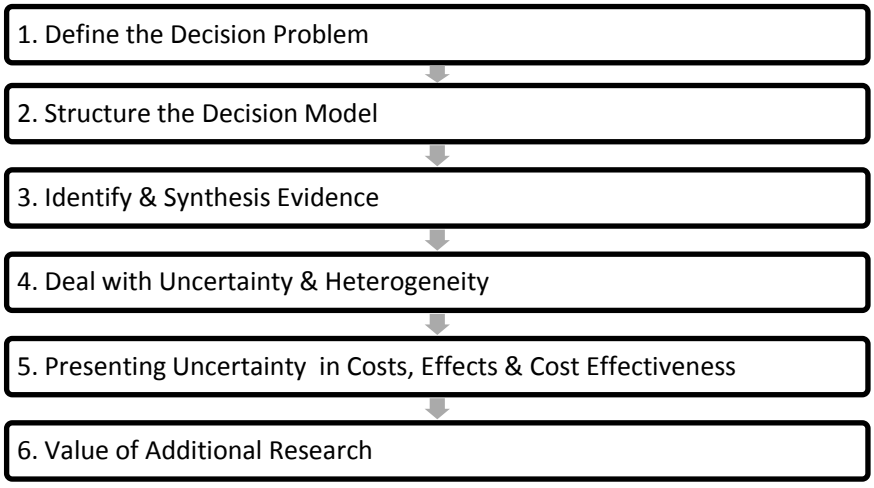
Source: Adapted from Drummond et al. (2007)

As discussed in Section 2.2, single point estimates are not sufficient for estimating the differences in costs and effects. In fact, it is likely that data from a number of sources will be required to inform each parameter thus requiring synthesis of the evidence (Spiegelhalter et al., 2004). Decision analytical modelling offers a means of representing the complexities of decision problems in a logical form and are especially useful where evidence is scarce and needs to be synthesised and used to extrapolate beyond trial endpoints (Buxton et al., 1997). Decision analytical modelling is not explicit in the eight step framework proposed by Drummond et al. (1987) (2007), but as discussed in Section 2.2 it is recommended. Also, the framework does not consider the value of collecting additional information, thereby overlooking the research priority setting decision.

2.5.2 A Framework Incorporating Decision Analytical Modelling into Economic Evaluations

Briggs et al. (2006) propose a framework for economic evaluations which explicitly includes decision analytical modelling and consideration of future research. This alternative framework, presented in Figure 2.8, indicates six distinctive stages to developing a decision model for conducting an economic evaluation, using the tools and techniques describes in Section 2.2-3.

Figure 2.8 Conducting Economic Evaluations with Decision Analytical Models



Source: Adapted from (Briggs et al., 2006)

This framework informs both adoption and research priority decisions using decision analytical modelling. However, with health technologies, especially novel medical devices, there can be incremental innovations and learning curves which result in an evolving evidence base. As new information becomes available during the lifecycle of the technology, the adoption and research decisions are influenced and could change. This framework, proposed by Briggs et al. (2006), does not account for evolving evidence, nor does it indicate how it should be captured and managed, both of which are imperative for medical devices, given their characteristics (described in Section 1.2.1).

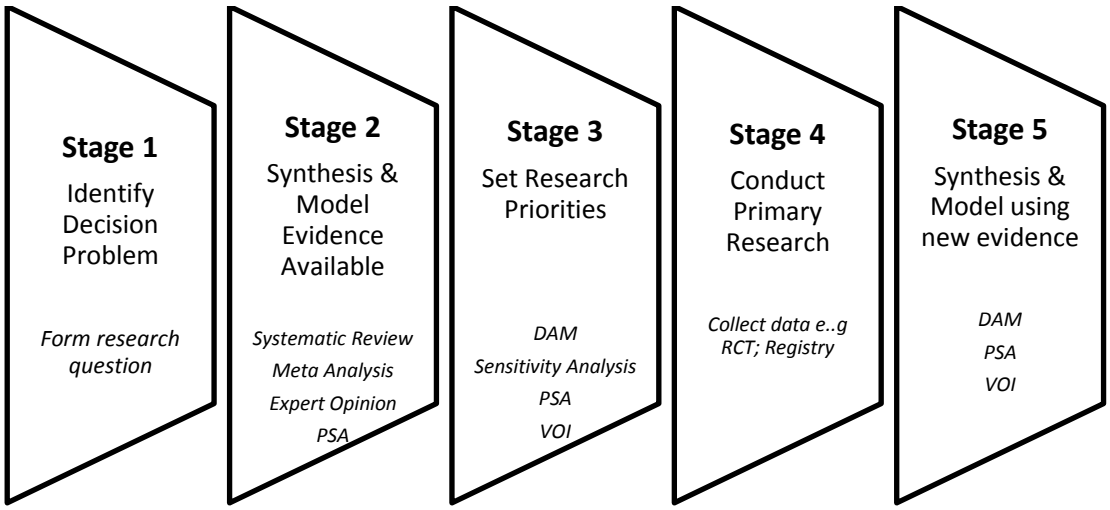
2.5.3 An Iterative Framework for Economic Evaluations

As suggested at the end of the previous sub-section, evidence bases for technologies can evolve, reflecting incremental innovations and movements along learning curves. The evolving nature of health technologies, their evidence bases and the effect of this on the aforementioned decisions, suggest an economic evaluation should not be a once off activity. According to Sculpher et al. (1997) and Fenwick et al. (2000), economic evaluations should be re-performed as evidence bases develop throughout the lifecycle of the technology. Thus, economic evaluations should be performed on an iterative basis so as to incorporate the learning about the technology. This implies that as new evidence becomes available the model should be updated to ensure consistency in decision making about the provision of the technology and research and development prioritisation to ensure access and value for money (Fenwick et al., 2000).

Sculpher et al. (1997) (2006) propose a five step framework which can be used for conducting economic evaluations on an iterative basis, illustrated in Figure 2.9. This iterative approach provides greater confidence in the cost effectiveness estimates used to inform decisions throughout the lifecycle of the technology, as they incorporate best available evidence at the time decisions are being made (Fenwick et al., 2000, Sculpher et al., 1997, Sculpher et al., 2006, Fenwick et al., 2006, Claxton, 2004, Claxton, 2005a, Vallejo-Torres et al., 2008, Boyd et al., 2010). Also, because the evaluations are performed throughout the lifecycle of the technology there are efficiency savings. For example, performing an economic evaluation early in a technology's lifecycle can avoid inefficient and costly studies on technologies which are unlikely to be considered cost effective. This promotes prioritisation of research monies for technologies which are more likely to be

considered cost effective. Thus, iterative economic evaluations can increase the speed of decision making, account for new information as it comes available and reduce costs in the long run, while reducing uncertainty surrounding cost effectiveness estimates (Boyd et al., 2010). In reducing uncertainty, evaluating technologies earlier and more frequently through the proposed iterative framework, decision makers aim to make better quality decisions.

Figure 2.9 Iterative Approach to Economic Evaluations



Source: Adapted from Sculpher et al. (2006)

The iterative framework proposed by Sculpher et al. (1997) (2006) is a step towards addressing the evolving nature of health technologies' evidence bases, while simultaneously accounting for uncertainty through the explicit inclusion of decision analytical modelling, especially for medical devices. However, it has two shortcomings. Firstly, while the framework proposed by Sculpher et al. (1997) (2006), indicates that economic evaluations should not be once off, the framework is linear. This suggests that following data collection and re-analysis in stage 5 the process is complete. However, this is often not the case, particularly for medical devices. As outlined in Section 1.2.1, the unique characteristics of medical devices give rise to incremental innovations and movements along the learning curve which lead to evolutions in the technology's evidence base. These evolutions take place throughout the lifecycle of the device. Consequently, two iterations of an economic evaluation may not be sufficient. Secondly, the framework proposed by Sculpher et al. (1997) (2006) does not consider the relationship between access and additional evidence collection. As discussed in Section 2.4, performance

tracking linked to reimbursement is increasingly important, as it provides a means of generating more evidence, which can reduce uncertainty and increase value for money. Consideration of such schemes therefore should be intrinsic in economic evaluations.

2.6 A CONTINUOUS ITERATIVE FRAMEWORK FOR ECONOMIC EVALUATIONS

Having considered the existing frameworks for conducting economic evaluations it is evident that they have developed overtime. The initial model proposed in 1987, developed in subsequent years by Drummond et al., is a concise and transparent framework. However, it does not explicitly provide provisions for the inclusion of decision modelling, which is an essential when evidence from different sources are required, necessitating extrapolation etc., and VOI. The framework proposed by Briggs et al. (2006), overcomes these omissions. However, it assumes economic evaluations are static and once off. While the latter is addressed in the Sculpher et al. (1997) (2006) framework, that too fails to adequately address the complexities arising from the unique characteristics of medical devices and excludes the consideration of performance based risk sharing agreements.

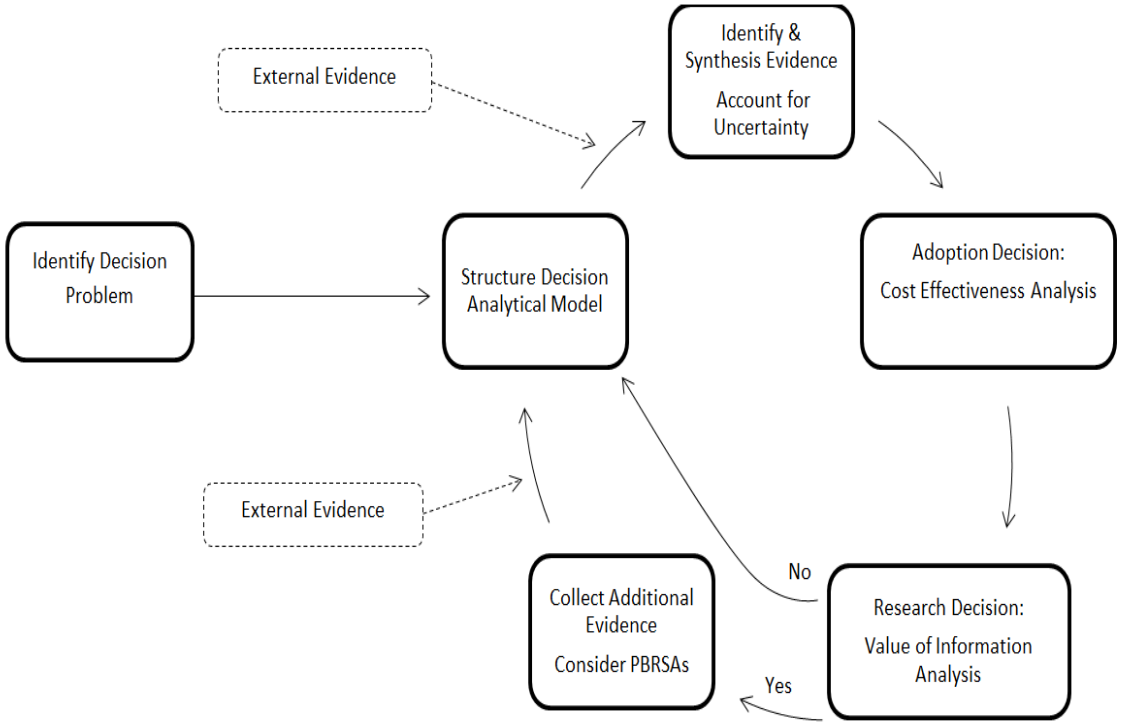
Thus, a framework for the cost effectiveness of novel expensive medical devices, capable of capturing evolving evidence is warranted. To address this, a continuous iterative framework is conceptualised here (presented in Figure 2.10).

The first stage of the proposed continuous iterative framework is to identify the decision problem, as per the frameworks considered in the previous section. In line with the ISPOR – SMDM guidelines (Roberts et al., 2012, Caro et al., 2012), a clear statement outlining the decision problem, disease, treatments etc. should be written at the outset. This will identify the technology under consideration, the alternatives, the time frame, perspective to be taken etc. (described further in Section 2.2.1).

Once the problem under consideration has been clearly identified a decision analytical model can be constructed. As discussed in Section 2.2.2, decision analytical modelling has become a requirement in economic evaluations owing to the need for evidence to be synthesised and extrapolated. An appropriate type of decision model should be selected

and constructed to accurately reflect current understanding of the theory and practice of the condition and treatment under review.

Figure 2.10 A Continuous Iterative Framework for Economic Evaluations



Source: Author's Own

Next, all relevant and available evidence should be identified; this may require a literature search. Having identified all relevant evidence it will need to be synthesised. As discussed in Section 2.2.3, given their flexible nature Bayesian approaches to synthesising evidence are advocated, as they provide a means of formalising the process of learning from experience.

Given the use of decision analytical modelling, parameter uncertainty is inevitable and needs to be accounted for. The most common means of handling parameter uncertainty is probabilistic sensitivity analysis (PSA). As explained in Section 2.2.4, this involves characterising uncertainty about the input parameters, by assigning probability distributions to each parameter and propagating the uncertainty throughout the model using a Monte Carlo simulation.

The Monte Carlo simulation provides a large number of expected costs and effects which can be used to reflect the joint parameter uncertainty in the decision model. These results can be used for a cost effectiveness analysis to estimate an Incremental Cost Effectiveness Ratio (ICER), Incremental Cost Effectiveness (ICE) plane and incremental net benefits to inform the adoption decision. Also, a Cost Effectiveness Acceptability Curve (CEAC) can be constructed to reflect decision uncertainty (see Section 2.2.5 for description of these methods). Therefore, using the results of the simulation decision makers can decide to adopt or not adopt the technology under review.

Irrespective of the adoption decision made, a Value of Information (VOI) analysis (using the model results) can be performed to assess the value in collecting further information. As outlined in Section 2.3, the Expected Value of Perfect Information (EVPI) assesses the value of eliminating all uncertainty about the adoption decision. The Expected Value of Perfect Parameter Information (EVPPI) considers for which parameters perfect information would be most valuable. Finally, Expected Value of Sample Information (EVSI) estimates the net benefit if the decision was based on sample information. This can be compared to the expected costs of sampling to estimate the Expected Net Benefit of Sampling (ENBS) to determine efficient research designs.

Hence, using the results of the simulation for the cost effectiveness and the VOI analyses decision makers can make one of four decisions (in line with Eckermann and Willan (2008)):

i. Adopt the technology and collect more information.
ii. Adopt the technology and do not collect more information.
iii. Do not adopt the technology and collect more information.
iv. Do not adopt the technology and do not collect more information.

Even if the decision not to collect more primary information (ii and iv) is made additional external information may become available over time. External information refers to evidence generated outside the health technology assessment (HTA) system where the evaluation is taking place and/or information generated outside the control of decision makers in that system. The latter could be a result of evidence generation (trial or registry) in another jurisdiction. For example, if a clinical trial conducted in the United States releases results, decision makers in the United Kingdom can avail of this information even though they had no control over its collection, dissemination etc. Alternatively, external

evidence may become available if the technology is being used in clinical practice and practitioners, professional organisations etc., record the outcomes in a database. Once available, this additional external evidence can be employed to re-assess the adoption and research priority setting decisions for that technology. In light of the new evidence, the decision model may require re-structuring, to reflect updated knowledge on the technology, all the available evidence will need to be synthesised and probability distributions will need to be assigned. The PSA can be performed again, the results of which can be used to inform the adoption decision and the VOI analysis for the research priority setting decision. After which, additional evidence can be collected if necessary and/or additional external evidence may become available and the decisions can be re-assessed as the evidence base evolves again.

Alternatively, if the decision to collect additional information is made (i and iii) consideration is given to how this additional evidence should be collected. As discussed in Section 2.4, Performance Based Risk Sharing Agreements (PBRSA), like Access with Evidence Development (AED), provide a means of collecting additional evidence by granting limited access to the technology for a specific patient group for a pre-defined time. This permits performance tracking, while generating further evidence, which can subsequently be linked to reimbursement. As outlined in Section 2.4, the suitability and value of a proposed PBRSA needs to be assessed. The results of the decision analytical model and VOI analysis (from previous steps in the framework) can be used to estimate the potential value of the evidence a proposed PBRSA will generate (Expected Value of Sample Information (EVSI)). This can be compared to the expected cost of the PBRSA to measure the Expected Net Benefit of Sampling (ENBS). If the ENBS is positive, the potential value is greater than the costs and the PBRSA is suitable. The additional evidence generated from a PBRSA, along with any additional external evidence available, can be used to re-structure the decision analytical model and all available evidence can be synthesised. This ensures that the model includes all available information on the technology. Following this, the PSA can be performed again to inform the adoption and research priority setting decisions and additional evidence can be collected and the decisions can be re-assessed as the evidence base evolves again.

This proposed framework encourages decision makers to perform iterations of the decision analytical model continuously. This ensures that evolutions in the evidence base, owing to incremental innovations, movements along the learning curve etc., are reflected and

decisions about adoption of the technology and further evidence generation are based on the best available data at that time.

Following on from the iterative approach describe by Sculpher et al. (1997) (2006) other frameworks (for example Vallejo-Torres et al. (2008) see below) have developed which aim to capture the HTA process in the UK whereby each guidance document identifies a date on which the decision will be reviewed. The framework proposed by Vallejo-Torres et al. (2008) also proposes conducting economic evaluations throughout the lifecycle of a technology, explicitly medical devices, employing Bayesian techniques iteratively. Their framework consists of three stages. Stage One, the early phase, captures the very early development phase of a device, in which expert opinion is elicited to inform the evaluation (see Section 2.2.3). Stage Two, the mid-phase, employs early evidence available which updates prior elicited beliefs. In stage three, the late stage, all available evidence is formally synthesised to inform external decision makers (Vallejo-Torres et al., 2008).

While the Continuous Iterative Framework for conducting economic evaluations proposed here has similarities with these existing frameworks and the HTA process in practice, it has several advantages. Firstly, the framework presented in this thesis is applicable to any health technology with evolving evidence. Secondly, the framework presented in this thesis is more flexible than that proposed by Vallejo-Torres et al. (2008); it does not restrict iterations to specific stages in the development of the technology. Thirdly, the framework presented in this thesis is designed to be both proactive and reactive to evolutions in the evidence base. Finally, it explicitly includes the consideration of how additional evidence could be collected and formally incorporates the consideration of PBRSAs.

2.7 CONCLUSION

As outlined in this Chapter, owing to scarce resources choices have to be made concerning the adoption and commissioning of further research for health technologies. Economic evaluations provide a means of assessing the costs and benefits of competing health technologies under consideration. Decision modelling and probabilistic analysis are increasingly being used to conduct such evaluations, the results of which can be presented

using ICERs, cost effectiveness planes, cost effectiveness acceptability curves and net benefits, which can be used to address the adoption decision. While VOI analyses can be employed to address the research priority setting decision.

In recent years, when there is value in collecting additional research health care providers, payers and manufacturers are increasingly interested in tracking performance of technologies to generate further evidence and link this to reimbursement. Such policies and agreements, collectively referred to as Performance Based Risk Sharing Agreements (PBRSA), aim to reduce uncertainty and increase value for money by generating further evidence on the technology.

As outlined in Section 2.5, frameworks for conducting economic evaluations have been developing over the years. These are employed routinely for medicines, capital projects etc. However, employing these frameworks for economic evaluations of medical devices is relatively unexplored. The lack of formal requirements for economic evaluations, as well as the distinctive characteristics of medical devices (presented in Section 1.2.1), contribute to a lack of evidence on long term outcomes and evolving evidence owing to incremental innovations which increase uncertainty. The latter present challenges in conducting economic evaluations of novel expensive medical devices. As a result, the existing frameworks taken into account in this thesis are considered insufficient for an economic evaluation of novel expensive medical devices, like the case study under consideration in this thesis.

To overcome the drawbacks of the existing frameworks, a continuous iterative framework, developed in Section 2.6, is proposed. This framework incorporates decision analytical modelling, probabilistic analysis and VOI analysis to inform the adoption and research priority setting decisions, on a continuous iterative basis as the evidence base evolves. The framework also includes the consideration of PBRSA and externally produced evidence. Therefore, it is capable of handling uncertainty and evolving evidence to inform the adoption and research priority setting decisions.

The remainder of the thesis presents an application of the proposed continuous iterative framework for the case study considering the cost effectiveness of Transcatheter Aortic Valve Implantation (TAVI). The thesis is arranged as follows: Chapter 3 presents a literature review of TAVI and Aortic Stenosis (AS), to identify the research question. Chapter 4 presents the decision analytical model and evidence synthesis. These are used to

estimate the cost effectiveness and VOI analysis of TAVI, for different patient groups (operable and inoperable) given current information (pre-trial). Chapters 5 and 6 reconsider the cost effectiveness of TAVI as the evidence base evolves with the publication of the first trial data in an iterative manner, for inoperable and operable patients respectively. Chapter 7 investigates where to go now with TAVI given evolved evidence for operable and inoperable patients. Finally, Chapter 8 concludes by discussing the challenges faced and lessons learnt from the economic evaluation performed, which are applicable when investigating the cost effectiveness of novel technologies with evolving evidence bases.

CHAPTER 3 LITERATURE REVIEW ON TRANSCATHETER AORTIC VALVE IMPLANTATION

3.1 INTRODUCTION

As outlined in Chapter 2, the rapid pace of innovation amongst health technologies presents a significant challenge for health care systems. This challenge is twofold. Firstly, decision makers within health systems must determine for whom technologies are suitable, while delivering an equitable health service. Secondly, as health care expenditures are rising, value for money is sought after. As discussed in the previous chapter, in response to these demands, economic evaluations are increasingly being incorporated into the decision making process. Economic evaluations can inform decision makers regarding the cost effectiveness of technologies, compared to its' alternative(s), for different patient groups and for setting research priorities. In the case of medical devices, this must be done while recognising their challenging characteristics (described in Chapter 1).

One discipline in medicine which has seen substantial developments in recent decades is cardiovascular disease. According to the British Heart Foundation (2012), cardiovascular disease is the main cause of death in the UK (responsible for approximately one third of all deaths). While there are numerous types of cardiac diseases, heart valve diseases, such as Aortic Stenosis (AS), are considered an important public health issue owing to poor prognosis and high prevalence amongst the increasing elderly population (Nkomo et al., 2006). The traditional treatment for severe AS is invasive and owing to the characteristics of the patient population (elderly with significant co-morbidities) approximately one third of patients are denied the procedure annually (Iung et al., 2005). Given the increasing patient population and the poor prognosis for those denied treatment, the development of a less invasive alternative, Transcatheter Aortic Valve Implantation (TAVI), is welcomed. Despite its potential, since being released in 2002, the evidence base for TAVI remains under developed and access to the procedure is limited across the US, Europe and the UK. Thus, TAVI represents a novel technology with high demand but scarce evidence, for which decision makers need to make recommendations on access and the collection of

further evidence early in its lifecycle. For these reasons, TAVI was chosen as a case study in this thesis, to examine how economic evaluations can be applied iteratively to examine the cost effectiveness of and value of collecting further evidence on novel expensive medical devices, with evolving evidence. To commence the process, this Chapter presents a description of the epidemiological background of AS, the traditional treatments available and the TAVI procedure. Following this, the evidence base for TAVI available at the point at which the case study commenced (2009) is reviewed. The subsequent chapters will examine the cost effectiveness of TAVI and the need for further research at key points in the evidence development of TAVI, in line with the continuous iterative framework developed in Chapter 2.

3.2 EPIDEMIOLOGICAL BACKGROUND OF AORTIC STENOSIS

Aortic Stenosis (AS) is the most common type of degenerative valvular heart disease (Van Brabandt and Neyt, 2008), present in 1-2% of the population aged over 65 (Chikwe et al., 2003). AS refers to the narrowing of the aortic valve (NHS, 2008b) and is caused by an age-dependent, progressive build-up of calcium in the aortic valve. The condition is particularly prevalent amongst the elderly, who have significant co-morbidities such as pulmonary hypertension, diabetes mellitus, renal failure, severe lung disease, mitral valve disease, hypertension, recent stroke, aortic regurgitation, cancer, porcelain aorta etc. (Cribier et al., 2006, Cribier et al., 2004, Vahanian et al., 2008, Webb et al., 2007).

The narrowing of the aortic valve, arising from AS, results in impaired outflow of blood from the heart (NHS, 2008b). Consequently, the left ventricle needs to pump harder to maintain a normal circulatory blood flow. Under normal conditions the aortic valve allows blood to flow forwards out of the heart and prevents back flow. With AS however, the aortic valve is narrowed so the valve is unable to open properly. Therefore, the blood cannot flow as effortlessly out of the heart. This puts a strain on the heart, as it must work harder, and over time the heart muscle may thicken so as to pump the blood harder through the narrowed valve (NICE, 2008). This results in symptoms such as chest pain brought on by exertion, angina, breathlessness, dizziness and fainting and ultimately ventricular hypertrophy (enlarged ventricles) and heart failure can result (NHS, 2008b). So without

intervention the increased pressure on the left ventricle results in symptoms of congestive cardiac failure and there is increased risk of sudden death (Chikwe et al., 2003, Legrand et al., 1991).

Risk factors for AS include a bicuspid aortic valve (where the aortic valve has only two leaflets instead of three), coronary artery disease, increased age, male gender and high cholesterol levels (Chikwe et al., 2003). Owing to the degenerative nature of valvular diseases, like AS, as populations age disease prevalence increases. In Europe, for example, it is estimated that 23% of the population will be older than 65 by 2030 (EuroStat, 2012). As a result, the related workloads and financial pressures on national health services are expected to continue (Majeed, 2005). While prevention of aortic valve disease is optimal, with 17.2% of the European population over 65 in 2009 (EuroStat, 2012) reducing symptoms and treating AS is an immediate priority.

3.3 TRADITIONAL TREATMENT FOR AORTIC STENOSIS

Treatment for Aortic Stenosis (AS) is usually required only when the disease is considered severe or symptomatic. Severe AS is defined as a valve area less than or equal to 0.6cm^2 of body surface area and/ or a mean aortic gradient of ≥ 50mmHg (Iung et al., 2005). This treatment requires replacement of the aortic heart valve, referred to as Aortic Valve Replacement (NHS, 2008b).

3.3.1 Surgical Aortic Valve Replacement

Over the past 40 years, patients with severe AS have received surgical valve replacement (AVR), which has been demonstrated to reduce the symptoms of AS and prolong life (Leon et al., 2006). AVR involves the replacement of the diseased valve with an artificial prosthesis. This is conducted through a median sternotomy approach, involving open heart surgery, where the patient is placed on a heart and lung machine (heart-lung bypass) (NHS, 2008b). To be eligible for AVR four pre-conditions are necessary, according to the American College of Cardiology/American Heart Association Guidelines (Leon et al., 2006). These include the presence of cardiac symptoms; concomitant coronary artery

bypass graft surgery; concomitant surgery of the aorta or other heart valves and left ventricular systolic dysfunction (ejection fraction less than 50%).

The artificial prosthesis inserted during AVR can be mechanical or biological. Mechanical prostheses are constructed from synthetic materials such as metals, whereas biological prostheses are made from biological materials such as porcine or bovine tissue (Van Brabandt and Neyt, 2008). Biological prostheses have a risk of structural failure resulting in the need for re-operation. While mechanical prostheses have a risk of thromboembolism and anticoagulant haemorrhage (Van Brabandt and Neyt, 2008).

Since its introduction, perioperative patient management techniques for AVR continue to improve and it has been proven to significantly improve AS symptoms and prolong life. As demonstrated by increases in valve durability and clinical benefits published over time (Leon et al., 2006). Owing to the ageing nature of AS patients however, AVR patients are often found to require prolonged hospital stays and have increased risks of renal failure, stroke and heart failure.

Also, during or post AVR there is a risk of death and complications. Operative mortality for symptomatic AS patients receiving AVR varies between 2% and 30%. Strokes are also a major concern owing to haemorrhage, aortic cannulation at the site, hypoperfusion and emboli from the calcified valve. Other major complications possible amongst these patients include chest infection, pleural effusion, post-operative bleeding, wound infections and acute renal failure (Chikwe et al., 2003).

Given the invasive nature of the procedure and risks associated with it, there are several risk indicators for surgical AVR. These are advanced age; female gender; severe chronic obstructive pulmonary disease; severely reduced left ventricular function; advanced renal or liver failure; diabetes mellitus; NYHA class III and IV; congestive heart failure and recurrent neurological insults (Leon et al., 2006, Van Brabandt and Neyt, 2008, Iung et al., 2005).

3.3.2 Medical Management

Since the 1980's, the number of patients being denied AVR has increased to approximately one third of patients, owing to high surgical mortality (Iung et al., 2005). In the absence of AVR, patients receive conservative treatment, which involves no valve replacement, just medical therapy and occasionally balloon valvuloplasty (Leon et al., 2006). Without valve replacement, the prognosis for patients with severe AS is poor. Even with aortic balloon valvuloplasty and pharmacological treatments, symptoms are only marginally relieved in the short term and the disease continues to progress, resulting in death. This is owing to significant complications, re-stenosis and further deterioration which can occur within 6-12 months (Braunwald, 2002). Thus, these patients require frequent and prolonged hospitalizations and consume a high level of health care resources. As a result, these patients are considered to be a significant economic burden to the health care system, with poor quality of life and high mortality (average survival is 2-3 years) (Legrand et al., 1991)).

3.3.3 Risk Groups

Given the nature of the disease, the associated risk factors and evidence to date, Aortic Stenosis (AS) patients can be categorised as operable or inoperable. To determine into which categories patients fit, predictive risk models and functional classification systems can be employed (Leon et al., 2006). These include functionality scales such as the New York Heart Association (NYHA) and the European System for Cardiac Operative Risk Evaluation (EuroScore) (Van Brabandt and Neyt, 2008).

European System for Cardiac Operative Risk Evaluation (EuroScore

The logistical EuroScore is a method for predicting the likelihood of death during or shortly after heart surgery, i.e. operative mortality. It identifies a number of risk factors and assigns a weight to each factor, which are used to estimate mortality on an individual basis. The factors include age, gender, previous cardiac surgery, pulmonary disease, angina, left ventricular ejection fraction, neurological dysfunction, pulmonary pressure etc. The EuroScore is widely used in Europe owing to its simplicity, user-friendly design and validity in predicting operative mortality on an individual basis for high risk patients (Roques et al., 2003). For example, patients with a logistical EuroScore > 20% would be

considered at high surgical risk. While the predictive nature of the scoring system is considered to be very good, a disadvantage is that it tends to overestimate mortality (Karabulut et al., 2003). To overcome this disadvantage the EuroScore can be used in conjunction with a functionality classification system, such as the New York Heart Association (NYHA) system.

New York Heart Association (NYHA)

The New York Heart Association (NYHA) functionality classification system indicates the functional status of patients with heart failure. It is a four-point semi-quantitative index, commonly employed owing to its useful ability to correlate clinical status with quality of life and survival (Kubo et al., 2004). The four classes are ordered by increasing disability. Patients in class I have cardiac disease without limitations on physical activity. Patients in class II have cardiac disease which impairs some physical activity. Patients in class III have cardiac disease with associated limitations in physical activity, though they are comfortable at rest. Finally, patients in class IV have cardiac disease which inhibits any physical activity without discomfort (NYHA, 1964). These classes are summarised in Table 3.1.

Table 3.1 New York Heart Association Classification

Class	Functional Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea or angina pain
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pain
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnoea or angina pain
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Source: (NYHA, 1964)

While these tools are useful, they can be imprecise by excluding less common risk factors. It is therefore recommended that patient classification be based on a combination of objective quantitative prediction models (e.g. NYHA and EuroScore) and subjective assessment by clinical teams (Leon et al., 2006).

So in the case of Aortic Stenosis patients using those tools, patients can be classified into inoperable and operable patients as follows. Those with high operative risk, e.g. Logistical EuroScore ≥ 20, and who are in NYHA class ≥ III (which is common amongst elderly patients with significant co-morbidities), require AVR but are often are denied the procedure, owing to the increase risk associated with surgery (Iung et al., 2005). Surgical mortality increases by 8.8% overall in patients aged over 65 years old (Leon et al., 2006). These patients are classified as inoperable patients, as AVR is not a viable treatment option. Thus, the treatments available for these patients are medical management or TAVI.

Patients with a lower operative risk, i.e. Logistical EuroScore < 20 and in NYHA Class II/III, are usually considered to be operable. For the purposes of this thesis, the operable patient group is further divided into low and high risk operable patients. Low risk, operable patients are those who are always considered suitable for surgery (low operative mortality ~5%, NYHA Class ≤ II). The treatments available for these patients are AVR and TAVI. High risk, operable patients are those who may be considered either eligible or ineligible for surgery depending on age, co-morbidities and other factors influencing operative mortality and function status (medium operative mortality ~ 15%, NYHA class II/III). The treatments available for these patients are AVR, TAVI and medical management.

3.4 TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

The increasing number of patients being denied AVR since the 1980's, as well as the intrusive nature of AVR has led to the development of an alternative method for valve replacement – Transcatheter Aortic Valve Implantation (TAVI). It involves the insertion of a new valve through a thin tube (a catheter) into the heart. Access to the aortic valve with TAVI is achieved transluminally through the femoral artery or vein. I.e. the catheter is inserted into the body via a large blood vessel, found for example in the groin

(transfemoral route) or via a mini-thoracotomy and apical puncture of the left ventricle (the transapical approach). In the latter, a small cut is made in the chest, through which the valve is inserted. In both procedures, a balloon catheter is advanced into the left ventricle over a guide wire and is positioned within the opening of the affected aortic valve (NHS, 2008b, NICE, 2008). After which, the existing aortic valve is dilated to make room for the new prosthetic valve. This new valve is mounted on a metal stent, following which it is directed into position and is expanded either by self-expansion or balloon inflation techniques. Once the new valve is installed, the existing aortic valve becomes redundant. A key advantage of the TAVI procedure is that it can be performed under a local anaesthetic. Therefore, it is considered minimally-invasive and avoids the emotional and physical trauma, prolonged hospital stay and long recovery associated with AVR. Consequently, it can be considered suitable for patients with high operative risk (NHS, 2008b).

There are currently two manufactures of TAVI which have earned the CE Mark approval in Europe, the Medtronic CoreValve device and the SAPIEN device by Edwards Lifesciences. For the purposes of this thesis, no differentiation is made between the devices or the insertion methods; they are all treated as one technology.

In contrast to AVR, there are several contradictions for TAVI which can limit its use (listed in Table 3.2). These include the diameter of the annulus; the presence of asymmetric heavy valvular calcification; dimension of the aortic root and presents of apical lung valve thrombus (Vahanian et al., 2008).

Table 3.2 Contraindications for TAVI

Universal Contraindications for TAVI

- Aortic annulus which is less than 18mm or greater than 25mm for balloon-expandable and less than 20mm or greater than 27mm for self-expandable devices.
- Bicuspid valves; because of the risk of incomplete deployment of the prosthesis (Zegdi 2008)
- The presence of asymmetric heavy valvular calcification, as it may compress the coronary arteries during TAVI (Webb 2007).
- Aortic root dimension greater than 45mm at the aorto-tubular junction for self-expandable prostheses.
- Presence of apical lung valve thrombus

Contraindications for the Transfemoral Approach

- Where the iliac arteries display severe calcification, tuortusosity, a small diameter or where aorto-femoral bypass was previously performed;
- Where there is severe angulation of the aorta; severe atheroma of the aorta arch; coarctation, aneurysm of the abdominal aortic with protruding mural thrombus;
- Where bulky atherosclerosis is present in the ascending aorta and the arch, as detected by TEE (transoesophageal echocardiography);
- Where the aorta is ascending transversely.

Contraindications for the Transapical approach

- If previous surgery was performed on the lung valve using a patch;
- Where there is calcified pericardium;
- If there is severe respiratory insufficiency;
- Where the lung valve apex in non-reachable.

Source: (Vahanian et al., 2008)

3.5 CURRENT EVIDENCE BASE FOR TRANSCATHETER AORTIC VALVE IMPLANTATION

To determine the effectiveness, cost effectiveness and availability of TAVI a literature review was conducted. The literature was identified through searches of PubMed, Google Scholar and from reference lists in retrieved articles in April 2009. In general, the literature providing clinical evidence reported on procedural death, mortality in the short term and events occurring post procedure. These events included stroke, myocardial infarction, cardiac tamponade, valve thromboembolism, paravavular leaks, vascular events etc. For the purposes of this thesis these events (defined in Appendix III) are termed “procedure related events” or PREs.

3.5.1 Effectiveness Evidence

Since the first use of TAVI in 2002, the annual number of procedures has been increasing, particularly for high risk patients. Between 2002 and 2008 over 1,000 high risk patients displaying symptoms of severe AS were treated using TAVI (Vahanian et al., 2008). These procedures were performed under special clinical arrangements and results were recorded in registries. No randomised clinical trials were performed at this time (Thomas, 2009). The procedures carried out up to 2009 were mainly on high risk patients, older than 80 years of age, with a Logistic EuroScore over 20% who displayed contraindications for surgery (Vahanian et al., 2008). Thus, despite first being used in 2002, by 2009, when this study commenced, TAVI's evidence base was still relatively immature. Given the characteristics of medical devices, discussed in Section 1.2.1, this was not surprising.

In 2008, Vahanian et al. (2008) published a review of early clinical results of TAVI. This review distinguished between transfemoral and transapical results and found the following. Procedure success for the transfemoral approach was found to be approximately 90%, with good valve function and valve area between 1.5 to 1.8 cm^2 (Vahanian et al., 2008). Mortality at 30 days ranged between 5-18%. While acute myocardial infarction occurred in 2-11% of cases, coronary obstruction was rare (<1%). Initially, approximately 50% of cases displayed mild-moderate aortic regurgitation; however with the development of prostheses this reduced to approximately 5%. The main causes of mortality and morbidity were vascular complications (10-15%). Stroke was experienced in 3% to 9% of patients and between 4% and 8% of patients had atrioventricular blocks which required the installation of pacemakers (Vahanian et al., 2008). Long term results (beyond 30 days or one year) were sparse in 2009. Of those that did report long term results, average survival with clinical improvement was 70-80% (Vahanian et al., 2008). For patients treated using the transapical aortic valve implantation the success rate was also approximately 90%. Here the mortality rate ranged between 9-18% and 0-6% of patients experienced a stroke (Vahanian et al., 2008). Table 3.3 summarises these results.

The evidence available on TAVI up to 2008, as reported by Vahanian et al. (2008), suggested that the technology was suitable for patients with symptoms of severe AS, it was haemodynamic and provided clinical improvement for up to two years (Vahanian et al., 2008). However, owing to questions regarding safety and long term durability it was recommended that the use of the procedure should be limited to high risk patients or those with contraindications for surgery (Vahanian et al., 2008).

Table 3.3 Effectiveness Results for TAVI 2002-2008

	Transfemoral Approach	Transapical Approach
Number of Cases	~ 900	> 300
Success Rate	~90%	~90%
Mortality Rate at 30 days	5-18%	9-18%
Stroke	3-9%	0-6%
Myocardial Infraction	2-11%	
Coronary Obstruction	<1%	
Aortic Regurgitation	~50% → ~5%	
Prosthesis embolization	~1%	
Vascular complications	10-15%	
Artioventricular blocks	4-8%	
Long Term Survival	70-80%	

Source: (Vahanian et al., 2008)

As suggested by Vahanian et al. (2008), the most representative and best data available in 2008 was evidence from early registries and case studies published in the literature. Such short term, non-randomised, high risk patient focused evidence is common amongst medical devices in the early stage of their lifecycle, as discussed in Chapter 1. In this thesis the review of effectiveness literature is expanded and developed beyond that from Vahanian et al. (2008). The literature review considered publications up to and including 2009. Here 17 papers with effectiveness evidence from case series and registries, reporting short term results for the TAVI procedure, were found. The studies are listed in Table 3.4 and are discussed below.

TAVI Literature

The literature review for TAVI revealed 17 papers with effectiveness evidence on short term results, from case series and small early TAVI registries from France, Germany, Austria, Canada and USA. USA (See Appendix II for search strategy). Sample sizes ranged from 1 to 86 patients and the average was 31 (median = 30). Having identified and reviewed the relevant literature, evidence on mortality and procedure related events (PREs) were extracted per patient following TAVI as follows. This evidence will be used to form a data base on the effectiveness of TAVI.

Table 3.4 Effectiveness Literature Reviewed

AUTHOR	Year	Location	N
TAVI Literature			
(Cribier et al., 2004)	2002-2003	France	6
(Hanzel et al., 2005)	2003	USA	1
(Sack et al., 2005)	June – July 2005	Germany	2
(Cribier et al., 2006)	2003	France	36
(Grube et al., 2006)	Feb - Nov 2005	Germany	25
(Lichtenstein et al., 2006)	-	Canada	7
(Webb et al., 2006)	Jan - July 2005	Canada	18
(Berry et al., 2007)	Mar 2005 – Feb 2007		13
(Eltchaninoff et al., 2007)	2003 - 2005	France	36
(Grube et al., 2007)	Aug 2005 – Feb 2007	Canada, Germany	86
(Marcheix et al., 2007)	Dec 2005 - Aug 2006	Canada	10
(Walther et al., 2007)	-	Germany, Austria, USA	59
(Webb et al., 2007)	-	Canada	50
(Descoutures et al., 2008)	Oct 2006- April 2007	France	66
(Svensson et al., 2008)	Dec 2006 – Feb 2008	-	40
(Walther et al., 2008)	Feb 2006 – Mar 2007	-	50
(Ye et al., 2009)	-	Canada	26
AVR Literature			
(Gehlot et al., 1996)	1987-1996	UK	103
(Milano et al., 1998)	1981-1995	Italy	355
(Gilbert et al., 1999)	1985-1996	Germany	455
(Aupart et al., 2006)	1984-2003	France	1,133
(Eichinger et al., 2008)	1971-1992	USA	322
Stroke Literature			
(Bando et al., 2003)	1977-2001	Japan	812
(Melby et al., 2007)	1993-2005	USA	245
(Alsmady et al., 2009)	2001-2008	-	64

- Indicates missing information

Criber et al. (2004) presented results on six patients, all in New York Heart Association (NYHA) Class IV, who received an anterograde TAVI procedure in France, between April 2002 and August 2003. Five patients were male and the average age was 75±12 years. The procedure was considered successful in five patients. Vascular events were reported for only one patient. One patient died immediately from cardiac causes, while three patients

died during the first eight weeks. One vascular event was reported within the first 30 days. This was an early study which concluded that TAVI may become an important treatment option for non-surgical patients in the future.

The first report of a technically successful retrograde TAVI procedure was made by Hanzel et al. (2005). Here a single TAVI procedure was performed on an 84 year old male, in the USA. The patient had severe AS, congestive heart failure and a previously failed valve replacement. There was no evidence of bleeding or myocardial infarction and the procedure was considered successful. In 2005 also, Sack et al. (2005) reported outcomes for two patients who received the TAVI procedure in Germany. At follow up, both patients were alive, aortic insufficiency was reduced and minimal regurgitation was reported for one patient.

Criber et al. (2006) reported results from a single centre pilot trial delivering TAVI in France in August 2003, with 36 patients. All patients were in NYHA Class IV; the average age of patients was 80±7 and 57% were male. Post-procedure, 27 procedures were considered successful. At nine month follow up, 11 patients were alive. Overall, the rate of major adverse events within 30 days was 26%. Five cases of major paravavular leakages were reported within the first 30 days. The study reported that zero cases of myocardial infractions and pacemaker insertions were reported in the same period, which is useful for constructing the data base.

Grube et al. (2006) reported results from a single centre registry study conducted in the Siegburg Heart Centre, Germany, with 25 patients. The average logistical EuroScore prior to receiving the procedure was 11%. The average age of patients was 80.3±5.4, of whom 80% were female. Grube et al. (2006) reported that two patients converted to AVR, i.e. did not receive the TAVI procedure. Device and procedural success was 88%, corresponding to 21 patients. Meanwhile, 18 patients survived to discharge with no adverse events occurring within 30 days of leaving the hospital. The study also reported that within the first 30 days zero cases of valve thromboembolism, myocardial infarction, endocarditis and major paravavular leaks were reported. There was one case of cardiac tamponade and five vascular events in the same period. Despite the small sample size, this study provides a thorough description of the clinical results of TAVI, especially with respect to procedure related events.

Lichtenstein et al. (2006) reported outcomes on seven patients who received the TAVI procedure in Canada. All patients were considered high risk, the average age of patients was 77±9 and five were male. The average NYHA classification was III and surgical mortality risk, measured by logistical EuroScore, was 35±6%. No intraprocedural deaths were reported and at follow up (average 87±56 days) six patients were alive. Unfortunately, this study did not report on any procedure related event, thus provides little contribution to the effectiveness evidence base.

Webb et al. (2006) reported results from 18 patients who received the TAVI procedure in Canada. The average age of these high risk patients was 81±6 years, 72% of who were male. The average logistical EuroScore was 26.2%±13.1% and 67% of patients had logistical EuroScore greater than 20%. The procedure was considered successful in 14 patients and no intraprocedural deaths were reported. At a follow up (75±55 days), 16 patients were alive. With respect to PREs, within 30 days zero cases of endocarditis and myocardial infarction were reported and two cases of vascular events were reported. Again, the reporting of zero events here is useful for when the evidence will be synthesised.

Berry et al. (2007) presented results for 11 patients who received the TAVI procedure, aged 82±10 years, of whom 54% were male. One patient suffered a stroke and five died post-procedure, while four others died within four months of discharge. One patient was reported as having vascular events within the first 30 days. It was also reported that three patients had pacemakers fitted within the first 30 days. No other events were reported here.

Grube et al. (2007) reported outcomes on 86 patients who received TAVI in Germany and the USA. This was the largest number of patients reported in a single study in the literature review. Here patients were either 80 years or more with a logistical EuroScore greater than 20% or 75 years or more with a logical EuroScore greater than or equal to 15% or aged greater than or equal to 65 with significant pre-specified risk factors. The average age of patients was 81.3±5.2 and the average logistical EuroScore was 23.4 ±13.5%. Reported device success was 88%, while procedural mortality was 6%. Also, six patients converted from TAVI to AVR. Over all 30-day mortality was reported as 22%. While combined death, stroke and myocardial infarction was 22%. Examining the incidence of procedural related events individually, zero cases of major paravavular leaks and endocarditis were reported within the first 30 days. While six patients experienced cardiac tamponade, one

had a myocardial infarction and one had a pacemaker inserted within the first 30 days. Despite reporting on the largest number of patients, this study did not report on any other events.

Marcheix et al. (2007) reported results from 10 patients who received the TAVI procedure between December 2005 and August 2006 in Canada. The average age of the patients was 81.3 years and 50% were male. The median NYHA class was III. The median logistical EuroScore was 32% and 80% of patients had a logistical EuroScore greater than 20%. The reported 30-day mortality rate was 20%. One patient died five days after the procedure from a major stroke and a second patient died at day 20, also from a stroke. With respect to PREs, one case of major paravavular leakage was reported; three cases of access site events; two cases of vascular events and three pacemakers were implanted within 30 days. Also, zero incidences of endocarditis and myocardial infarction were reported within the first 30 days. Albeit reporting on small patient numbers, the reporting of zero events occurring in this study is very useful.

Walther et al. (2007) reported outcomes on 59 patients from a clinical study which collected evidence from February 2006 until October 2006. The patients were enrolled in clinics in Leipzig, Vienna, Frankfurt and Dallas. The average age of patients was 81.4±5.8 years and 74.6% were female. The average logistical EuroScore for these patients was 26.8%±13.5%. Successful valve positioning was performed in 53 patients and two patients had to convert to AVR. Eight patients died in hospital without valve dysfunction (13.6%) and survival was 75.7±5.9% at follow up (110±77 days). With respect to PREs, four myocardial infractions were reported within the first 30 days. Despite the large study population, the authors did not report on any other PREs.

Webb et al. (2007) reported results from 50 patients who received the TAVI procedure in Canada. All patients were high risk and severely symptomatic. The average age of patients was 82±7 years and 40% were female. The average logistical EuroScore was 28%. Mortality at 30 days was 12% and procedure success was reported to increase from 76% in the first 25 patients to 96% in the second 25 patients. One patient had to be converted to AVR from TAVI. This study reported on a wide range of PREs occurring within 30 days, as follows: zero cases of endocarditis; one case of cardiac tamponade; one incidence of myocardial infarction; two patients had access site events; two patients has vascular events;

and one patient had to have a pacemaker implanted. This study is very useful as it reports on a wide range of procedure related events for a substantial number of patients.

Descoutures et al. (2008) reported outcomes for 66 patients who received TAVI in France. Here, the average logistical EuroScore was 20±14%, 39 patients were considered unsuitable for AVR, 12 of which underwent TAVI and 27 were treated medically or redirected to AVR. This is the first study to consider AVR and TAVI side by side. Of the eleven considered suitable for TAVI, one patient converted to AVR. Following the TAVI procedure major paravavular leak was reported for one patient; one case of cardiac tamponade was reported and zero myocardial infractions. In addition, six cases of vascular events were reported. Another French study, Eltchaninoff et al. (2007), reported results for TAVI procedures performed between 2003 and 2005 in France for 36 patients. A 57% success rate was reported. With respect to procedure related events, five cases of major paravavular leaks were reported. Unfortunately, no other events were reported on in this study; a disappointment considering the size of the study population.

Svensson et al. (2008) reported outcomes from 40 patients who received a TAVI procedure between December 2006 and February 2008 in the USA. The average age of patients was 83.61 years and 48% were female. The average logistical EuroScore was 35.5%±15.3%. All valves were successfully delivered and 35 were considered to be successfully seated. Owing to complications, two cases required conversion to AVR. There were seven deaths within 30 days and another two deaths occurred before discharge at day 42 and 72. No strokes were reported immediately post procedure. Kaplan-Meier survival was estimated to be 81.8%±6.2% at one month and 71.7±7.7% at three months. With respect to PREs, zero incidents of valve thromboembolism were reported; two cases of major paravavular leaks and six incidents of myocardial infarction were reported within the first 30 days. Considering the size of the study population and the range of events reported on, this study is a useful contribution for this thesis.

Walther et al. (2008) reported on 50 patients who received the TAVI procedure at a single centre in Germany. All patients had a high perioperative risk profile and the logistical EuroScore was 15.8±9.1%. The average age of patients was 82.4±4.6 years and 78% were female. TAVI was successfully performed in 47 patients. Three patients had to be converted to AVR. No prosthesis migration or embolization was observed. Survival at one month was 92±3.8%; at six months 73.9±6.2% and at one year survival was 71.4±6.5%.

Mortality observed was owing to the overall health condition and was not valve related. With respect to PREs, within the first 30 days two patients had pacemakers fitted. No other PREs were reported on here, which is unfortunate given the size of the patient group.

Finally, Ye et al. (2009) reported outcomes for 26 patients who underwent TAVI in Canada between October 2005 and January 2007. The average age of patients was 80±9 years and 50% were male. With respect to functionality, 77% were in NYHA Class III or IV and logistical EuroScore was 11±6%. Six patients died within the first 30 days. Of those patients who survived 30 days, three subsequently died. With respect to complications, zero cases of valve thromboembolism and access site events were reported within the first 30 days. Meanwhile, during this time period one patient had a myocardial infarction and two reported vascular events. Given the modest patient population considered here, a reasonable range of procedure related events were reported upon.

AVR Literature

At the same time, a literature review for long term effectiveness of the AVR procedure was also conducted, using similar methods to those described earlier (See Appendix II for search strategy). This was necessary owing to the scarce evidence on long term TAVI results. The literature review revealed five papers reporting short and longer term results for patients following AVR. The results of which were from registries in the USA, France, Germany, UK and Italy, with an average of 457 patients (ranging from 103 to 1,049).

Gehlot et al. (1996) reported the outcomes from 322 patients who received the AVR procedure between June 1971 and December 1992 in the USA. The average age of patients was 82.7 years, 53% were male and 86% of the patients were in NYHA Class III or IV. Survival at five years was 60.2%. Within the first 30 days, two cases of endocarditis were reported and 35 patients had to have pacemakers fitted. Unfortunately, no other procedure related events were reported on here.

Milano et al. (1998) reported outcomes from 355 patients who received the AVR procedure (63% with mechanical prosthesis and 37% with bio prosthesis) between 1981 and 1995 in Italy. The average age of patients was 74±4 years, 53% were males and 78% of patients were in NYHA class III or IV. In-hospital mortality was 7.6%, which decreased to 4.6% in the latter three years. There were 55 late deaths. With respect to procedure related events (PREs), within 30 days seven cases of valve thromboembolism, two cases of major

paravavular leaks and one incidence of endocarditis were reported. With respect to PREs after 30 days and up to one year, Milano et al. (1998) reported 23 cases of repeat hospitalisations; 18 cases of valve thromboembolism; two cases of major paravavular leaks and three cases of endocarditis. Also, 27 patients were reported to have had a fatal procedure related event after 30 days and within one year. Reporting of results in this study is very comprehensive and will be valuable for this thesis.

Gilbert et al. (1999) reported outcomes for 103 patients over 80 years of age who received an AVR procedure between 1987 and 1996 in the UK. The median age was 82 years and 92% of patients were in NYHA class III or IV. Overall mortality was 18.4%, late complications were uncommon and 92% of patients were in NYHA class I or II at follow up. With respect to PREs within 30 days, zero incidences of myocardial infarction and four cases of vascular events were reported. In addition, 11 patients had to have pacemakers implanted. Beyond 30 days and up to one year following AVR, eight patients had to be re-hospitalised and one patient had endocarditis. The reporting of short and long term results in this study is valuable owing to TAVI's underdeveloped evidence base.

Aupart et al. (2006) reported outcomes for 1,113 patients who received the AVR procedure in France between 1984 and 2003. The average age of patients was 72.6 years and 63% were male. The average NYHA class of the patients was 2.3 and 36% of patients were in NYHA class III or IV. Operative mortality was 2.8% and there were 330 late deaths reported. At follow up, 98% of patients were in NYHA classes I or II. Aupart et al. (2006) did not report outcomes on PREs occurring within 30 days. PREs occurring post one year were reported as follows: 18 cases of vascular events; 22 re-hospitalisations; 39 valve thromboembolisms and 24 cases of endocarditis. With respect to fatal PREs post 30 days, 19 were reported. The large study population and detailed reporting of procedure related events here is valuable for this study.

Eichinger et al. (2008) reported outcomes for 455 patients who received AVR in Germany between January 1985 and December 1996. The average age of patients enrolled in the study was 72.5±9 years and 53% were male. With respect to functional status, 44.8% of patients were in NYHA class III or IV. Mortality at 30 days was 5.3%. The most frequent cause of death was congestive heart failure. Eichinger et al. (2008) only reported PREs post 30 days the following were reported: 16 access site events; 56 re-hospitalisations; 70 cases of valve thromboembolism; 10 major paravavular leaks and 18 cases of endocarditis.

With respect to late fatal PREs 36 were reported. This study provides strong evidence on long term outcomes.

Stroke

Stroke is a significant complication following any cardiac surgery, including valve replacement (Caswell, 2003). In particular, according to Chikwe et al. (2003), stroke is a risk associated with valve replacement owing to the emboli of the calcified valve, the aortic annulation site, hypo-perfusion and haemorrhage. The TAVI and AVR literature presented above did not provide sufficient evidence on the incidence of strokes so an additional literature review was conducted, using the same approach as described earlier, to identify stroke risk. Chikwe et al. (2003) summarised the natural history of AS and regurgitation and reported 3% stroke risk for patients undergoing AVR. This stroke risk was confirmed by Caswell et al. (2003), who reported that 3% stroke rates have been observed in several studies including Puvimanasinghe et al. (2001) (based on a meta-analysis) and Bando et al. (2003) reported the results from 812 patients who received the AVR procedure in Japan, between May 1977 and December 2001. The median age of the patients 58 years, 41% were male and 60% of patients were in NYHA class II or IV.

This stroke rate was maintained in later studies. Melby et al (2007) reviewed the outcomes from 245 patients who received the AVR procedure at a single site in the US between 1993 and 2005. The average age of the patients was 83.6±2.9 years and 53% were women. With respect to functional status, the average NYHA class was 3.1±0.9 and 78% of patients were in NYHA class III or IV. Operative mortality at 30 days was 9% and survival after surgery at one year was 82%. Permanent stroke was observed in 8 patients (3%). In addition, Alsmady et al. (2009) reported the outcomes from 64 patients who received AVR between January 2001 and December 2008. The average age of patients was 49.4±16.9 years and 39% of the patients were female. With respect to functional status 75% of patients were in NYHA class III or IV. Operative mortality was 3.1% and two patients (3%) experienced major stroke post operatively.

Estimating Probabilities

The procedure related events (PREs) extracted from the 25 papers, discussed above, are presented as a data set examining the effectiveness of TAVI in Table 3.5 below. The

probabilities are estimated as the number of events occurring as a proportion of event that could have occurred. The number of events which occurred is denoted by α, the number of events that could have occurred is denoted by n and the number of events which did not occur is denoted by β (n- α). The probabilities are estimated using these parameters. For example, Webb et al. (2007) reported one conversion from TAVI to AVR, there were 49 patients who could have converted to AVR. Thus, α=1, n=49, so the probability of conversion as reported by Webb et al. (2007) is 0.02 (1/49). Similarly, Criber et al. (2006) reported five cases of major paravavular leaks (α=5). A total of 34 patients could have incurred a major paravavular leak (n =34) and 29 patients did not incur a major paravavular leak (β=29). The probability of major paravavular leaks, as reported by Criber et al. (2006), is 0.15 (5/34).

Having reviewing the effectiveness literature, it became apparent that there was little consistency in how the studies reported procedure related events (PREs). Some studies explicitly reported where zero incidences of an event occurred. Other studies did not report where zero incidents of an event occurred. So it is unclear if non-reporting meant zero events occurred or if that the event had just been omitted from the reported results. Thus, in extracting data from the publications a distinction is made between non-reporting of an event and no events occurring. Where it is reported in a paper that zero events occurred for a PRE, these were counted in estimating the probability. Where an event is not reported, it is assumed to be missing information and was not included in estimating the probability. For example, Webb et al (2006) reported zero cases of endocarditis and myocardial infarction and two cases of vascular events. However, there was no mention of pacemaker implantations or valve thromboembolism. So in extracting evidence, to build a data set, 0 was recorded as the number of endocarditis and myocardial infractions and 2 was recorded for vascular events as reported by Webb et al (2006). For all other PREs, nothing is recorded for Webb et al. (2006) in the constructed data set. These results and those for the remaining studies and procedure related events (PREs) are presented in Table 3.5.

Table 3.5 Effectiveness Literature Review Findings

Paper	Event	α	β	N	Probability
TAVI LITERATURE					
Criber et al 2004	Vascular Events	1	4	5	0.20
Hanzel et al (2005)	-	-	-	-	-
Sack et al 2005	-	-	-	-	-
Criber et al 2006	Major Paravavular Leak	5	29	34	0.15
	Myocardial Infarction	0	34	34	0.00
	Pacemaker Implantation	0	34	34	0.00
Grube et al 2006	Probability Of Converting To AVR	2	20	22	0.09
	Valve Thromboembolism	0	22	22	0.00
	Major Paravavular Leak	0	22	22	0.00
	Endocarditis	0	22	22	0.00
	Cardiac Tamponade	1	21	22	0.05
	Myocardial Infarction	0	22	22	0.00
	Vascular Events	5	17	22	0.23
Lichtenstein et al 2006	-	-	-	-	-
Walther et al 2006	Probability Of Converting To AVR	3	43	46	0.07
	Pacemaker Implantation	2	44	46	0.04
Webb et al 2006	Endocarditis	0	18	18	0.00
	Myocardial Infarction	0	18	18	0.00
	Vascular Events	2	16	18	0.11
Berry et al 2007	Vascular Events	1	10	11	0.09
	Pacemaker Implantation	3	8	11	0.27
Eltchaninoff et al 2007	Major Paravavular Leak	5	29	34	0.15
Grube et al 2007	Probability Of Converting To AVR	6	70	76	0.08
	Major Paravavular Leak	0	76	76	0.00
	Endocarditis	0	76	76	0.00
	Cardiac Tamponade	6	70	76	0.08
	Myocardial Infarction	1	75	76	0.01
	Pacemaker Implantation	1	75	76	0.01
Marcheix et al 2007	Major Paravavular Leak	1	9	10	0.10
	Endocarditis	0	10	10	0.00
	Myocardial Infarction	0	10	10	0.00
	Access Site Events	3	7	10	0.30
	Vascular Events	2	8	10	0.20
	Pacemaker Implantation	3	7	10	0.30
Walther et al 2007	Probability Of Converting To AVR	2	55	57	0.04
	Myocardial Infarction	4	53	57	0.07
Webb et al 2007	Probability Of Converting To AVR	1	48	49	0.02
	Endocarditis	0	49	49	0.00
	Cardiac Tamponade	1	48	49	0.02
	Myocardial Infarction	1	48	49	0.02

Table 3.5 Continued

Paper	Event	α	β	n	Probability
	Access Site Events	2	47	49	0.04
	Vascular Events	2	47	49	0.04
	Pacemaker Implantation	1	48	49	0.02
Descoutures et al 2008	Probability Of Converting To AVR	1	10	11	0.09
	Major Paravavular Leak	1	10	11	0.09
	Cardiac Tamponade	1	10	11	0.09
	Myocardial Infarction	0	11	11	0.00
	Vascular Events	6	5	11	0.55
Svensson et al 2008	Probability Of Converting To AVR	2	35	37	0.05
	Valve Thromboembolism	0	37	37	0.00
	Major Paravavular Leak	2	35	37	0.05
	Myocardial Infarction	6	31	37	0.16
Ye et al 2009	Valve Thromboembolism	0	26	26	0.00
	Myocardial Infarction	1	25	26	0.04
	Access Site Events	2	24	26	0.08
	Vascular Events	0	26	26	0.00
AVR LITERATURE					
Geholt et al 1996	Endocarditis	2	285	287	0.01
	Pacemaker Implantation	35	243	278	0.13
Milano et al 1998	Valve thromboembolism	7	321	328	0.02
	Major paravavular leak	2	326	328	0.01
	Late Hospitalisations	23	305	328	0.07
	Late Valve Thromboembolism	18	310	328	0.05
	Late Major Paravavular Leak	2	326	328	0.01
	Late Endocarditis	3	325	328	0.01
	Late Fatal PRE	27	46	73	0.37
Gilbert et al 1999	Myocardial infarction	0	82	82	0.00
	Vascular Events	4	78	82	0.05
	Pacemaker implantation	11	71	82	0.13
	Late Hospitalisations	8	76	84	0.10
	Late Endocarditis	1	83	84	0.01
Aupart et al 2006	Vascular Events	18	707	725	0.02
	Late Hospitalisations	22	1079	1101	0.02
	Late Valve Thromboembolism	39	1062	1101	0.04
	Late Endocarditis	24	1077	1101	0.02
	Late Fatal PRE	19	85	104	0.18
Eichinger et al 2008	Access Site Events	16	415	431	0.04
	Late Hospitalisations	56	375	431	0.13
	Late Valve Thromboembolism	70	361	431	0.16
	Late Major Paravavular Leak	10	421	431	0.02
	Late Endocarditis	18	413	431	0.04
	Late Fatal PRE	36	154	190	0.19
Stroke	Bando et al 2003	20	759	779	0.03
	Meldby et al 2007	8	237	245	0.03
	Alsmady et al 2009	2	60	62	0.03

- Indicates no events were reported

3.5.2 Cost Effectiveness Evidence

As indicated above, evidence surrounding Transcatheter Aortic Valve Implantation (TAVI) was scarce in 2009 and accordingly access to TAVI was limited for patients. There were no published randomised control trials (RCTs) comparing TAVI to surgical valve replacement (AVR) or medical management; there was little evidence on long-term outcomes following TAVI and information on the quality of life impact of TAVI relative to comparators was limited. Consequently, it could be considered that the potential for TAVI to increase life years and quality of life for AS patients was yet to be fully demonstrated.

Despite immature evidence, decision makers like NICE, needed to make access decisions and set research priorities while balancing safety concerns and pressures from stakeholders. For example, patients want access to the technology; manufactures want their technology on the market etc. Balancing these pressures, while collecting further evidence and reducing access delays, has associated opportunity costs. Granting access prior to establishing sufficient efficacy can result in mortalities and morbidities and increases litigation risks. While delaying access to a technology, which is later shown to have adequate efficacy and to be cost effective, results in mortalities and morbidities and reduces manufactures profits. As outlined in Chapter 2, economic evaluations can aid decision makers in making these coverage decisions and setting research priorities, even when evidence is scarce. Using an iterative framework the adoption and research decisions can be re-assessed as new evidence becomes available.

In addition to the literature review on the clinical effectiveness of TAVI, a comprehensive literature search was conducted for literature relating to costs, cost effectiveness and quality of life associated with TAVI (See Appendix II for search strategy). Two reports were identified: a Belgian Health Care Knowledge Centre (KEC) report (Van Brabandt and Neyt, 2008) and one by Bazian Ltd (Bazian, 2008) from the UK. Both of these reports found that no previous cost effectiveness analysis had been performed.

The Belgian KEC report (Van Brabandt and Neyt, 2008) contained a systematic review of the published evidence up to 2008 which consisted of registries and single patient outcomes (as discussed above). The report found that there were no data available on the performance of TAVI from randomised clinical trials (RCTs). Only evidence on short term outcomes was available, from published observational series. According to the report,

these publications indicated that TAVI was feasible in eligible patients but there are risks of complications and mortality, influenced by age and co-morbidities. Based on their observations, Van Brabandt and Neyt (2008) concluded that evidence from RCTs were needed to confirm TAVI performance. Without such clinical studies they considered it difficult to perform a reliable economic evaluation. They reported AVR device costs as €3,000 and TAVI device costs ranging from €19,610 to €20,398, depending on manufacturer chosen (this was equivalent to £18,565 to £19,311 at the time (Oanda, 2012)). Also, the report stated that while it is anticipated that TAVI will offer shorter lengths of stay and improve quality of life (QoL) outcomes, data on safety, efficacy, effectiveness, QoL and cost data are yet to be gathered.

The Bazian report (Bazian, 2008) presents an economic analysis, commissioned by the East Midlands Specialist Commissioning Group in the UK, employing a model which considers the local clinical and cost impact of TAVI in the East Midlands region. A one year time horizon is used and severe AS patients aged 75 years of age or older, unsuitable for AVR were considered. The base case results revealed that the cost of the procedure was approximately £18,000 (2008 prices). With 50 patients per annum in the patient group in the region, costs were estimated as £900,000, per annum. If TAVI was extended to all AS patients costs were estimated as £2.8 million, per annum. No comparator was used in the evaluation and no effectiveness measures were included, thus this can only be considered a partial evaluation.

So not only was clinical effectiveness evidence scarce at the time, so too were economic evaluations. Both reports discussed above (Van Brabandt and Neyt, 2008, Bazian, 2008) indicated that the TAVI evidence base was immature and further evidence was needed. While this scarcity was highlighted, it was recognised that evidence from early case studies and series do exist. In addition, health outcomes from surgical valve replacement (AVR) existed at time. Thus, despite scarce data, economic evaluations using decision analytical modelling (see Chapter 2 for methods) are feasible, so long as current understanding of theory and practice can be reflected in the model (Roberts et al., 2012, Caro et al., 2012). Thereby, the adoption and research priority setting decisions can be informed.

While previous efforts at establishing the cost effectiveness of TAVI were incomplete, in this thesis the importance of capturing early experiences with the technology is acknowledged. This in line with Lilford et al. (2000), who indicate that the learning curve

should not be ignored. Despite the challenges associated with collecting evidence prior to the technology stabilising, it is important that randomised evidence is collected before it is too late to randomise. The latter can occur when clinicians firmly consider the technologies not to be in equipoise even if such claims are not substantiated) (Lilford et al., 2000). Waiting for the technology to stabilise can give rise to larger numbers of clinicians who are prematurely optimistic (Fitch et al., 1999).

3.5.3 Availability of TAVI in the UK

As outlined above, TAVI is a less invasive treatment for patients with severe AS. Therefore, patients considered at too high a risk for AVR could potentially benefit from the less invasive valve procedure that is TAVI. Since the first use of TAVI in 2002, the rate of TAVI procedures has been increasing, particularly for high risk patients (Cribier et al., 2004, Cribier et al., 2002a, Vahanian et al., 2008, Iung et al., 2005, Van Brabandt and Neyt, 2008). Despite the increase in usage and the release of early registry results, evidence surrounding the effectiveness and cost effectiveness of TAVI is still scarce. Evidence available when this case study began (2009) was based on early generations of devices, inserted in relative inexperienced centres only reporting short-term outcomes. As discussed in Chapter 1, this is a common phenomenon for medical devices.

Consequently, the NICE Interventional Procedure Guidance (Number 266, 2008) (Thomas, 2009) at this time, recommended the use of TAVI only where special arrangements for clinical governance, consent, audit and research are in place. This guidance was owing to the lack of evidence, particularly with respect to long term outcomes. While acknowledging the safety concerns associated with scarce data it also recognised that patients who are denied the treatment are at risk of death and complications. So it was recommended that a team of professionals including specialist doctors with experience, cardiac surgeons, cardiac anaesthetist and interventional cardiologists should be involved in deciding the suitability of a candidate for the procedure. Also, the procedure could only be carried out in units which have specialists in heart and blood vessel surgery available in case of emergency (NICE, 2008). This recommendation was to be considered for revision in May 2011. In addition, NICE Guidelines recommend that all TAVI procedures performed in the UK since 2007 are recorded through the Central Cardiac Audit Database

to form the UK TAVI Registry. At the time this case study commenced, results from this registry had not been published.

Similarly in the USA at this time, the U.S. Food and Drug Administration had not granted approval for TAVI for operable or inoperable patients. Which meant neither TAVI manufacturers could market their device in the US and its use was limited to investigational use (Edwards, 2010). In Europe however, TAVI devices were approved since 2007 (Piazza et al., 2008b, Bauernschmitt et al., 2009) and an increasing number of procedures were being performed. These informed the registries and case series presented in the literature review in Section 3.5.1.

So when this case study commenced, clinical and cost effectiveness evidence on TAVI was scarce and concerns regarding vascular complications; stroke rates; long term consequences of paravavular leaks and the incidence time and predictors of atrioventricular blocks persisted. More and longer term evidence, expected to resolve uncertainties, was required. In 2009, collection of this evidence had begun, via the PARTNER trial in the US and other European trials and registries (Vahanian et al., 2008), however evidence from these was not expected for some time.

3.6 CONCLUSION

As outlined in the sections above, Transcatheter Aortic Valve Replacement (TAVI) is a novel treatment which has the potential to offer a real treatment alternative to patients with severe AS. Although evidence is currently scarce, decision makers still need to make adoption research priorities setting decisions. As demonstrated in Chapter 2, economic evaluations can inform such decisions, using decision analytical modelling.

TAVI therefore presents an opportunity to investigate the cost effectiveness of a novel technology with high demand for access but an immature evidence base. This study aims to estimate the cost effectiveness of TAVI to determine the suitability of adoption and to assess the value of generating further information, using decision analytical modelling and probabilistic sensitivity analysis considering the uncertainty surrounding the parameter estimates.

In subsequent chapters, a decision analytical model (DAM) is constructed and employed iteratively to estimate the costs and benefits of TAVI compared to AVR and medical management. While previous economic assessments, reviewed in Section 3.5.2, suggested that further research is necessary, no formal quantitative assessment of the value this additional evidence could generate was performed. Rather than waiting for the trial evidence, early economic evaluations, which include a formal assessment of the value of additional information a trial will provided, are advocated. Therefore, in this thesis a decision analytical model is constructed and populated with evidence as available, to determine the cost effectiveness of TAVI and value of generating further evidence, using the continuous iterative framework conceptualised in Chapter 2.

CHAPTER 4 ESTIMATING THE COST EFFECTIVENESS OF TRANSCATHETER AORTIC VALVE IMPLANTATION

4.1 INTRODUCTION

To test the suitability of the continuous iterative framework for economic evaluations of expensive medical device technologies, a case study is warranted. The case study chosen is Transcatheter Aortic Valve Implantation (TAVI) for the treatment of severe, symptomatic patients with AS in the United Kingdom (UK), as it is expensive novel technology with an immature evidence base for which demand is great.

As discussed in Chapter 3, at the time this case study began (2009) evidence on TAVI outcomes (particularly long term outcomes) were scarce and previous efforts to examine its cost effectiveness were only partial evaluations (Van Brabandt and Neyt, 2008, Bazian, 2008). Employing the methods for conducting economic evaluations (described in Chapter 2) and what is known about the natural disease history of AS and the treatment effects of TAVI and its comparators (explained in Chapter 3), a decision analytical model (DAM) is constructed. This facilitates a probabilistic sensitivity analysis (PSA) and Bayesian value of information (VOI) analysis for a full economic evaluation to address the following questions (in line with objectives two and three): Is TAVI cost effective compared to its alternative(s) given current evidence? Is it worthwhile collecting further evidence on TAVI?

4.2 PATIENT GROUPS

In evaluating the cost effectiveness of TAVI for treating AS, the NHS perspective is taken and consideration is given to three patient groups based on risk (discussed in Section 3.3.3). Patient characteristics vary across patient risk groups, influencing model parameters, which in turn influences cost effectiveness results. Thus, considering different risk groups of patients allows the study to incorporate the heterogeneous nature of AS

patients. The three AS patient sub-groups considered in this study are low risk operable, high risk operable and high risk inoperable.

For the purposes of this study, low risk operable patients are defined by an operative mortality of 5% and are assumed to be eligible for surgical valve replacement (AVR). So the treatment choice is between TAVI and AVR. While six age/gender groups are considered in the analysis, the base case is assumed to be 60 year old males with an operative mortality of 5%.

The treatment options available to high risk operable patients, with an operative mortality of 15%, are more ambiguous. Currently, these patients may be considered eligible or ineligible for AVR depending on co-morbidities and other factors. So for these patients the choice is between TAVI, AVR and medical management. Again, six age/gender groups are considered in the analysis, however the base case for these patients is assumed to be 70 year old males with an operative mortality of 15%.

High risk inoperable patients are assumed to be ineligible for surgery, owing to their high operative mortality (20%) and co-morbidities. Therefore, currently only medical management is available to these patients. So in the analysis of high risk inoperable patients the treatment choice is between TAVI and medical management. Again, six age/gender groups are considered in the analysis and the base case is assumed to be 80 year old males with an operative mortality of 20%.

The operative mortality rates reported above are based on, although not identical to, the EuroSCORE measure (see Section 3.3.3) and aim to reflect various risk factors related to patient characteristics, type and severity of disease, as well as risks associated with the procedures (Nashef et al., 1999, Roques et al., 1999). Table 4.1 summarises the base case characteristics for each risk-group and the devices considered.

Table 4.1 Patient Groups

Patient Group	Operative Mortality	Alternative Treatments
Low Risk Operable Patients	5%	TAVI versus AVR
High Risk Operable Patients	15%	TAVI versus AVR versus Medical Management
High Risk Inoperable Patients	20%	TAVI versus Medical Management

4.3 THE DECISION ANALYTICAL MODEL TO INVESTIGATE THE COST EFFECTIVENESS OF TRANSCATHETER AORTIC VALVE IMPLANTATION

Employing a decision analytical model (DAM) (explained in Chapter 2) provides a means of using all available information to inform decision makers when making coverage decisions and setting research priorities for novel expensive technologies where evidence is scarce. This is particularly suitable as it facilitates evidence synthesis, an important step in the evaluation where the evidence base is underdeveloped. For this case study, a DAM is constructed and populated with the best available evidence from published literature at the time (2009). The model was conceptualised to reflect current understanding of theory and practice of the disease and treatment pathways for patients with severe symptomatic AS receiving TAVI or one of its comparators (AVR or medical management). Including AVR and medical management ensures that all possible interventions are incorporated. In conceptualising the model, the guidelines and practices outlined by the ISPOR-SMDM Task Force on Modelling Good Research Practices (Roberts et al., 2012, Caro et al., 2012) (discussed in Chapter 2), were adhered to.

The identification of the decision problem and conceptualisation of the model were informed by reviewing effectiveness literature on AS and the devices (described Chapter 3). In addition, the model structure and development was informed by a steering group. This group included clinical and policy experts (as advocated by Roberts et al. (2012) and Caro et al. (2012)), including cardiologists, cardiac surgeons, public and private (industry based) health economists and other public and private representatives (see Appendix I for group member details). The steering group formally met on two occasions[2]. The first meeting in May 2009, provided background information on the disease, technology and access arrangements for TAVI in the UK. A second meeting was held eight months later where the conceptualisation of the DAM constructed and data sources identified were

[2] 11th May 2009 in University of Glasgow and 12th January 2010 in University of Glasgow

presented to the committee for approval. Following this a report on the model was circulated to the steering group members for further comments and agreement[3].

4.3.1 Decision Analytical Model Structure

To depict the nature of the disease and outcomes of the technologies (TAVI, AVR and medical management) a DAM, split into two components, corresponding to two time periods in the model, was employed. The first component considered the initial phase of treatment for a patient with AS, who could be managed medically; receive an AVR or TAVI procedure, corresponding to a 30 day period. This initial phase took the patient up to the point at which they have recovered from any procedure received and its short term outcome (success or failure) is known. The second phase involved a longer term projection of costs and life-expectancy after the initial phase over the estimated lifetime of the patient (20 years). These time horizons are suitable as they capture the anticipated health effects associated with the disease and interventions.

Decision Tree

The initial 30 day phase was modelled using a decision tree, Figure 4.1. The decision tree began with a decision, represented by a decision node, between the three treatment options available for those suffering from AS: AVR, TAVI, and medical management. The alternatives included in the specific analysis depended on the risk group under consideration, as discussed above. As explained in the review of the treatment (in Chapter 3), for those who receive AVR there is a risk of operative mortality, stroke and major or minor procedure related event (PRE). These PREs incur costs and impact utility. The model distinguishes between minor PREs, which are assumed to resolve with appropriate medical care, and major PREs, which are assumed to result in a state equivalent to valve implantation failure. Within the model, major disabling stroke is assumed to be equivalent to death in terms of utility in the short term, while incurring a substantial cost. Other major PREs include valve thromboembolism, major paravavular leak, endocarditis and myocardial infarction. Minor PREs for the purpose of the model include: access site events, minor vascular events and pacemaker implantation. (These PREs are defined in

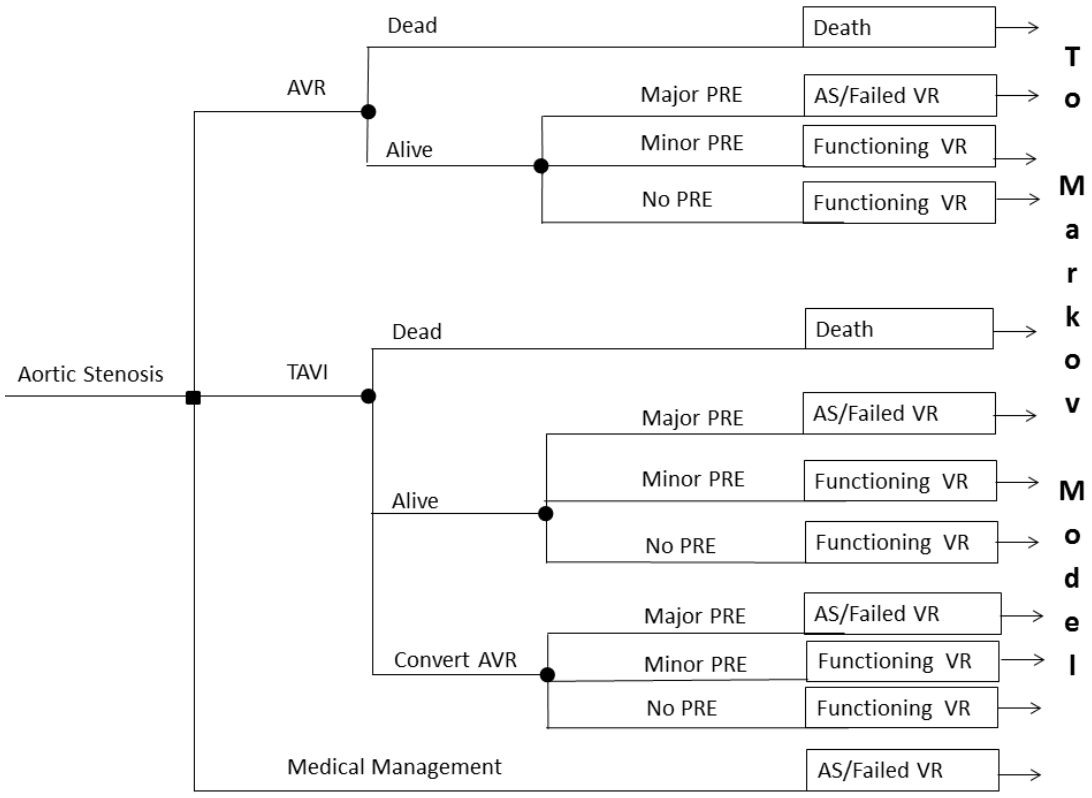
[3] This report was subsequently submitted to the Scottish Health Technologies Group on 29th November 2010.

Appendix III.) For patients who experience minor or no PREs, the procedure is assumed to be successful and patients are deemed to have experienced a successful valve replacement. Patients who experience major disabling stroke or major PREs (shown on one branch on Figure 4.1) are assumed to be left in a state no better than their original manifestation of AS (termed persistent AS/failed valve replacement (VR)). In this state, the valve is assumed to be no longer offering benefits to utility.

Patients receiving TAVI follow the same pathway as those receiving AVR, except that during the TAVI procedure there may be a need to convert to AVR. If this occurs the outcomes are assumed to be equivalent to AVR for those patients.

Finally, patients receiving medical management receive appropriate medical care and no valve replacement. This does not cure AS but offers transient relief and these patients remain in a state no better than their original manifestation of AS (persistent AS/ failed VR).

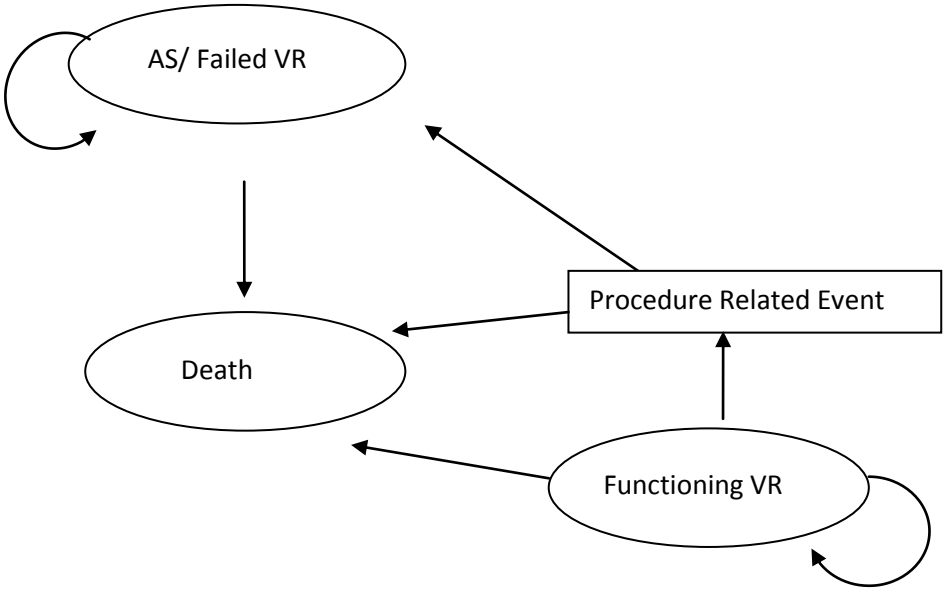
Figure 4.1 Decision Analytical Model: Short Term Component - The Decision Tree



Markov Model

The second phase of the model was presented using a Markov state transition model, Figure 4.2. This component of the DAM represents the longer term prognosis of the patient. There are three states in the Markov model: functioning valve replacement, persistent AS/failed valve replacement and death. Outcomes from the initial 30 day phase (the decision tree) determine in which of these three states a patient enters the longer-term model. Each cycle of the Markov model is one year in duration and the model is run for 20 years (by which time most patients have died). The cycle length is considered enough to capture anticipated clinical events, side effects of the interventions etc.

Figure 4.2 Decision Analytical Model: Long Term Component – The Markov Model



In the initial cycle, the functioning valve replacement state is populated with patients who had a successful valve replacement (TAVI or AVR), with or without minor PREs, within the first 30 days. The persistent AS/ failed valve replacement state is populated with patients who had a valve replacement (TAVI or AVR) but suffered a major disabling stroke or major PREs or patients who received the medical management treatment in the first 30 days. The death state is populated with those who did not survive either valve replacement procedure in the first 30 days.

In subsequent cycles, patients in the functioning valve replacement state are at risk of a late major procedure related event (PRE) that could be fatal, or if non-fatal results in loss of valve functioning, meaning that they move to the persistent AS/failed valve replacement state. In addition, patients in the functioning valve replacement state are at risk of death from natural causes. Patients in the persistent AS/failed valve replacement state are at risk of death from both AS and natural causes.

4.3.2 Decision Analytical Model Parameters

Transition probabilities

There are ten transition probabilities in the decision tree and four in the Markov Model. For patients receiving a valve procedure (TAVI or AVR) there is the risk of death within 30 days (this includes intra-procedural death), for those who survive there is the risk of major disabling stroke, major and minor PREs. In addition, for TAVI patients there is a probability of converting to AVR. Finally, for those who receive medical management, there is the probability that AS persists. In the longer term, there is a risk of death risk (from both valve functioning and persistent AS) of major non-fatal, late PREs and risk of fatal late PREs.

Costs

Throughout the DAM, costs are applied to both states and events to estimate the costs of the alternatives. In the decision tree, the cost of the intervention is applied. This includes the cost of the device, procedure, in-patient care and any necessary follow-up care. Where patients convert from TAVI to AVR the costs of both interventions are applied. Where PREs are experienced, costs are applied to reflect the costs of treatment. Also, there is an annual cost associated with each health state. These state costs are based on expected hospitalisations for each state, medication costs, costs of long-term care and costs associated with any late PREs.

Utilities

To estimate the impact on QALYs, owing to the procedures, utility values were applied to the health states and events in the DAM. Disutilities were assigned to the AVR and TAVI procedures; these were incorporated to reflect the impact of the initial valve procedures. Disutilities were also applied to any PREs experienced as a result of the valve procedure. In addition, utilities were applied to the persistent AS/failed valve replacement and functioning valve replacement health states. These state utilities are based on estimated utility by NYHA class per state and are reduced by the disutility associated with PREs where relevant.

The Decision Analytical Model TAVI Specific Parameters

One of the principles of the modelling reported here is to explore the potential uncertainty related to the relative effectiveness of TAVI compared to AVR. This is imperative in this early TAVI model owing to scarce TAVI evidence. Thus, while the base case assumption of the model is that TAVI is comparable to AVR in a number of key respects, flexibility is built into the model for the possibility that TAVI differs in a number of key areas.

4.4 POPULATING THE DECISION ANALYTICAL MODEL

To populate the DAM, point estimates for the transition probabilities, costs and utilities for events and states were required. As outlined in Chapter 3, TAVI is a novel treatment for which data is scarce, so following the identification of relevant evidence (presented in Chapter 3), it needed to be synthesised.

4.4.1 Transition Probabilities

Short Term – Decision Tree

As discussed above, the decision tree component of the DAM includes the probability of converting from TAVI to AVR and procedure related events (PREs) immediately

following the procedure and in the long term. Here, the PREs likely to occur (as identified at the model conceptualisation stage) are grouped into major and minor PREs. To populate the DAM, the results from the literature (presented in Chapter 3) were synthesised to provide estimates of major PREs causing persistent AS/valve failure within 30 days; minor PREs within 30 days, which do not result in valve failure; probability of major disabling stroke within 30 days; probability of converting from TAVI to AVR and major PREs in the follow up period. In doing so, the number of events per study was pooled across all the studies and divided by the total number of patients to give the probability of that event occurring. The total number of patients was pooled from all the studies. The pooling process employed was a fixed effects meta-analysis, which assumed that information is exchangeable and the baseline being measured is identical (see Chapter 2 for description).

However, as mentioned in Chapter 3, there were inconsistencies across the studies with respect to how the results were reported. While some authors explicitly reported zero cases of an event occurring, others excluded events in their reporting. Thus, in synthesising the evidence a distinction between non-reporting of an event and no events occurring was required. For papers reporting zero events occurring for a PRE, they were included in the denominator for estimating the probability. In contrast, where an event was not reported, it was assumed to be missing and the study was excluded from the denominator for calculating the probability. For example, to estimate the probability of a myocardial infarction in the first 30 days post procedure for TAVI, 17 papers were examined. Of the 17 papers only 10 reported on myocardial infarction, of which five papers reported zero observations of myocardial infarction in this time period. To estimate the probability of myocardial infarction, the observations from the 10 papers reporting on myocardial infarction are included. The number of events occurring was summed, which is equal to 13 (α) and the number of events that could have occurred is 340 (n, the total number of patients in the 10 papers reporting on myocardial infarction). The probability of myocardial infarction is estimated by dividing 13 by 340 which equates to 0.05. This was repeated for other PREs, conversions and stroke. These data and calculations are presented in Table 4.2. Where, as outlined in Chapter 3, α refers to the number of events which occurred, β refers to the number of events which did not occur, n is the total number of events which could have occurred ($\alpha + \beta = n$). The probability was calculated as the proportion of events which occurred from the total number of events which could have occurred (α /n).

The data in Table 4.2 was used to estimate the probability of total major and minor PREs. These are calculated by grouping the PREs into major and minor (as per Table 4.2) and summing each category. The results of these calculations are provided in Table 4.3. Note, for the probability of operative mortality within 30 days; major stroke following valve replacement within 30 days; major procedure related events following valve replacement within 30 days and major procedure related events after 30 days within one year a baseline absolute risk was employed in the AVR arm and relative risks were applied to calculate the risk in the TAVI arm. Absolute risks were employed in both arms of the model for all other probabilities.

Table 4.2 Data Extracted From Literature – Grouped by Procedure Related Event

Event/ Literature	α	β	n	Probability
CONVERSION TAVI TO AVR				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	2	20	22	0.09
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	3	43	46	0.07
Webb et al 2006	-	-	-	-
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	6	70	76	0.08
Marcheix et al 2007	-	-	-	-
Walther et al 2007	2	55	57	0.04
Webb et al 2007	1	48	49	0.02
Descoutures et al 2008	1	10	11	0.09
Svensson et al 2008	2	35	37	0.05
Ye et al 2009	-	-	-	-
	17	**281**	**298**	**0.06**
MAJOR DISABLING STROKE - AVR				
Bando et al 2003	20	759	779	0.03
Meldby et al 2007	8	237	245	0.03
Alsmady et al 2009	2	60	62	0.03
	30	**1056**	**1086**	**0.03**
MAJOR PROCEDURE RELATED EVENTS – TAVI				
Valve thromboembolism				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	0	22	22	0.00
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	-	-	-	-
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	-	-	-	-
Marcheix et al 2007	-	-	-	-
Walther et al 2007	-	-	-	-
Webb et al 2007	-	-	-	-
Descoutures et al 2008	-	-	-	-
Svensson et al 2008	0	37	37	0.00
Ye et al 2009	0	26	26	0.00
	0	**85**	**85**	**0.00**
Major paravavular leak				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	5	29	34	0.15
Grube et al 2006	0	22	22	0.00

Table 4.2 Continued

Event/ Literature	α	β	n	Probability
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	-	-	-	-
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	5	29	34	0.15
Grube et al 2007	0	76	76	0.00
Marcheix et al 2007	1	9	10	0.10
Walther et al 2007	-	-	-	-
Webb et al 2007	-	-	-	-
Descoutures et al 2008	1	10	11	0.09
Svensson et al 2008	2	35	37	0.05
Ye et al 2009	-	-	-	-
	14	**210**	**224**	**0.06**
Endocarditis				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	0	22	22	0.00
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	0	18	18	0.00
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	0	76	76	0.00
Marcheix et al 2007	0	10	10	0.00
Walther et al 2007	-	-	-	-
Webb et al 2007	0	49	49	0.00
Descoutures et al 2008	-	-	-	-
Svensson et al 2008	-	-	-	-
Ye et al 2009	-	-	-	-
	0	**175**	**175**	**0.00**
Cardiac tamponade				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	1	21	22	0.05
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	-	-	-	-
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	6	70	76	0.08
Marcheix et al 2007	-	-	-	-
Walther et al 2007	-	-	-	-
Webb et al 2007	1	48	49	0.02
Descoutures et al 2008	1	10	11	0.09
Svensson et al 2008	-	-	-	-
Ye et al 2009	-	-	-	-
	9	**149**	**158**	**0.06**
Myocardial infarction				
Criber et al 2004	-	-	-	-

Table 4.2 Continued

Event/ Literature	α	β	n	Probability
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	0	34	34	0
Grube et al 2006	0	22	22	0.00
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	0	18	18	0.00
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	1	75	76	0.01
Marcheix et al 2007	0	10	10	0.00
Walther et al 2007	4	53	57	0.07
Webb et al 2007	1	48	49	0.02
Descoutures et al 2008	0	11	11	0.00
Svensson et al 2008	6	31	37	0.16
Ye et al 2009	1	25	26	0.04
	13	**327**	**340**	**0.04**
MINOR PROCEDURE RELATED EVENTS - TAVI				
Access site events				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	-	-	-	-
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	-	-	-	-
Berry et al 2007	-	-	-	-
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	-	-	-	-
Marcheix et al 2007	3	7	10	0.30
Walther et al 2007	-	-	-	-
Webb et al 2007	2	47	49	0.04
Descoutures et al 2008	-	-	-	-
Svensson et al 2008	-	-	-	-
Ye et al 2009	0	26	26	0.00
	5	**80**	**85**	**0.06**
Vascular Events				
Criber et al 2004	1	4	5	0.20
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	-	-	-	-
Grube et al 2006	5	17	22	0.23
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	-	-	-	-
Webb et al 2006	2	16	18	0.11
Berry et al 2007	1	10	11	0.09
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	-	-	-	-
Marcheix et al 2007	2	8	10	0.20
Walther et al 2007	-	-	-	-
Webb et al 2007	2	47	49	0.04
Descoutures et al 2008	6	5	11	0.55

Table 4.2 Continued

Event/ Literature	α	β	n	Probability
Svensson et al 2008	-	-	-	-
Ye et al 2009	2	24	26	0.08
	21	**131**	**152**	**0.14**
Pacemaker				
Criber et al 2004	-	-	-	-
Hanzel et al (2005)	-	-	-	-
Sack et al 2005	-	-	-	-
Criber et al 2006	0	34	34	0.00
Grube et al 2006	-	-	-	-
Lichtenstein et al 2006	-	-	-	-
Walther et al 2006	2	44	46	0.04
Webb et al 2006	-	-	-	-
Berry et al 2007	3	8	11	0.27
Eltchaninoff et al 2007	-	-	-	-
Grube et al 2007	1	75	76	0.01
Marcheix et al 2007	3	7	10	0.30
Walther et al 2007	-	-	-	-
Webb et al 2007	1	48	49	0.02
Descoutures et al 2008	-	-	-	-
	10	**216**	**226**	**0.04**
MAJOR PROCEDURE RELATED EVENTS – AVR				
Valve thromboembolism				
Geholt et al 1996	-	-	-	-
Gilbert et al 1999	-	-	-	-
Milano et al 1998	7	321	328	0.02
	7	**321**	**328**	**0.02**
Major paravavular leak				
Geholt et al (1996)	-	-	-	-
Milano et al (1998)	2	326	328	0.01
Gilbert et al (1999)	-	-	-	-
	2	**326**	**328**	**0.01**
Endocarditis				
Geholt et al (1996)	287	2	285	0.01
Milano et al (1998)	328	1	327	0.00
Gilbert et al (1999)	-	-	-	-
	615	**3**	**612**	**0.00**
Cardiac tamponade				
Geholt et al (1996)	-	-	-	-
Milano et al (1998)	-	-	-	-
Gilbert et al (1999)	-	-	-	-
Myocardial infarction				
Geholt et al (1996)	-	-	-	-
MINOR PROCEDURE RELATED EVENTS – AVR				
Access Site Events				
Geholt et al (1996)	-	-	-	-
Milano et al (1998)	-	-	-	-
Gilbert et al (1999)	-	-	-	-
Aupart et al (2006)	-	-	-	-
Eichinger et al (2008)	16	415	431	0.04
	16	**415**	**431**	**0.04**

Table 4.2 Continued

Event/ Literature	α	β	n	Probability
Vascular Events				
Geholt et al (1996)	-	-	-	-
Milano et al (1998)	-	-	-	-
Gilbert et al (1999)	4	78	82	0.05
Aupart et al (2006)	18	707	725	0.02
Eichinger et al (2008)	-	-	-	-
	22	**785**	**807**	**0.03**
Pacemaker Implantation				
Geholt et al (1996)	35	243	278	0.13
Milano et al (1998)	-		-	
Gilbert et al (1999)	11	71	82	0.13
Aupart et al (2006)	-	-	-	-
Eichinger et al (2008)	-	-	-	-
	46	**314**	**360**	**0.13**
LATE PROCEDURE RELATED EVENTS - AVR				
Hospitalisations				
Gilbert et al (1999)	8	76	84	0.10
Milano et al (1998)	23	305	328	0.07
Aupart et al (2006)	22	1079	1101	0.02
Eichinger et al (2008)	56	375	431	0.13
	109	**1835**	**1944**	**0.06**
Valve thromboembolism				
Gilbert et al (1999)	-	-	-	-
Milano et al (1998)	18	310	328	0.05
Aupart et al (2006)	39	1062	1101	0.04
Eichinger et al (2008)	70	361	431	0.16
	127	**1733**	**1860**	**0.07**
Major paravavular leak				
Gilbert et al (1999)	-	-	-	-
Milano et al (1998)	2	326	328	0.01
Aupart et al (2006)	-	-	-	-
Eichinger et al (2008)	10	421	431	0.02
	12	**747**	**759**	**0.02**
Endocarditis				
Gilbert et al (1999)	1	83	84	0.01
Milano et al (1998)	3	325	328	0.01
Aupart et al (2006)	24	1077	1101	0.02
Eichinger et al (2008)	18	413	431	0.04
	46	**1898**	**1944**	**0.02**
Cardiac tamponade				
Gilbert et al (1999)	-	-	-	-
Milano et al (1998)	-	-	-	-
Aupart et al (2006)	-	-	-	-
Eichinger et al (2008)	-	-	-	-
	0	**0**	**0**	**0.00**
Late Fatal PREs				
Gilbert et al (1999)	-	-	-	-
Milano et al (1998)	27	46	73	0.37
Aupart et al (2006)	19	85	104	0.18
Eichinger et al (2008)	36	154	190	0.19
	82	**295**	**367**	**0.22**

- Indicates missing information

Table 4.3 Transition Probability Estimation

Procedure Related Event	α	β	n	Probability
Conversion from TAVI to AVR	17	281	298	**0.06**
Major disabling stroke	30	1056	1086	**0.03**
Major Procedure Related Events – TAVI *see Box 4.1*				**0.12**
Minor Procedure Related Events - TAVI				
Access site events	5	80	85	0.06
Vascular Events	21	131	152	0.14
Pacemaker	10	216	226	0.04
				0.24
Major Procedure Related Events – AVR *see Box 4.1*				**0.12**
Minor Procedure Related Events - AVR				
Access site events	16	415	431	0.04
Vascular Events	22	785	807	0.03
Pacemaker	46	314	360	0.13
				0.19
Late Procedure Related Events				
Hospitalisations	109	1835	1944	0.06
Valve thromboembolism	127	1733	1860	0.07
Major paravavular leak	12	747	759	0.02
Endocarditis	46	1898	1944	0.02
Cardiac tamponade	0	0	0	0.00
				0.17
Fatal Procedure Related Events	**82**	**295**	**367**	**0.22**

As discussed above, the probability of minor and major PREs were calculated by summing the probabilities of each PRE in that category. As the evidence base here was underdeveloped, concerns around the suitability of the point estimates calculated were raised, particularly the probability of major PREs occurring within 30 days following AVR and TAVI. The estimates produced, using the methods described above, were inconsistent with what was expected from consultation with literature and experts owing to the poor evidence base. In light of these concerns, the probability of major PREs was assumed to be the same for AVR and TAVI in the base case. This common probability was calculated by averaging the absolute probabilities obtained from the literature across AVR and TAVI. In addition, in cases where no incidences of a major PRE were reported, but expert opinion

indicated it may occur, a small amount (0.01) is added to each estimate to allow for the small chance of such events occurring. Using this method, the probability of major PREs occurring within 30 days is estimated at 0.12. This calculation is shown in Box 4.1.

Box 4.1 Calculation of Major Procedure Related Events within 30 Days Following Valve Replacement

Major procedure related complications	Probability AVR	Probability TAVI	Pooled + 0.01			
			Probability	α	β	n
Valve thromboembolism	0.021	0.000	0.02	6	407	413
Major paravavular leak	0.006	0.063	0.04	22	530	552
Endocarditis	0.005	0.000	0.01	6	784	790
Cardiac tamponade	0.000	0.057	0.03	5	153	158
Myocardial infarction	0.000	0.038	0.02	10	412	422
Probability of Early Major PRE			**0.12**			

Therefore, the transition probabilities employed in the DAM were as follows (presented in Table 4.4). The probability of major PREs following AVR and TAVI was 0.12. The probability of minor PREs for AVR was 0.19. The probability of minor PREs following a TAVI procedure was greater than that for AVR, at 0.24. This is owing to the catheter insertion with TAVI. The probability of a major disabling stroke was estimated to be 0.03 for AVR and TAVI. Also, there was a probability of converting from TAVI to AVR, 0.06.

Operative mortality varies in the model according to patient type. As outlined in Table 4.1, low risk operable patients were assumed to have a 5% operative mortality rate, high risk operable patients were assumed to have 15% operative mortality and for high risk inoperable patients' operative mortality was assumed to be 20%.

As outlined earlier, a principle of the modelling reported here was to explore the potential uncertainty related to the relative effectiveness of TAVI compared to conventional valve replacement. The base case assumption of the model was that TAVI is comparable to AVR in a number of key respects (Table 4.4). However, flexibility was built into the model to represent the potential for differential outcomes for TAVI in a number of key areas. Here the relative impact of TAVI was represented by a ratio parameter which if set to unity

represents equality of outcomes, while values below unity represent superiority for TAVI. For example, the relative cost of TAVI compared to AVR with respect to the procedure, hospital stay and post discharge care were all set to a value below unity reflecting the assumption that TAVI is cheaper than AVR with respect to each of these outcomes.

Long Term Model – Markov Model

In the long-term component of the DAM, the Markov model, similar techniques for estimating the transition probabilities were employed. Again, the available published evidence was synthesised to estimate the transition probabilities. For those in the functioning valve replacement state the probability of a PRE occurring is 0.17 per cycle, this was estimated in a similar way to the adverse events in the decision tree (Table 4.3). Whereby, the probability of non-fatal PREs in the long run was estimated by summing across the different PREs considered. For those who have a late PRE, 22% of those events were expected to be fatal. While the remaining non-fatal PREs result in failure of the valve, returning the patient to a state equivalent to the original AS state (persistent AS/valve failure state). In addition to experiencing a fatal PRE, patients in the functioning valve state of the model were at risk from death from natural causes. This natural mortality rate is assumed to follow the background age/gender adjusted mortality rates, but with a standardised mortality ratio of 1.5, to adjust for the fact that patients undergoing valve replacement are likely to be at higher risk of death than the average patient population of the same age/gender.

For patients in the persistent AS/ Failed valve replacement state of the model, the life expectancy is assumed to be just 3 years (Legrand et al., 1991) or three cycles of the model. In the model this was presented as a 0.33 probability of death. Table 4.4 presents the complete transition probabilities employed in the model, including details of the Beta distributions applied to reflect uncertainty.

Table 4.4 Transition Probabilities for TAVI Decision Analytical Model

TRANSITION PROBABILITIES	Dist	Probability (95% CI)	α	β	N
Short term - 0-30 days					
Probability of converting from TAVI to AVR	Beta	0.06 (0.03-0.09)	17	281	298
Probability of major stroke following AVR	Beta	0.03 (0.02-0.05)	30	1056	1086
Probability of major stroke following TAVI	Beta	0.03 (0.02-0.05)	30	1056	1086
Probability of early major PREs AVR	Beta	0.12 (0.09-0.17)	See Table 4.3		
Probability of early major PREs TAVI	Beta	0.12 (0.09-0.17)			
Probability of early minor PREs AVR	Beta	0.19 (0.15-0.23)			
Probability of early minor PREs TAVI	Beta	0.24 (0.17-0.32)			
Probability of death 30 days all causes AVR	Beta	+		-	
Probability of death 30 days all causes TAVI	Beta	+		-	
Probability AS persisting following MM	Beta	1		-	
Long term - post 30 days					
Probability fatal PRE	Beta	0.22 (0.18-0.27)	82	285	367
Probability of late non-fatal PRE	Beta	0.17 (0.13-0.18)	See Table 4.3		
Probability death from AS state [¶]	Beta	0.33 (0.23-0.43)	33	67	100
Probability death from AS state - Medical Management[¶]	Beta	0.33 (0.24-0.43)	33	67	100
			mean		**se**
Mortality from natural causes (mr)		‡	-		-
Relative risk of death due to AS (rrsmrAS)	Log N	1.5 (0.96-2.24)	0.38		0.22
Mortality from persistent AS/ failed valve replacement		mr* smrAS			
TAVI SPECIFIC PARAMETERS					
Relative stroke risk	Log N	1.00 (0.82-1.21)	-0.01		0.1
Relative risk of operative mortality with TAVI	Log N	0.90 (0.74-1.09)	-0.11		0.1
Relative risk of major PREs causing valve failure	Log N	1.00 (0.82-1.21)	-0.01		0.1
Relative risk of PREs causing valve failure	Log N	1.00 (0.56-1.76)	-0.01		0.29
Relative cost of procedure	Log N	0.73 (0.59-0.88)	-0.32		0.1
Relative cost of hospital stay	Log N	0.51 (0.42-0.62)	-0.67		0.1
Relative cost of post-discharge care	Log N	0.16 (0.13-0.19)	-1.84		0.1

+ Low risk 5%; medium risk 15% and high risk 20%. ‡ Standard life tables ¶(Legrand et al., 1991) Note as the model is a highly stylised version of the complexities of everyday clinical practice in this challenging patient group there are a number of limitations to the modelling developed and implemented. In particular, the co-morbidities for patients with higher operative mortality risks are likely to increase, and this is not explicitly modelled at present. α: the number of events occurring; β the number of events which did not occur and n the number of events which could have occurred; Log N = Log Normal.

The Decision Analytical Model TAVI Specific Parameters

As outlined earlier, a principle of the modelling reported here was to explore the potential uncertainty related to the relative effectiveness of TAVI compared to AVR. The base case assumption of the model was that TAVI is comparable to AVR in a number of key respects (listed in Table 4.3) and flexibility was built into the model to vary TAVI outcomes in a number of key areas. These included: relative stroke, operative mortality, probability of PREs and the relative cost of TAVI compared to AVR with respect to the procedure, hospital stay and post discharge care. The relative impact of TAVI was represented by a ratio parameter which was initially set to unity to represent equality of outcomes. This was varied in an analysis of uncertainty and could be set to non-unity values to give different outcomes of TAVI (in either direction) compared to AVR. To account for the uncertainty surrounding these parameters a log normal distribution was applied. This distribution was suitable as the confidence limits for these parameters are calculated on the log scale owing to the relative risks being made up of ratios.

4.4.2 Cost Parameters

Costs were applied to the states and events through the DAM. Firstly, in the decision tree the costs per branch were identified, measured and valued. The branch costs include the device, procedure, length of stay and follow-up care costs. The cost of the AVR device was £2,000 and the TAVI device was £12,000 (Kennon et al., 2008), indicating that the TAVI device is six times more expensive than the AVR device. (Note the costs of the devices are only approximate, due to the commercial nature of these data.) The procedure cost for AVR was £3,580 and for TAVI it was £2,360 (Kennon et al., 2008). Meanwhile, for patients who only receive medical management the cost of that medication was estimated to be £16 per month. Balloon valvuloplasty was not included in the model as it was only recommended in specified circumstances, according to the American College of

Cardiology/American Heart Association (Leon et al., 2006) and was not widely used in the UK.

With respect to length of stay costs time spent in the intensive care unit (ICU), high dependency unit (HDU) and on the general ward were all included. AVR patients were estimated to spend two days in ICU, two days in HDU and six days on a general ward, so the total length of stay was ten days (Expert opinion and (Gehlot et al., 1996, Straumann et al., 1994)). TAVI patients meanwhile were estimated to spend half a day in ICU, one and half days in HDU and six days on the general ward. So total length of stay for TAVI patients was eight days (Expert opinion (Gehlot et al., 1996, Straumann et al., 1994). The expected costs for ICU stay was £1,690 per day, HDU £570 per day and the general ward was estimated to cost £210 per day (Kennon et al., 2008). Therefore, while the costs of the procedures were assumed to have a slight advantage towards AVR, it was in the hospital length of stay that the main advantage of the TAVI procedure was realised, with TAVI patients spending less time in the more costly departments (ICU and HDU). However, it was assumed that time on the general ward will be similar for the two devices. These costs are presented on Table 4.5.

Table 4.5 Decision Tree Branch Costs

					AVR	TAVI	MM
	Resource Use AVR	**Resource Use TAVI**	**Resource Cost £**	**SE**	**(95% CI)**	**(95% CI)**	
Device Cost*					2,000	12,000	16
Procedure Cost*					3,580 (2,986-4,167)	2,360 (1,990-3,349)	
Hospital Stay (Days)							
ICU	2^N	0.5^	1,690*N	300	3,380	845	
HDU	2^N	1.5^	570*N	200	1,140	855	
General Ward	6^N	6^	210*N	50	1,260	1,260	
Hospital Stay Total	10	8			5,780 (4,143-7,492)	2,960 (1,997-4,110)	
Post Discharge (Probability of Requiring)							
Cardiac Rehab	0.9*B	0.1*	2940*N	500	2,646	294	
Nursing Home	0.5*B	0.23*	854†‡N	50	427	196	
Post Discharge Total					3,073 (2,198-3,968)	490 (1,997-4,110)	
Total					**14,433**	**18,080**	**16**

*(Kennon et al., 2008) ^ Expert opinion (Gehlot et al., 1996, Straumann et al., 1994) †(Netten, 1996) ‡ 14 Days at £61/day N Indicates Normal Distribution is applied B Indicates Beta Distribution is applied. MM: Medical Management.

Following discharge from hospital, a greater proportion of patients who received AVR will require cardiac rehabilitation and/or temporary nursing home care. The probability of AVR patients requiring cardiac rehabilitation was 90%, while for TAVI patients there was only a 10% chance of requiring it (Kennon et al., 2008). In addition, there was a 50% chance that following AVR patients will require temporary nursing home care, while for TAVI patients this was reduced to 23% (Kennon et al., 2008). Cardiac rehabilitation was estimated to cost £2,940 while temporary nursing home stays were estimated to last 14 days and cost £61 per day (Kennon et al., 2008). So the total costs of each technology in the decision tree were £14,433 for AVR, £17,810 for TAVI and £16 for medical management (Table 4.5).

To calculate the costs per state in the Markov model, expected hospitalisations based on NYHA class, probability of requiring permanent nursing home care and routine drug therapy were included. Applying hospitalisation rates per NYHA class (Ahmed et al., 2006) to the proportion of patients per NYHA class from the Revive Trials (Cribier, 2008) provided estimates of the probability of requiring hospitalisation. This was estimated to be 53% for those in the persistent AS/failed valve replacement state and 7% for those in the functioning valve replacement state. Average hospitalisation costs (estimated to be £3,316 (Kennon et al., 2008)) were applied to these probabilities. It was also recognised that even with functioning valve replacement some patients would require permanent nursing home care. So for patients in the persistent AS/failed valve replacement state, the likelihood of requiring nursing home care was assumed to be 50% (Kennon et al., 2008). While for patients in the functioning valve replacement state, the probability of requiring nursing home care was only 10% (Kennon et al., 2008). These probabilities were applied to the cost per nursing home stay (£11,133 (Netten, 1996)). In addition, routine drug therapy medication costs (£188 (Kennon et al., 2008)) were added to estimate the cost of the functioning valve replacement and persistent AS/failed valve replacement states. The annual costs for each health state were estimated as £1,533 for functioning valve replacement and £7,512 for failed valve replacement (Table 4.6).

Table 4.6 Costs of Functioning & Persistent AS/ Failed Valve Replacement Health States

	Probability	α	β	Dist	Unit Cost £	Cost £ (95% CI)
Functioning Valve Replacement State						
Hospitalisations	0.07*	53	704	Beta	3,316†	232
Nursing Home	0.10†	76	681	Beta	11,133‡	1,113
Routine Drug Therapy	1.00				£188†	188
Total						**1,533 (1,300-1,790)**
Persistent AS/Failed Valve Replacement State						
Hospitalisations	0.53*	401	356	Beta	3,316†	1,757
Nursing Home	0.50†	379	379	Beta	11,133‡	5,567
Routine Drug Therapy	1.00				188†	188
Total						**7,512 (7,096-7,919)**

* (Ahmed et al., 2006) †(Kennon et al., 2008) ‡(Netten, 1996)

Procedure Related Event Costs

The costs of the procedure related events (PREs) were determined from the event costs and a weighting, representing each event as a proportion of the total events (Table 4.7). Box 4.2 presents an example of how the weights were estimated. Column A in Box 4.2 lists the probability of each major PRE (A_i) and the total probability of major PREs ($\sum A = 0.12$). To estimate the weight for each major PRE, the probability of it occurring was divided by the probability of all major PREs ($A_i/\sum A$). For example, the probability of valve thromboembolism was 0.02 and the total probability of major PREs was 0.12; so the weight assigned to valve thromboembolism is 0.13 (0.02/0.12). Thus, valve thromboembolism represents 13% of all the major PREs. This was repeated for the other four PREs. Note, the weight assigned to the five PREs sums to one ($\sum B = 1$). To estimate the total cost of major PREs, the weight of each PRE was multiplied by its unit cost ($B_i * C_i$) and these were summed ($\sum C$). For example, the weight assigned to valve thromboembolism was 0.13; this is multiplied by £639 to give £83. This was repeated for the other PREs and summed to get the total cost of major PREs, £985. This process was repeated for minor and late major PREs (Table 4.7). Note a Bayesian technique was used such that zero probabilities of events in the data are assigned a non-zero weight to allow for a small chance of such events occurring. Normal distributions were applied to the costs of treating PREs. This distribution was suitable in this model, as a tight distribution was applied and no negative values were yielded. A discount rate of 3.5% was applied.

Box 4.2 Calculation of Procedure Related Event Costs

Major Procedure Related Events	Probability*	Weight^{+}	Event Cost £^	Cost £ (95% CI)
	A	$B = A_i/\sum A$	*C*	*B*C*
Valve thromboembolism	0.02	0.13	639	83
Major paravavular leak	0.04	0.33	210	69
Endocarditis	0.01	0.06	5,149	319
Cardiac tamponade	0.03	0.28	630	176
Myocardial infarction	0.02	0.20	1,683	338
Total	**0.12**	**1.00**		**985**

4.4.3 Utility Parameters

Utility values were applied to the states and events in the DAM. Firstly, to reflect the disutility associated with the TAVI procedure a disutility of 0.0035 QALYS (Rao et al., 2007) was applied for six weeks (four weeks in the decision tree and two weeks in Markov model). Similarly, to reflect the disutility associated with the AVR procedure a disutility 0.012 QALYS (Rao et al., 2007) was applied for 13 weeks (four weeks in the decision tree and nine weeks in Markov model).

Secondly, utilities were applied to the health states (persistent AS/failed valve replacement and functioning valve replacement). To estimate these, the proportion of patients per NYHA class per state (from the Revive Trials (Cribier, 2008)) was multiplied by utility estimates for each NYHA class (provided by Maliwa et al. (2003)). For example, it was estimated that in the functioning valve replacement state, 59% of patients were in NYHA I, 28% in NYHA II, 10% in NYHA III and 3% in NYHA IV. These proportions were multiplied by the utility associated with each class and summed to estimate the utility associated with that class. So the utility associated with functioning valve replacement was 0.77 and the utility of being in the persistent AS/ failed valve replacement state was 0.54. These calculations are shown in Table 4.8. A Dirichlet distribution was applied to model the uncertainty surrounding the proportion of patients in each NYHA class, to estimate the utility associated with having AS, a failed valve replacement resulting in persistent AS and functioning valve replacement as there were categories in the variable.

Table 4.7 Decision Analytical Model Procedure Related Events Costs

	Probability*	Weight[+]	Event Cost £^	SE	Dist	Cost £ (95% CI)
Major Disabling Stroke	0.03	1.00	11,450	500	Normal	**344 (193-562)**
Major PREs AVR						
Valve thromboembolism	0.02	0.13	639	100	Normal	83
Major paravavular leak	0.04	0.33	210	50	Normal	69
Endocarditis	0.01	0.06	5,149	300	Normal	319
Cardiac tamponade	0.03	0.28	630	95	Normal	176
Myocardial infarction	0.02	0.20	1,683	300	Normal	338
	0.12	**1.00**				**985 (717-1,309)**
Major PREs TAVI						
Valve thromboembolism	0.02	0.13	639	100	Normal	83
Major paravavular leak	0.04	0.33	210	50	Normal	69
Endocarditis	0.01	0.06	5,149	300	Normal	319
Cardiac tamponade	0.03	0.28	630	95	Normal	176
Myocardial infarction	0.02	0.20	1,683	300	Normal	338
	0.12	**1.00**				**985 (717-1,309)**
Minor PREs AVR						
Access site events	0.04	0.19	198	48	Normal	38
Vascular Events	0.03	0.14	198	48	Normal	28
Pacemaker	0.13	0.66	4,649	500	Normal	3,091
	0.19	**1.00**				**3,158 (2,397-3,954)**
Minor PREs TAVI						
Access site events	0.06	0.24	198	48	Normal	48
Vascular Events	0.14	0.57	198	48	Normal	113
Pacemaker	0.04	0.18	4,649	500	Normal	853
	0.24	**1.00**				**1,014 (587-1,608)**
Late PREs – Non-Fatal						
Hospitalisations	0.06	0.32	3,316	500	Normal	1,070
Valve thromboembolism	0.07	0.39	639	100	Normal	251
Major paravavular leak	0.02	0.09	210	50	Normal	19
Endocarditis	0.02	0.14	5,149	300	Normal	791
Cardiac tamponade	0.01	0.06	630	95	Normal	36
	0.17	**1.00**				**2,077 (1,764-2,590)**

* Probabilities were estimated in Table 4.2. [+] Weights are calculated from the absolute probabilities such that costs can be presented as conditional on the event occurring. A Bayesian technique is used such that zero probabilities of events in the data are assigned a non-zero weight to allow for a small chance of such events occurring. [^] Event costs were sourced from: (Kalra et al., 2005, Kennon et al., 2008, NHS, 2008a)

Procedure Related Event Utilities

The procedure related event (PRE) utilities were determined from the event utility and a weighting, representing each event as a proportion of the total events (Table 4.9), as per the PRE costs. The utility of major PREs following AVR and TAVI was 0.03, utility of minor PREs following AVR and TAVI were 0.04 and 0.02 and the utility of longer term PREs was 0.03. Normal distributions were applied to the utilities of treating PREs. This was feasible as the utility was transformed in to a utility decrement X (X = 1-U) (see Section 2.2.4 for description). A discount rate of 3.5% was applied.

Table 4.8 Decision Analytical Model Health State Utilities

Event / State[¥]	Utility by NYHA Class*	Proportion†	Dist	Utility (95% CI)	Duration (wks.)
Utility of AS					
I	0.85	0.01	Dirichlet	0.01	
II	0.71	0.09	Dirichlet	0.06	
III	0.57	0.57	Dirichlet	0.32	
IV	0.43	0.34	Dirichlet	0.15	
				0.54 (0.54-0.55)	
Utility of Functioning Valve Replacement					
I	0.85	0.59	Dirichlet	0.5	
II	0.71	0.28	Dirichlet	0.2	
III	0.57	0.10	Dirichlet	0.06	
IV	0.43	0.03	Dirichlet	0.01	
				0.77 (0.75-0.79)	
Utility Hit following TAVI				0.0035‡	6
Utility Hit following AVR				0.012‡	13

*(Maliwa et al., 2003) †(Cribier, 2008) ‡(Rao et al., 2007) [¥] See Table 3.1 for definition of NYHA states.

Table 4.9 Decision Analytical Model Procedure Related Event Utilities

	Prob*	Weight+	Utility^	SE	Dist	Utility (95% CI)
Major Disabling Stroke	0.03	1.00	0.00	0	-	**0.00**
Major PREs AVR						
Valve thromboembolism	0.02	0.13	0.04	0.008	Normal	0.01
Major paravavular leak	0.04	0.33	0.04	0.008	Normal	0.01
Endocarditis	0.01	0.06	0.01	0.002	Normal	0.00
Cardiac tamponade	0.03	0.28	0.02	0.005	Normal	0.01
Myocardial infarction	0.02	0.20	0.04	0.008	Normal	0.01
	0.12	**1.00**				**0.03 (0.02-0.04)**
Major PREs TAVI						
Valve thromboembolism	0.02	0.13	0.04	0.008	Normal	0.01
Major paravavular leak	0.04	0.33	0.04	0.008	Normal	0.01
Endocarditis	0.01	0.06	0.01	0.002	Normal	0.00
Cardiac tamponade	0.03	0.28	0.02	0.005	Normal	0.01
Myocardial infarction	0.02	0.20	0.04	0.008	Normal	0.01
	0.12	**1.00**				**0.03 (0.02-0.04)**
Minor PREs AVR						
Access site events	0.04	0.19	0.01	0.002	Normal	0.00
Vascular Events	0.03	0.14	0.01	0.002	Normal	0.00
Pacemaker	0.13	0.66	0.05	0.004	Normal	0.03
	0.19	**1.00**				**0.04 (0.03-0.04)**
Minor PREs TAVI						
Access site events	0.06	0.24	0.01	0.002	Normal	0.00
Vascular Events	0.14	0.57	0.01	0.002	Normal	0.01
Pacemaker	0.04	0.18	0.05	0.004	Normal	0.01
	0.24	**1.00**				**0.02 (0.01-0.02)**
LATE PREs						
Hospitalisations	0.06	0.32	0.02	0.005	Normal	0.01
Valve thromboembolism	0.07	0.39	0.04	0.008	Normal	0.02
Major paravavular leak	0.02	0.09	0.04	0.008	Normal	0.00
Endocarditis	0.02	0.14	0.01	0.002	Normal	0.00
Cardiac tamponade	0.01	0.06	0.02	0.005	Normal	0.00
	0.17	**1.00**				**0.03 (0.02-0.04)**

*Probabilities were estimated in Table 4.2. + Weights are calculated from the absolute probabilities such that costs can be presented as conditional on the event occurring. A Bayesian technique is used such that zero probabilities of events in the data are assigned a non-zero weight to allow for a small chance of such events occurring. ^ (Sullivan, 2006)

4.5 INVESTIGATING THE TAVI DECISION ANALYTICAL MODEL

As outlined above, owing to scarce evidence the TAVI decision analytical model (DAM) model was populated with data extracted from published literature, early registry data and expert opinion in 2009. To ensure plausibility of estimates and to verify the model a variety of checks were performed to examine the stability in the model and the distributions around the model input and output parameters.

Firstly, suitability of the distributions around the input parameters was examined. As discussed earlier, a distinction was made between the reporting of zero events occurring and non-reporting of events. The effect of this differentiation was investigated by generating the descriptive statistics for model inputs (See Appendix IV Table a) for two scenarios. In the first scenario, the literature which did not report events were excluded (as per the parameterisations above), this yielded a smaller sample size (NS) for the denominator. In the second scenario the literature which did not report events were included, yielding a larger sample size (NL) for the denominator. The Monte Carlo simulation was run for each scenario (NS and NL) and the resulting descriptive statistics were analysed. This analysis resulted in the following concerns: the different sample sizes yielded differences in the range around the point estimates for the PREs and some of the relative risk parameters and the standard errors around the event costs and event utilities were inconsistent.

To address these concerns a number of steps were taken. Firstly, with respect to constructing the probability of PREs, only literature reporting events was included (corresponding with NS). Secondly, as the relative risk parameters were considered too narrow to reflect expert opinions on the expected differences between TAVI and AVR they were widened. Specifically, the range for the relative risk of having a major PRE within 30 days following TAVI was increased from 0.85-1.17 to 0.50-1.50. Also, the range for the relative risk of death due to AS was increased from 1.27-1.75 to 1.00-2.00. Thirdly, the standard errors surrounding the event costs and utilities were examined to ensure no negative costs or utilities were yielded in the PSA (the latter are feasible owing to the employment of the normal distribution).

Secondly, the descriptive statistics were examined for stability. Firstly, the DAM model was run twice (NS1 and NS2) where it was expected that the range surrounding the parameters would be constant. This however was not the case, so to improve stability in the model the number of iterations was increased tenfold, from 1,000 to 10,000 (See Appendix IV Tables b and c). Secondly, how the random numbers were being drawn was investigated. In Microsoft Excel (the programme used to operate this model) when using the randomise statement in Visual Basic macros, the random number generator in the random function should generate a new series of random numbers each time you use it as the seed is reset each time. In previous versions of Excel resetting the "seed" was an issuing when making random draws. This was investigated for the model by amending the macro to include resetting the seed after every draw and the model was run. The results were not found to be different as Microsoft Excel 2003 or newer was used. Thirdly, the model outputs were examined to confirm stability. This included producing ICERs; incremental cost effectiveness planes; plotting incremental net benefit and incremental net benefit curves for two runs of the model (NS1 and NS2). The latter, along with the descriptive statistics and analysis of outputs for two runs of the model confirmed stability in the model.

Thirdly, covariance in the model was examined using an ANOVA analysis, which estimates the variance between the parameters in the model. Here the proportion sum of squares for the incremental cost and incremental benefit parameters were estimated. This determined that a small number of variables were having a consistent influence on the outputs. These are relative risk of procedure related event following TAVI (rrvre_TAVI); relative risk of death due to aortic stenosis (rrsmras) and probability of death owing to aortic stenosis (pdeath_as) (See Appendix IV Table d). Following the ANOVA analysis, the correlation co-efficient was estimated for each version of the model (low and high risk operable and high risk inoperable) between the two output parameters i.e. costs and effects. The results indicate correlation between costs and effects is high, especially for the costs and effects of TAVI and medical management (see Appendix IV Table e). Given this strong correlation a second ANOVA analysis was performed on the costs, effects and life years for each intervention against all input parameters. The results indicated that the following variables had a consistent influence on the outputs: probability of fatal procedure related event (platefatalvre); relative risk of death due to aortic stenosis (rrsmrAS); relative risk of procedure related event following TAVI (rrevre_TAVI); probability of death owing to aortic stenosis (pdeath_AS); cost of failed valve replacement or aortic stenosis

(cfv_AS); cost of functioning valve replacement (cfn) and the residual (see Appendix IV Table f).

These investigations concluded that the Monte Carlo simulation should use 10,000 iterations (increased from 1,000 initially) and there is plausibility and stability in the inputs (confirmed though the ANOVA and correlation coefficients).

4.6 COST EFFECTIVENESS ANALYSIS

Using the DAM, the economic evaluation was undertaken from the perspective of the UK National Health System (NHS). A Monte Carlo simulation with 10,000 iterations was used to propagate the uncertainty in the individual model parameters, reflected by the probability distributions assigned, through the model to produce a distribution of expected costs and expected QALYs associated with each procedure (methods described in Chapter 2). The mean values of these distributions are used to calculate the incremental cost-effectiveness ratio (ICER) in terms of the expected incremental costs associated with TAVI compared to AVR per incremental QALY gained, for low risk operable patients. This is repeated for high risk operable patients and inoperable patients.

A sensitivity analysis is performed to determine the effect of changes in the price of the TAVI device on the cost effectiveness of TAVI. Currently, the TAVI device is expensive, as expected with a new, innovative, high-tech device. However, over time owing to erosion of patents, recouping research and development costs, incremental innovations and increased competition it is anticipated the price may decrease. Similarly, future evidence owing to incremental innovations and movements along the learning curve, may illustrate greater reductions in the relative risk of operative mortality associated with TAVI than the 10% conservatively assumed here, this would give a much greater potential health gain. The impact of such changes on the cost effectiveness of TAVI is explored through a sensitivity analysis.

Having examined if TAVI is cost effective compared to its comparators, for the three patient groups, a Bayesian VOI is employed to investigate if there is value in collecting additional evidence. The Expected Value of Perfect Information (EVPI) investigates what

society would be willing to pay to eliminate all the uncertainty surrounding the coverage decision. This is calculated as the difference in the net benefit of the decision made with perfect information and that with current information (Fenwick et al., 2008) for the three patient groups. (See Chapter 2 for a description of these methods.)

4.7 COST EFFECTIVENESS ANALYSIS RESULTS FOR TAVI

4.7.1 Cost Effectiveness Results for Low Risk Operable Patients – TAVI versus AVR

The first patient-group considered is the low risk operable patient group. As these patients are eligible for AVR, with an operative mortality of 5%, a cost effectiveness analysis of TAVI versus AVR is performed. A cohort of 1,000 patients enter the decision tree and Markov model and using the parameter estimates and transition probabilities, the cost and QALYs per person over a 20 year period are estimated for AVR and TAVI. This facilitates the calculation of an ICER and is repeated for a number of age/gender groups. The results are presented in Table 4.10.

The results indicate only a 0.005 reduction in all-cause mortality at the end of year one between TAVI and AVR. The survival estimates from the model (Figure 4.3), illustrate for TAVI and AVR survival is considerably similar over the 20 years considered. With respect to quality of life, the estimates from the model suggest that TAVI offers marginally more QALYs per patient at the end of year one (0.01 QALYs) (Figure 4.4.)

Figure 4.3 Survival Estimates for AVR and TAVI

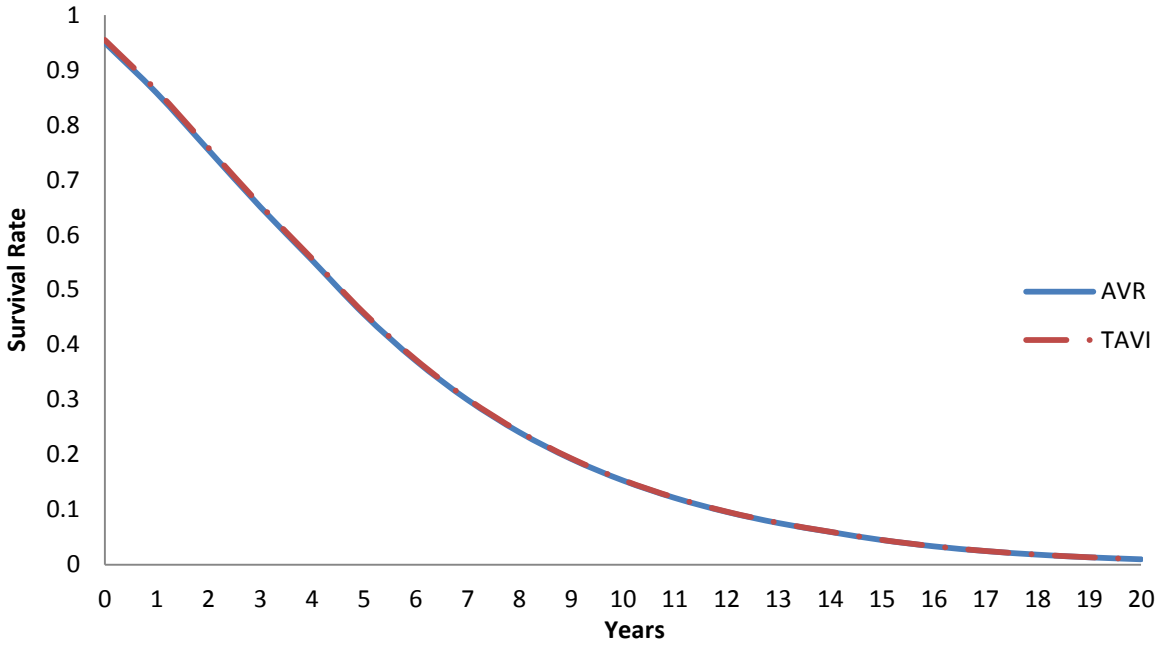


Figure 4.4 Quality of Life Estimates for AVR and TAVI

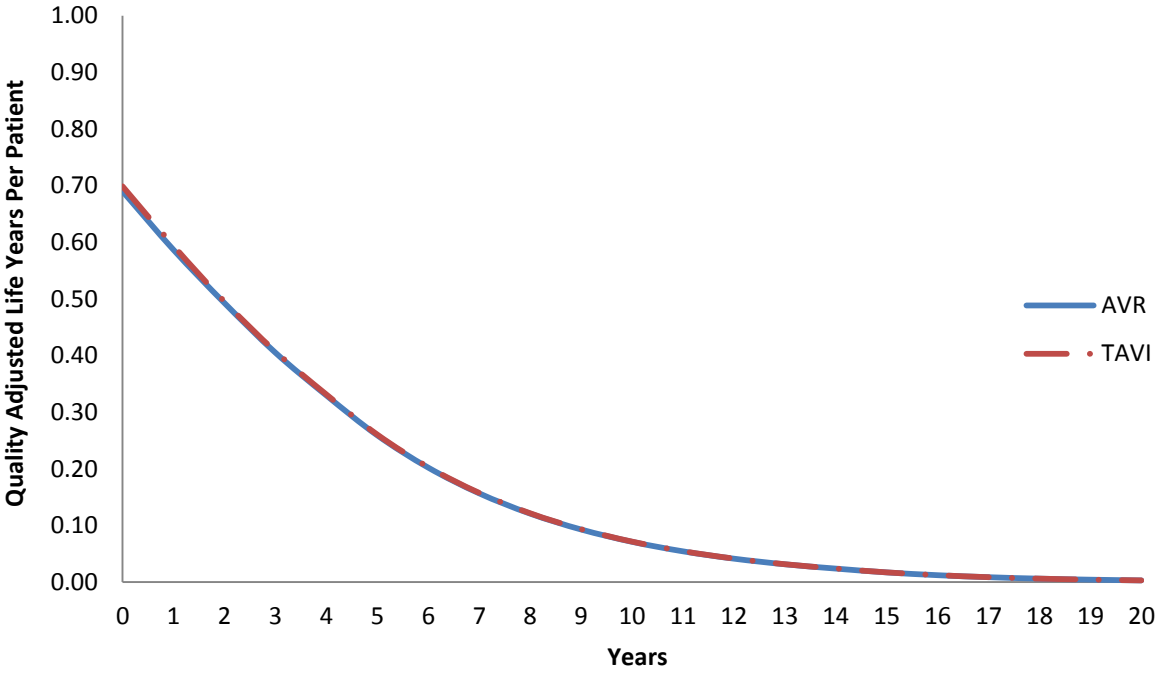


Table 4.10 Cost Effectiveness Analysis Results: Low Risk Operable Patients* - TAVI versus AVR

	AVR			TAVI			TAVI vs. AVR		
	LYs (95% CI)	Costs £ (95% CI)	QALYs (95% CI)	LYs (95% CI)	Costs £ (95% CI)	QALYs (95% CI)	Δ Costs	Δ QALYs	ICER £/QALY
Deterministic:		**Males (age, yrs)**							
60	5.98	31,421	3.61	6.01	35,802	3.64	4,381	0.03	155,669
70	5.09	29,169	3.13	5.11	33,538	3.16	7,407	0.03	171,487
80	3.96	26,132	2.49	3.98	30,538	2.51	4,406	0.02	199,953
		Females (age, yrs)							
60	6.27	32,095	3.76	6.30	36,480	3.79	4,384	0.03	151,529
70	5.54	30,336	3.38	5.57	34,711	3.41	4,375	0.03	162,867
80	4.39	27,335	2.74	4.41	31,694	2.77	4,359	0.02	187,201
Probabilistic:		**Males (age, yrs)**							
60	6.14	31,509	3.68	6.18	35,906	3.71	4,397	0.03	147,617
	(5.47-6.94)	(27,859-35,897)	(3.33-4.04)	(5.43-7.08)	(32,069-40,730)	(3.33-4.14)	(2,047-6,958)	(-0.11-0.19)	
70	5.20	29,270	3.18	5.23	33,641	3.21	4,371	0.03	163,815
	(4.50-5.98)	(25,725-33,4510	(2.80-3.57)	(4.49-6.09)	(30,044-38,096)	(2.81-3.63)	(2,196-6,728)	(-0.90-0.16)	
80	4.04	26,168	2.52	4.06	30,528	2.54	4,360	0.02	191,811
	(3.34-4.80)	(22,805-29,991)	(2.12-2.94)	(3.33-4.88)	(27,302-34,496)	(2.13-2.98)	(2,520-6,306)	(-0.07-0.13)	
		Females (age, yrs)							
60	6.45	32,239	3.84	6.49	36,622	3.87	4,383	0.03	154,364
	(5.77-7.25)	(28,585-36,609)	(6348-4.23)	(5.73-7.38)	(32,703-41,472)	(3.48-4.29)	(1,942-7,064)	(-0.12-0.20)	
70	5.68	30,426	3.44	5.71	34,788	3.46	4,362	0.03	164,202
	(4.97-6.47)	(26,790-34,665)	(3.07-3.83)	(4.96-6.57)	(31,086-39,425)	(3.07-3.89)	(2,119-6,802)	(-0.11-0.18)	
80	4.46	27,332	2.77	4.49	31,697	2.80	4,365	0.02	181,220
	(3.77-5.25)	(23,940-31,321)	(2.39-3.18)	(3.77-5.32)	(28,343-35,763)	(2.40-3.22)	(2,365-6,461)	(-0.08-0.14)	
Sensitivity Analysis:		**TAVI Cost Neutral**							
	6.14	31,520	3.68	6.17	32,259	3.71	739	0.03	26,190
	(5.46-6.93)	(27,898-35,861)	(3.324.07)	(5.42-7.05)	(28,546-36,897)	(3.32-4.13)	(-1,642-3,273)	(-0.12-0.19)	
		Lower Relative Risk of Operative Mortality							
	6.15	31,556	3.69	6.31	36,356	3.79	4,800	0.10	45,723
	(5.46-6.97)	(27,961-35,905)	(3.39-4.22)	(5.55-7.22)	(32,467-41,250)	(3.39-4.22)	(2,406-7,437)	(-0.04-0.26)	

*Operative mortality risk assumed to be 5% Shaded row – base case: 60 year old males

Deterministic Cost Effectiveness Results

The cost effectiveness of TAVI compared to AVR is estimated for low risk operable patients based on evidence synthesised from the literature, as discussed earlier. The deterministic cost effectiveness results (Table 4.10) are estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. For the base case (60 year old males) the results illustrate that for these patients TAVI is more costly (£4,381) and more effective (0.03 QALYs) than AVR. The ICER is estimated at £199,942, which is outside the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)). Therefore, compared to AVR, TAVI cannot be considered cost effective in treating severe AS amongst low risk operable patients. Similarly, for the other five patient groups (males aged 70 and 80 and females aged 60, 70 and 80) TAVI is also more expensive and generates more QALYs than AVR. However, each of the ICERs are greater than £30,000/QALY (Table 4.10).

Probabilistic Cost Effectiveness Results

The mean costs and QALYs produced from the probabilistic sensitivity analysis (PSA) and Monte Carlo simulation are presented in Table 4.10 also. The probabilistic cost effectiveness results reveal for the base case (60 year old males) TAVI is more expensive (£4,397; 14%) and more effective (0.03; 1%) than AVR. Using the mean costs and effects generated in the PSA, the ICER is estimated as £147,617/QALY. This is outside the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)) so TAVI cannot be considered cost effective compared with AVR for treating low risk operable patients with severe AS. The probabilistic results for the remaining five patient groups also indicate that TAVI is more expensive and generates more QALYs than AVR, however the ICERs are greater than £30,000/QALY (Table 4.10).

The incremental cost effectiveness (ICE) plane (Figure 4.5) illustrates the existence and extent of uncertainty surrounding the incremental cost and effect (measured by QALYs) by plotting the additional benefits and costs of the TAVI procedure over AVR for 60 year old males. The ICE Plane for low risk operable patients indicates that there is considerable uncertainty surrounding the existence of a benefit advantage for TAVI compared to AVR, as well as some uncertainty surrounding the extent of this benefit advantage. The average incremental QALYs are 0.03 and range from -0.23 to 0.42 (95% CI provided in Table

4.10). However, there is little uncertainty surrounding the fact that TAVI is more expensive than AVR, although the extent of the additional cost is uncertain. The average incremental cost is £4,397 and ranges from -£59 to £10,127 (95% CI provided in Table 4.10). The ICE plane illustrates there is high correlation between the costs and QALYs. This was confirmed by estimating the correlation coefficient between the cost and effects for each treatment (r_{AVR} = 0.61; r_{TAVI} =0.85). The high correlation may be as a result of how the costs and QALY parameters were both constructed using the procedure related events (PREs).

The cost effectiveness acceptability curve (CEAC) (Figure 4.6), shows the decision uncertainty surrounding the cost effectiveness of each procedure, by plotting the probability of TAVI and AVR being cost effective against a range of ceiling ratios. For example, at a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective is 85% and the probability that TAVI is cost effective is just 15%.

Figure 4.5 Incremental Cost Effectiveness Plane: Low Risk Operable Patients -TAVI versus AVR

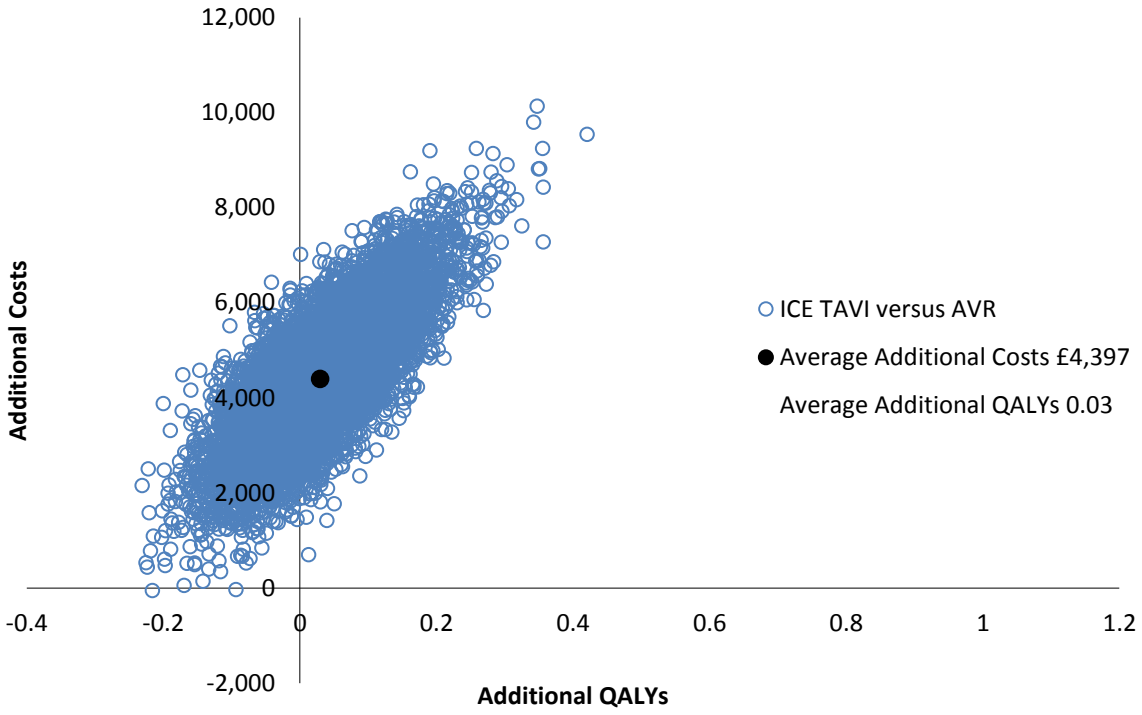
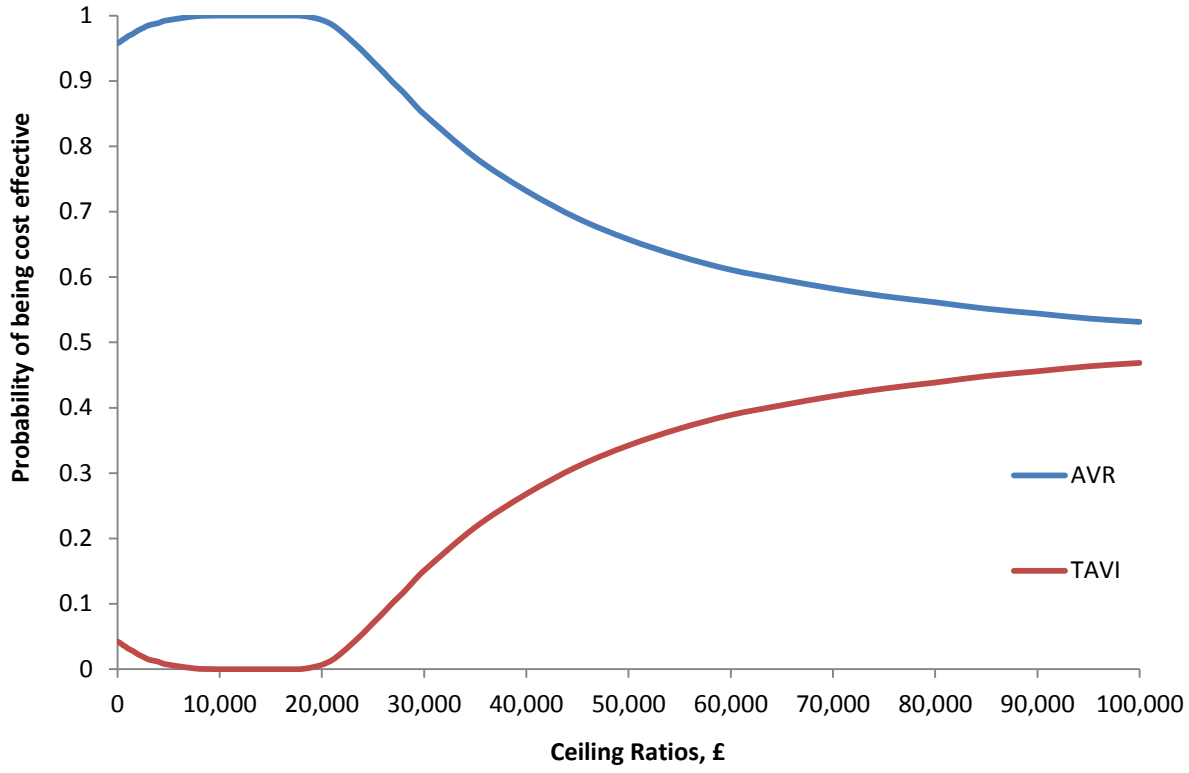


Figure 4.6 Cost Effectiveness Acceptability Curve: Low Risk Operable Patients - TAVI versus AVR



Sensitivity Analysis

As outlined earlier, it is anticipated that over time the price of the TAVI device will decrease owing to erosion of patents, as more competitors enter the market etc. A sensitivity analysis is used here to examine the impact of a reduction in the price of the TAVI device on its cost effectiveness. Reducing the cost of the device by £3,647 would result in TAVI being cost neutral (i.e. total cost of TAVI equals total cost of AVR). This is calculated as the difference in total procedural costs for AVR and TAVI (£18,080-£14,433, Table 4.5). With TAVI cost neutral there would only be slight health advantage due to the lower operative mortality associated with this risk-group. In this scenario, the ICER is £26,190/QALY which is within the usually accepted range making TAVI cost effective compared to AVR amongst low risk operable patients in this scenario.

Future evidence may also illustrate greater reductions in the relative risk of operative mortality associated with TAVI than the 10% conservatively assumed here, owing to incremental innovations and movements along the learning curve. A second sensitivity analysis was performed to assess the impact of such reductions in relative risk assuming a

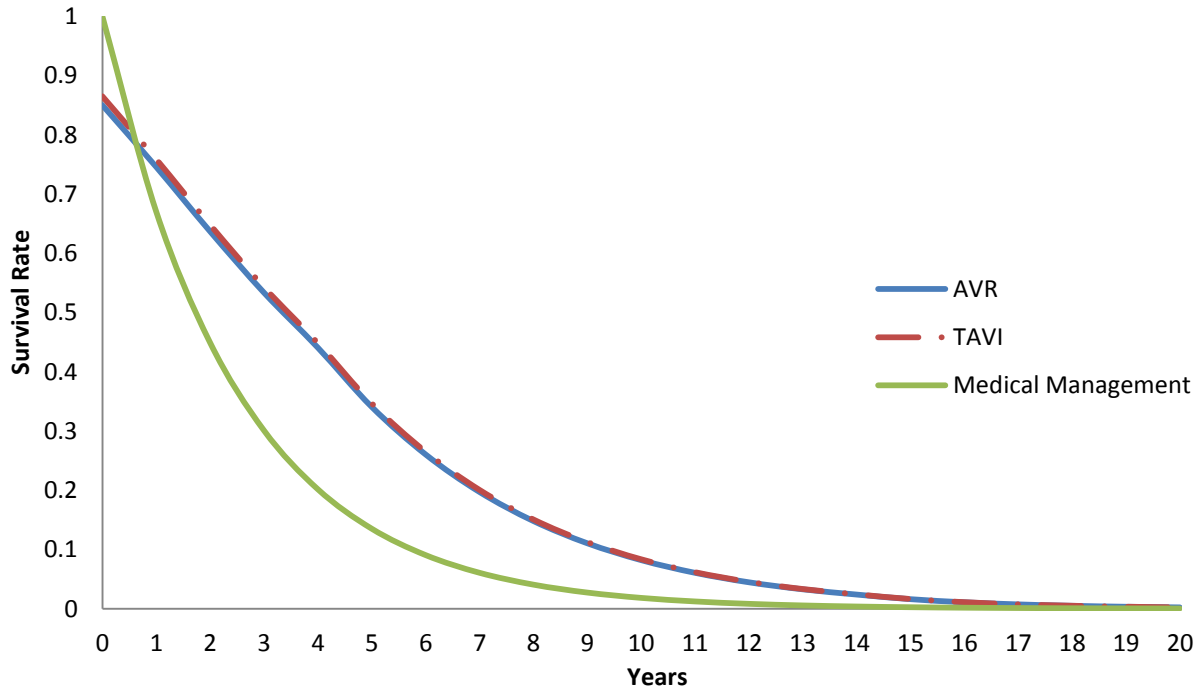
50% reduction in operative mortality. The analysis revealed that this would reduce the ICER to £45,723. These sensitivity analysis results are presented in Table 4.10.

4.7.2 Cost Effectiveness Results for High Risk Operable Patients – TAVI versus AVR and AVR versus Medical Management

The second patient group to be considered is the high risk operable group. Patients in this risk group are assumed to have an operative mortality of 15%. Owing to this operative mortality and potential co-morbidities, patients in this group may or may not be deemed eligible for AVR. A cohort of 1,000 patients enter the decision tree and Markov model and using the parameter estimates and transition probabilities the cost and QALYs per person over a 20 year period are estimated for AVR, TAVI and medical management. This facilitates the calculation of an ICER. This is repeated for a number of age/gender groups and the results are presented in Table 4.11.

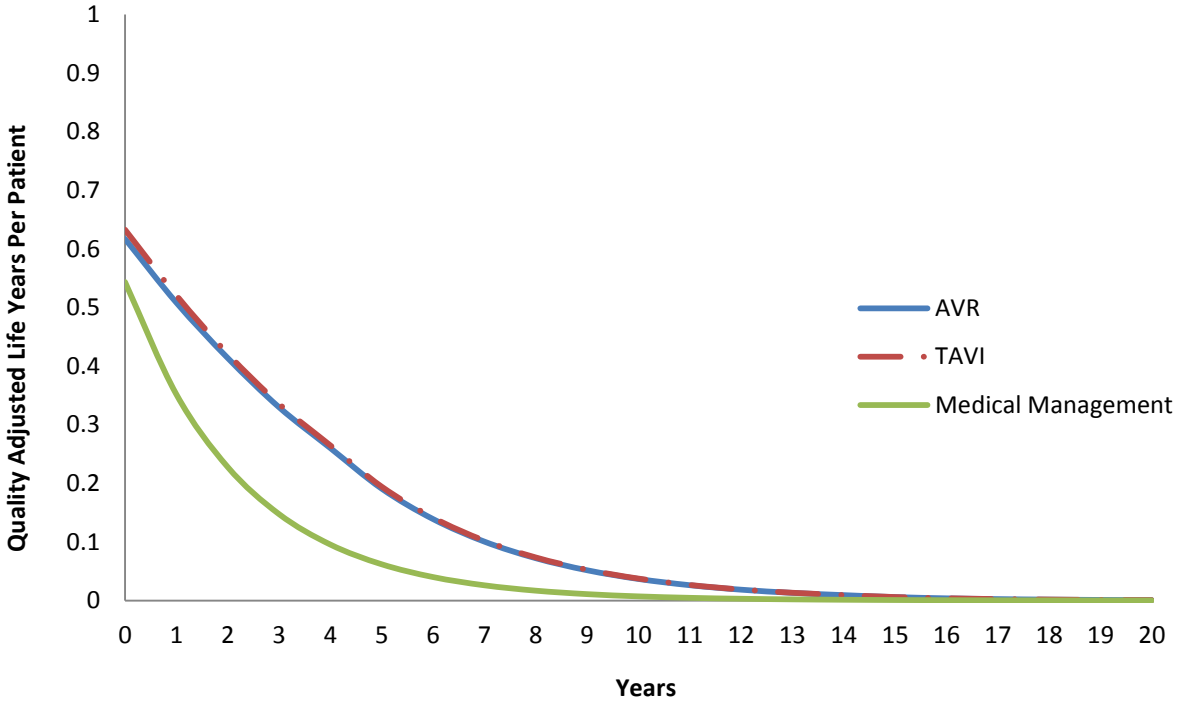
The results indicate only a 2% reduction in all-cause mortality at the end of year one between TAVI and AVR. While AVR provides a 7.5% reduction in all-cause mortality at the end of year one compared with medical management. The survival estimates from the model for TAVI, AVR and medical management are presented on Figure 4.7.

Figure 4.7 Survival Estimates for AVR, TAVI and Medical Management



With respect to quality of life (Figure 4.8), TAVI offers marginally more QALYs per patient at the end of year one (0.01 QALYs). While AVR offers substantially better quality of life than medical management with a difference of 0.16 QALYs.

Figure 4.8 Quality of Life Estimates for AVR, TAVI and Medical Management



Deterministic Cost Effectiveness Results

The deterministic cost effectiveness results (Table 4.11) are estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. For the base case (70 year old males) the results illustrate that TAVI is more costly (£5,140) and more effective (0.06 QALYs) than AVR. The ICER is estimated at £89,142/QALY which is outside the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)). Therefore, compared to AVR, TAVI cannot be considered cost effective in treating severe AS amongst high risk operable patients. Similarly, for the other five patient groups (males aged 60 and 80 and females aged 60, 70 and 80) TAVI is also more expensive and generates more QALYs than AVR and the ICERs are greater than £30,000/QALY for each age/gender group (Table 4.11).

With respect to AVR compared with medical management, for the base case (70 year old males) AVR was found to be more expensive (£12,777) and more effective (1.31 QALYs) than medical management. The ICER is estimated at £9,721/QALY, which is below the range usually considered cost effective in the UK (£20,000-£30,000 per (Rawlins et al., 2009)). Therefore, amongst high risk operable patients AVR can be considered cost effective compared to medical management in treating severe AS. For the other five patient groups (males aged 60 and 80 and females aged 60, 70 and 80) AVR is also more expensive and generates more QALYs than AVR. Each of the ICERs are less than £30,000/QALY, so across the patient groups AVR can be considered cost effective compared with medical management in treating severe AS amongst high risk operable patients (Table 4.11).

Probabilistic Cost Effectiveness Results

The probabilistic cost effectiveness results (Table 4.11) revealed for the base case (70 year old males) TAVI is more expensive (£5,157; 19%) and more effective (0.06; 2%) than AVR. The ICER is estimated as £85,982/QALY. This is outside the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)) so TAVI cannot be considered cost effective compared with AVR for treating high risk operable patients with severe AS. The probabilistic results for the remaining five patient groups also indicate that TAVI is more expensive and generates more QALYs than AVR, however the ICERs are greater than £30,000/QALY (Table 4.11).

With respect to AVR compared to medical management the probabilistic cost effectiveness results indicate in the base case (70 year old males) AVR is more expensive (£12,777; 93%) and more effective (1.31; 82%) than medical management. The ICER is estimated as £9,721/QALY which is below the range usually considered cost effective. So AVR can be considered cost effective compared with medical management for treating high risk operable patients with severe AS. The probabilistic results for the remaining five patient groups also indicated that AVR is more expensive and generates more QALYs than medical management and the ICERs are less than £30,000/QALY (Table 4.11). So across the patient groups AVR can be considered cost effective compared with medical management in treating severe AS amongst high risk operable patients (Table 4.11)

Table 4.11 a) Cost Effectiveness Results: High Risk Operable Patients* - TAVI Versus AVR & AVR Versus Medical Management

	AVR			TAVI			Medical Management		
	LYs (95% CI)	**Costs £ (95% CI)**	**QALYs (95% CI)**	**LYs (95% CI)**	**Costs £ (95% CI)**	**QALYs (95% CI)**	**LYs (95% CI)**	**Costs £ (95% CI)**	**QALYs (95% CI)**
Deterministic:		**Males (age, yrs)**							
60	5.35	28,691	3.23	5.45	33,867	3.30	3.03	13,802	1.54
70	4.55	26,676	2.80	4.63	31,817	2.86	3.03	13,802	1.54
80	3.54	23,958	2.23	3.61	29,051	2.27	3.03	13,802	1.54
		Females (age, yrs)							
60	5.61	29,295	3.36	5.70	34,481	3.43	3.03	13,802	1.54
70	4.96	27,721	3.02	5.04	32,879	3.08	3.03	13,802	1.54
80	3.93	25,035	2.45	4.00	30,147	2.51	3.03	13,802	1.54
Probabilistic:		**Males (age, yrs)**							
60	5.50	28,805	3.30	5.60	33,980	3.36	3.06	13,987	1.53
	(4.88-6.20)	(25,555-32,646)	(2.97-3.65)	(4.90-6.41)	(30,478-38,369)	(2.33-4.07)	(2.33-4.07)	(9,217-20,330)	(1.20-1.98)
70	4.65	26,698	2.84	4.73	31,854	2.90	3.05	13,920	1.53
	(4.00-5.35)	(23,5019-30,358)	(2.50-3.20)	(4.03-5.53)	(28,532-35,930)	(2.53-3.30)	(2.23-4.01)	(9,292-20,172)	(1.20-1.98)
80	3.61	23,963	2.25	3.67	29,051	2.30	3.06	13,944	1.53
	(2.99-4.01)	(20,984-27,380)	(1.90-2.63)	(3.02-4.43)	(26,091-32,742)	(1.93-2.70)	(2.33-4.09)	(9,254-20,377)	(1.20-1.99)
		Females (age, yrs)							
60	5.78	29,444	3.44	5.88	34,610	3.50	3.06	13,978	1.53
	(5.17-6.50)	(26,165-33,311)	(3.12-3.78)	(5.17-6.71)	(31,062-39,006)	(3.13-3.91)	(2.33-4.08)	(9,244-20,352)	(1.19-1.98)
70	5.07	27,772	3.07	5.17	32,947	3.14	3.05	13,900	1.53
	(4.45-5.76)	(24,580-31,433)	(2.74-3.41)	(4.47-5.94)	(29,547-37,096)	(2.77-3.52)	(2.32-4.03)	(9,166-20,022)	(1.19-1.96)
80	4.01	25,060	2.49	4.08	30,184	2.54	3.06	13,986	1.53
	(3.38-4.49)	(21,947-28,598)	(2.14-2.84)	(3.41-4.82)	(27,118-33,934)	(2.14-2.93)	(2.33-4.11)	(9,287-20.620)	(1.20-2.93)
Sensitivity Analysis:		**TAVI Cost Neutral**							
	4.65	26,712	2.84	4.73	28,194	2.90	3.06	13,952	1.53
	(4.02-5.37)	(23,561-30,461)	(2.51-3.20)	(4.06-5.54)	(24,927-32,235)	(2.53-3.30)	(2.33-4.09)	(9,202-20,410)	(1.19-1.99)

*Operative mortality risk assumed to be 15%; shaded row – base case

Table 4.11 b) Cost Effectiveness Results: High Risk Operable Patients* - TAVI Versus AVR & AVR Versus Medical Management

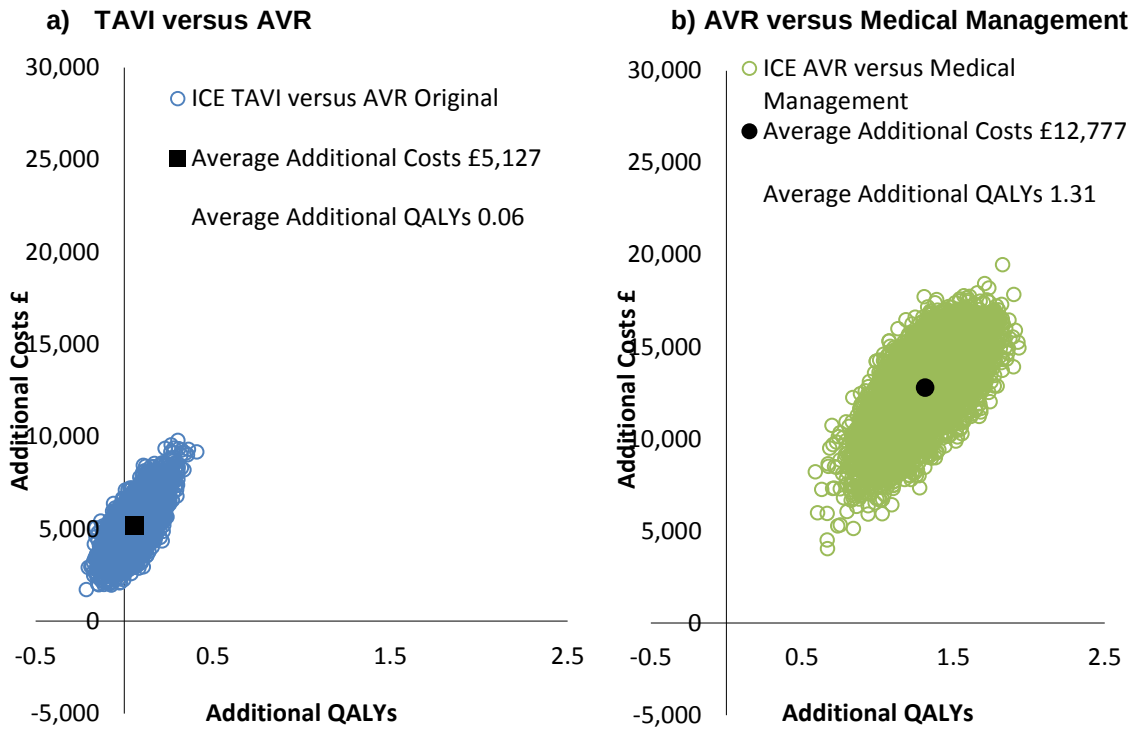
	TAVI versus AVR			AVR versus Medical Management		
	Δ Costs	**Δ QALYS**	**ICER £/QALY**	**Δ Costs**	**Δ QALYS**	**ICER £/QALY**
Deterministic:	**Males (age, yrs)**					
60	5,176	0.07	79,178	14,889	1.69	8,810
70	5,140	0.06	89,142	12,874	1.26	10,213
80	5,092	0.05	107,832	10,156	0.69	14,815
	Females (age, yrs)					
60	5,186	0.07	76,623	15,492	1.82	8,512
70	5,159	0.06	83,676	13,918	1.48	9,390
80	5,111	0.05	99,442	11,233	0.91	12,303
Probabilistic:	**Males (age, yrs)**					
60	5,175	0.07	78,245	14,818	1.76	8,401
	(2,892-7,590)	(-0.10-0.24)		(11,219-17,874)	(1.43-2.08)	
70	5,157	0.06	85,982	12,777	1.31	9,721
	(3,141-7,337)	(-0.08-0.21)		(8,820-16,082)	(0.94-1.67)	
80	5,088	0.05	107,377	8,820	0.94	13,850
	(3,299-6,908)	(-0.06-0.16)		(5,500-13,7290	(0.30-1.11)	
	Females (age, yrs)					
60	5,166	0.07	76,380	15,466	1.90	8,120
	(2,860-7,590)	(-0.12-0.25)		(12,005-18,446)	(1.58-2.12)	
70	5,174	0.06	81,960	13,873	1.55	8,972
	(3,043-7,488)	(-0.09-0.22)		(10,157-17,121)	(1.21-1.88)	
80	5,124	0.05	96,040	11,074	0.95	11,616
	(3,289-7,043)	(-0.07-0.18)		(6,673-14,610)	(0.54-1.33)	
Sensitivity Analysis:	**TAVI Cost Neutral**					
	1,482	0.06	26,653	12,761	1.31	10,406
	(-421-3,560)	(-0.09-0.20)		(8,802-16,044)	(0.93-1.66)	

*Operative mortality risk assumed to be 15%; shaded row – base case

The incremental cost effectiveness (ICE) planes (Figure 4.9a and 4.9b) illustrate the existence and extent of the uncertainty surrounding the incremental cost and incremental effect by plotting the additional benefit and costs of TAVI over AVR and AVR over medical management, presented side by side. With respect to TAVI versus AVR, there is no uncertainty with respect to the existence of differences in costs; TAVI is more expensive than AVR. However, there is considerable uncertainty surrounding the existence of differences in effectiveness. There is uncertainty surrounding the extent of the uncertainty in costs and effects. Similarly, AVR is more expensive and offer greater health benefit than medical management. However, there is considerable uncertainty surrounding the extent of differences in effects and costs for high risk operable patients. The average incremental cost of TAVI compared with AVR is £5,157 (ranging from £1,705 to £9,756) and incremental QALY is 0.06 (ranging from -0.21 to 0.41). The average incremental cost of AVR compared to medical management is £12,777 (ranging from £4,024 to £19,456) and the average incremental QALY is 1.31 (ranging from 0.59 to 1.93).

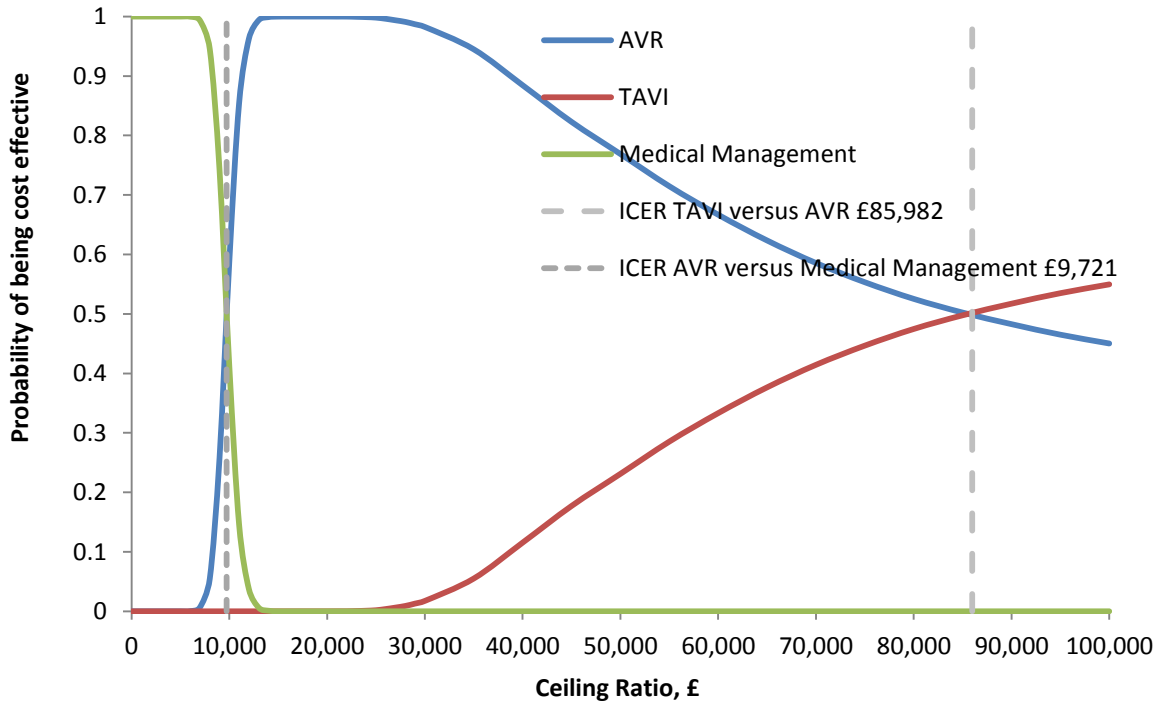
The ICE plane illustrates there is high correlation between the costs and QALYs. This is confirmed by estimating the correlation coefficient between the cost and effects for each treatment (r_{AVR} = 0.64; r_{TAVI} =0.72 and $r_{\text{Medical management}}$ =0.98). This high correlation can be explained by the construction of the costs and QALY parameters, which are both heavily reliant on the transition probabilities.

Figure 4.9 Cost Effectiveness Plane: High Risk Operable Patients



The CEAC (Figure 4.10) shows the decision uncertainty surrounding the cost effectiveness of each procedure, by plotting the probability of TAVI, AVR and medical management being cost effective against a range of ceiling ratios. For example, at a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective is 98%, the probability that TAVI is cost effective is 2% and the probability that medical management is cost effective is 0.

Figure 4.10 Cost Effectiveness Acceptability Curve: High Risk Operable Patients - TAVI versus AVR versus Medical Management



Sensitivity Analysis

As outlined earlier, TAVI is costly and its price is expected to decrease over time. A sensitivity analysis demonstrates that small changes in the base case assumptions of the modelling could change these results. For example, reducing the cost of the device by £3,647 (£18,080- £14,433 – Table 4.5) would result in TAVI being cost neutral. However, despite being cost neutral there is only a slight health advantage due to the lower operative mortality associated with this risk-group. This reduction in treatment costs results in an ICER of £10,401/QALY. This ICER is below the usually accepted range making TAVI cost effective compared to AVR amongst low risk operable patients in this scenario.

4.7.3 Cost Effectiveness Results for High Risk Inoperable Patients – TAVI versus Medical Management

The third patient group considered is the high risk inoperable group. Patients in this risk-group are assumed to have an operative mortality of 20%. Owing to this high operative mortality and potential co-morbidities, these patients are not deemed eligible for AVR. A cohort of 1,000 patients enter the decision tree and Markov model and using the parameter estimates and transition probabilities the costs and QALYs per person over a 20 year period are estimated for TAVI and medical management, facilitating the calculation of an ICER. This is repeated for a number of age/gender groups and the results are presented in Table 4.12.

The results indicate a marginal difference in all-cause mortality at the end of year one between TAVI and medical management. This increases in year two to 8%, 11% in year three and 12% in year four. The survival estimates (Figure 4.11) demonstrate the superiority of TAVI after year one until year 11. With respect to quality of life TAVI offers more QALYs (0.10) per patient at the end of year one than medical management (Figure 4.12).

Figure 4.11 Survival Estimates for TAVI and Medical Management

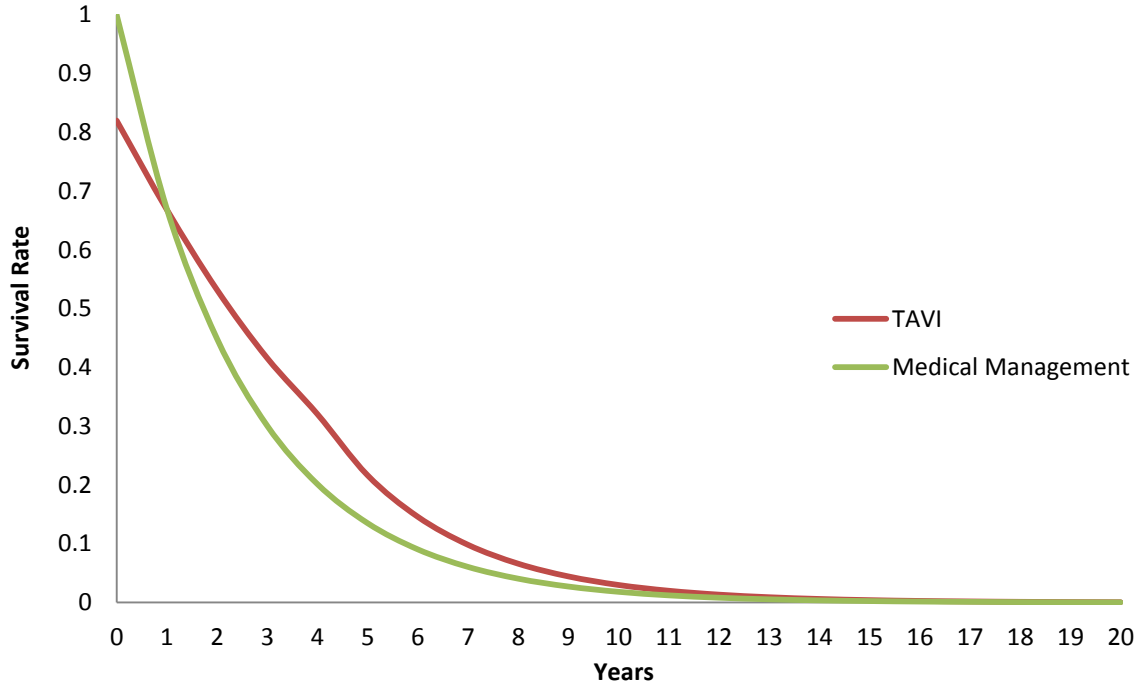
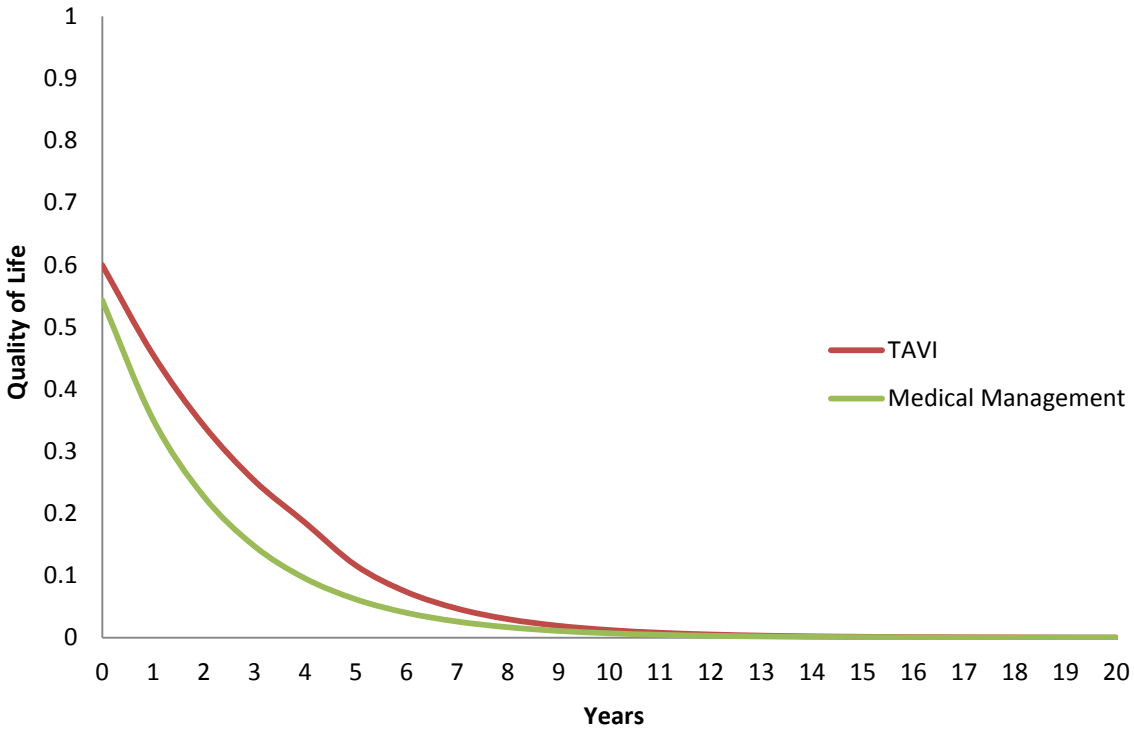


Figure 4.12 Quality of Life Estimates for TAVI and Medical Management



Deterministic Cost Effectiveness Results

The deterministic cost effectiveness results (Table 4.12) are estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. For the base case (80 year old males) the results illustrate that for these patients TAVI is more costly (£14,531) and more effective (0.61 QALYs) than medical management. The ICER is estimated at £23,650/QALY, which is within the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)). Therefore, compared to medical management, TAVI can be considered cost effective in treating severe AS amongst high risk inoperable patients. For the other five patient groups (males aged 60 and 70 and females aged 60, 70 and 80) TAVI is also more expensive and generates more QALYs than medical management and the ICERs are less than £30,000/QALY for each group. So across the age/gender groups TAVI can be considered cost effective compared with medical management in treating severe AS amongst high risk inoperable patients.

Probabilistic Cost Effectiveness Results

The probabilistic cost effectiveness results (Table 4.12) reveal for the base case (80 year old males) TAVI is more expensive (£14,531; 103%) and more effective (0.65 QALYs; 43%) than medical management. The ICER is estimated as £22,108, which is within the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)) so TAVI can be considered cost effective compared with AVR for treating high risk inoperable patients with severe AS. The probabilistic results for the remaining five patient groups also indicated that TAVI is more expensive and generates more QALYs than medical management. The ICERs are also less than £30,000/QALY for the remaining patient groups, so TAVI can be considered cost effective compared with medical management for these groups.

The ICE plane (Figure 4.13) illustrates the existence and extent of the uncertainty surrounding the incremental cost and incremental effect by plotting the additional benefit and costs of the TAVI procedure over medical management. Here, there is some uncertainty with respect to the existence of differences in effectiveness and little uncertainty with respect to differences in costs. However, TAVI is likely to be more expensive and offer greater health benefits than medical management. The difference in costs is driven by the cost of the TAVI device. There is also considerable uncertainty surrounding the extent of differences in effects and costs. The average incremental cost of TAVI compared to medical management is £14,411 (ranges from £3,948 to £20,520) and the average incremental QALY is 0.65 (ranges from -0.34 to 1.39).

The ICE plane illustrates there is high correlation between the costs and QALYs. This correlation was confirmed by estimating the correlation coefficient between the cost and effects for each treatment (r_{TAVI} =0.74 and $r_{Medical\ Management}$ =0.99). An explanation for this high correlation lies in the construction of the costs and QALY parameters, which are both based on the transition probabilities.

The CEAC (Figure 4.14) shows the decision uncertainty surrounding the cost effectiveness of each procedure, by plotting the probability of TAVI and medical management being cost effective against a range of ceiling ratios. For example, at a ceiling ratio of £30,000 per QALY the probability that TAVI is cost effective is 86% and the probability that medical management is cost effective is just 14%.

Table 4.12 Cost Effectiveness Results: High Risk Inoperable Patients* - TAVI versus Medical Management

	TAVI			Medical Management			TAVI versus Medical Management		
	LYs (95% CI)	Costs £ (95% CI)	QALYs (95% CI)	LYs (95% CI)	Costs £ (95% CI)	QALYs (95% CI)	Δ Costs (95% CI)	Δ QALYS (95% CI)	ICER £/QALY
Deterministic:		**Males (age, yrs)**							
60	5.16	32,900	3.12	3.03	13,802	1.54	19,097	1.58	12,057
70	4.39	30,956	2.71	3.03	13,802	1.54	17,154	1.17	14,669
80	3.42	28,334	2.16	3.03	13,802	1.54	14,531	0.61	23,650
		Females (age, yrs)							
60	5.23	32,706	3.02	3.35	13,802	1.64	17,769	1.38	12,906
70	4.78	31,963	2.92	3.03	13,802	1.54	18,161	1.38	13,128
80	3.79	29,373	2.38	3.03	13,802	1.54	15,570	0.83	18,668
Probabilistic:		**Males (age, yrs)**							
60	5.31	33,002	3.19	3.06	13,962	1.53	19,040	1.66	11,500
	(4.63-6.11)	(29,607-37,106)	(2.83-3.58)	(2.34-4.07)	(9,269-20,212)	(1.20-1.97)	(14,973-22,508)	(1.28-2.03)	
70	4.49	30,988	2.75	3.06	13,948	1.53	17,040	1.22	13,971
	(3.82-4.26)	(27,874-34,811)	(2.39-3.14)	(2.35-4.07)	(9,334-20,284)	(1.20-1.98)	(12,890-20,526)	(0.81-1.60)	
80	3.48	28,353	2.18	3.06	13,942	1.53	14,411	0.65	22,108
	(2.86-4.19)	(25,491-31,820)	(1.83-2.56)	(2.33-4.06)	(9,251-20,274)	(1.19-1.98)	(9,767-18,075)	(0.22-1.05)	
		Females (age, yrs)							
60	5.57	33,608	3.32	3.06	13,963	1.53	19,645	1.79	10,976
	(4.88-6.36)	(30,173-37,779)	(2.96-3.71)	(2.35-4.08)	(9,295-20,476)	(1.20-1.99)	(15,584-23,047)	(1.41-2.16)	
70	4.90	32,049	2.98	3.07	14,002	1.53	18,047	1.44	12,512
	(4.25-5.68)	(28,789-36,136)	(2.63-3.36)	(2.33-4.09)	(9,208-20,329)	(1.20-1.99)	(13,912-21,508)	(1.06-1.81)	
80	3.86	29,403	2.40	3.06	13,955	1.53	15,448	0.87	17,689
	(3.22-4.60)	(26,432-33,039)	(2.04-2.78)	(2.33-4.07)	(9,180-20,204)	(1.19-1.98)	(11,019-19,083)	(0.46-1.27)	

*Operative mortality risk assumed to be 20%; shaded row – base case

Figure 4.13 Incremental Cost Effectiveness Plane: High Risk Inoperable Patients - TAVI versus Medical Management

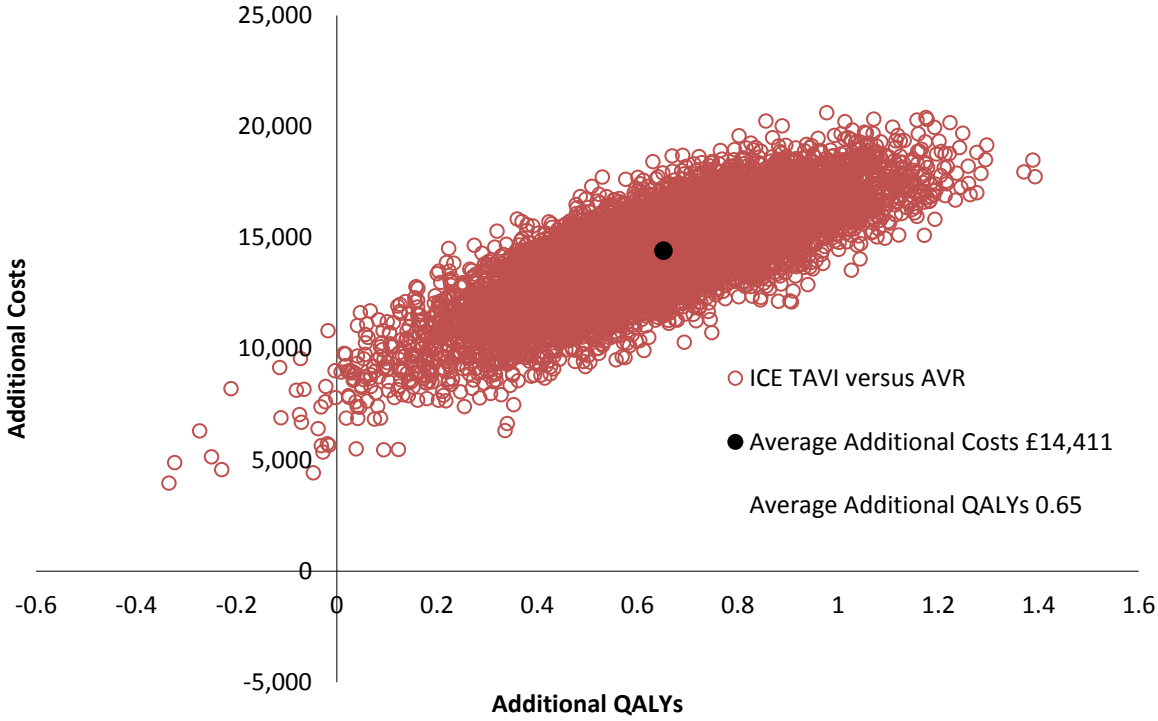
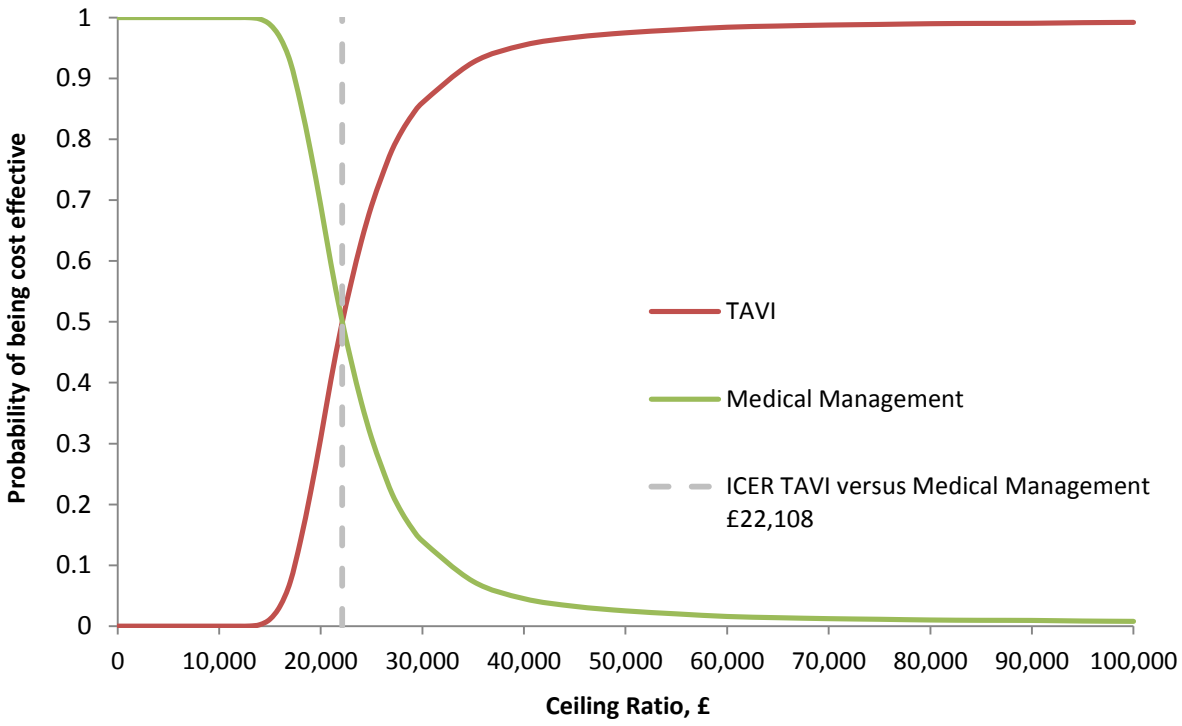


Figure 4.14 Cost Effectiveness Acceptability Curve: High Risk Inoperable Patients - TAVI versus Medical Management



4.8 VALUE OF FURTHER RESEARCH

The potential value of undertaking further research is estimated using a Bayesian VOI analysis (described in Chapter 2). The expected value of perfect information (EVPI), estimates the value of eliminating all the uncertainties within the model, providing a maximum value for the return on further research. Having estimated EVPI per patient, the population EVPI (pEVPI) for one year is estimated, using the population estimates presented in Table 4.13. The annual population estimates for those with severe AS in the UK per patient risk group are as follows: 3,000 low risk operable patients; 2,250 high risk operable patients and 2,750 high risk inoperable patients (SHTG, 2009). As discussed in Chapter 2, it can be difficult to assess what is an appropriate time frame. Here one year is chosen as the timeframe, as it is the expected period over which a choice between TAVI, AVR and medical management is considered a viable decision. That is to say, beyond one year it is expected that advances in the medical device technology would make the decision obsolete/invalid, as per the characteristics of medical devices discussed in Section 1.2.1.

Table 4.13 Population Estimates per Patient Group in the UK

Patient Group	UK*
Low risk operable patients currently getting AVR	3,000
High risk operable patients currently getting AVR or medical management	2,250
High risk inoperable patients currently not getting AVR just medical management	2,750
Total	8,000

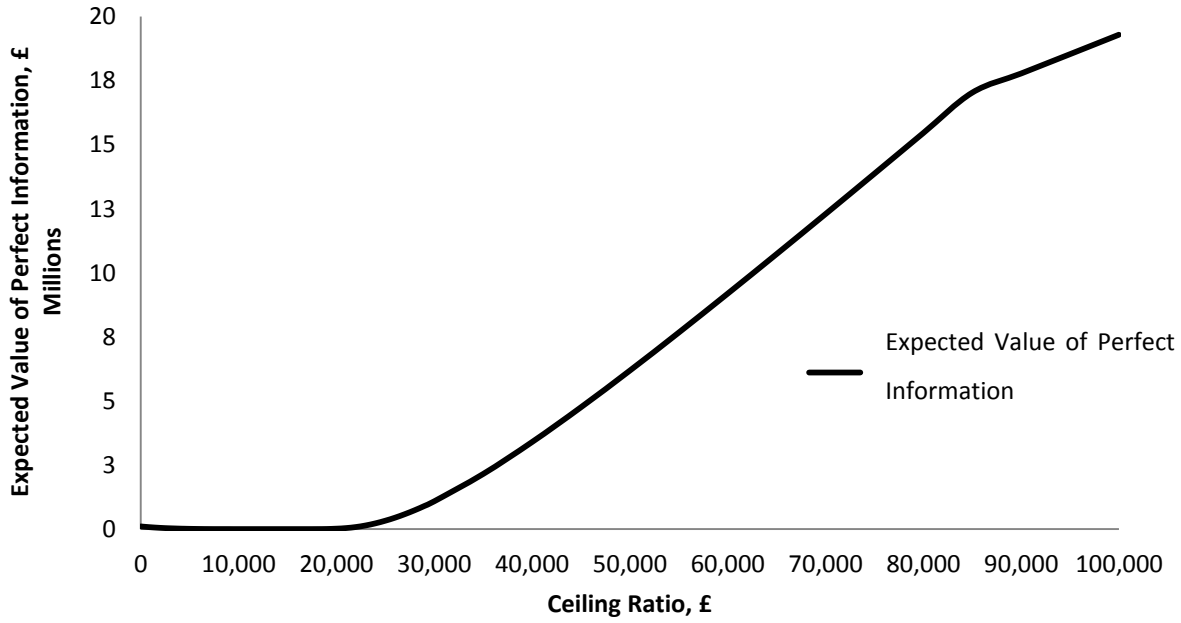
*Scottish Health Technologies Group (2009)

Low Risk Operable Patients

The EVPI per patient, when deciding between TAVI and AVR, is estimated using the net benefits from the PSA results. Here, the EVPI ranges from £5 to £360 per low risk operable patient, over the range usually considered cost effective (£20,000-£30,000/QALY) (Rawlins et al., 2009) for one year.

Given the public good characteristics displayed by information, the EVPI for the population (pEVPI) can be estimated for the low risk operable population in the UK (3,000 (SHTG, 2009). The pEVPI, over the range usually considered cost effective, is estimated to range from £15,917 to £1.08 million (Figure 4.15). These estimates provide a maximum value for the return of further research, suggesting there is value in collecting further information on low risk, operable patients.

Figure 4.15 Expected Value of Perfect Information: Low Risk Operable Patients – TAVI versus AVR

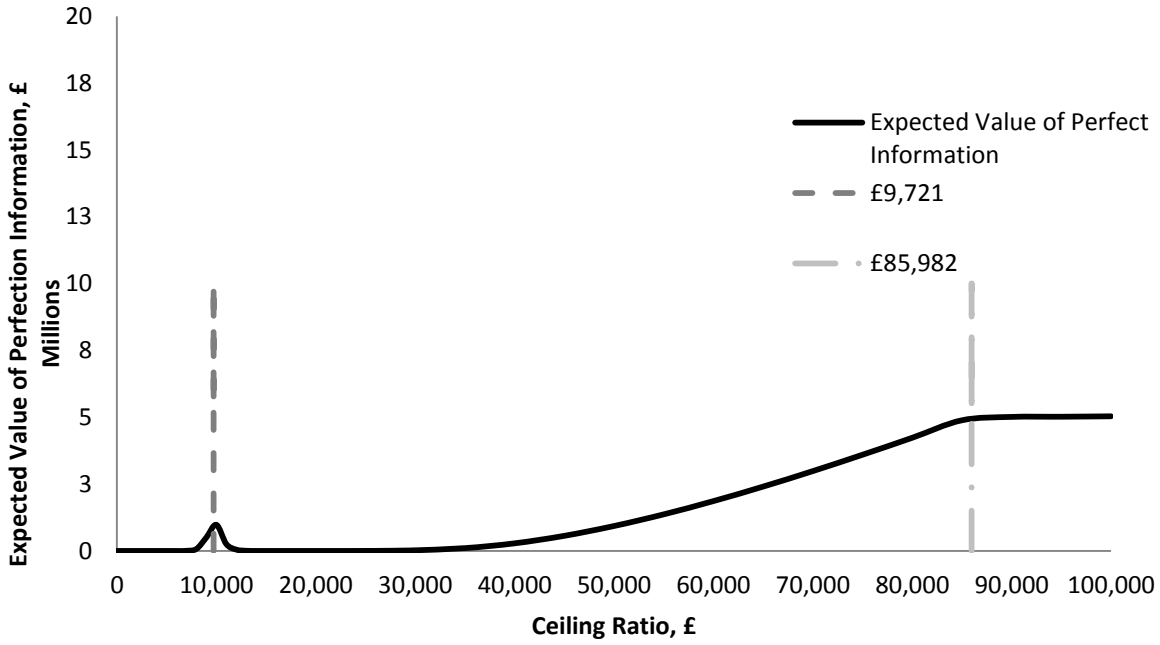


High Risk Operable Patients

The EVPI per patient, when deciding between TAVI, AVR and medical management ranges from £0 to £10 per high risk operable patient over the range usually considered cost effective (£20,000-£30,000/QALY). Using the population estimates from Table 4.13, the pEVPI was calculated for one year for a population of 2,250. The pEVPI (2,250 (SHTG, 2009), over the range usually considered cost effective, ranges from £0 to £23,433 (Figure 4.16). The EVPI provide a maximum value for the return on further research, suggesting there is very little value in collecting further information on high risk, operable patients.

Meanwhile, the results indicate that the pEVPI reaches an inflection point at a ceiling ratio equal to the ICER £9,721/QALY. This corresponds to the point on the CEAC (Figure 4.10) where the decision between AVR and medical management is most uncertain. Here, the probability that medical management is cost effective is 41% and the probability that AVR is cost effective is 59%. Beyond this ceiling ratio the optimal treatment changes and AVR is more likely to be cost-effective compared with medical management. The pEVPI curve has a second inflection point at the ICER for TAVI versus AVR (£85,982/QALY). This is where the decision about the cost effectiveness of TAVI versus AVR is most uncertain. At a ceiling ratio greater than £85,000/QALY, TAVI is more likely to be cost effective compared with AVR.

Figure 4.16 Expected Value of Perfect Information: High Risk Operable Patients – TAVI versus AVR versus Medical Management



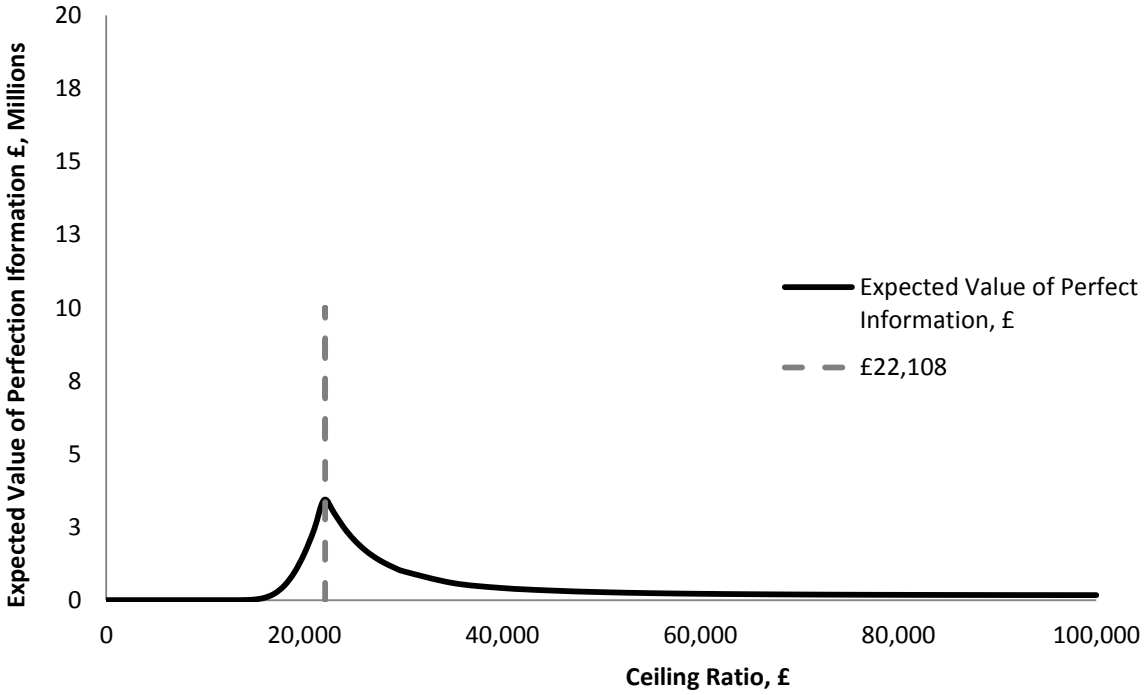
High Risk Inoperable Patients

The EVPI per patient, when deciding between TAVI and medical management, ranges from £360 to £1,247 per high risk inoperable patient, over the range usually considered cost effective (£20,000-£30,000/QALY). For these high risk inoperable patients the pEVPI over the range usually considered cost effective ranges from £998,775 to £3.43 million (Figure 4.17). These estimates provide a maximum value for the return of further research

and suggest there is some value in collecting further information on high risk, inoperable patients.

The pEVPI curve has an inflection point at a ceiling ratio equal to the ICER (£22,108/QALY), corresponding to the point on the CEAC (Figure 4.14) where the decision is most uncertain. Here, the probability that TAVI is cost effective is 49% and the probability that medical management is cost effective is 51%. Beyond this ceiling ratio (i.e. > £22,108/QALY) the optimal treatment changes and TAVI is more likely to be cost-effective compared with medical management. As there are only two technologies considered here (TAVI and medical management) this inflection point is also the maximum pEVPI point.

Figure 4.17 Expected Value of Perfect Information: High Risk Inoperable Patients – TAVI versus Medical Management

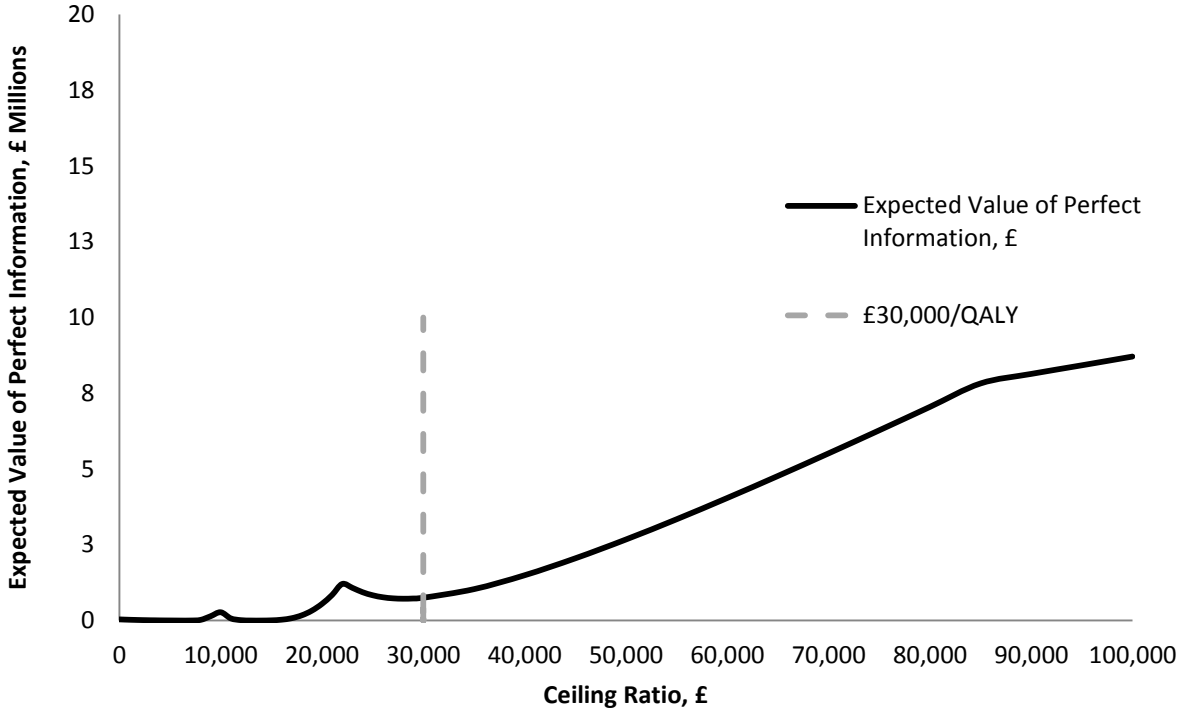


Severe AS Population in the UK

To estimate the pEVPI for the entire severe AS population in the UK the pEVPI for the three risk groups are weighted and summed. Recalling that the pEVPI ranges from £15,917 to £1.08 million for low risk operable patients; £0 - £23,433 for high risk operable

patients and £998,775 - £3.43 million for high risk inoperable patients, weighting these pEVPI estimates by the number of patients per group gives the total pEVPI for the total UK population of severe AS patients. This ranges from £486,641 - £1.27 million at the usually acceptable threshold (£20,000-£30,000 per QALY) (Figure 4.18). This provides an upper bound on the potential value for additional research in the UK context, indicating there is value in generating evidence for TAVI within these bounds, where the evidence is appropriate for all patients irrespective of risk. This additional information can be employed in a subsequent cost effectiveness and VOI analysis in line with the continuous iterative framework developed in Chapter 2.

Figure 4.18 Expected Value of Perfect Information for the UK Population



4.9 SUMMARY OF COST EFFECTIVENESS ANALYSIS RESULTS AND RESEARCH RECOMMENDATIONS

This chapter presented a detailed description of the decision analytical model (DAM) proposed to estimate the cost effectiveness of TAVI in treating severe AS compared with AVR and medical management. The DAM contains a decision tree to model the initial 30 days and a Markov model to capture the next 20 years in yearly cycles. Owing to data scarcity, the model is populated using a combination of data extracted from published literature, expert opinion etc., which yields parameter uncertainty.

The results illustrate that for low and high risk operable patients TAVI cannot be considered cost effective compared to AVR and is subject to uncertainties. In particular, there are two short-term uncertainties that must be taken into account when trying to understand the potential for TAVI to provide a cost effective treatment. The first is the extent to which the high acquisition cost of the device can be offset by the reduction in hospital length of stay, particularly in high-dependency units. The second is the potential for TAVI to reduce the operative mortality rate. This analysis chooses a conservative 10% reduction; if a more optimistic view point could have been supported by evidence the ICER is reduced (though still outside the range usually considered cost effective).

The cost effectiveness analysis of TAVI for high risk inoperable patients appears more positive. This is largely due to the poor prognosis for AS patients who do not receive AVR, meaning that the potential patient benefit in this group is much higher. Nevertheless, with few costs to offset, the health service would have to fund the full cost of the device, which may prove a practical challenge in current resource constrained environments.

Given the results and the novel nature of the device the appropriate question to ask is what further research could be performed to help improve decisions regarding TAVI in the future? The VOI analysis presented here attempts to summarise this potential. If all uncertainties in the model could be resolved, the ‘value’ of this is estimated to be £751,967 (Figure 4.18) for UK severe AS population in terms of the reduced cost of this uncertainty associated with making the incorrect decision (either to reject a cost effective technology or adopt a cost-ineffective one) at a ceiling ratio of £30,000/QALY. Suggesting there is some value in collecting further evidence on TAVI amongst the UK severe AS population.

There is however, a number of limitations to the analysis presented here. The model provides a highly stylised version of the complexities of everyday clinical practice in this challenging patient group. In particular, the co-morbidities for patients with higher operative mortality risks are likely to increase, and this is not explicitly modelled at present. For the low risk operable patients, it is not clear that the QALY approach adequately captures patient preferences for the less invasive technique compared to conventional surgery. Nevertheless, decisions do have to be made and it is clear that the potential for TAVI to bring huge patient benefits should not be ignored.

The cost effectiveness and VOI analyses presented here represent the first cycle of the continuous iterative framework proposed in Chapter 2. Whereby, a decision problem is identified and employing available evidence the cost effectiveness of TAVI and the value of generating further evidence is investigated. The analysis reports that TAVI is cost effective for high risk inoperable patients, compared to medical management only. But there is some value in collecting additional evidence on operable patients also.

As described previously, the analysis presented here is based on early evidence from pre-trial published small single centre registries and case series up to 2009. According to Leon et al. (2006) evidence generation for new devices, such as TAVI, follow a natural sequence. Whereby, initially the first experiences with the device from small single centre registries and case series are published. Here the general operating principles are ascertained and feasibility is tested. Subsequently, multicentre registries are established where techniques are improved upon and efficacy is compared with the natural history of the disease and alternatives. Following this, random control trials (RCTs) begin to appear.

Evidence generation for TAVI appears to be following this sequence. Subsequent to the initial evidence from the registries and case series employed in this analysis (described in Chapter 3), RCTs for high risk operable and inoperable patients are emerging. (Currently there are no plans for trials for low risk operable patients.) The results of these trials, when published, can be incorporated into this DAM in line with the proposed iterative framework. This will provide the opportunity to update the model parameters to reflect the best available data which may improve the fit of the model and reduce some uncertainties, in line with the continuous iterative framework proposed in Chapter 2.

CHAPTER 5 EVOLVING DATABASE FOR TRANSCATHETER AORTIC VALVE IMPLANTATION - INTEGRATING THE PARTNER TRIAL RESULTS FOR HIGH RISK INOPERABLE PATIENTS

5.1 INTRODUCTION

Despite the increasing number of TAVI procedures performed (detailed in Chapter 3), little evidence on the long term outcomes of the procedure were available for the first iteration of the decision analytical model (DAM) presented in Chapter 4. As outlined in Chapter 1, this is a common problem for novel expensive medical devices, where there are no regulatory requirements for clinical trials etc. Currently, in England and Wales the National Institute for Clinical Excellence (NICE) Interventional Procedure Guidance (Number 266, 2008) (NICE, 2008) recommends the use of TAVI only where special arrangements for clinical governance, consent, audit and research are in place. While in Scotland, the Scottish Health Technologies Group (SHTG) advice statement (Number 005/11) does not recommended TAVI for routine treatment of patients with AS (NHS, 2008b). Therefore, strict clinical and anatomical criteria are still required when recommending TAVI, which is yet to be demonstrated as being cost effective.

So the publication of results from the Placement of Aortic Transcatheter Valves (PARTNER) trial in 2010 - 11 (Leon et al., 2010, Smith et al., 2011) was a welcomed evolution in the TAVI evidence base (Leon et al., 2006). In this Chapter, evidence from the PARTNER trial (Leon et al., 2010) was incorporated into the TAVI DAM (developed in Chapter 4) to estimate the long term cost effectiveness of TAVI compared to medical management for high risk inoperable patients with severe AS. While the short term efficacy and effectiveness of TAVI for inoperable patients has been hinted at by case studies and published literature, it is yet to be demonstrated. This re-analysis is in line with the proposed iterative framework for economic evaluations (Chapter 2), as the role of TAVI in treating patients with AS needs to be further investigated to inform adoption and

research priority setting decisions. Upon publication of the trial results there was no accompanying cost effectiveness analysis.

5.2 EVOLVING TAVI EVIDENCE – THE PARTNER TRIAL

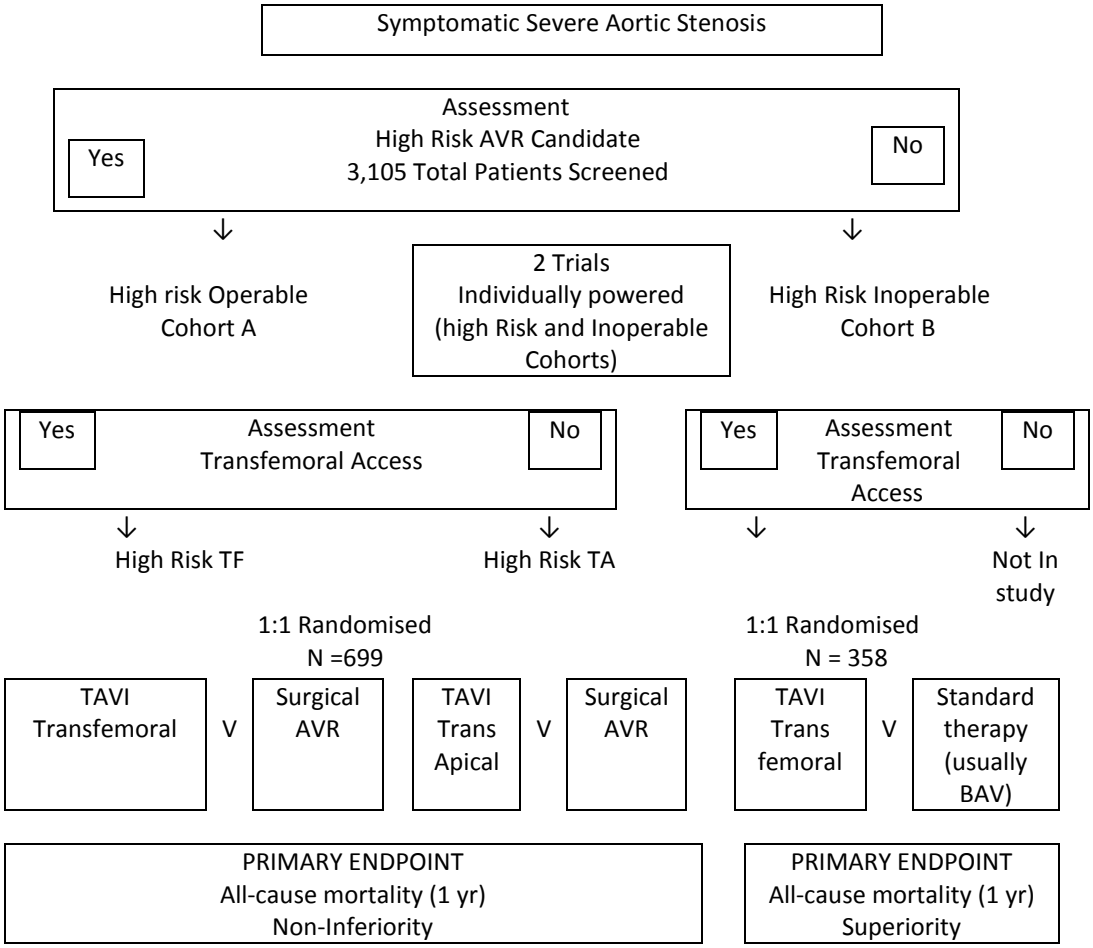
The aforementioned PARTNER Trial, sponsored by Edwards Lifesciences[4], began in April 2007 and enrolled patients with severe AS in 25 centres (see Appendix V Table a for inclusion and exclusion criteria). One of the centres was in Germany (Leipzig), three were in Canada (Quebec, Vancouver and Toronto) and the remaining 21 were across 15 states in the US (Leon et al., 2010). Motivation for the trial came from the lack of safety and effectiveness data surrounding the procedure and specifically the Edwards device (Penn, 2012). Severe AS was defined in the trial as an aortic valve area of less than $0.8cm^2$, a mean aortic valve gradient of 4mm Hg or more or a peak aortic-jet velocity of 4.0m per second or more (Leon et al., 2010). In addition, all patients were in New York Heart Association (NYHA) classes greater than I (see Table 3.1 for definition of NYHA classes) (Leon et al., 2010). The patients were then divided into two treatment groups, defined by their eligibility for surgery, determined by at least two surgeons.

The study design (Figure 5.1) illustrates that a total of 3,105 patients were screened for inclusion in the trial. Of whom, 699 were considered operable and were included in the cohort comparing TAVI with surgical valve replacement (i.e. AVR) (Cohort A). A further 358 patients were considered inoperable and were included in a second cohort comparing TAVI with standard therapy (i.e. medical treatment) (Cohort B).

In the context of this thesis, Cohort A corresponds to high risk operable patients and Cohort B corresponds to high risk inoperable patients, in line with the previous chapter. Cohort B results were published in October 2010 and the Cohort A results were published in June 2011. In this Chapter, published Cohort B results will be used to re-examine the cost effectiveness of TAVI amongst high risk inoperable patients. The Cohort A results are incorporated in Chapter 6 to re-evaluate TAVI for high risk operable patients.

4 Edwards Lifesciences Corporation, Irvine, CA, manufacture of the Edwards Sapien Valve, one of two TAVI devices on the market at the time.

Figure 5.1 PARTNER Trial Design



Source: Adapted from Figure 1, Supplementary Appendix, Leon et al. (2010)

5.3 INCORPORATING EVIDENCE FROM PARTNER COHORT B – INOPERABLE PATIENTS

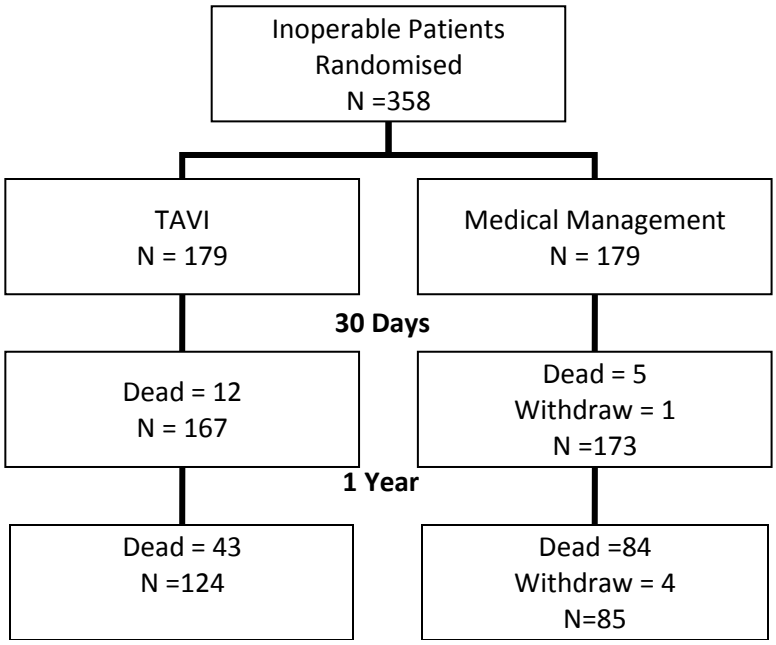
Incorporating the PARTNER evidence into the model, where available, resulted in some adjustments to the TAVI DAM, developed in Chapter 4 and revisions to the parameters.

5.3.1 PARTNER B Evidence

In October 2010, the results of PARTNER Cohort B were published. This cohort compared inoperable patients receiving TAVI to those receiving medical management (Leon et al., 2010). The study design and patient flows (Figure 5.2) show that this cohort initially included 358 patients, who were considered to have severe AS and deemed inoperable (unsuitable for cardiac surgery). Of these 179 patients were allocated to each of

the TAVI and medical management arms of the trial. In the medical management arm one patient withdrew from the trial and five died within the first 30 days. While 12 TAVI patients died in the same period. So at the end of the first 30 days, 173 patients received medical management and 167 received the TAVI procedure. During follow up (30 days to one year) a further four patients withdrew from the medical management arm and 84 more patients died. While in the TAVI arm, an additional 43 patients died during this time period. Thus, at one year follow up information on the clinical endpoints were available for all those who died; 85 medical management survivors and 124 TAVI survivors. This (pre-model) data is presented in Appendix V Table b.

Figure 5.2 PARTNER Trial Cohort B Patient Flow: TAVI versus Medical Management



Source: Adapted from Figure 2, Supplementary Appendix, (Leon et al., 2010)

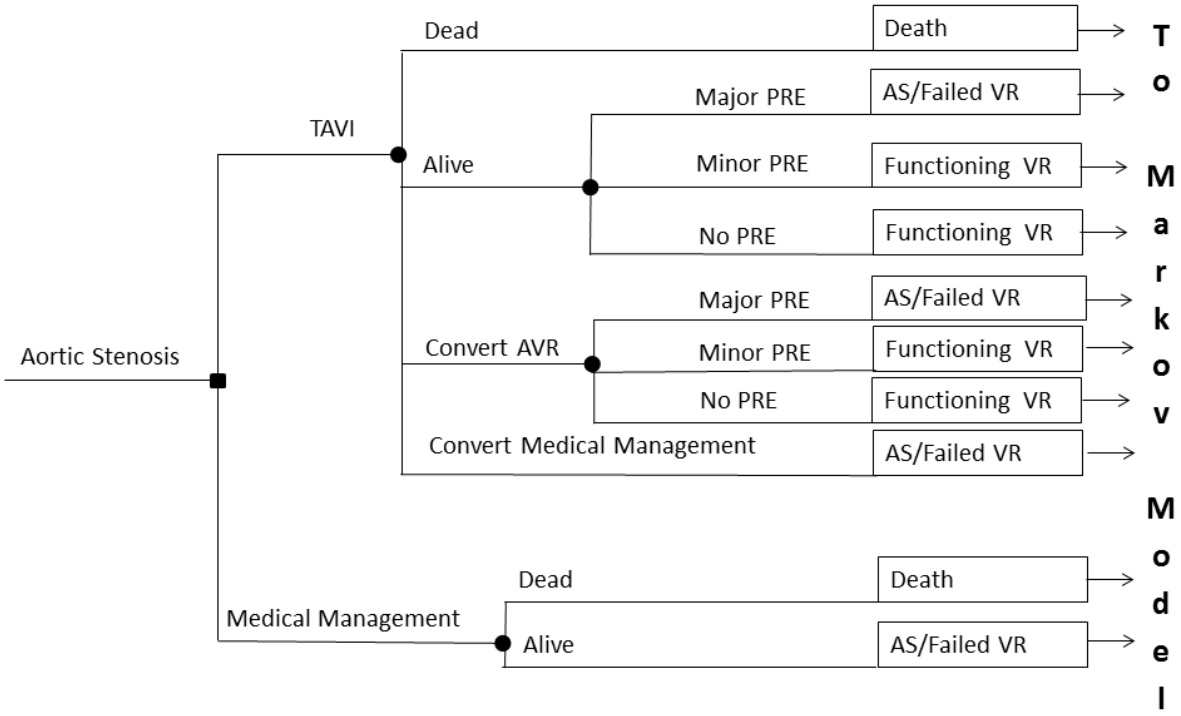
5.3.2 Changes to the Decision Analytical Model

Incorporating PARTNER B evidence, where available, into the DAM model (developed in Chapter 4) to investigate the cost effectiveness of TAVI compared with medical management, resulted in some adjustments to the decision tree component of the model. The initial conceptualisation of the DAM was dependent on knowledge about AVR and early TAVI experiences. The latter was based on early registries and small case series. As

the PARTNER Cohort B trial is the first to consider medical management compared to TAVI directly, evidence from the trial updates knowledge and understanding of the procedures and the disease pathways. Specifically, this informed the inclusion of conversions from TAVI to medical management, repeat TAVI procedures and death from medical management in the decision tree. These changes are illustrated on the revised decision tree (Figure 5.3).

Prior to the PARTNER trial, experience with TAVI was limited, particularly with respect to late outcomes. While evidence from the PARTNER trial did not result in any structural amendments to the Markov model, it did offer the distinction between major and minor late procedure related events (PREs) (the latter incur a cost and utility hit only and do not result in valve failure). In addition, the data provided revised estimates for long run point estimates, such as late major procedure related events, which were previously informed by experience with AVR.

Figure 5.3 Revised Decision Analytical Model for Inoperable Patients: Short Term Component – The Decision Tree



5.3.3 Parameterisation of the Decision Analytical Model – Inoperable Patients

Transition Probabilities

Cohort B of the PARTNER Trial compared TAVI to standard therapy (i.e. medical management) for severe AS patients considered inoperable. Outcomes and clinical endpoints from the two treatment arms presented by Leon et al. (2010) for 30 days and 1 year (presented in Appendix V Table b) permitted the revision of the parameters used in the model to reflect the best data available. Here evidence from PARTNER B was used to replace the previously used evidence from the literature, where available, to revise the point estimates for the model parameters. A "replacement" strategy was adopted as PARTNER B evidence reflects the best available data at the time of publication. Whereas, the evidence used to populate the original model was based on early short term TAVI results and AVR experience. This is in line with the view that expert opinion can become irrelevant in the presence of large RCTs. Where it is considered that the accumulated empirical evidence dominates the expert opinion (NICE, 2004). Therefore, an "updating" strategy would not have reflected optimal data at the time. For parameters where PARTNER evidence was unavailable, the point estimates from the original model (from published literature) were maintained.

The point estimates for the transition probabilities using PARTNER Cohort B evidence (Leon et al., 2010) were calculated as follows. Leon et al. (2010) provided the number of times each event occurred (α). The total number of times that the event could have occurred was estimated as the number of patients at risk of the event (n) (i.e. those who had already died were removed). The probability of the event occurring is estimated as the proportion of events occurring (α) from the total that could have occurred (n).

Box 5.1 provides an example. Leon et al. (2010) reported 30 cases of major bleeding within 30 days for TAVI patients and 40 cases within one year. It was deduced that 10 major bleeding occurred post discharge up to one year. The arm consisted of 179 patients, six withdrew, one converted to AVR and four converted to medical management, so 168 patients received the TAVI procedure. The probability of having a major bleeding in the first 30 days was the proportion of events which occurred ($\alpha = 30$) from the total that could have occurred ($n=168$), which is 0.179 ($\alpha/n = 30/168$). The probability of having a major

bleeding in the longer term was estimated similarly. The number of events that occurred (α =10) as a proportion of the total that could have occurred (n=118) which was 0.085 (α/n =10/118). The total number of events that could have occurred in the longer term was calculated as the number of patients who received the treatment minus those who died, had a major stroke or major PREs within the initial 30 days.

Box 5.1 Example of Probability of Procedure Related Event Calculation for Inoperable Patient Group

Randomised to TAVI		179
Withdrew		6
Conversion to AVR		1
Conversion to Medical Management		4
Received TAVI Procedure (n)		168
Major Complications, Major Stroke or Death within 30 days		50
Functioning Valve Replacement after 30 days (n)		118
TAVI: Major Bleeding - 30 days (α)		30
TAVI: Major Bleeding - Within 1 Year		40
TAVI: Major Bleeding - Post Discharge to 1 year: (α)		10
Probability of Major Bleeding - 30 days	(α/n) → (30/168)	0.179
Probability of Major Bleeding - Post Discharge to 1 year	(α/n) → (10/118)	0.085

Using the technique described above, the transition probabilities for the DAM were revised as follows (Tables 5.1-2). For the short term model, as one patient out of a potential 170 converted from TAVI to AVR, the probability of converting from TAVI to AVR was estimated at 0.01. With respect to converting from TAVI to medical management, four patients experienced this out of 173 so the probability was 0.02. There was also a chance that the TAVI procedure would have to be repeated (0.02). Eleven patients died from all causes within 30 days following TAVI (0.07), while the risk of stroke was 0.05. The likelihood of early major PREs was 0.18 and early minor PREs was 0.58, estimated from the sum of the individual major and minor PREs (details provided in Table 5.2). For patients managed medically, the likelihood of requiring a balloon valvuloplasty was 0.83 (114 out of a potential 138 patients). Finally, five patients managed medically, out of 138

died within 30 days, giving 0.04 probability of death from all causes from medical management.

In the long term model, incorporating PARTNER B evidence revised the transition probabilities as follows for the TAVI arm: the probability of late fatal PREs was 0.23, late major PREs are 0.20 and late minor PREs were 0.19. The latter were estimated from the sum of the individual major and minor PREs (details provided in Table 5.2). While there was a 0.50 probability that medically managed patients in the persistent AS/failed valve replacements state will require a balloon valvuloplasty in the long run. One limitation of the PARTNER B results is that they are for 12 months duration only. So while it was feasible to isolate a mortality rate from natural causes from the functioning state (0.14) and persistent AS /failed valve replacement state for TAVI (0.60) and medical management (0.57) for year one, these were employed in the first cycle only. Subsequent cycles employ the natural mortality rate adjusted for age-sex and disease for mortality from the functioning valve state and a probability of death from persistent AS /failed valve replacement state of 0.33 (Legrand et al., 1991), as per the original model. These latter probabilities were employed so as to reflect the life-stage of the patients and to account for the diminishing benefits of the valve procedure as forecasted by Leon et al. (2010). These transition probabilities for the long term model are presented in Tables 5.1-2.

As per the original model, the uncertainty surrounding each of the parameters was incorporated into the model through the assignment of probability distributions. The PARTNER B results identified the total number of patients and the number for whom events occurred. This information was used to specify a beta distribution for each probability. This information, along with the distributions, facilitated the running of a Monte Carlo simulation for a probabilistic sensitivity analysis (PSA). These distributions and the number of events occurring and not occurring are shown in Tables 5.1-2. All of the transition probabilities provided on Tables 5.1-2 represent absolute risk for each arm of the model, TAVI and medical management.

As outlined previously, where PARTNER Cohort B provided no evidence for events expected to occur (and included in the original model, Chapter 4) point estimates from previously published literature, used in the original model, were maintained. This was the case for early and late cardiac tamponade and early access site events. Table 5.3 presents the evidence that was employed to calculate the estimates shown in Table 5.2 for the

aforementioned PREs. Whereby, for each event the number of cases per study is pooled across and divided by the total number of patients to give the probability of that event occurring. For example, with respect to early access site events, Eichinger et al. (2008) reported 16 incidences of early access site events from a potential 431, giving a probability of early access site events of 0.04. For early major PREs evidence was scarce prior to PARTNER so evidence from AVR studies were employed also and an average was taken across the studies (see Section 4.4.1). Here the total number of patients was pooled from all the studies. In addition, where no incidences of an event occurring were reported but expert opinion and priors indicated it may occur, a small amount was added to the data for each event in order to adjust for those with an observed zero probability to allow for the small chance of such events occurring. This was the case for the early major procedure related event cardiac tamponade, where 0.01 was added to each estimate. So the estimate of cardiac tamponade occurring therefore is 0.00 (from (Gilbert et al., 1999, Gehlot et al., 1996, Milano et al., 1998)) added to 0.06 (from (Webb et al., 2007, Descoutures et al., 2008, Grube et al., 2007, Grube et al., 2006)) plus 0.01, averaged to give 0.03 (Table 5.3).

Table 5.1 Transition Probabilities for TAVI Decision Analytical Model Updated For PARTNER B

Transition probabilities	Distribution	Probability¶ (95% CI)	α	β	n
Short term - 0-30 days					
Probability of converting from TAVI to AVR	Beta	0.01 (0.00 - 0.02)	1	169	170
Probability of converting from TAVI to medical management	Beta	0.02 (0.01-0.05)	4	169	173
Probability of repeat TAVI procedure	Beta	0.02 (0.00-0.04)	3	165	168
Probability of major stroke following TAVI	Beta	0.05 (0.03-0.09)	9	159	168
Probability of death 30 days all causes TAVI	Beta	0.07 (0.03-0.11)	11	157	168
Probability AS persisting following medical management	Beta	0.96 (0.93-0.99)	133	5	138
Probability of death following medical management 30 days	Beta	0.04 (0.01-0.07)	5	133	138
Probability of balloon valvuloplasty (MM)	Beta	0.83 (0.76-0.88)	114	24	138
Probability of early major PRE	Beta	0.18 (0.12-0.24)	Table 5.2		
Probability of early minor PRE	Beta	0.58 (0.48-0.69)			
Long term - post 30 days					
Probability PRE fatal (TAVI)	Beta	0.23 (0.15-0.31)	27	91	118
Probability PRE major (TAVI	Beta	0.20 (0.13-0.29)			
Probability PRE minor (TAVI)	Beta	0.19 (0.12-0.27)	Table 5.2		
Probability death from AS state – TAVI (year 1)	Beta	0.60 (0.44-0.74)	23	15	38
Probability death from AS state - Medical Management (year 1)	Beta	0.57 (0.49-0.65)	76	57	133
Probability death from AS state – post 1 year*	Beta	0.33 (0.24-0.42)	33	67	100
Probability of requiring balloon valvuloplasty	Beta	0.50 (0.41-0.58)	66	67	133
Mortality from natural causes – TAVI (year 1)	Beta	0.14 (0.09-0.21)	17	101	118
Mortality from natural causes+	Log normal	-	-	-	
Relative risk of mortality from AS (rrsmras)	Log normal	1.50 (0.95-2.27)	0.38	0.22	

¶ (Leon et al., 2010) *(Legrand et al., 1991) + Applied post one year. Mortality estimated according to standard life tables adjusted by rrsmras. α = number of events occurring.
β= n- α (where n is the number of events which could have occurred).

Table 5.2 Procedure Related Event Probabilities for TAVI Decision Analytical Model Updated For PARTNER B

Transition Probability	Distribution	Probability (95% CI)	Weight	α	β	n
Major PREs – TAVI						
Valve Thromboembolism¶	beta	0.01	0.03	1	167	168
Major paravavular leak¶	beta	0.14	0.78	23	145	168
Endocarditis¶	beta	0.00	0.00	0	168	168
Cardiac tamponade†	beta	0.03	0.19	6	162	168
Myocardial infarction¶	beta	0.00	0.00	0	168	168
Total		**0.18 (0.12-0.24)**				
Minor PREs – TAVI						
Access site events†	beta	0.04	0.07	7	161	168
Vascular Events¶	beta	0.15	0.27	26	142	168
Pacemaker implantation¶	beta	0.04	0.06	6	162	168
Major Vascular Event¶	beta	0.17	0.30	29	139	168
Major Bleeding¶	beta	0.18	0.31	30	138	168
Total		**0.58 (0.48-0.69)**				
Probability late PREs* TAVI						
Valve Thromboembolism†	beta	0.00	0.00	0	118	118
Major paravavular leak¶	beta	0.13	0.62	15	103	118
Endocarditis¶	beta	0.02	0.08	2	116	118
Cardiac tamponade†	beta	0.01	0.05	1	117	118
Stroke ¶	beta	0.04	0.21	5	113	118
Myocardial infarction¶	beta	0.01	0.04	1	117	118
Total		**0.20 (0.13-0.29)**				
Late Minor PREs TAVI						
Repeat hospitalisations ¶	beta	0.06	0.32	109	1835	1835
Major vascular complications ¶	beta	0.01	0.05	1	156	157
Minor vascular complications ¶	beta	0.02	0.09	2	155	157
Major bleeding ¶	beta	0.08	0.46	10	147	157
New pacemaker ¶	beta	0.02	0.09	2	155	157
Total		**0.19 (0.12-0.27)**				

α = number of events occurring. β= n- α (where n is the number of events which could have occurred). ¶(Leon et al., 2010) †(Webb et al., 2007) (Descoutures et al., 2008) (Grube et al., 2007) (Grube et al., 2006) (Gilbert et al., 1999) (Gehlot et al., 1996) (Milano et al., 1998) (Eichinger et al., 2008) (Aupart et al., 2006) See Table 5.3.

Table 5.3 Estimation of Procedure Related Event Probabilities Using Literature

Study	Probability	α	β	n
MAJOR PRE				
Cardiac tamponade – TAVI				
Webb et al. (2007)	0.02	1	48	49
Descoutures et al. (2008)	0.09	1	10	11
Grube et al. (2007)	0.08	6	70	76
Grube et al. (2006)	0.05	1	21	22
	0.06^	**9**	**149**	**158**
Cardiac tamponade – AVR				
Gilbert et al. (1999)	0.00	0	0	0
Geholt et al. (1996)	0.00	0	0	0
Milano et al. (1998)	0.00	0	0	0
	0.00*	**0**	**0**	**0**
Cardiac tamponade - Total [¥] [(0.00* + 0.06^) + (0.01)]/2 = 0.03				
MINOR PRES - TAVI				
Access site events				
Eichinger et al. (2008)	0.04	16	415	431
	0.04	**16**	**415**	**431**
LATE MAJOR PRES -				
Cardiac tamponade				
Gilbert et al. (1999)	0.00	0	0	0
Milano et al. (1998)	0.00	0	0	0
Eichinger et al. (2008)	0.00	0	0	0
Aupart et al. (2006)	0.00	0	0	0
	0.00	**0**	**0**	**0**

[¥] Here no incidences of an event occurring are reported but expert opinion and priors indicated it may occur so a small amount is added to the data for each event in order to adjust for those with an observed zero probability to allow for the small chance of such events occurring. So the estimate of cardiac tamponade occurring therefore is the 0.00* added to 0.06^ plus 0.01 averaged to give 0.03.

Cost Parameters

For the cost analysis the value of the following resources were estimated: TAVI device; TAVI and medical management procedures; length of stay; hospitalisations and other costs incurred with PREs. The published PARTNER trial results provide no additional information on the cost of the TAVI procedure or length of stay but did provide information on the probability of medical management patients having a balloon valvuloplasty in the short (0.83) and long term (0.50). Therefore, the procedural costs for TAVI employed are as per the original model (updated to reflect 2010 prices using purchasing power parity (Officer and Williamson, 2011)). No additional UK resource costs or cost effectiveness analyse are published either at this time.

The state costs were updated using a revised rate of hospitalisations per state. As per the original model, hospitalisations per health state are estimated using probabilities of hospitalisations per NYHA state (Ahmed et al., 2006) applied to the proportion of patients per NYHA state provided in Leon et al. (2010). This provided an updated cost for the functioning valve replacement state of £1,533 and £7,512 for the persistent AS/failed valve replacement state (Table 5.4).

The costs of the procedure related events (PREs) were determined from the event costs and a weighting, representing each event as a proportion of the total events, as per Chapter 4. The PARTNER B data provided no additional unit cost information so the unit costs from Chapter 4 are maintained (but updated to reflect 2010 prices (Officer and Williamson, 2011)) and the weights were updated with the revised probabilities. The costs of major and minor PREs, within 30 days, following TAVI were £310 and £618. For major and minor PREs occurring beyond 30 days following TAVI the costs were estimated as £3,091 and £1,652 respectively. Normal distributions are applied to the cost of treating PREs. As per the original model the costs were discounted at a rate of 3.5%.

Quality of Life Parameters

As per the original model, QALYs were derived for each health state adjusting for the condition, the procedure and PREs, as no additional quality of life information was available at the time. As with the costs, the impact on utility associated with the PREs was adjusted to account for the revised PRE probabilities. Here the utilities associated with the procedure related events (PREs) were determined using the event utilities and a weighting, representing each event as a proportion of the total events, as per Chapter 4. The utilities of major and minor PREs following TAVI within 30 days were 0.04 and 0.03, respectively. For major and minor PREs occurring beyond 30 days, following TAVI, the utilities were 0.03 and 0.02 respectively.

The PARTNER B data also provided additional information on NYHA classification of patients in each state. This permitted a re-estimate of the proportion of patients per class to update the utility of functioning valve replacement and failed valve replacement. The utility associated with AS was estimated at 0.54; utility of functioning valve replacement was 0.75 and the utility associated with failed valve replacement following TAVI was 0.63 (Table 5.5). Normal distributions were applied to the utilities associated with the PREs.

While (as they are categories), a Dirichlet distribution was applied to model the uncertainty surrounding the proportion of patients in each NYHA class, to estimate the utility per health state. As per the original model the QALYs were discounted at a rate of 3.5%.

Table 5.4 Revised Cost of Functioning & Persisting AS/ Failed Valve Replacement Health States for the TAVI Decision Analytical Model Updated for PARTER B

COSTS	Unit Cost £	Dist	Prob	α	β	Total Cost £ (95% CI)
Cost of Functioning Valve Replacement						
Hospitalisations	3,390*	beta	0.07¶	11	146	246
Nursing home	11,382+	beta	0.10*	16	141	1,138
Drug Therapy	192*					192
						1,578 (1,313-1,871)
Cost of Failed Valve Replacement						
Hospitalisations	3,390*	beta	0.67¶	106	51	2,280
Nursing home	11,382+	beta	0.50*	79	79	5,691
Drug Therapy	192*					188
						8,163 (7,694-8,634)

¶(Leon et al., 2010) * (Ahmed et al., 2006) + (Netten, 1996) Costs updated to reflect 2010 prices using purchasing power parity (Officer and Williamson, 2011)).

Table 5.5 Revised Utilities by NYHA Class for TAVI Decision Analytical Model Updated for PARTNER B

NYHA Class	Distribution	Utility*	Proportion¶	Utility
Utility of AS				
I	Dirichlet	0.82	0.00	0.00
II	Dirichlet	0.72	0.08	0.06
III	Dirichlet	0.59	0.48	0.28
IV	Dirichlet	0.51	0.44	0.22
				0.56
Utility of Functioning Valve Replacement TAVI				
I	Dirichlet	0.82	0.54	0.44
II	Dirichlet	0.72	0.29	0.21
III	Dirichlet	0.59	0.14	0.08
IV	Dirichlet	0.51	0.02	0.01
			1.00	**0.75**
Utility of Failed Valve Replacement TAVI				
I	Dirichlet	0.82	0.02	0.02
II	Dirichlet	0.72	0.39	0.28
III	Dirichlet	0.59	0.45	0.27
IV	Dirichlet	0.51	0.14	0.07
				0.63

*(Maliwa et al., 2003) ¶(Leon et al., 2010)

5.3.4 Analysis – Inoperable Patients

An analysis similar to that employed in Chapter 4, was applied here for inoperable patients, with a UK NHS perspective. A Monte Carlo simulation with 10,000 iterations was used to propagate the uncertainty in the individual model parameters (reflected by the probability distributions assigned) through the model (methods described in Chapter 2). This produces a distribution of expected costs and QALYs associated with each procedure. The mean values of these distributions are used to calculate the incremental cost effectiveness ratio (ICER) in terms of the expected incremental costs associated with TAVI compared to medical management per incremental QALY gained. The uncertainty associated with the incremental costs and QALYs are presented through incremental cost effectiveness (ICE) planes. The decision uncertainty associated with the cost effectiveness of TAVI compared to medical management is presented in terms on a cost effectiveness acceptability curve (CEAC). These can be used to re-address the adoption decision. A sensitivity analysis is performed to assess the impact of improved TAVI outcomes on the cost effectiveness of TAVI. Finally, to re-address the research priority setting decision a Bayesian Value of Information (VOI) analysis is performed to investigate whether there is potential value in collecting additional evidence. The Expected Value of Perfect Information (EVPI) investigates what society would be willing to pay to eliminate all the uncertainty surrounding the coverage decision. The Expected Value of Perfect Parameter Information (EVPPI) investigates the potential value in collecting further information about specific parameters or groups of parameters. The Expected Value of Sample Information (EVSI) estimates the benefit of sampling. Following which a sensitivity analysis is performed.

5.4 COST EFFECTIVENESS ANALYSIS RESULTS – INOPERABLE PATIENTS

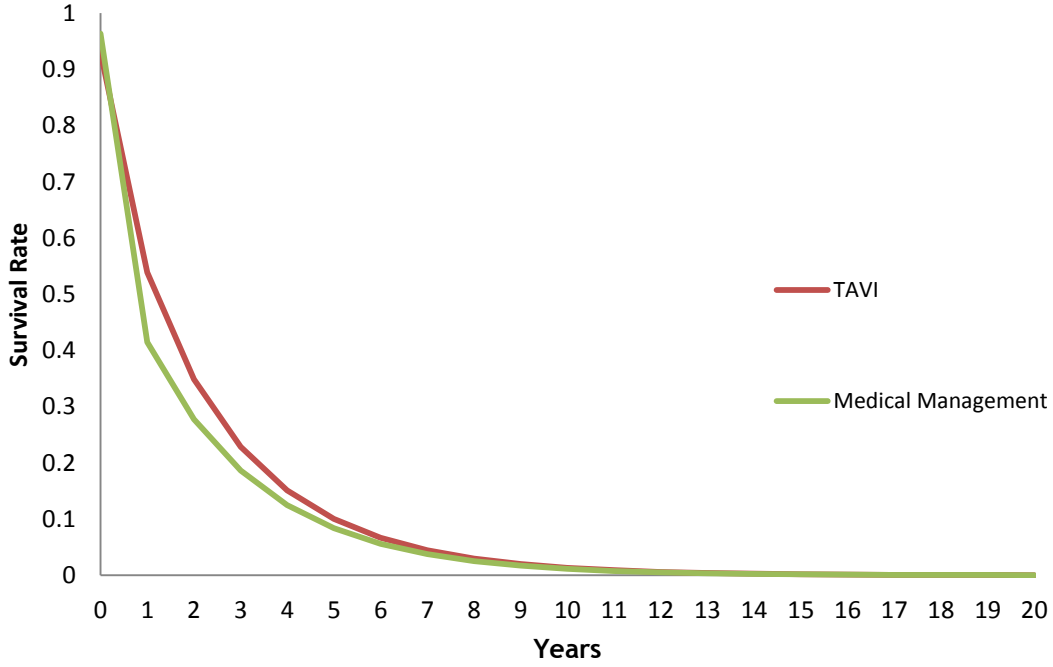
The cost effectiveness of TAVI versus medical management is estimated for high risk inoperable patients based on a mix of evidence from Cohort B of the PARTNER trial and the original estimates from the literature. The results indicate a 12% reduction in absolute risk in terms of all-cause mortality, at the end of year one, between TAVI and medical management. The model predicts that this steadily declines from year two onwards (Figure

5.4). Also, the results indicate that TAVI offers greater quality of life (14%) than medical management as per the PARTNER results in year 1.

5.4.1 Deterministic Cost Effectiveness Results

The deterministic cost effectiveness results (Table 5.6) are estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. The results illustrate that for inoperable patients TAVI is both more costly (£16,111) and more effective (0.42 QALYs) than medical management. The ICER is estimated as £38,724 per QALY gained, which is just outside the level usually considered cost effective (£20,000-£30,000 per QALY (Rawlins et al., 2009)).

Figure 5.4 Survival Estimates for TAVI and Medical Management



5.4.2 Probabilistic Cost Effectiveness Results

The Monte Carlo simulation produced the mean cost and QALYs for TAVI and medical management (Table 5.6). Here it is illustrated that for inoperable patients TAVI is both more costly (£16,183) and more effective (0.43 QALYs) than medical management. The

95% confidence interval around the incremental costs is £12,869-£19,365. The 95% confidence interval around the incremental benefits is 0.20-0.69. The probabilistic ICER is estimated as £37,390 per QALY gained, which is outside the level usually considered cost effective (£20,000-£30,000 per QALY(Rawlins et al., 2009)).

Table 5.6 Cost Effectiveness Results: Inoperable Patients - TAVI versus Medical Management

	LYs	Costs (£) (95% CI)	Δ Costs	QALYs (95% CI)	Δ QALYS	ICER £/QALY
Deterministic Results						
Medical Management	2.22	12,290		1.18		
TAVI	2.50	28,401	16,111	1.59	0.42	£38,724
Probabilistic Results						
Medical Management	2.24 (1.86-2.75)	12,446 (9,353-16,468)		1.19 (1.00-1.43)		
TAVI	2.54 (2.12-3.06)	28,629 (25,737-32,145)	16,183	1.62 (1.37-1.92)	0.43	£37,390

The ICE plane (Figure 5.5) illustrates the existence and extent of the uncertainty surrounding the incremental effect (measured in QALYs) and cost (these are the red points plotted on Figure 5.5). In this case, there is some uncertainty surrounding the existence of benefit for TAVI (over medical management), with TAVI being more effective. There is considerable uncertainty surrounding the extent of the differences in effects, owing to the probability PREs. Furthermore, there is no uncertainty with respect to the existence of differences in costs, with TAVI being more expensive than medical management: this is driven by the cost of the TAVI device. However, there is some uncertainty surrounding the extent of the differences in cost. This is potentially driven by uncertainties surrounding the probability of PREs.

The CEAC (Figure 5.6) represents the decision uncertainty surrounding the cost effectiveness of each treatment. At a ceiling ratio of £30,000 per QALY, the probability that TAVI is cost effective is 18% while the probability that medical management is cost effective is 82%. If the acceptable ceiling ratio was increased to £40,000 per QALY the probability that TAVI is cost effective increases to 59%.

Figure 5.5 Incremental Cost Effectiveness Plane: Inoperable Patients - TAVI versus Medical Management

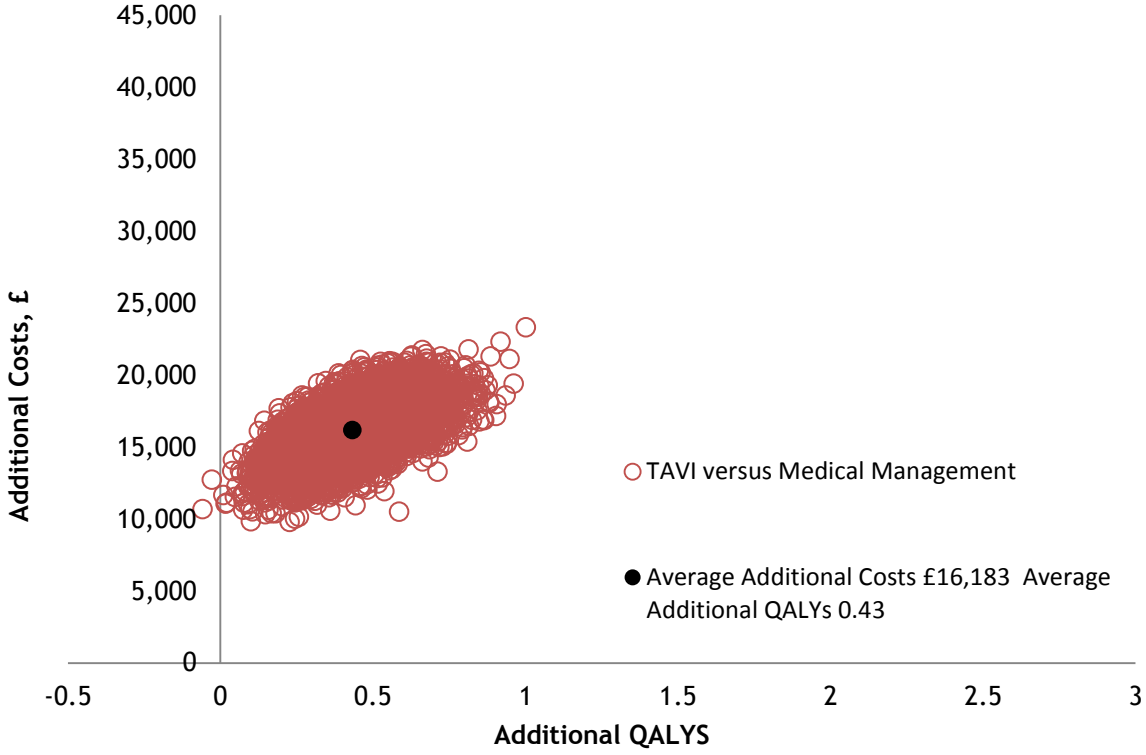
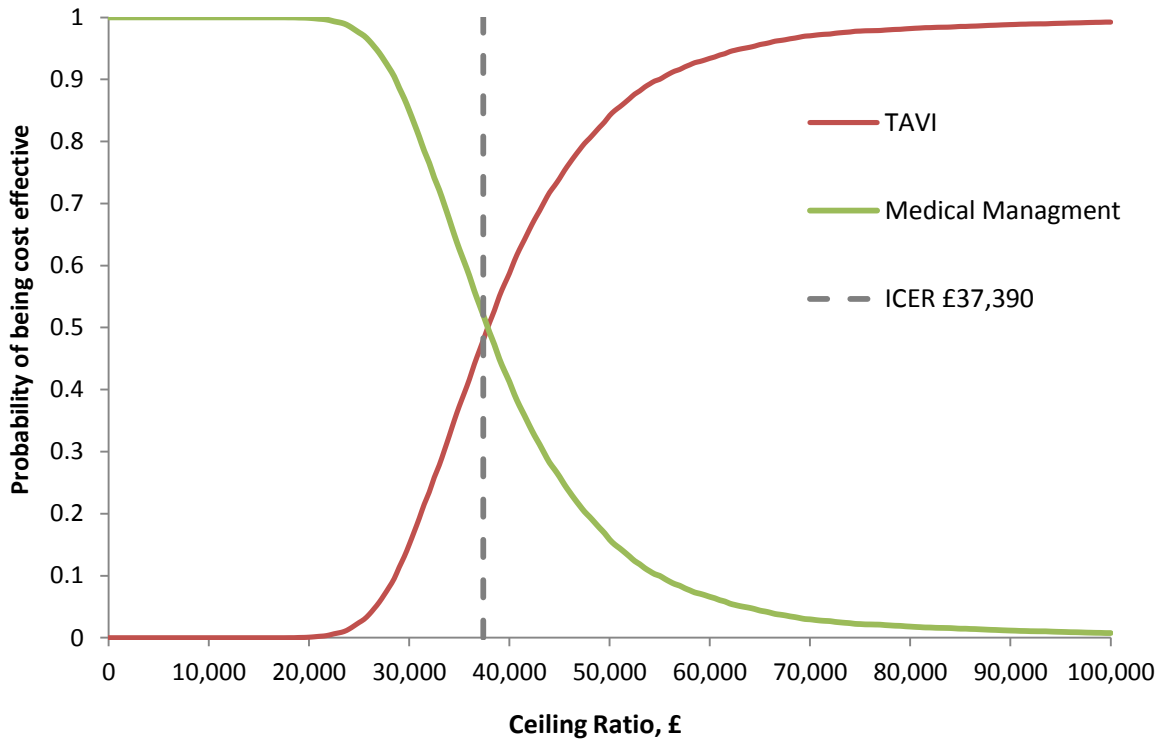


Figure 5.6 Cost Effectiveness Acceptability Curves: Inoperable Patients - TAVI versus Medical Management

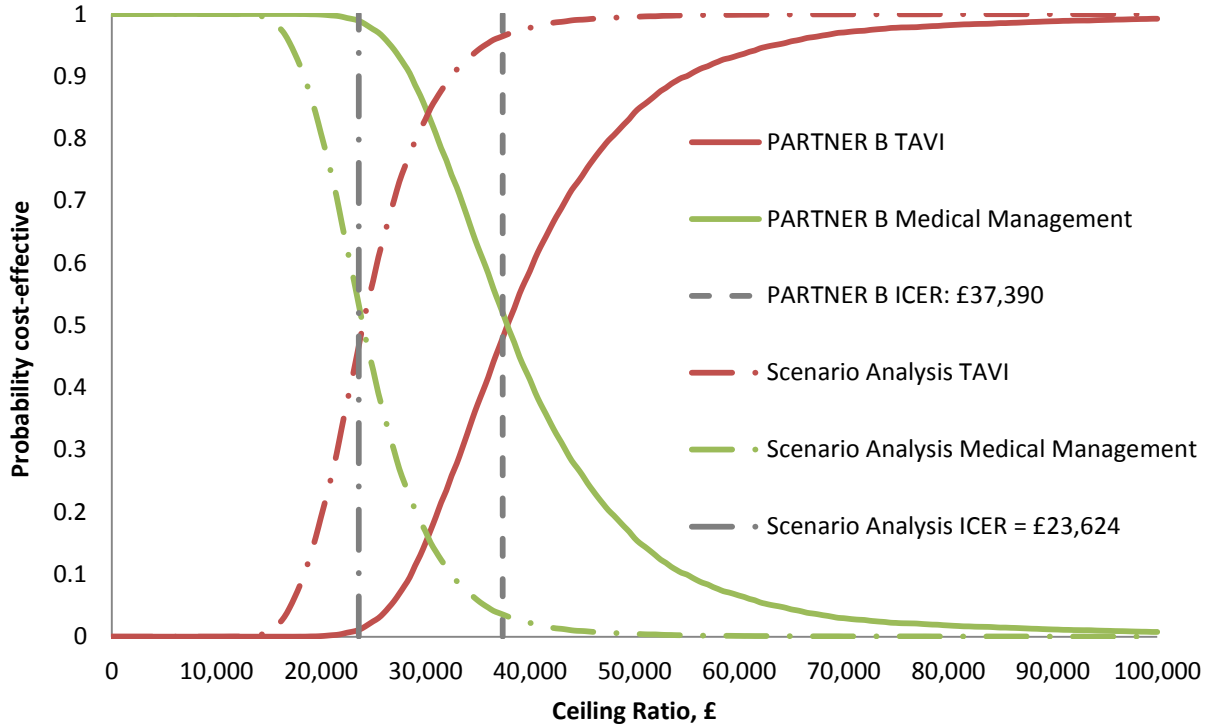


5.5 SCENARIO ANALYSES

To date there is limited evidence of TAVI outcomes beyond one year. Commentators suggest that current data, from published trials and registries including PARTNER, relate to older generations of devices used in centres that were inexperienced at the time (Schaff, 2011, Webb and Cribier, 2011). This is attributable to the characteristics of medical devices, such as incremental innovations, the device-clinician learning curve etc. (see Section 1.2.1). It is suggested that these shortcomings contribute to the high rate of PREs following TAVI, which may be resolved in the future (Schaff, 2011, Webb and Cribier, 2011). Collecting further evidence, via trial or registry, could demonstrate if this is the case or if the high incidence of PREs is part of treating elderly ailing patients with severe AS. The value of such data collection is examined in the next section through a Bayesian VOI analysis. Before examining the value of collecting further information however, a scenario analysis is performed to analyse the impact of the suggested improvements in PREs on the cost effectiveness of TAVI.

The scenario analysis indicates that if all PREs reported for TAVI are reduced by 25% (expert opinion (Toff, 2011)), TAVI would remain more expensive (£7,856; 41%) and more effective (0.56; 44%) than medical management. However, in such a scenario the ICER falls to £23,642/QALY, bringing it within the range considered cost-effective in the UK (£20,000-£30,000/QALY). The CEAC (Figure 5.7) demonstrates that at a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective increases to 83% and the probability that medical management is cost effective falls to 17%. Thus, if future evidence demonstrates improved TAVI outcomes, in the form of reduced PREs, then TAVI could be considered cost effective for high risk inoperable patients in the UK.

Figure 5.7 Scenario Analysis: Cost Effectiveness Acceptability Curve: TAVI versus Medical Management



5.6 VALUE OF INFORMATION ANALYSIS – INOPERABLE PATIENTS

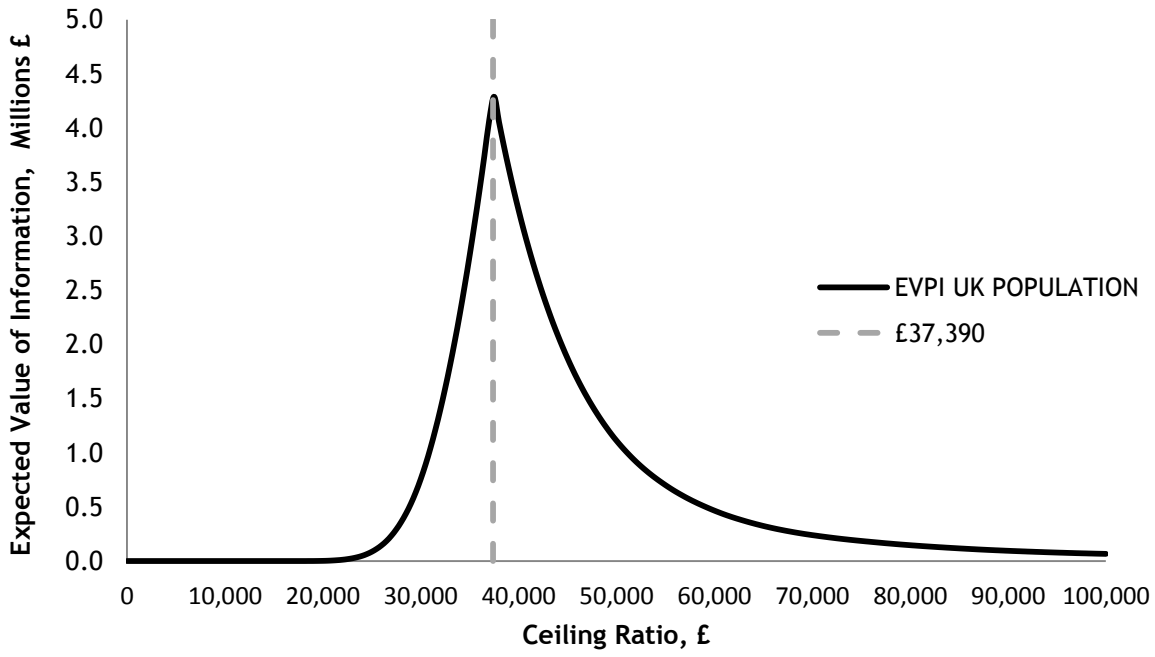
As mentioned in the previous section, commentators expect future evidence to demonstrate improved longer term outcomes for TAVI, which would increase the probability of TAVI being considered cost effective. To demonstrate this, additional evidence is needed. The value of this additional evidence, which parameters additional evidence is most valuable for and the optimal data collection strategy for collecting this additional evidence can be estimated using Bayesian VOI techniques. This includes Expected Value of Perfect Information (EVPI), Expected Value of Partial Perfect Information (EVPPI) and Expected Value of Sample Information (EVSI) (described in Chapter 2).

5.6.1 Is There Value in Collecting Further Evidence?

The potential value of undertaking further research is estimated by determining the value of eliminating all the uncertainties in the model (i.e. the EVPI). The EVPI per patient, when deciding between TAVI and medical management ranges from £1 to £275 per inoperable patient for one year (based on PSA results in Section 5.4.2).

The population expected value of perfect information (pEVPI) for the inoperable population in UK (2,750 from Table 4.13 (SHTG, 2009)), over the range usually considered cost effective, ranges from £1,441 to £756,649 over one year (Figure 5.8). These estimates provide a maximum value for the return of further research, suggesting there is some value in collecting further information on inoperable patients. The pEVPI reaches a point of inflection at a ceiling ratio equal to the ICER £37,390/QALY. This corresponds to the CEAC (Figure 5.6) where at £37,390/QALY the decision is most uncertain. Here the probability that TAVI is cost effective is 0.48 and probability that medical management is cost effective is 0.52. Beyond this ceiling ratio, the optimal treatment changes and TAVI is more likely to be cost effective compared with medical management. As there are only two technologies considered here the point of inflection is also the maximum pEVPI.

Figure 5.8 Expected Value of Perfect Information: UK Inoperable Population



5.6.2 On Which Parameters Is There Value In Collecting Further Information?

As shown by the pEVPI, given current evidence there is some value in collecting additional information on inoperable patients. On which parameters this future evidence will be most valuable and how it should be collected is examined using expected value of perfect parameter information (EVPPI). Additional evidence could be collected using a specific UK clinical trial or expanding the existing UK TAVI Registry[5]. It is anticipated that both of these methods would have the power to collect additional information regarding short term transition probabilities; long term transition probabilities; resources consumed and quality of life/utility information for TAVI patients. In addition, a trial could collect this evidence on medical management as well as TAVI. This expectation is informed by what is currently collected in the UK TAVI registry (as per Ludmann (2010)) and what was collected in the PARTNER trial (see Appendix VI). These groups of parameters are shown in Table 5.7.

Table 5.7 Parameter Groups for Further Evidence Generation

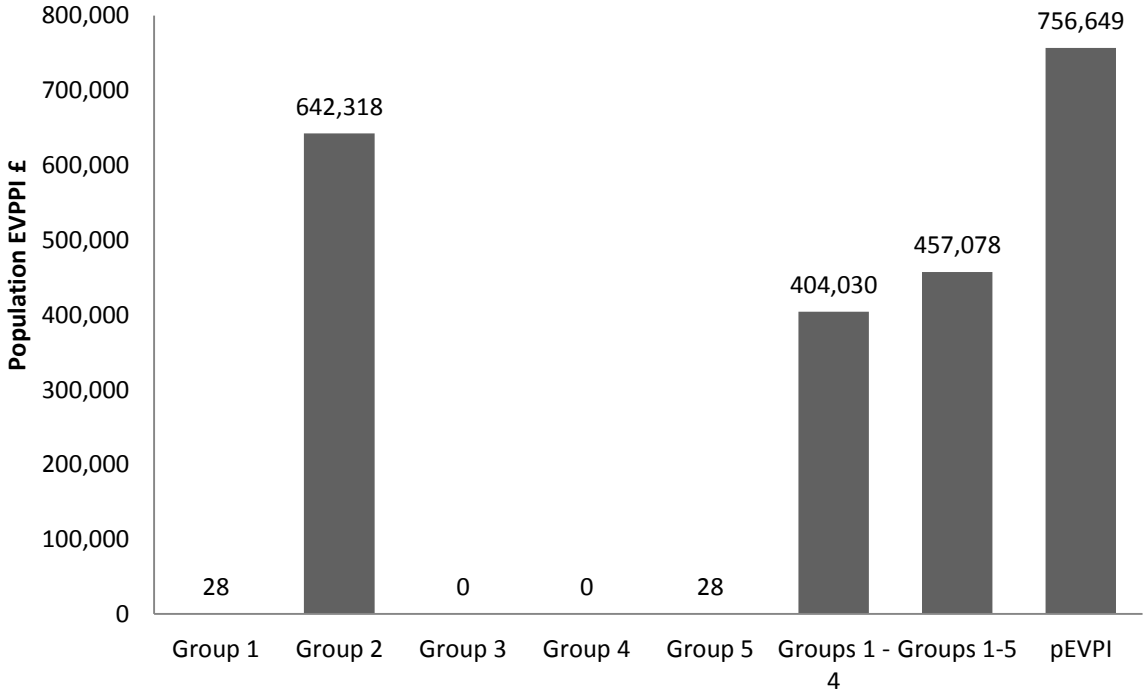
1 Short Term Outcomes	*2 Short & Long Term Outcomes*	*3 Quality of Life*	*4 Resources*	*5 Medical Management*
- Major PRE TAVI - Minor PRE TAVI - Converting To AVR - Converting To MM - Repeat TAVI - Death 30 Days TAVI - Major Stroke TAVI	- Major PRE TAVI - Minor PRE TAVI - Converting To AVR - Converting To MM - Repeat TAVI - Death 30 Days TAVI - Major Stroke TAVI - Late PRE TAVI - Late PRE AVR - Late Minor PRE TAVI - Late Fatal PRE TAVI - MR TAVI - Death AS TAVI	- Utility Functioning TAVI - Utility Persistent AS TAVI	- Total LOS TAVI - Post Discharge TAVI - Cost Functioning TAVI - Cost Persistent AS TAVI	- Death 30 Days Medical Management - Early Balloon Valvuloplasty - MR Medical Management – 1 Yr - MR Medical Management > 1 Yr - Late Balloon Valvuloplasty

[5] As per NICE Guidelines all TAVI procedures performed in the UK since 2007 are recorded through the Central Cardiac Audit Database to form the UK TAVI Registry.

Using the expected net benefit (ENB) for TAVI compared to medical management, generated from the Monte Carlo simulation (Section 5.4), the EVPPI analysis measures the potential value in collecting further evidence on the parameter groups. This was performed for each group of parameters individually (groups 1- 5), for all the groups simultaneously to represent a clinical trial and for groups 1-4 simultaneously to represent a registry, using a ceiling ratio of £30,000/QALY.

The results of the EVPPI analysis are as follows (Figure 5.9). At a ceiling ratio of £30,000/QALY, the EVPPI for group 2 individually was the highest of the five groups, at £642,318. For the rest of the groups individually (1, 3, 4 and 5) there is little value in collecting information on them in isolation. When all the groups are considered simultaneously to represent a registry (groups 1 to 4) the EVPPI was £404,030 and to represent a clinical trial (groups 1 to 5) the EVPPI was £457,078, for the UK inoperable population (2,750 (SHTG, 2009)). The lower EVPPI results for the groups simultaneously, compared to those for Group 2 individually, are owing to the interactions between the variables. Figure 5.9 includes the pEVPI at £30,000/QALY to demonstrate that not all the uncertainty is resolved in assuming perfect information about the five groups of parameters. To determine how additional evidence should be collected the expected value and costs of the data collection methods need to be compared.

Figure 5.9 Expected Value of Partial Perfect Information: UK Inoperable Population



5.6.3 How Should the Additional Evidence be Collected?

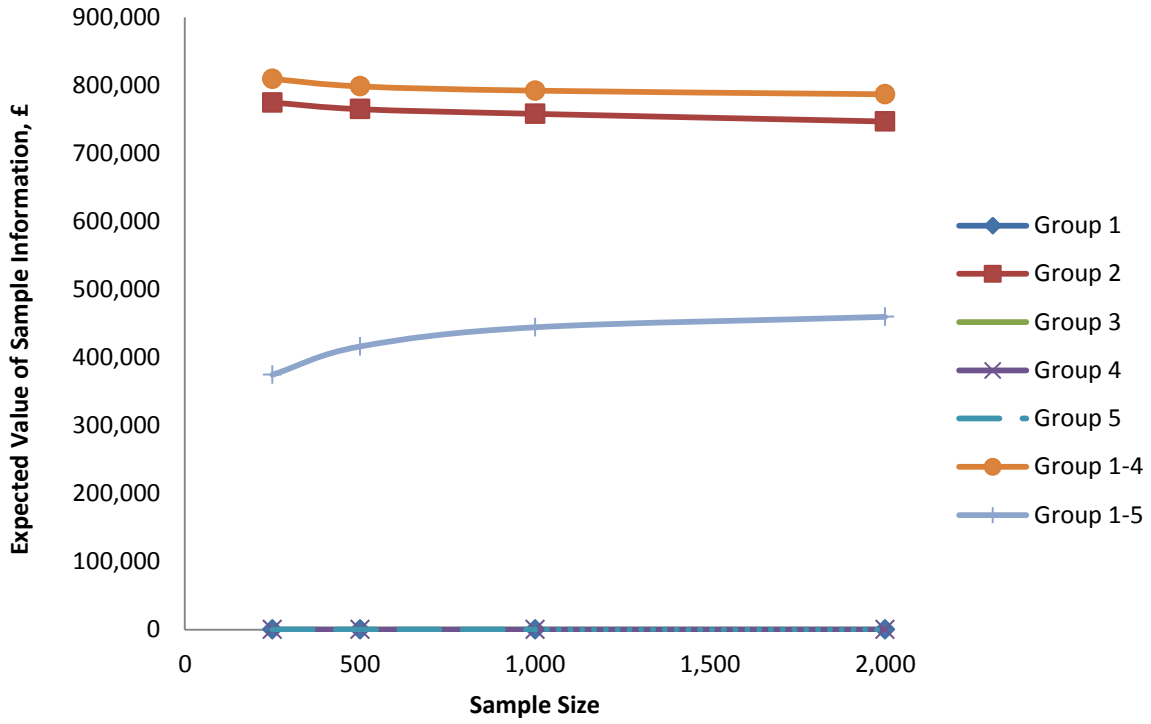
As outlined above, the additional evidence could be collected via a registry or clinical trial. Registries use observation methods to collect data on specific outcomes, thus collect evidence on real clinical practice settings (Gliklich and Mack, 2009, Gliklich and Dreyer, 2007). In contrast, clinical trials are usually randomised and focus on collecting information on efficacy in a controlled setting where conditions are ideal (Gliklich and Mack, 2009). It is recognised that some features of the two are similar; however clinical trials are more reliant on protocol development, guidance from advisory panels and biostatistics. While registries are thought to be a lower cost mode of collecting evidence (Gliklich and Mack, 2009). The expected value of both methods is considered here through the Bayesian VOI analysis, using EVSI for inoperable patients.

Clinical Trial

The potential value of a hypothetical UK TAVI Trial for inoperable patients is considered here. This is calculated using the estimates of ENB from the PSA analysis (Section 5.4) and evaluates the worth of conducting a clinical trial, with five year follow up, by estimating the difference between the expected value of a decision made with sample information and the expected value of a decision made with current information. It is anticipated that such a trial would be powered to collect information on all five groups of parameters presented in Table 5.7.

The EVSI analysis was conducted for a variety of trial sizes: 250, 500, 1,000 and 2,000 for the parameter groups (Table 5.7) individually and simultaneously. The results (Figure 5.10) reveal that clinical trial collecting information on Groups 1-5 simultaneously has the highest EVSI, £459,663, at the largest sample size (2,000). Trials collecting information on the parameter groups individually have little value, across the sample sizes (except Group 2, seventh series on Figure 5.10).

Figure 5.10 Expected Value of Sample Information for All Groups - Different Trial Sizes



As outlined in Chapter 2, it is anticipated that there is a positive relationship between EVSI and sample size: as sample size increases there is more information, which reduces uncertainty, therefore increasing EVSI. As is evident from Figure 5.10 however, in this case the EVSI is downward sloping, illustrating the practical challenges associated with estimating EVSI. An initial solution to overcoming this problem would be to increase the number of iterations employed in the simulation. The results illustrated on Figure 5.10 are produced from a simulation employing 10,000 iterations for both the inner and outer loops. Without access to a *super computer* this is the maximum number of iterations feasible. Other possible solutions for future work include employing methods such as meta-models or space searching strategies, which are currently under development in the Centre for Bayesian Statistics in Health Economics (CHEBS) at the University of Sheffield.

As there are currently no plans for a UK TAVI trial for inoperable patients no formal costs exist. So to compare the expected benefit to costs for such a trial fixed costs are estimated at £2.25 million and variable costs are estimated as £15,000 per patient. (These estimates are based on consultation with TAVI trial experts in the UK (Toff, 2012).) Using the sample sizes from before (250, 500, 1,000 and 2,000) the costs of the trial can be compared

to the expected value of the sample information (EVSI) of the hypothetical trial. The difference between the expected costs and EVSI is the expected net benefit of sampling (ENBS).

For example, the expected value (EVSI) for a trial with 2,000 patients is £459,663. The expected cost of this trial is £32,250,000 (estimated using fixed cost of £2.25 million and variable costs £30 million (£15,000 * 2,000 patients)). Comparing the expected costs and benefits gives a negative ENBS (-£31.8 million), indicating that a trial of this size and magnitude cannot be considered cost effective. This is repeated for different sample sizes. The ENBS results indicate that at a ceiling ratio of £30,000/QALY, across the four sample sizes, the ENBS for the trial is negative. Thus, the trial cannot be considered cost effective at the £30,000/QALY ceiling ratio (used to estimate EVSI).

Supposing the nationally accepted ceiling ratio was increased to £50,000/QALY, across the sample sizes the trial would have a positive ENBS. Specifically, a trial with sample size of 2,000 would have the highest net benefit, £32.74 million. These ENBS results are presented on Figure 5.11.

Using the expected cost estimates above, an approximation of for how long the information from the trial would have to be relevant for, for the costs of the trial to be recouped, can be calculated. This is estimated by dividing the expected trial cost by the EVSI. For example, a trial with sample size of 250 patients is estimated to cost £6.5 million (based on the fixed and variable costs from above). A clinical trial capable of collecting information on all parameters in groups 1-5 with this sample size has an EVSI of £306,540. Thus, to recoup the costs of the trial, the information collected from it would need to be relevant for over 20 years. Similarly for a trial with 2,000 patients, the expected costs are £32.5 million (including NHS service costs) and the EVSI is £376,088. Thus, to recoup the costs of the trial, the information collected from it would need to be relevant for over 86 years (Table 5.8). Given the nature of novel medical devices like TAVI, such trials are unlikely to yield information which is relevant for such long periods.

These results indicate that at the current range for the nationally accepted ceiling ratio, i.e. what society is willing to for an extra QALY (£20,000-£30,000/QALY) and current evidence for high risk inoperable patients, there is little benefit in conducting a clinical trial.

Figure 5.11 Expected Net Benefit of Sampling – Clinical Trial for Inoperable Patients

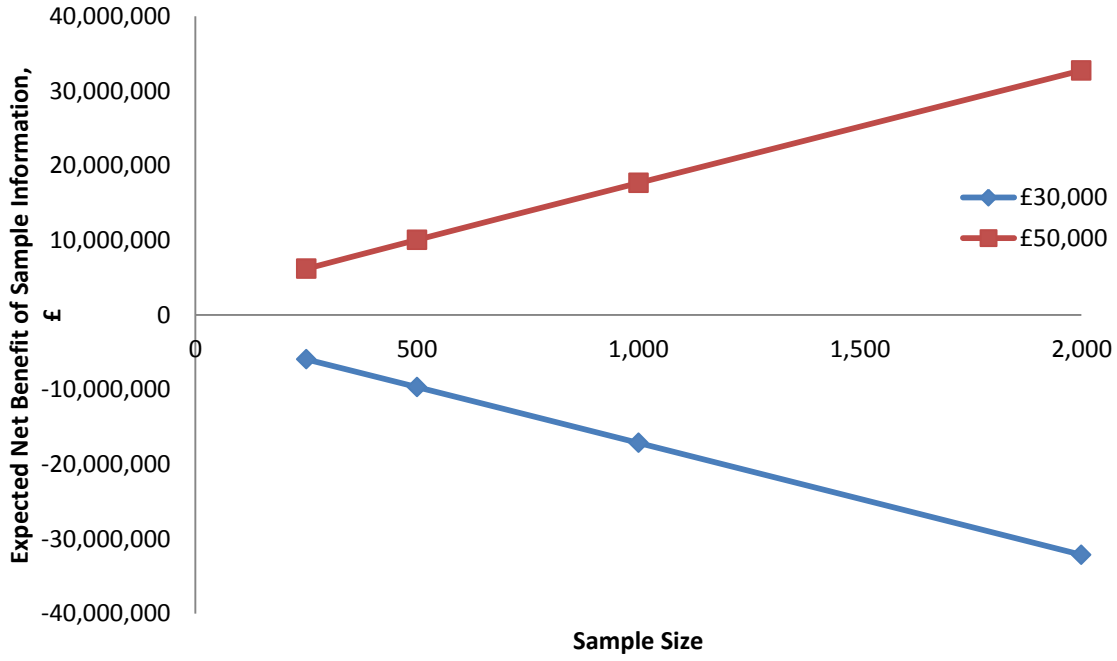


Table 5.8 Expected Value of Sample Information: Clinical Trial - Inoperable Patients

Sample Size	EVSI @ £30,000/QALY Groups 1-5	Cost of Trial* £ Millions			
		6.25 (n=250)	10 (n=500)	17.5 (n=1,000)	32.5 (n=2,000)
		Years To Recoup Costs			
250	306,540	20.39			
500	340,425		32.62		
1,000	363,510			48.14	
2,000	376,088				86.42

*Costs are based on fixed costs £2.25 million and variable costs of £15,000 per patient (Toff, 2012), include NHS service costs.

Registry

As per NICE guidelines details on all TAVI procedures performed in the UK since 2007 are recorded through the Central Cardiac Audit Database (CCAD) (Ludmann, 2010). From

this database the UK TAVI Registry has developed through collaboration between the BSCIS and STCTS[6], Department of Health and Special Commissioners and Health Technology Assessment and NICE. Appendix VI shows the evidence currently being collected in the UK TAVI Registry and what additional evidence could be collected through a registry.

An alternative to a clinical trial would be to expand the existing UK TAVI Registry (Ludmann, 2010) to collect additional evidence. It is anticipated that an extension of the TAVI Registry could collect additional evidence on the following types of parameters associated with the TAVI procedure: short term probabilities only, all short and long term probabilities (including long term mortality), utility and resources consumed. These correspond to parameter groups 1-4 listed in Table 5.7.

The EVPPI analysis performed in Section 5.6.2 illustrated the maximum potential worth of collecting data on TAVI only through an expanded UK TAVI Registry (consideration of groups 1-4 simultaneously). So if further data collection was to provide evidence on all the parameters contained in groups 1-4, it would be worth a maximum of £404,030 for the UK population, at a ceiling ratio of £30,000/QALY (see Figure 5.9).

An EVSI analysis is conducted for a variety of sample sizes: 250, 500, 1,000 and 2,000, for the parameter groups 1 to 4 (Table 5.7) simultaneously to represent a registry. The results reveal that a registry collecting information on groups 1-4 simultaneously on 2,000 patients has an EVSI of £643,680. This is repeated for the other trial sizes, illustrated on Figure 5.10 (orange line) and Table 5.9.

With respect to the expected costs of such a registry, it is estimated that the fixed costs of establishing such a registry would be £100,000 and the variable costs per patient would be £50 (based on expert opinion (Cunningham, 2012)). Using the sample sizes from before (250, 500, 1,000 and 2,000) the costs of the trial can be compared to the expected value of the sample information (EVSI) of the registry. The difference between the expected costs and EVSI is the expected net benefit of sampling (ENBS).

For example, the expected value (EVSI) for a registry with 2,000 patients is £643,680. The expected cost of this trial is £200,000 (estimated using fixed cost of £100,000 and variable

[6] British Cardiovascular Intervention Society (BCIS), Society of Cardiothoracic Surgeons (SCTS)

costs of £100,000 (£50 * 2,000 patients)). Comparing the expected costs and benefits gives a positive ENBS, £443,680, indicating that a registry of this size and magnitude can be considered cost effective. This is repeated for different sample sizes. The ENBS results indicate that at a ceiling ratio of £30,000/QALY across the four sample sizes the ENBS for the trial is positive. Thus, the registry can be considered cost effective at the £30,000/QALY ceiling ratio (used to estimate EVSI) (Figure 5.10).

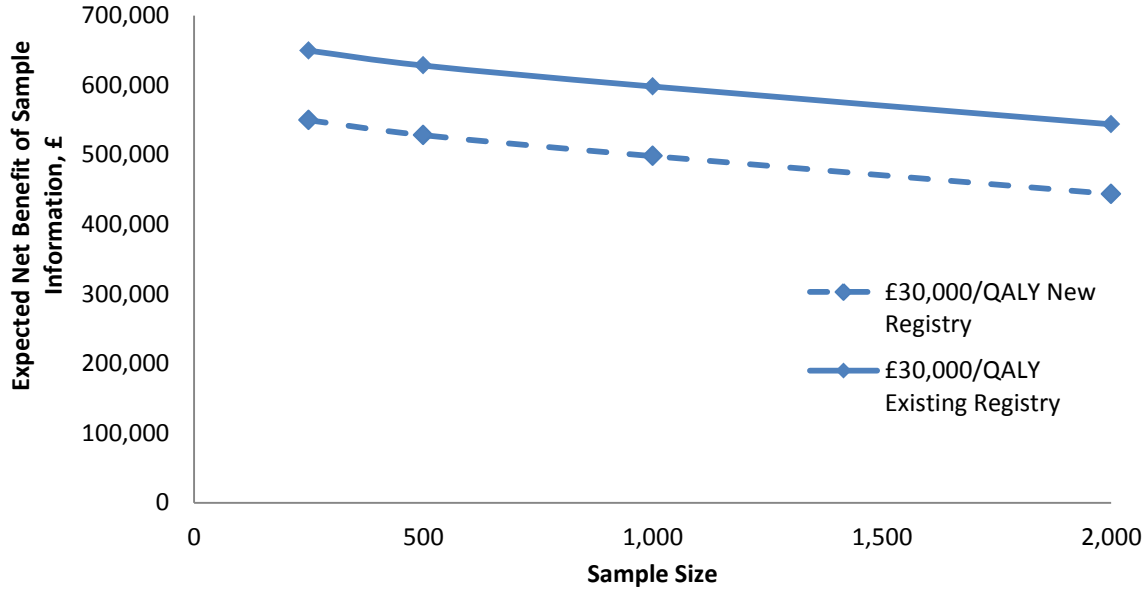
Using the expected costs estimates an approximation for how long the information from the registry would have to be relevant for, to recoup the costs of the registry can be estimated. This is calculated by dividing the expected registry cost by the EVSI. For example, a trial with sample size of 250 patients is estimated to cost £112,500 (based on the fixed and variable costs from above). A registry capable of collecting information on all parameters in groups 1-4 with this sample size has an EVSI of £662,085. Thus, to recoup the costs of the trial, the information collected from it would need to be relevant for just over two months. Similarly for a trial with 2,000 patients, the expected costs are £200,000 and the EVSI is £643,680. Thus, to recoup the costs of the trial the information collected from it would need to be relevant for almost 4 months. These results are summarised in Table 5.9.

Table 5.9 Expected Value of Sample Information: Registry - Inoperable Patients

Sample Size	EVSI @ £30,000/QALY	Cost of Registry* £			
	Groups 1-4	**112,500** (n=250)	**125,000** (n=500)	**150,000** (n=1,000)	**200,000** (n=2,000)
		Years to Recoup Costs			
250	662,085	0.17			
500	653,153		0.19		
1,000	648,000			0.23	
2,000	643,680				0.31

*Costs are based on fixed costs £100,000 and variable costs of £50 per patient (Cunningham, 2012).

Figure 5.12 Expected Net Benefit of Sampling – Proposed & Existing Registry for Inoperable Patients



However, given that a TAVI Registry already exists in the UK one could assume that the fixed costs are sunk and only the variable costs (£50/patient) are applicable. In this instance, the ENBS is estimated as follows, for four sample sizes, ranging between 250 and 2,000. At a ceiling ratio of £30,000/QALY the highest ENBS is for a trial with sample size of 250 patients, at £649,585. These results are presented as the solid line on Figure 5.12. This indicates that at the current nationally accepted ceiling ratio, i.e. what society is willing to for an extra QALY, there is benefit in collecting additional information using the existing UK TAVI Registry.

The results from VOI analysis and ENBS indicate that there is value in collecting additional information. In particular, the results indicate that a registry would be a more cost efficient means of collecting the additional evidence than a trial. In line with the continuous iterative framework, presented in Chapter 2, this additional evidence could be collected using a Performance Based Risk Sharing Agreement (PBRSA) like Access with Evidence Development (AED). Whereby, the registry could be integrated into an AED scheme. This would ensure that evidence is collected while controlling who gets TAVI on a simultaneous basis.

5.7 COMPARISON OF ORIGINAL MODEL WITH UPDATED MODEL INCORPORATING PARTNER (COHORT B) EVIDENCE - INOPERABLE PATIENTS

Model and Parameters

As outlined previously, incorporating evidence from PARTNER B into the inoperable patient model, affords the opportunity to use the best data available to reflect current understanding of the treatment pathways and technologies. This facilitates a re-assessment of the cost effectiveness of TAVI on an iterative basis. This resulted in some structural changes to the model: inclusion of conversion from TAVI to medical management, repeat TAVI, death from medical management within 30 days and the distinction between major and minor PREs in the Markov model. It also provided current evidence for the transition probabilities in the short and long term such as stroke, PREs and mortality estimates. Previously, early short term experiences with TAVI, expert opinion and experiences with AVR had to be relied on to inform the model.

These changes to the model and evidence resulted in the following changes to the transition probabilities (See Appendix VII). With respect to conversions, the original model only included conversions from TAVI to AVR; updating the evidence with PARTNER B results reduced the probability of this by 83% to 0.01. Incorporating PARTNER B evidence increased the stroke risk associated with TAVI to 0.05. This is a 67% increase on the baseline stroke rate employed in the original model (although it does fall within the upper range of the uncertainty modelled for the parameter). For inoperable patients, the original model assumed a 30 day all-cause mortality rate of 20% after TAVI, based on operative mortality risk. This is reduced to 7% following the inclusion of PARTNER B evidence. While for medically managed patients, a 30 day mortality rate of 0 was used in the original model, based on expert opinion, this increased to 4% in the revised model.

Incorporating PARTNER B evidence also increased early major PREs following TAVI by 50% to 0.18. This is mainly attributable to the increase in paravavular leaks. The probability of early minor PREs also increased, by 120%, from 26% to 58%. This is attributable to the high incidence of major vascular events and major bleeding. The

likelihood of late fatal PREs increased slightly for TAVI patients from 0.22 to 0.23. While late major PREs increased by 17% for TAVI patients to 0.20. This is explained by the increase in paravavular leaks following TAVI and the inclusion of late strokes and late myocardial infarction (0.04 and 0.01 respectively).

With respect to late mortality, there were also some changes from the original model. Death from the functioning valve replacement state in year 1 increased to 0.14 owing to the inclusion of PARTNER evidence. However, for subsequent years the natural mortality rate for age and sex, adjusted for the disease was maintained. Similarly, death from the persistent AS/failed valve replacement state increased for TAVI and medically managed patients by 82% and 73% respectively in year 1, however the mortality rate of 0.33 (Legrand et al., 1991) is maintained for subsequent years.

With regard to the cost parameters, the revised model included the costs of balloon valvuloplasty for 83% of medically managed patients in the short term and 50% of those in the persistent AS/failed valve state in the long run. The costs of long term care per state were also revised, to account for increased probability of requiring hospitalisation. These increased in the annual cost associated with the persistent AS/failed valve replacement state by 6% and the annual cost associated with the functioning valve replacement state by 1%. These increases are explained by the 26% increase in the probability of requiring annual hospitalisations associated with the persistent AS/failed valve replacement state (0.67); and a less than 1% increase in the probability of requiring annual hospitalisations for those in the functioning valve replacement state (0.07).

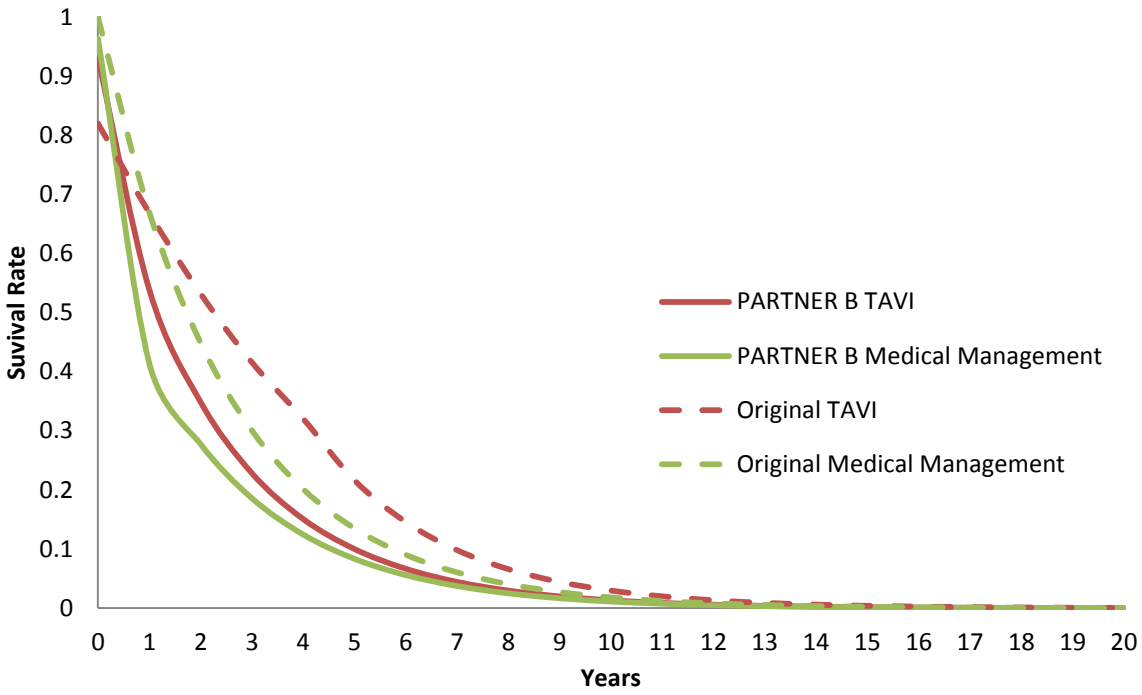
PARTNER provided updated estimates for the proportion of patients per NYHA class and these were used to replace estimates used in the original analysis, as per the PRE estimates. This ensures consistency for the patient population under consideration. Revising the utilities per state reduced the utility associated with having AS (by 4%) to 0.54, representing the greater severity of AS amongst this inoperable patient group. The utility associated with the functioning valve replacement state also decreased in the revised model by 3% to 0.75. However, the utility associated with the persistent AS/failed valve state increased by 22% for patients who received TAVI (0.63). This provided a differentiation between TAVI and medical management patients while in the same state, thus reflecting the benefit of the TAVI procedure, despite major PREs. In the original model, the state utilities were not varied to reflect heterogeneity between the patient types or procedures.

Thus, incorporating the PARTNER B evidence into the model provided revised parameters to reflect the best currently available data and facilitate differentiation between patient types and procedures to reflecting heterogeneity. Specifically, the PARTNER B evidence provided evidence on early and late outcomes following TAVI. This generally reduced the mortality parameters in the short run but increased them in year one. It increased major and minor PREs associated with TAVI in the short and long term. Also, additional costs associated with medical management and persistent AS/failed valve state were incorporated (balloon valvuloplasty). Previously, utilities were applied homogenously across patient and procedure types based on state only. The developed evidence base permitted the reflection of heterogeneity between patient groups and the different treatments through different state utilities varied by treatment. In contrast, the original model only incorporated heterogeneity between patient groups via treatment choice, operative mortality rates and the use of relative risk parameters between TAVI and AVR. Thus, the revised model provided an updated reflection of TAVI in practice.

Cost Effectiveness Results

The revised cost effectiveness analysis demonstrated that TAVI both extends life and improves quality of life in the longer term for those patients who otherwise would not receive a valve replacement. The average life years gained was 2.55 for patients receiving TAVI and 2.24 for patients receiving medical management. This was a decrease compared to the original model (3.50 following TAVI and 3.05 following medical) which is explained by the increase in mortality in year 1 of the Markov model and higher rates of PREs. The latter resulted in more patients entering the persistent AS/failed valve replacement state which has a higher mortality rate than the functioning valve state. Figure 5.13 presents the survival estimates from each model for comparative purposes, illustrating that the revised model has much steeper survival estimates than the original model. In addition, the difference between TAVI and medical management is narrower in the revised model. This steeper curve is explained by the higher one year mortality estimates for each state in the Markov model as informed by PARTNER B evidence.

Figure 5.13 Comparisons of Survival Estimates



Results from both the original and the revised models indicate that TAVI is more costly and more effective when compared to medical management for inoperable patients. The incremental costs in the PARTNER B model are 12% greater and the incremental QALYs are 34% less than the original model. In the original model, the ICER (£22,108) was within the range usually considered acceptable but in the revised model the ICER is above this range (£37,390) (Table 5.10).

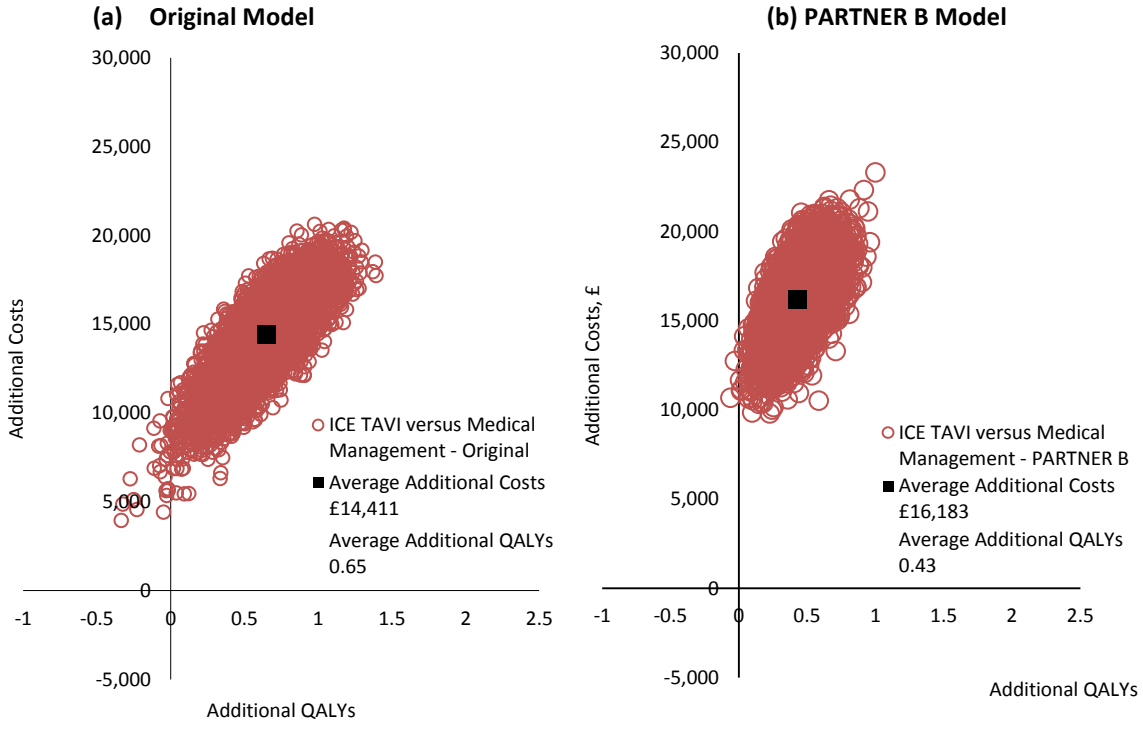
Table 5.10 Cost Effectiveness Results Comparison PARTNER B and Original Model: Inoperable Patients

	TAVI			Medical Management			Δ Costs	Δ QALYs	ICER
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs			£/ QALY
ORIGINAL*									
	28,353	2.18	3.48	13,942	1.53	3.06	14,411	0.65	22,108
PARTNER B‡									
	28,629	1.62	2.54	12,176	1.19	2.24	16,453	0.43	37,390

*Presented in Chapter 4 ‡Presented in Section 5.4

Specifically, the costs associated with TAVI were estimated to be greater than suggested by the original model (£276; 0.9%) and the QALYs produced are less (0.56; 26%). Similarly, the costs and QALYs associated with medical management, based on the revised analysis, were both less than the values produced by the original model (£1,748; 13% and 0.34; 22% respectively). These differences are explained by the higher probability of PREs and stroke associated with TAVI, the greater probability of death from the persistent AS/Failed valve replacement state and the inclusion of death within 30 days with medical management. The ICE plane compares the additional costs and benefits of TAVI over medical management. As discussed in Section 5.4, there is little uncertainty surrounding the existence of benefit and cost differences for TAVI (over medical management) with TAVI being more effective and more expensive than medical management. There is however, some uncertainty surrounding the extent of the differences in effects and costs, though considerably less than that in the original model.

Figure 5.14 Incremental Cost Effectiveness Plane Comparison: Inoperable Patients: Original and PARTNER B Models

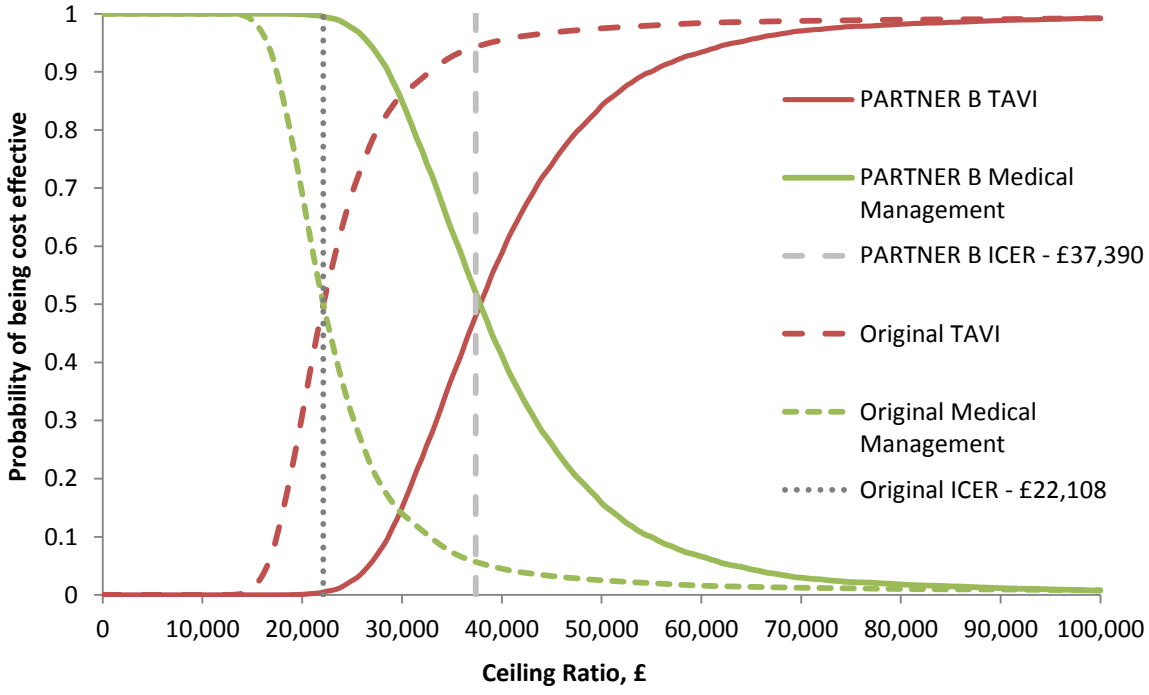


Comparing the ICE planes (Figure 5.14) it is evident that the new evidence has reduced and shifted the amount of uncertainty present. Figure 5.14a illustrates the incremental cost effectiveness plane from the original model and Figure 5.14b represents this uncertainty

for the revised model with PARTNER B data. Here it is illustrated that the uncertainty surrounding the extent of differences in QALYs and costs particularly, has reduced compared to the original model. This is confirmed in the reduction of the 95% confidence interval around the incremental QALYs between the original model (0.22-1.05) and the PARTNER B model (0.22-0.68). Similarly, the 95% confidence interval around the incremental costs narrowed from the original model (£9,766-£18,075) and the PARTNER B model (£12,674-£18,902) indicating a decrease in uncertainty surrounding the input parameters. So incorporating the new evidence reduced the uncertainty.

Comparing the CEACs from the re-analysis and the original analysis (Figure 5.15) demonstrates that the decision uncertainty in the original model was also reduced when the new evidence is incorporated. The probability that TAVI is cost effective compared with medical management (at a ceiling ratio of £30,000 per QALY) was 86% in the original and 18% in the revised model. Figure 5.15 presents the two CEACs side by side, to illustrate the change in decision uncertainty.

Figure 5.15 Cost Effectiveness Acceptability Curve Comparison: Inoperable Patients



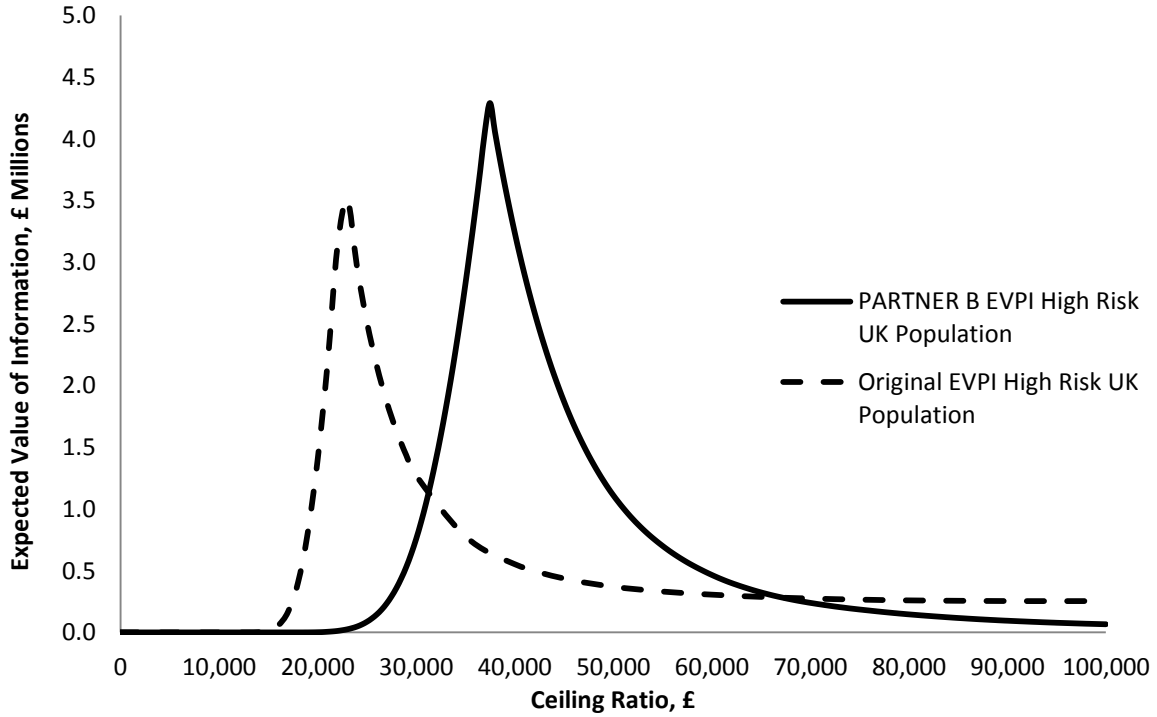
Thus, both the original model, employing data from published literature, and the revised model, which incorporates PARTNER Cohort B evidence, suggest that TAVI is more

costly and more effective compared with medical management in treating inoperable AS patients.

Value of Information Analysis

The VOI analysis estimated that the pEVPI between TAVI and medical management for the UK inoperable patient population (2,750 (SHTG, 2009)), using PARTNER evidence, over the range usually considered cost-effective, ranged from £1,270,699 to £3,512,503, over one year. This was marginally higher than that estimated in the original model which ranged from £988,775 to £3,428,480 for the UK inoperable population over one year. Figure 5.16 presents the pEVPI for the original model and PARTNER model side by side for comparative purposes. As illustrated here, the additional evidence marginally increased the pEVPI. So uncertainty remains and there is still some value in collecting further evidence on the costs and effects of TAVI compared with medical management, as confirmed by the EVPPI and EVSI.

Figure 5.16 Expected Value of Perfect Information Comparison: Inoperable Population



5.8 COMPARISON WITH OTHER COST EFFECTIVENESS ANALYSES

US Cost Effectiveness Analysis

Subsequent to the cost effectiveness analysis employing the optimal data available (including PARTNER B) presented in this Chapter, a cost effectiveness analysis of TAVI compared to medical management was published by Reynolds et al. (2012). This analysis was exclusively based on the PARTNER Cohort B trial with a US perspective and estimated an ICER of $61,889 (£39,027[7]) per QALY. The paper concluded that at an acceptable ceiling ratio of $50,000 (£44,142[7]), TAVI is cost effective compared to medical management. Table 5.11 presents the results of the Reynolds et al. (2012) cost effectiveness analysis alongside the results produced in this study. Upon examination it is evident that the incremental costs between TAVI and medical management are higher in the Reynolds et al. (2012) paper, as are incremental life years gained and QALYs.

Table 5.11 Comparison of Cost Effectiveness Results with Reynolds et al. (2012)

		Costs	Δ Costs	LYs	LYGs	QALY	Δ QALY	ICER £/ LYG	ICER £ /QALY
Reynolds $	**TAVI**	149,740		2.78		2.03			
	Control	69,903	79,837	1.20	1.58	0.73	1.30	50,212	61,889
Reynolds £*	**TAVI**	94,426		2.78		2.03			
	Control	44,081	50,345	1.20	1.58	0.73	1.30	31,664	39,027
PARTNER B	**TAVI**	28,629		2.54		1.62			
	Control	12,446	16,183	2.24	0.30	1.19	0.43	53,943	37,390

*Applied average USD GBP exchange rate March 2011-12 of 0.6306 (Oanda, 2012)
"Reynolds" are the results of the Reynolds et al. (2012) cost effectiveness analysis and "PARTNER B" is the cost effectiveness results from the model developed in this thesis.

[7] Average USD GBP exchange rate March 2011-12 of 0.6306 applied (OANDA, 2012).

The higher costs and resource utilisation between the two models is explained by the difference in treatment pathways beyond the initial intervention: UK practice is reflected in this study, while Reynolds et al. (2012) reflects US practice. Specifically, there are differences in length of stay between the two models. Reynolds et al. (2012) report a higher length of stay[8], particularly in the intensive care unit (4 versus 0.5 days). A key advantage of TAVI is the reduced length of stay particularly in high dependency unit (HDU) compared with surgical valve replacement. However, the length of stay reported by Reynolds et al. (2012) is similar to the total length of stay expected for AVR (as employed in Chapter 4). Also, Reynolds et al. (2012) only employs evidence from the PARTNER trial which is an account of early experiences with early generations of the TAVI devices. However, over time length of stay is reducing and particularly savings in higher dependency units are being seen, as there are incremental innovations and movements along the device-clinician learning curve. This is incorporated into the model in this study through a reduced length of stay and subsequent lower costs.

The costs for medical management also differ significantly between the two models. This reflects the difference in routine care provided for medically managed patients in the US compared to the UK. In the UK a proportion receive balloon valvuloplasty and all receive some medication. With respect to follow up costs there are also significant differences reported. In the US (as indicated by Reynolds et al. (2012)) there are higher follow up hospitalisations, rehabilitation days etc. compared to that modelled in this study. This reflects differences in routine care and costs of medicine in the two jurisdictions.

With regard to differences in life expectancy, long term evidence (beyond two years) is scarce for TAVI and medically managed patients. So employing PARTNER only evidence (as per Reynolds et al. (2012)) and a mix of evidence (as per the model presented in this study) yields different projections for life expectancy from the two procedures. Reynolds et al. (2012) employed a survival analysis to estimate long term survival estimates, employing evidence from a locked data set and parametric survival models. In addition, EQ-5D results directly from the patient were used to estimate QALYs. While, the model developed in this thesis, explicitly includes the likelihood of PREs in the longer term based on evidence for 1 year. These have a negative impact on life expectancy and quality of life following TAVI. Also, the utilities employed in the study are generally similar. For

[8] These length of stay estimates were not provided in the original trial results publication.

example, baseline utility in Reynolds et al. (2012) was 0.57 for control group and 0.59 for TAVI patients while the model in this thesis used a utility of 0.56 with a range of 0.55-0.58 in the probabilistic analysis for all patients.

The key distinctions between the models therefore lie in the perspective taken and the evidence sources employed. The Reynolds et al. (2012) model employs evidence from PARTNER B only, a US based clinical trial. This trial is subject to limitations as indicated by the authors themselves (Reynolds et al. 2012) and others (Schaff, 2011) such as: early generation devices used, centres studied had early experience and in trial practice differs from typical community practice. The latter was highlighted in the differences in post discharge care for non-TAVI patients between Reynolds et al. (2012) and model developed here. Aside from the caveats outlined above, employing evidence from a single trial to inform a cost effectiveness analysis could potentially lead to a partial and/or biased economic evaluation (Griffin et al., 2011). In contrast, the model developed in this thesis attempts to reflect current understanding of the TAVI practice, by employing data from a variety of sources, i.e. PARTNER B evidence and evidence from published registries and case studies where PARTNER evidence is unavailable.

Another explanation for the difference in conclusions drawn lies in location. Different jurisdictions by their nature have different "benchmarks" and standards owing to economic environment, costing systems and values. That is to say, what represents value for money in one economy may be higher or lower compared to another. The Reynolds et al. (2012) model was US based, where health care costs are higher than the UK and clinical practice differs. Therefore, the conclusions drawn in the two models are different, despite similar ICERs. While Reynolds et al. (2012) concludes that TAVI is cost effective they do issue limitations of the study and hint that the study may not be representative to wider populations owing to these limitations. These limitations are that PARTNER collected on early experience with early device generations, care delivered in the trial differs to routine practice and the long term projections of survival and quality of life go beyond the time horizon of the trial so are subject to uncertainties (Reynolds et al. 2012). Meanwhile, the model developed in this thesis could not conclude that TAVI is cost effective using the UK national standard of £20,000 to £30,000/QALY for the cost effectiveness threshold. However, if a ceiling ratio of £44,000/QALY been employed in this study (as suggested by Reynolds et al. (2012)) it would also have found TAVI to be cost effective (72% probability that TAVI is cost effective – Figure 5.6).

While the two studies disagree on their conclusions, they agree that this is not the end as far as investigating the cost effectiveness of TAVI. Where this thesis contributes to the literature specifically is that it ventures beyond a mere statement that further evidence is required by providing a quantitative estimate of the potential worth of this future evidence and investigating potential data collection strategies through VOI, namely the estimation of EVPI, EVPPI and EVSI.

Belgian Cost Effectiveness Analyses

In addition to the PARTNER cost effectiveness analysis published by Reynolds et al. (2012), a cost effectiveness analysis of TAVI for inoperable patients was also conducted by the Belgian Health Care Knowledge Centre (Neyt et al., 2011). This study employed a mix of evidence from PARTNER B and Belgian resource data. Neyt et al. (2011) estimated an ICER of €37,432/QALY for the baseline model (equivalent to £32,700 on date of publication[9] (OANDA, 2011)). As illustrated in Table 5.12, the incremental costs, QALYs and LYGs were higher in the Belgian analysis than those produced in the analysis in this thesis. The key differences evident between the two models were the cost of the TAVI device and procedure (€40,917 (£35,744[9] versus £18,302); Neyt et al. (2011) employed EQ-5D estimates when calculating quality of life; and the following procedure related events (PREs) were excluded from the baseline analysis: strokes, repeat procedures, vascular complications and major bleeding. In the model produced in this chapter, the PREs had a negative impact on mortality and utility. (In the scenario analysis, the ICER increased to over €40,000/QALY when repeat hospitalisations, strokes etc. were included (Neyt et al., 2011)).

Despite the ICER being greater than £30,000/QALY, Neyt et al. (2011) concluded that for inoperable patients the benefits of TAVI do seem to outweigh the risks and so it may be appropriate to consider TAVI with inoperable patients. This analysis therefore had similar findings to the model constructed in this thesis: TAVI is more effective and more expensive than medical management with an ICER greater than £30,000 and less than £40,000/QALY. However, similar to the Reynolds et al. (2012) analysis, a different conclusion is drawn based on a different acceptable ceiling ratio. (Note in Belgium there is no nationally suggested cost effectiveness threshold ((Cleemput, 2008)). This suggests that

[9] Converted as per Euro – GBP exchange rate on 22nd September 2011 (date of publication) (OANDA, 2011)

there is flexibility around the cost effectiveness decision in other jurisdictions, indicating there is scope for promising technologies like TAVI to be considered cost-effective despite high ICERs.

Table 5.12 Comparison of Cost Effectiveness Results with Neyt et al. (2011)

	Δ Costs *(95% CI)*	**LYGs** *(95% CI)*	**Δ QALY** *(95% CI)*	**ICER: Cost/LYGS**	**ICER: Cost/QALY**
Neyt €	31,856 (29,900, 38,600)	1.16 (0.65-1.75)	0.92 (-0.29-1.90)	31,856	37,432
Neyt £*	27,829 (26,120 - 33,720)	1.16 (0.65-1.75)	0.92 (-0.29-1.90)	27,829	32,700
PARTNER B	16,183 (12,869-19,365)	0.30 (-0.11 - 0.73)	0.43 (0.20 - 0.69)	53,399	37,390

*Applied average EUR GBP exchange rate on 22nd September 2011 (date of publication) (OANDA, 2011) "Neyt" are the results of the Neyt et al. (2011) cost effectiveness analysis and "PARTNER B" is the cost effectiveness results from the model developed in this thesis. Note only total incremental costs were provided in Neyt et al. (2011).

Other UK Cost Effectiveness Analyses

A study by Watt et al. (2011), published in late 2011, examined the cost effectiveness of TAVI amongst severe AS patients considered unsuitable for AVR. This study concluded that TAVI was highly likely to be considered cost effective in the UK, with an ICER of approximately £16,100. The analysis employed PARTNER B data where appropriate and other data where PARTNER B data was unavailable. For example, for device failure rates, results from AVR only studies were employed, elsewhere values from a clinical steering group were employed. Table 5.13 presents a comparison of the results from Watt et al. (2011) and this thesis.

The key differences between the model employed in Watt et al. (2011) and the model developed and employed in this thesis, lie in QALY results. Watt et al. (2011) report 45% higher QALYs for TAVI patients compared with the model presented here. This difference can be explained by the omission of long term PREs in Watt et al. (2011). Some adverse events are included in the post-operative period but none thereafter. Whereas, the model developed in this thesis explicitly includes short and long term PREs which have a

disutility attached to them. Thus, the estimation of survival following TAVI between the two models is different which impacts on the QALY results. However, Watt et al. (2011) do not report life expectancy results so it is difficult to determine how big this difference is. Survival estimates are also clearly different for medically management patients leading to an estimate of 49% higher QALYs for medically managed patients compared to Watt et al. (2011).

Other differences lie in treatment of PREs and inclusion of long term costs of care. As mentioned above, Watt et al. (2011) only included some early PREs such as stroke, paravavular leaks, pacemaker implantation, major vascular events and major bleeding. This is considerably less than those considered in the model in this thesis. With respect to costs, the costs for medically managed patients are more than twice those reported in Watt et al. (2011). These high costs for medical management are attributable to the long term costs of care and balloon valvuloplasty (83% in short run and 50% in the long run). Meanwhile, there is only an 8% difference in costs for TAVI between the models. Watt et al. (2011) also cite the lack of longer term evidence as a limitation of the study but no formal quantitative analysis for the value of this additional information would yield is included.

Table 5.13 Comparison of Cost Effectiveness Results with Watt et al. (2011)

		Costs	ΔCosts	QALYs	ΔQALYs	ICER: £/QALYs
Watt	TAVI	30,200		2.36		
	Control	5,000	25,200	0.80	1.56	£16,200
PARTNER B Model	TAVI	28,629		1.62		
	Control	12,446	16,183	1.19	0.43	£37,930

"Watt" are the results of the Watt et al. (2011) cost effectiveness analysis and "PARTNER B Model" is the cost effectiveness results from the model developed in this thesis.

Another UK, though unpublished[10](NHS, 2012), study is also underway, employing PARTNER B evidence. This is a study funded by the NIHR HTA programme to

[10] Report expected February 2013 NHS (2012)

investigate the cost effectiveness of TAVI amongst patients who cannot undergo AVR. Preliminary (unpublished) results (Orlando, 2011) demonstrate they too employed PARTNER Cohort B data and survival analysis techniques to estimate the cost effectiveness of TAVI compared to medical management for inoperable patients. The results to date conclude that TAVI appeared cost effective for treating inoperable patients compared to medical management. Again the authors recommend future research is warranted and should be conducted but it is unclear on what basis this recommendation is made as it was not supported by a VOI analysis.

5.9 DISCUSSION

The publication of results from the first TAVI clinical trial, the PARTNER trial, with 12 month follow-up, provided the eagerly awaited one year outcomes for inoperable patients. The DAM built in Chapter 4, to estimate the cost effectiveness of TAVI for inoperable patients with pre-trial information, is employed here again and populated with evidence from the first clinical trial, to re-assess the cost effectiveness of TAVI for inoperable patients, in line with the iterative approach conceptualised in Chapter 2.

Having revised the model, to reflect current understanding about the intervention and treatment pathways available, an ICER of £37,390 per QALY is estimated for TAVI for inoperable patients compared to medical management. This ICER is just outside the range usually considered cost effective. Comparing the results from the two versions of the model indicated that in both cases TAVI is more expensive but offers greater benefit than medical management. Comparing the 12 month results of the original model with this revised PARTNER B model, illustrated that both models demonstrate mortality and health gains for TAVI over medical management. But as the ICER is outside the range considered cost effective, given current information, TAVI cannot be considered cost effective for high risk inoperable patients.

The additional evidence provided by the clinical trial reduced the uncertainty surrounding differences in QALYs between TAVI and medical management. There is still however, value in collecting additional information, as demonstrated in the EVPI. The EVPPI and EVSI indicate there is most value in collecting additional evidence on short and long term transition probabilities (including mortality). This additional evidence could be collected

via a trial or registry. The expected trial and registry costs employed in the VOI analysis here suggest that a registry is more cost effective. A scenario analysis demonstrated that if this future information reported reduced PREs, TAVI could be considered cost effective.

The cost effectiveness analysis performed here employs the best data available at the time. Demand for TAVI is growing, with significant vested interests in the UK, across Europe and the US. It is not surprising then that others have also examined the cost effectiveness analysis of TAVI compared to medical management for high risk inoperable patients. The comparison across studies here indicates that the perspective taken and the ceiling ratio employed as a benchmark, influence the conclusions drawn with respect to TAVI's cost effectiveness. Consequently, different conclusions have been drawn across studies though the ICERs are comparable. Some recommendations however are common across the studies.

Firstly, each study acknowledged the heterogeneity amongst the different patient groups (operable and inoperable) and the need to consider the cost effectiveness of TAVI for both. Subsequent to the publication of Cohort B results, PARTNER published results on operable patients comparing TAVI to AVR (Cohort A). This evidence is employed in the next chapter, along with some exchangeable evidence from PARTNER B, to re-assess the cost effectiveness of TAVI for high operable patients in light of the evolving evidence base using the DAM on an iterative basis.

Secondly, there is a need for further information. This was quantified in this thesis, through a Bayesian VOI analysis, which found there is some value in collecting additional evidence for this patient group. As indicated in the scenario analysis performed if commentators' predictions are accurate and TAVI outcomes improve over time the ICER will decrease and TAVI may be considered cost effective in accordance within the acceptable ceiling ratio in the UK.

Thirdly, linked to the need for further information, the conclusions drawn by the cost effectiveness study performed here and other published analyses indicate TAVI is a promising technology with persistent uncertainty around outcomes. Thus, further information is required to reduce this uncertainty. This is acknowledged in the guidance procedures published by NICE and Scottish Health Technologies Group (SHTG). Where subsequent to publication of the PARTNER B evidence in England and Wales, NICE Interventional Procedure Guidance (Number 266, 2008) still held, recommending the use

of TAVI only where special arrangements for clinical governance, consent, audit and research are in place (Thomas, 2009). There is not however an outright rejection of TAVI, particularly in England and Wales where decision making is non-dichotomous. Here it is recognised that uncertainty persists and further information is required before making an outright decision. Through special arrangements evidence is being collected on suitable cases through the UK TAVI Registry. While in Scotland, the SHTG advice statement (Number 005/11) does not recommended TAVI for routine treatment of patients with AS (SHTG, 2011). In Scotland, where the decision making system is currently dichotomous, there is a negative ruling on TAVI but this is reviewed at regular intervals. Such recommendations confirm the predictions of the model that TAVI evidence is evolving and is not yet considered sufficient to recommend TAVI, uncertainty persists and further information is required.

Evolving evidence presents a persistent challenge for economic evaluations of medical devices. This is owing to the characteristics of novel expensive medical devices in the early stage of the technology lifecycle like TAVI. One means of gathering this evidence, while not delaying access, is to design and implement a Performance Based Risk Sharing Agreement (PBRSA) like an Access with Evidence Development (AED) scheme. This could ensure that evidence is collected while controlling who gets TAVI on a simultaneous basis. The UK TAVI Registry, as advocated previously, is an example of such an AED scheme, whereby every procedure performed is recorded in the registry under the 2007 NICE Guidance on TAVI. These schemes are complex in design and organisation. These challenges are discussed for TAVI in a later chapter as the evidence base evolves even further with the anticipated publication of two and three year outcomes from the previously employed registries.

CHAPTER 6 EVOLVING DATABASE FOR TRANSCATHETER AORTIC VALVE IMPLANTATION – INTEGRATING THE PARTNER TRIAL RESULTS FOR OPERABLE PATIENTS

6.1 INTRODUCTION

While some short term efficacy and effectiveness results of TAVI for high risk operable patients have been published, AVR remains the standard therapy for treating severe AS (Smith et al., 2011). For example, in England and Wales, the National Institute of Clinical Excellence (NICE) Interventional Procedure Guidance (Number 266, 2008) (NICE, 2011) recommends the use of TAVI only where special arrangements for clinical governance, consent, audit and research are in place. While in Scotland, the Scottish Health Technologies Group (SHTG) advice statement (Number 005/11) does not recommended TAVI for routine treatment of patients with severe AS (SHTG, 2011). However, owing to the characteristics of novel expensive medical devices it is anticipated that their evidence evolves over time. After which, procedure guidance and advice statements can be reviewed and revised accordingly. This is demonstrated here for high risk inoperable AS patients with publication of the first TAVI RCT, PARTNER.

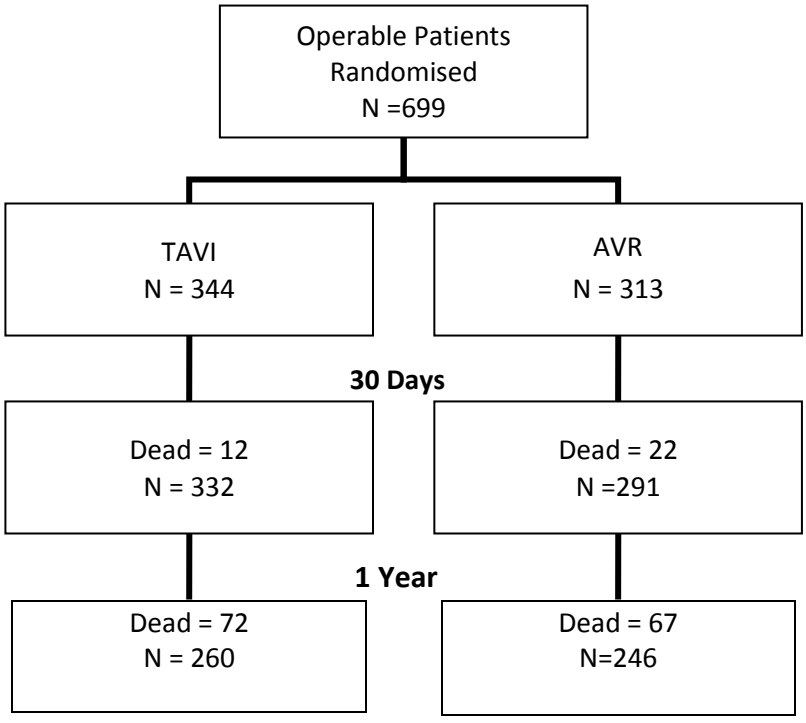
In light of this evolving evidence, the cost effectiveness of TAVI compared to AVR and medical management is re-evaluated here. This provides the opportunity to re-consider the adoption decision, in an iterative manner to reflect the current understanding of TAVI in practice, for high risk operable patients. A Bayesian value of information (VOI) analysis is also performed to re-assess the research priority setting decision. How the data is incorporated into the model and the cost effectiveness analysis results of TAVI using the new evidence are presented here to determine whether TAVI can be considered cost effective for high risk operable patients and given updated evidence whether there is value in collecting additional evidence. The revised results are compared to the original model for high risk operable patients as well as other cost effectiveness analysis.

6.2 TRANSCATHETER AORTIC VALVE IMPLANTATION'S EVOLVING EVIDENCE BASE

As outlined in Chapter 5, the first results from the first TAVI RCT, the Placement of Aortic Transcatheter Valves (PARTNER), were published in 2010. The trial commenced in April 2007 and was sponsored by Edwards Lifesciences. All of the patients enrolled had severe AS and were in New York Heart Association (NYHA) classes greater than I (see Table 3.1) (Leon et al., 2010). In the trial, Cohort A compared TAVI with surgical valve replacement (AVR). Given the treatment choices and risk profile, this cohort corresponds to high risk operable patients in Chapter 4.

Initially, 699 patients were allocated to the two cohorts for randomisation. Of these, 348 patients were randomised into the TAVI arm and 351 into the AVR arm. Following randomisation, 38 patients withdrew from the AVR arm, leaving 313 receiving the procedure. Similarly, four patients allocated to the TAVI arm withdrew from the trial, leaving 344 patients receiving the TAVI procedure. After 30 days, 22 patients who received AVR had died, while only 12 TAVI patients died during the same period.

Figure 6.1 PARTNER Trial Cohort A Patient Flow Operable Patients: TAVI versus AVR



Source: Adapted from Smith et al. (2011) :(S)28

Thus, at 30 day follow up information on the clinical endpoints were available for those who had died; 291 surviving AVR patients and 332 surviving TAVI patients. Between 30 days and one year a further 67 patients died in the AVR arm. From the TAVI arm a further 72 patients died in the same period. Thus, at one year follow up information on the endpoints were available for those who died; 246 AVR surviving patients and 260 surviving TAVI patients. This evidence is used to update the transition probabilities as the TAVI DAM model is employed in an iterative manner.

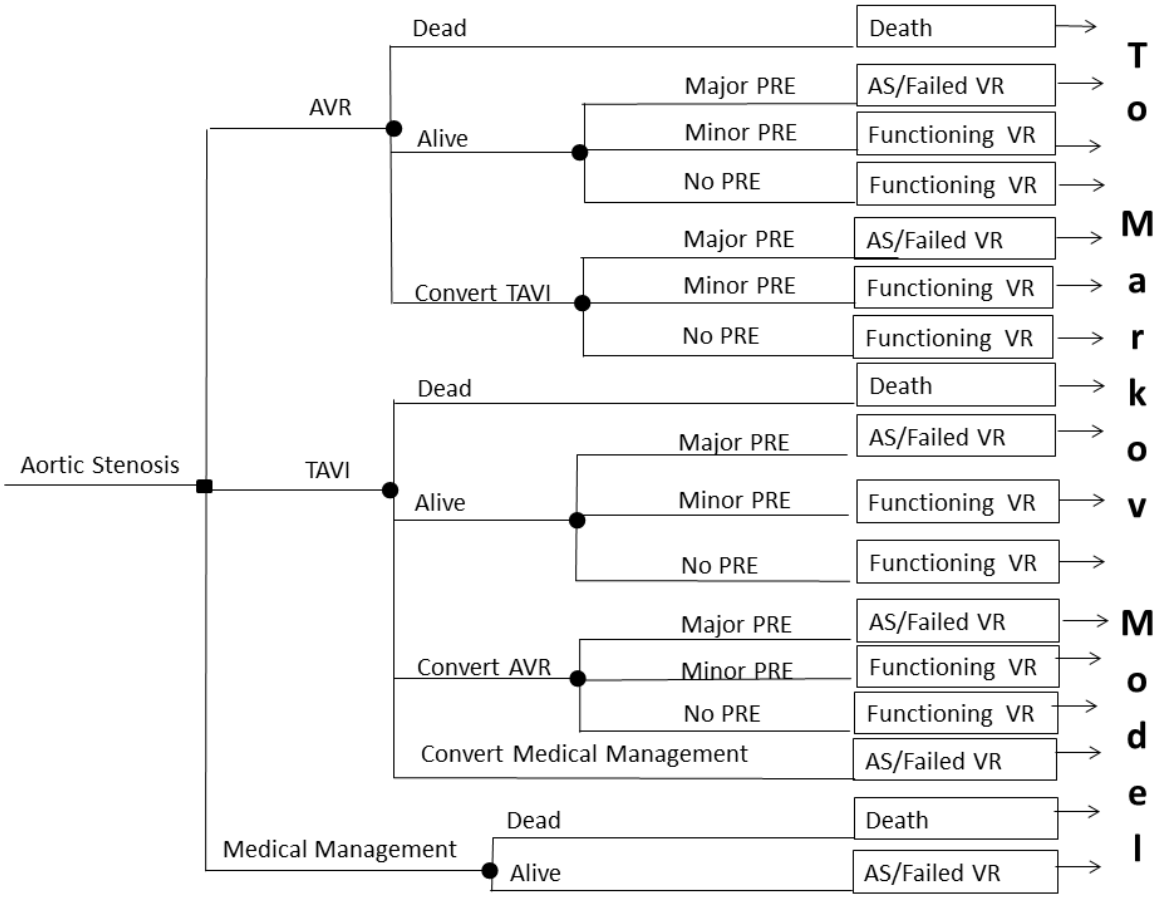
6.3 INCORPORATING EVIDENCE FROM PARTNER COHORT A – HIGH RISK OPERABLE PATIENTS

6.3.1 Changes to the Decision Analytical Model

As the PARTNER trial was the first to consider AVR compared to TAVI directly, evidence from the trial updates knowledge and understanding of the procedures and the disease pathways. This affords the opportunity to reflect the heterogeneity between technologies and make some structural changes to the decision tree. The latter being the inclusion of conversions from AVR to TAVI and TAVI to medical management and repeat TAVI (the latter two changes were made in Chapter 5 for inoperable patients also). These changes are illustrated on Figure 6.2 below.

As per the model for inoperable patients, evidence and experience from the PARTNER trial did not result in any structural amendments to the Markov model but did offer the distinction between major and minor late procedure related events (PREs) (the latter incur a cost and utility hit only and do not result in valve failure) and provided revised point estimates. Prior to the PARTNER trial, experience with TAVI was limited, particularly on late outcomes. The PARTNER trial has therefore revised knowledge and understanding of the intervention beyond the initial 30 day in-hospital period.

Figure 6.2 Revised Decision Analytical Model: Short Term Component – The Decision Tree



6.3.2. Parameterisation of the Decision Analytical Model for High Risk Operable Patients

Transition Probabilities

Cohort A of the PARTNER Trial compared TAVI with AVR for severe high risk operable AS patients. Extracting the outcomes and clinical endpoints from Smith et al. (2011) for 30 days and 1 year (pre model data is presented in Appendix V, Table c) permitted the revision of the parameters used in the model, thus reflecting the best data available. So PARTNER A evidence, where available, replaced previously employed evidence from the literature. A "replacement" strategy was adopted as PARTNER Cohort A evidence reflected the best available data at the time of analysis. As the original model was populated with early short term TAVI results and AVR experience, an "updating" strategy would not have reflected best data available at the time. (Recall that the original model was

populated with very early TAVI experience and experiences with AVR.) Where PARTNER Cohort A did not provide evidence, the point estimates employed in the original model were maintained. The provision of evidence directly on TAVI from PARTNER Cohort A eliminated the need for the relative risk parameters employed in Chapter 4

The revised transition probabilities were calculated as follows. Using the evidence presented in Smith et al. (2011) (Appendix V Table c) the number of times each event occurred was identified (α). The total number of times that an event could have occurred was estimated as the number at risk of that event (i.e. by removing those who died, converted and withdrew during the time frame in the data set (n)). The probability of each event occurring was estimated as the number of events that did occur (α) as a proportion of the total that could have occurred (n). Box 6.1 provides an example of this using major bleeding. The data set reported 32 cases of major bleeding within 30 days for TAVI patients and 49 major bleeding within one year. It was deduced that 17 cases of major bleeding occurred post discharge up to one year. The arm consisted of 344 patients, nine of whom converted to AVR and five who converted to medical management; thus 330 patients received the procedure. The probability of having a major bleeding in the first 30 days was the proportion of events which did occur (α = 32) from the total that could have occurred (n = 330), 0.097 (α/n, 32/330). The probability of having a major bleed in the longer term was estimated in a similar manner. Where the number of events that occurred (α = 17) estimated as a proportion of the total that could have occurred (n = 245), 0.069 (α/n, 17/245). Using this method for all other events the point estimates for the DAM were re-calculated to incorporate the PARTNER A data.

PARTNER A provided no evidence on medical management, which is also considered a treatment option in the model for high risk, operable patients in this thesis. The original model did not account for balloon valvuloplasty and had a 100% survival rate within the first 30 days, based on expert opinion. However, prior to publication of PARTNER Cohort A results, PARTNER Cohort B results were published (Leon et al., 2010) which provided estimates of mortality (0.04) and provision of balloon valvuloplasty for medical managed patients (0.83) within first 30 days. While the patients in the PARTNER Cohort B were considered high risk inoperable and, as such, are not the same as those considered high risk operable, these outcomes do update current knowledge and understanding of the medical management treatment. Thus, exchanging information between the two cohorts facilitates

the incorporation of the optimum evidence into the model to best reflect current practice. In the absence of other evidence, it was assumed that the data is directly exchangeable and medical management outcomes are the same for all patient risk groups.

Box 6.1 Example of Probability of Procedure Related Event Calculation for Operable Patient Group

Randomised to TAVI		344
Conversion to AVR		9
Conversion to Medical Management		5
Received TAVI Procedure (n)		330
Major Complications, Major Stroke or Death w/in 30 days		85
Functioning Valve Replacement after 30 days (n)		245
TAVI: Major Bleeding - 30 days (α)		32
TAVI: Major Bleeding - Within 1 Year		49
TAVI: Major Bleeding - Post Discharge to 1 year (α)		17
Probability of Major Bleeding - 30 days	(α/n) → (32/330)	0.097
Probability of Major Bleeding - Post Discharge to 1 year	(α/n) → (17/245)	0.069

Decision Tree

Using the PARTNER evidence to estimate the transition probabilities in the short term model provided the following revised probabilities. As one patient from a potential 313 patients converted from AVR to TAVI the probability of converting was 0.003 (1/313). With respect to major stroke within the first 30 days, 19 patients out of 312 had a major stroke giving a probability of a major stroke following AVR of 0.03. With respect to all-cause mortality within 30 days following AVR, 22 patients out of 312 died giving a probability of 0.07. With respect to early PREs, there was a 0.05 probability of major PREs occurring following AVR and a 0.33 chance of minor PREs. These PREs are estimated by summing the probabilities of the individual PREs, shown in Table 6.2.

For the TAVI arm, the likelihood of converting to AVR was 0.03, as nine patients from a potential 344 converted. Meanwhile, five patients out of a potential of 344 converted from TAVI to medical management, giving a probability of converting of 0.01. There is also a small chance that the TAVI procedure will have to be repeated. In the PARTNER Cohort A trial, seven out of 344 patients had to have a repeat TAVI procedure (0.02). Within the first 30 days, 12 patients had died from all causes within 30 days, giving a probability of

0.04. While for the same period, 19 patients suffered a stroke after TAVI, giving a probability of 0.06. The likelihood of early major PREs is 0.16 and early minor PREs 0.38 following TAVI. These PREs are estimated by summing the probabilities of the individual PREs shown in Table 6.2.

Finally, for the medical management arm the probability of death from all causes is 0.04 and the likelihood of requiring a balloon valvuloplasty is 0.83 (these estimates are informed by PARTNER Cohort B evidence presented in Chapter 5).

Markov Model

The late PREs for the long term model are estimated by summing the probabilities of the individual PREs shown in Table 6.2. The probability of late fatal PREs was 0.10, late major PREs were 0.11 and late minor PREs were 0.22, following AVR. For the TAVI arm the probability of late fatal PREs was 0.12, late major PREs was 0.18 and late minor PREs was 0.28.

One limitation of the PARTNER A results is that they are for 12 months duration only. While it was feasible to isolate a mortality from natural causes and mortality from the functioning and persistent AS /failed valve replacement state for one year these were employed in the first cycle only. For AVR patients, death from the functioning valve replacement state was 0.14, while death from persistent AS /failed valve replacement state was 0.18. While for TAVI patients, death from the functioning valve replacement state was 0.15, while death from persistent AS /failed valve replacement state was 0.08. This allows for differentiation between technologies. Applying different mortality rates for the same state reflects the longer term implications of each treatment, which differ.

Subsequent cycles (beyond one year) employed the natural mortality rate adjusted for age-sex and disease and a probability of death from persistent AS /failed valve replacement state of 0.33 (Legrand et al., 1991), as per the original model. These probabilities were employed so as to reflect the life-stage of the patients and to account for the diminishing benefits of the valve procedure, as forecasted by Smith (2011). For medically managed patients in each cycle, the probability of death from the persistent AS /failed valve replacement state employed was 0.33 (as per (Legrand et al., 1991). These transition probabilities for the short and long term model are presented in Tables 6.1. All of the

transition probabilities provided on Tables 6.1-2 represent absolute risk for each arm of the model, AVR, TAVI and medical management.

As per the original model, the uncertainty surrounding each of the parameters was incorporated into the model through the assignment of probability distributions (shown in Tables 6.1-2). The PARTNER Cohort A results identified the total number of patients and the number for whom events occurred. This information was used to specify a beta distribution for each probability.

Where the PARTNER results did not provide information on an event occurring, the original estimate, as calculated in Chapter 4, was maintained (as per Chapter 5). This was the case for cardiac tamponade in estimating early major PREs and access site events for early minor PREs. Where for each event the number of cases per study was pooled across and divided by the total number of patients to give the probability of that event occurring. With respect to late PREs, the original estimate for hospitalisations was used. For early major PREs evidence was scarce prior to PARTNER so evidence from AVR studies was included also. Here the total number of patients was pooled from all the studies (AVR and TAVI together) and the average was estimated. Also, where no incidences of an event occurring were reported but expert opinion and priors indicated it may occur a small amount is added to the data for each event in order to adjust for those with an observed zero probability to allow for the small chance of such events occurring (see Table 5.3 for further details of the calculation).

Cost Parameters

In the cost analysis the value of the following resources were estimated: TAVI, AVR and medical management devices; procedures; length of stay; hospitalisations and other costs incurred with PREs. No additional information on the cost of the TAVI, AVR or medical management procedure was provided in the published PARTNER A results. So the costs as per the original model are maintained but updated to reflect 2010 prices using purchasing power parity (Officer and Williamson, 2011)[11].

PARTNER A did however provide information on length of stay for patients in the operable arm. For AVR patients the length of stay in the intensive care unit reported was

[11] The costs as per Chapter 4 were employed but updated to reflect 2010 prices.

five days and seven days on the general ward. For TAVI patients PARTNER A reported three days in intensive care and eight days in the general ward. The revised cost of hospital stay for AVR patients was £10,142 and for TAVI patients £6,257. PARTNER A also provided data on the proportion of patients per NYHA class. These were used to update the probability of requiring hospitalisations in the long term model, which was used to estimate the cost of the functioning valve replacement and AS/Failed valve replacement states. While the cost of the functioning valve state for AVR patients was £1,561 and for TAVI patients was £1,514. The difference is explained by the two percentage point difference in probability of requiring hospitalisations (0.07 versus 0.05 for AVR and TAVI respectively). The cost of the persistent AS/failed valve replacement state was £8,214 for AVR patients and £8,295 for TAVI patients. The variation is explained by the difference in probability of requiring hospitalisations (0.71 versus 0.78 for AVR and TAVI respectively, determined by NYHA classification) when the valve is no longer offering benefits to utility.

These state and procedural costs are presented in Table 6.3, along with the distributions applied to the unit costs and resources consumed. Normal distributions were applied to procedure related costs, hospitalisation costs and post discharge care costs. With respect to the amount of resources consumed, a normal distribution was applied to the length of stay parameters and beta distributions to the probability of requiring post discharge care and resources consumed in each health state.

The costs of the PREs were estimated as previously (but updated to reflect 2010 prices using purchasing power parity (Officer and Williamson, 2011) as per Chapter 5), with a weight assigned to each event and the unit cost. The PARTNER Cohort A data provided no additional unit cost information but the weights (which are a proportion of each event occurring) were updated to reflect the revised probabilities (Table 6.2)). The cost of major and PREs following AVR with the first 30 days were £1,055 and £781 respectively. Following TAVI, the cost of major and minor PREs within the first 30 days was £367 and £819. The cost of late major and minor PREs occurring after 30 days but within one year following AVR were £2,707 and £2,341. Following TAVI the cost of late major and minor PREs occurring after 30 days but within one year were £2,700 and £2,594 respectively. Normal distributions were applied to cost of treating PREs. Again here the costs are discounted at a rate of 3.5%.

Table 6.1 Transition Probabilities for TAVI Decision Analytical Model Updated for PARTNER A

Transition Probability	Distribution	Probability (95% CI)	α	β	n
Short term - 0-30 days					
Probability of converting from TAVI to AVR¶	Beta	0.03 (0.01-0.04)	9	335	344
Probability of converting from TAVI to medical management¶	Beta	0.01 (0.00-0.03)	5	339	344
Probability of converting from AVR to TAVI¶	Beta	0.003 (0.00-0.12)	1	312	313
Probability of repeat TAVI procedure¶	Beta	0.02 (0.01-0.04)	7	337	344
Probability of major stroke following AVR¶	Beta	0.03 (0.01-0.05)	8	304	312
Probability of major stroke following TAVI¶	Beta	0.06 (0.03-0.08)	19	311	330
Probability of death 30 days all causes AVR¶	Beta	0.07 (0.04-0.10)	22	290	312
Probability of death 30 days all causes TAVI¶	Beta	0.04 (0.02-0.06)	12	332	344
Probability death 30 days all causes medical management‡	Beta	0.04 (0.01-0.07)	5	133	138
Probability of balloon valvuloplasty medical management	Beta	0.83 (0.76-0.88)	114	24	138
Probability of early major PRE AVR	Beta	0.05 (0.02-0.07)	Table 6.2		
Probability of early major PRE TAVI	Beta	0.16 (0.12-0.21)			
Probability of early minor PRE AVR	Beta	0.33 (0.29-0.40)			
Probability of early minor PRE TAVI	Beta	0.38 (0.31-0.44)			
Long term - post 30 days					
Probability PRE fatal (AVR) ¶	Beta	0.10 (0.06-0.14)	26	242	268
Probability PRE fatal (TAVI) ¶	Beta	0.12 (0.08-0.17)	30	215	268
Probability PRE late major (AVR)	Beta	0.11 (0.08-0.16)	Table 6.2		
Probability PRE late major (TAVI)	Beta	0.18 (0.13-0.24)			
Probability PRE late minor (AVR)	Beta	0.22 (0.17-0.27)			
Probability PRE late minor (TAVI)	Beta	0.28 (0.22-0.35)			
Probability death from AS state - AVR¶^	Beta	0.18 (0.05-0.36)	4	18	22
Probability death from AS state - TAVI¶^	Beta	0.08 (0.03-0.15)	6	67	73
Probability death from AS state - Medical Management*^	Beta	0.33 (0.25-0.41)	44	94	138
Probability death from AS state – Post 1 year*	Beta	0.33 (0.24-0.42)	33	67	100

Table 6.1 Continued

Transition Probability	Distribution	Probability (95% CI)	α	β	n
Morality from natural causes - AVR¶¤	Beta	0.14 (0.10 - 0.18)	37	231	268
Mortality from natural causes - TAVI¶¤	Beta	0.15 (0.10 -0.19)	36	209	245
Mortality from natural causes	Log normal	†	-	-	
Relative Risk of Death from AS	Log normal	1.50 (0.95-2.25)	0.38	0.22	

¶ (Smith et al., 2011) *(Legrand et al., 1991) † Standard life tables ‡(Leon et al., 2010)^ Only applied in year 1, there after Probability of death from AS state – Post 1 year is used ¤ Only applied in year 1, there after mortality from natural causes adjusted for AS is used. α = number of events occurring. β= n- α (where n is the number of events which could have occurred).

Table 6.2 Procedure Related Events Probabilities for TAVI Decision Analytical Model Updated for PARTNER A

Procedure Related Events	Dist	Probability (95% CI)	Weight	α	β	n
Major PREs AVR						
Valve Thromboembolism¶	beta	0.00	0.00	0	312	312
Major paravavular leak¶	beta	0.01	0.14	2	310	312
Endocarditis¶	beta	0.00	0.07	1	311	312
Cardiac tamponade*	beta	0.03	0.65	9	303	312
Myocardial infarction¶	beta	0.01	0.14	2	310	312
Total		**0.05 (0.02-0.07)**				
Major PREs - TAVI						
Valve Thromboembolism¶	beta	0.03	0.17	9	321	330
Major Paravavular leak¶	beta	0.11	0.64	35	295	330
Endocarditis¶	beta	0.00	0.00	0	330	330
Cardiac tamponade†	beta	0.03	0.19	10	320	330
Myocardial infarction¶	beta	0.00	0.00	0	330	330
Total		**0.16 (0.12-0.21)**				
Minor PREs - AVR						
Access site events*	beta	0.04	0.12	12	300	312
Vascular Events¶	beta	0.01	0.02	2	310	312
Pacemaker implantation¶	beta	0.04	0.12	12	300	312
Major Vascular Event¶	beta	0.04	0.11	11	301	312
Major Bleeding¶	beta	0.21	0.64	67	245	312
Total		**0.33 (0.29-0.40)**				
Minor PREs - TAVI						
Access site events†	beta	0.06	0.16	20	310	330
Vascular Events¶	beta	0.06	0.17	21	309	330
Pacemaker implantation¶	beta	0.04	0.10	13	317	330
Major Vascular Event¶	beta	0.12	0.31	38	292	330
Major Bleeding¶	beta	0.10	0.26	32	298	330
Total		**0.38 (0.31-0.44)**				
Probability late PREs* - AVR						
Valve Thromboembolism*	beta	0.07	0.59	18	250	268
Major paravavular leak¶	beta	0.01	0.10	3	265	268
Endocarditis¶	beta	0.01	0.07	2	266	268
Cardiac tamponade*	beta	0.01	0.09	3	265	268
Stroke ¶	beta	0.02	0.16	5	263	268
Myocardial infarction¶	beta	0.00	0.00	0	268	268
Total		**0.11 (0.08-0.16)**				

Table 6.2 Continued

Procedure Related Events	Dist	Prob (95% CI)	Weight	α	β	n
Probability late PREs* TAVI						
Valve Thromboembolism†	beta	0.07	0.37	17	228	245
Major paravavular leak¶	beta	0.06	0.33	15	230	245
Endocarditis¶	beta	0.01	0.04	2	243	245
Cardiac tamponade†	beta	0.01	0.05	2	243	245
Stroke ¶	beta	0.03	0.18	8	237	245
Myocardial infarction¶	beta	0.00	0.02	1	244	245
Total		**0.18 (0.13-0.24)**				
Late minor PREs AVR						
Repeat hospitalisations ¶	beta	0.12	0.57	33	235	268
Major vascular complications ¶	beta	0.00	0.02	1	267	268
Minor vascular complications ¶	beta	0.01	0.03	2	266	268
Major bleeding ¶	beta	0.07	0.31	18	250	268
New pacemaker ¶	beta	0.01	0.07	4	264	268
Total		**0.22 (0.17-0.27)**				
Late minor PREs TAVI						
Repeat hospitalisations ¶	beta	0.18	0.63	43	202	245
Major vascular complications ¶	beta	0.00	0.01	1	244	245
Minor vascular complications ¶	beta	0.01	0.03	2	243	245
Major bleeding ¶	beta	0.07	0.25	17	228	245
New pacemaker ¶	beta	0.02	0.09	6	239	245
Total		**0.28 (0.22-0.35)**				

¶(Smith et al., 2011) * (Gehlot et al., 1996, Gilbert et al., 1999, Milano et al., 1998, Aupart et al., 2006, Eichinger et al., 2008) †See Table 5.3 α = number of events occurring. n = number of events which could have occurred β= n- α.

Table 6.3 Cost Parameters for TAVI Decision Analytical Model Revised for PARTNER A

COSTS	Dist	Unit Cost £	SE	Dist				Total Cost £ (95% CI)
Short term costs								
AVR Device		2,045*						**£2,045**
AVR Procedure	normal	3,660*	300					**£3,660**
In hospital stay -AVR					**LOS [D]**	**SE**		
ICU	normal	1,728†	300	normal	5[¶]	0.19		8,639
General Ward	normal	215†	50	normal	7[¶]	0.04		1,503
								10,142
								(6,875-12,988)
In hospital stay -TAVI					**LOS [D]**	**SE**		
ICU	normal	1,728†	300	normal	3[¶]	0.19		5,183
General Ward	normal	215†	50	normal	8[¶]	0.04		1,073
								6,257
								(4,242-8,013)
Post Discharge Care- AVR					**Prob**	**α**	**β**	
Cardiac Rehab	normal	3006*	500	beta	0.90*	90	10	2,705
Nursing home	normal	873+	50	beta	0.50*	50	50	437
								3,142
								(2,177-3,995)
Post Discharge Care - TAVI								
Cardiac Rehab	normal	3006*	500	beta	0.10*	10	90	300
Nursing home	normal	873+	50	beta	0.23*	23	77	201
								501
								(347-637)
Long term costs								
Cost of Functioning Valve Replacement AVR								
Hospitalisations		3,390*		beta	0.07[¶‡]	20	270	231
Nursing home		11,382[+]		beta	0.10[*]	76	681	1,138
Drug Therapy		192*						192
								1,561
								(1,282-1,794)
Cost of Functioning Valve Replacement TAVI								
Hospitalisations		3,390*		beta	0.05[¶‡]	17	301	184
Nursing home		11,382[+]		beta	0.10[*]	76	681	1,138
Drug Therapy		192*						192
								1,514
								(1,243-1,743)
Cost of Failed Valve Replacement AVR								
Hospitalisations		3,390*		beta	0.78[¶‡]	226	64	2,641
Nursing home		11,382[+]		beta	0.50[*]	379	379	5,691
Drug Therapy		192*						192
								8,214
								(7,915-8,770)
Cost of Failed Valve Replacement TAVI								
Hospitalisations		3,390*		beta	0.71[¶‡]	225	92	2,412
Nursing home		11,382[+]		beta	0.50[*]	379	379	5,691
Drug Therapy		192*						192
								8,295
								(7,681-8,537)

* (Kennon et al., 2008) [+] (Netten, 1996) †(Kalra et al., 2005, Kennon et al., 2008, NHS, 2008a) ¶ (Smith et al., 2011) ‡ Based on hospitalisations by NYHA class. [D] Days

Quality of Life Parameters

As per the original model QALYs were also derived for each health state adjusting for the condition, the procedure and PREs. PARTNER Cohort A (Smith et al., 2011) also published evidence on NYHA classification of patients. This permitted a re-estimation of the proportion of patients per class to revise the utility of functioning valve replacement and persistent AS/failed valve replacement states (in line with the revised transition probabilities). As PARTNER Cohort A (Smith et al., 2011) provided different proportions of patients in NYHA classifications for TAVI and AVR patients, different utilities for the functioning valve replacement state for each procedure could be estimated. This captures the heterogeneity between treatments. The utility associated with AS or persistent AS was 0.55. While the utility associated with the functioning valve replacement state following AVR was 0.75 and following TAVI was 0.78. Table 6.4 presents the expected utilities employed in the model and the range employed in the probabilistic analysis. Normal distributions were applied to the disutility hits associated with the PREs, while Dirichlet distributions were applied to the disutility associated with each NYHA classification. Again here the QALYs were discounted at 3.5%.

As with the costs, the impact on utility associated with the PREs were adjusted to account for the revised probabilities of events occurring. The utility hit associated with major and minor PREs within one year following AVR were 0.03 and 0.04 respectively. Following TAVI, the utility hit associated with major and minor PREs within one year were 0.04 and 0.03 respectively. With respect to late major and minor PREs the utility hit was 0.04 and 0.02 for both TAVI and AVR.

Table 6.4 Utilities by NYHA Class for TAVI Decision Analytical Model Revised for PARTNER Cohort A

NYHA Class	Dist	Utility*	Proportion¶	Utility (95% CI)
Utility of AS				
I	Dirichlet	0.815	0.00	0.00
II	Dirichlet	0.720	0.05	0.04
III	Dirichlet	0.590	0.43	0.25
IV	Dirichlet	0.508	0.52	0.26
				0.55
				(0.55-0.56)
Utility of Functioning Valve Replacement AVR				
I	Dirichlet	0.815	0.55	0.45
II	Dirichlet	0.720	0.30	0.22
III	Dirichlet	0.59	0.13	0.08
IV	Dirichlet	0.508	0.02	0.01
				0.75
				(0.74-0.76)
Utility of Functioning Valve Replacement TAVI				
I	Dirichlet	0.815	0.72	0.59
II	Dirichlet	0.72	0.19	0.14
III	Dirichlet	0.59	0.08	0.05
IV	Dirichlet	0.508	0.02	0.01
				0.78
				(0.77-0.78)

*(Maliwa et al., 2003) ¶(Smith et al., 2011)

6.3.3. Analysis – High Risk Operable Patients

Similar to the analyses conducted in Chapters 4 and 5, the economic evaluation here is undertaken from the perspective of the UK NHS. A Monte Carlo simulation with 10,000 iterations is used to propagate the uncertainty in the individual model parameters (reflected by the probability distributions assigned) through the model to produce a distribution of expected costs and expected QALYs associated with each procedure. The mean values of these distributions are used to calculate the incremental cost effectiveness ratio (ICER) in terms of the expected incremental costs associated with TAVI compared to AVR and medical management per incremental QALY gained. The uncertainty associated with the incremental costs and incremental QALYs are presented through incremental cost effectiveness (ICE) planes. The uncertainty associated with the cost effectiveness of TAVI compared to AVR and medical management is presented in terms of a cost effectiveness acceptability curve (CEAC), to re-assess the adoption decision. Following this a Bayesian

VOI analysis is performed to estimate the value of collecting further information, given current, revised information. This corresponds with the research priority setting decision.

6.4 COST EFFECTIVENESS ANALYSIS RESULTS – HIGH RISK OPERABLE PATIENTS

When the DAM is revised to incorporate the best data available, including data from PARTNER Cohort A, the results indicate only a 3% reduction in all-cause mortality at the end of year one between TAVI and AVR. This is consistent with the 3% reported from PARTNER by Smith et al. (2011). Meanwhile, the model predicts a 33% reduction in all-cause mortality at the end of year one between AVR and medical management. The survival estimates (Figure 6.3) illustrate the initial sharp decline, followed by a diminishing decrease for AVR and TAVI patients. This may be attributable to the underlying patient characteristics, especially age and co-morbidities, which dominate the benefits of the valve replacement over time.

Figure 6.4 illustrates the difference in quality of life between the three treatment groups. For the first two years TAVI is marginally better than AVR and both are considerably better than medical management. Between years two and six AVR is better than TAVI, possibly owing to the rate of late PREs and mortality rates. After six years the model predicts that patients who received TAVI will have similar quality adjusted life years to AVR patients until death. Particularly, after year ten all patients have similar quality of life, irrespective of treatment. Again, this may be attributable to the underlying patient characteristics, which can over-ride the benefits of the valve replacement over time.

6.4.1 Deterministic Cost Effectiveness Results

The cost effectiveness of TAVI compared to AVR and medical management was estimated for operable patients based on a mix of evidence from the PARTNER Cohort A trial and the original estimates from the literature, as discussed earlier. The deterministic cost effectiveness results (Table 6.5) were estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. The results illustrate that

for high risk patients TAVI is more costly (£6,995) and less effective (-0.11 QALYS) than AVR. As TAVI is more expensive and less effective than AVR, TAVI is dominated by

Figure 6.3 Survival Estimates for AVR, TAVI and Medical Management

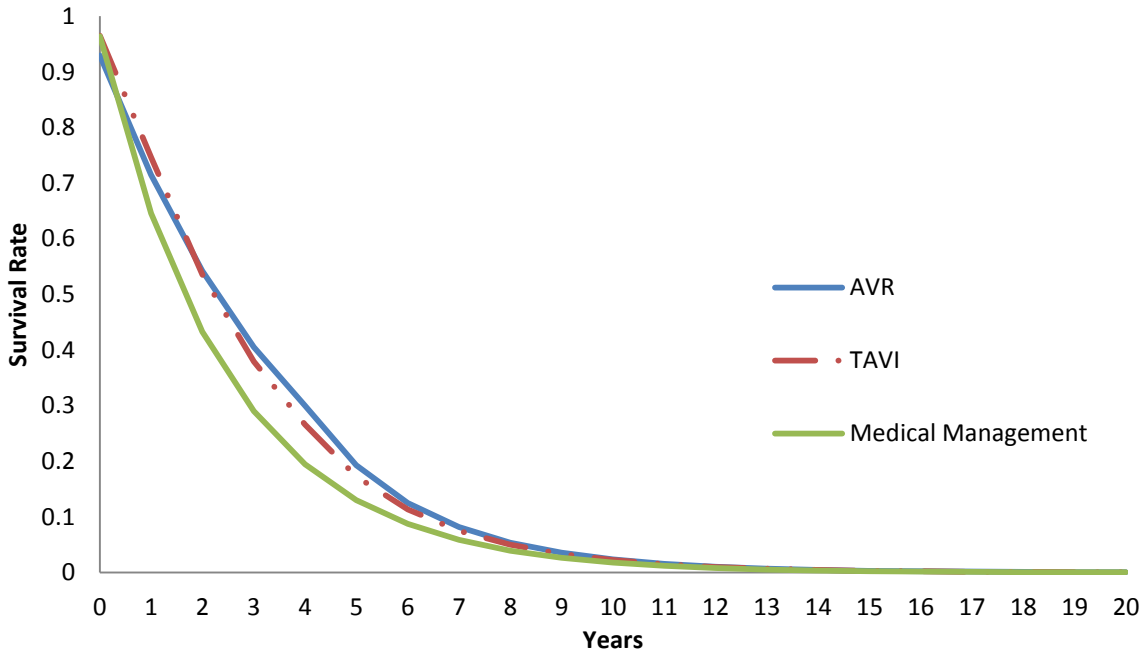


Figure 6.4 Quality Of Life Estimates for AVR, TAVI And Medical Management Per Patient

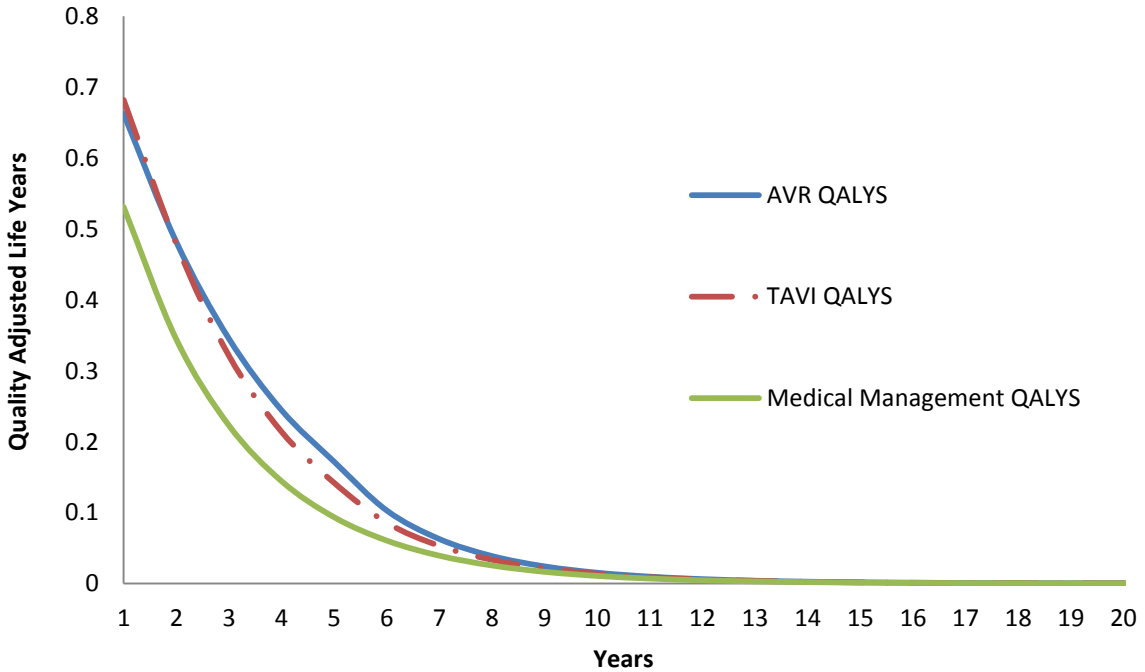


Table 6.5 Cost Effectiveness Results: High Risk Operable Patients - AVR versus TAVI versus Medical Management

	LYs	Costs (£) (95% CI)	Change in Costs	QALYs (95% CI)	Change in QALYS	ICER £/QALY
Deterministic Results						
Medical Management	2.92	18,681		1.51		
AVR	3.45	29,561	10,880	2.18	0.67	16,276
TAVI	3.45	36,557	6,995	2.07	-0.11	TAVI Dominated
Probabilistic Results						
Medical Management	2.96	19,012		1.54		
	(2.43-3.70)	(14,570-24,797)		(1.28-1.87)		
AVR	3.49	29,695	10,684	2.20	0.66	16,118
	(2.99-4.08)	(25,657-34,082)	(5,424-15,696)	(1.92-2.52)	(0.33-1.00)	
TAVI	3.44	36,813	7,117	2.09	-0.11	TAVI Dominated
	(2.96-4.06)	(32,974-41,435)	(3,802-10,605)	(1.83-2.40)	(-0.41-0.17)	

AVR and cannot be considered cost effective. With respect to AVR compared to medical management, AVR is more expensive (£10,880) and more effective (0.67 QALYs). The ICER is estimated at £16,276, which is within the range usually considered cost effective in the UK (£20,000-£30,000 per QALY (Rawlins et al., 2009)). Therefore, compared to medical management, AVR is cost effective in treating severe AS amongst high risk operable patients.

6.4.2 Probabilistic Cost Effectiveness Results

The probabilistic cost effectiveness results (Table 6.5) reveal that TAVI is more expensive (£7,117; 24%) and less effective (-0.11; 5%) than AVR, and is dominated by AVR. The incremental cost effectiveness (ICE) plane (Figure 6.5) illustrates the existence and extent of uncertainty surrounding the incremental cost and effect (measured by QALYs) by plotting the additional benefits and costs of the TAVI procedure over AVR. As the ICE plane shows there is uncertainty surrounding the existence of differences in effectiveness of TAVI compared to AVR. There is also uncertainty surrounding the extent of differences in effects and costs of AVR versus TAVI for high risk operable patients owing to uncertainty surrounding the PREs. However, there is little uncertainty about the existence of differences in costs, with TAVI being more expensive than AVR. This is driven by the cost of the TAVI device.

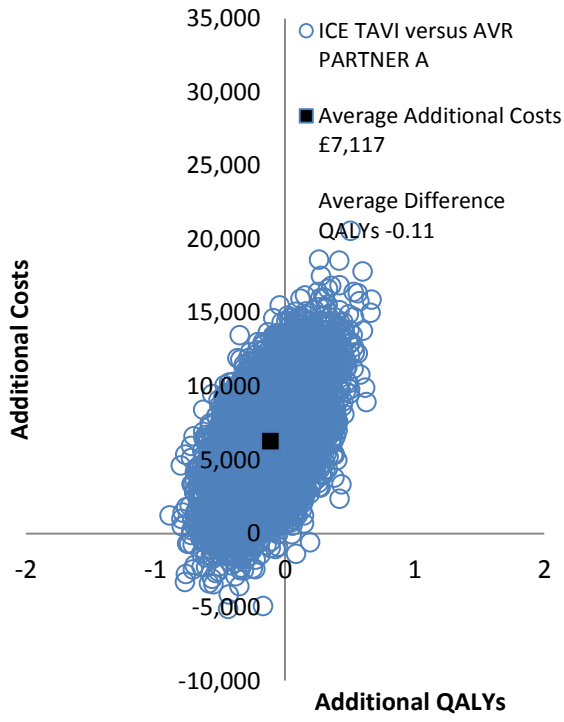
In addition, in comparing AVR with medical management for high risk operable patients the ICER is £16,118 per QALY gained (Table 6.5). This is below the ceiling ratio level usually considered cost effective (£20,000-£30,000 per QALY (Rawlins et al., 2009)). So while AVR is more expensive (£10,684), it generates substantively higher benefits (0.66 QALYs) than medical management, so is considered cost effective compared with medical management. The ICE plane (Figure 6.5b) shows there is some uncertainty with respect to the existence of differences in costs and effectiveness. The majority of co-ordinates are in the north-eastern quadrant, indicating that AVR is more expensive and offers greater health benefit than medical management. There is however considerable uncertainty surrounding the extent of differences in effects and costs (AVR versus medical management) for high risk operable patients. The higher cost is explained by the cost of the AVR device, procedure and in hospital stay and the greater benefit is owing to the mere transient relief

that medical management offers. Meanwhile, the extent of the differences is owing to uncertainty surrounding the PREs following AVR.

The CEAC (Figure 6.6) shows the uncertainty surrounding the cost effectiveness of each procedure by plotting the probability of TAVI, AVR and medical management being cost effective against a range of ceiling ratios. For example, at a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective is 98.7%, the probability that TAVI is cost effective is 0.2% and that medical management is cost effective is 1.1%. The vertical line is the ICER (£16,118) for AVR versus medical management, which is within the range considered cost effective.

Figure 6.5 Incremental Cost Effectiveness Plane: High Risk Operable Patients

a) TAVI versus AVR



b) AVR versus Medical Management

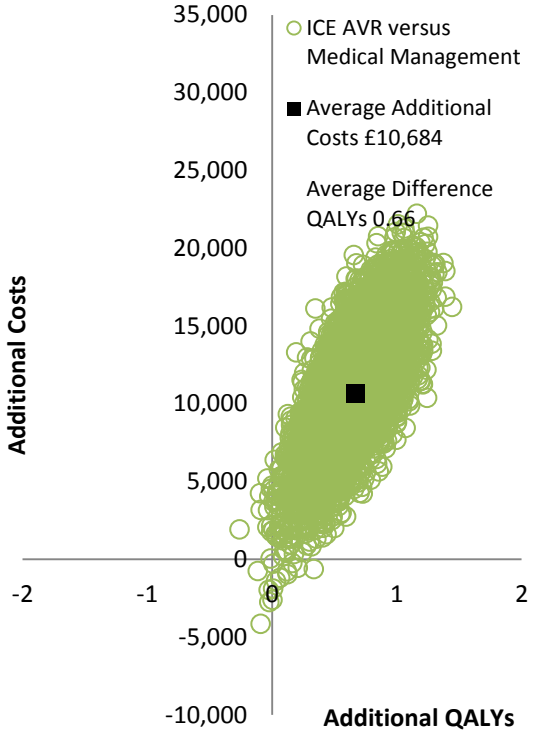
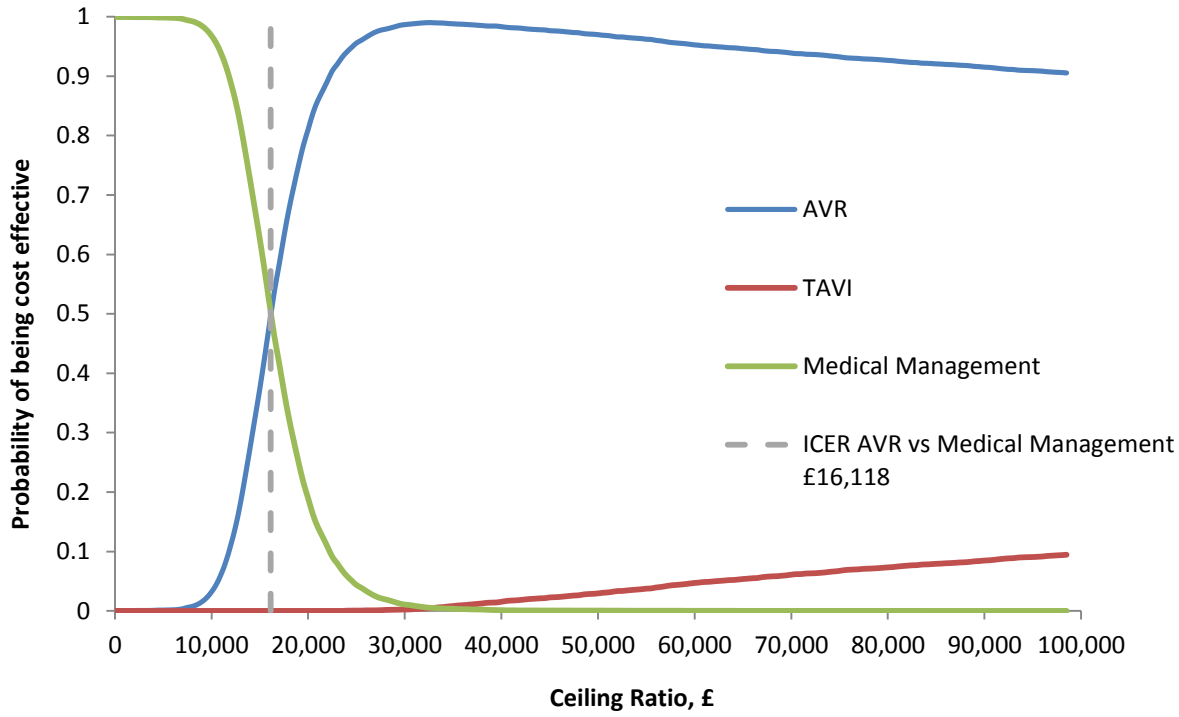


Figure 6.6 Cost Effectiveness Acceptability Curve: High Risk Operable Patients - TAVI versus AVR versus Medical Management



6.5 VALUE OF INFORMATION ANALYSIS – HIGH RISK OPERABLE PATIENTS

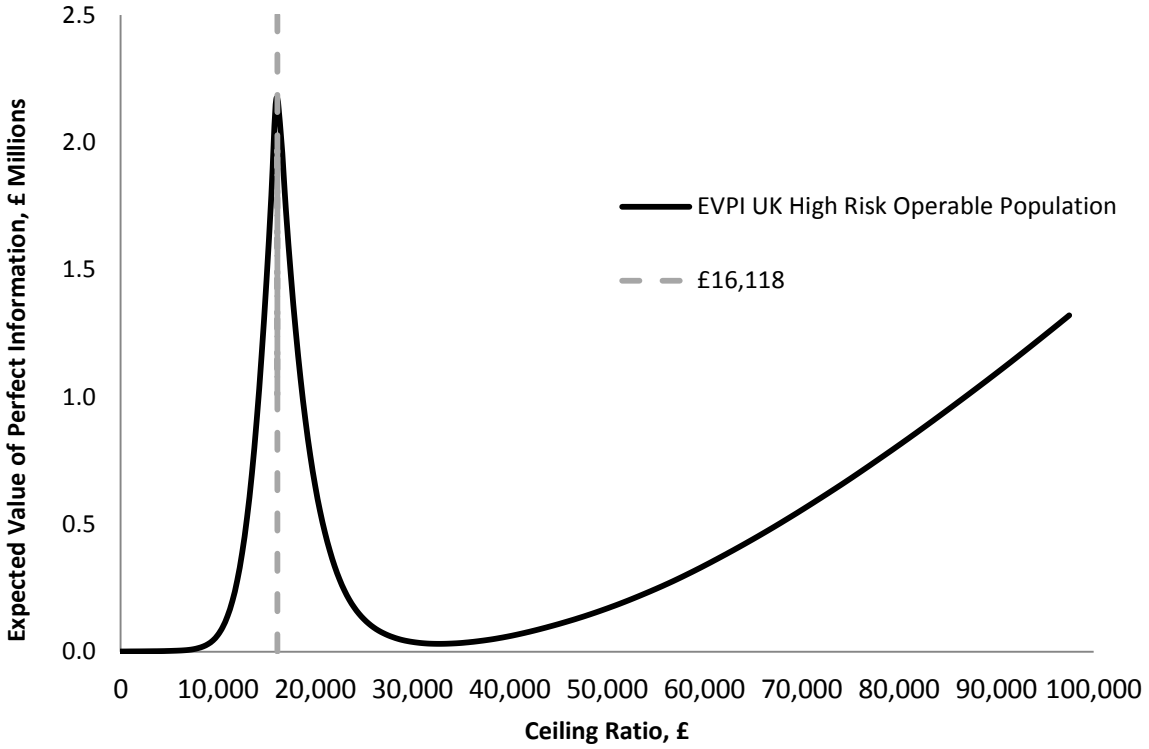
The potential value of undertaking further research is estimated by determining the value of eliminating all the uncertainties within the model (i.e. the EVPI). The EVPI per patient, when deciding between TAVI, AVR and medical management, over the range usually considered cost effective (£20,000 - £30,000 per QALY (Rawlins et al., 2009)) ranges from £17-£290 per high risk operable patient, for one year.

Given the public good characteristics of information the EVPI for the population (pEVPI) can also be estimated. Over a one year lifetime for the technology, the pEVPI for the UK high risk operable population (2,250 (SHTG, 2009)) ranges from £37,948 to £651,917, over the range usually considered cost effective (Figure 6.7). A one year lifetime is chosen to reflect the evolving evidence base and early life cycle stage of the technology, as beyond one year evidence may no longer represent the best evidence available. This is owing to the characteristics of medical devices such as incremental innovations, movements along the

learning curve etc. (as discussed in Section 1.2.1). These estimates provide a maximum value for the return on further research, indicating there is some value in collecting further information on per patient basis here. This modest pEVPI corresponds with the little decision uncertainty present in the cost effectiveness analysis.

As shown on Figure 6.7, the pEVPI reaches a point of inflection at a ceiling ratio equal to the ICER £16,118/QALY. This corresponds to the CEAC (Figure 6.6) where at ceiling ratio of £16,118/QALY, the decision between AVR and medical management is most uncertain. Here the probability that AVR is cost effective is 0.51 and probability that medical management is cost effective is 0.48. Beyond this ceiling ratio, the optimal treatment changes and AVR is more likely to be cost effective compared with medical management.

Figure 6.7 Expected Value of Perfect Information: UK High Risk Operable Population



6.6 COMPARISON OF ORIGINAL MODEL WITH REVISED MODEL INCORPORATING PARTNER (COHORT A) EVIDENCE FOR HIGH RISK OPERABLE PATIENTS

Model and Parameters

Incorporating evidence from PARTNER into the high risk operable model afforded the opportunity to reflect the current understanding of TAVI amongst operable patients. This resulted in some changes to the model such as the inclusion of conversions from TAVI to medical management, repeat TAVI procedures, death from medical management within 30 days and the distinction between major and minor PREs in the Markov model. These revisions reflect current practice and provide the opportunity to incorporate the best evidence available for the transition probabilities in the short and long term such as stroke, PREs and mortality estimates. Previously, early short term experiences with TAVI, expert opinion and experiences with AVR were relied upon to inform the TAVI and medical management arms of the model.

The changes to the model and revised evidence resulted in the following changes to the transition probabilities (See Appendix VII). The original short term model only included conversions from TAVI to AVR. Updating the evidence with PARTNER Cohort A evidence, resulted in a 50% reduction in the probability of converting from TAVI to AVR to 0.03. Incorporating PARTNER Cohort A evidence resulted in the probability of stroke following AVR remaining constant at 0.03, but widened the 95% confidence interval from 0.02-0.05 to 0.01-0.05. While the additional evidence increased the stroke risk associated with TAVI to 0.06. This is a 100% increase on the baseline stroke rate employed in the original model and widens the 95% confidence interval from 0.02-0.05 to 0.03 -0.09. The original model assumed a 15% mortality rate for 30 day all-cause mortality for AVR and TAVI, based on operative mortality risk. However, employing evidence from PARTNER Cohort A reduced this 30 day all-cause mortality rate to 7% for AVR patients and 4% for TAVI patients and allowed for differentiation between technologies.

As outlined above, the PARTNER evidence also revised the PREs. This resulted in a decrease in early major PREs following AVR by 58% to 0.05. This was attributable to the reduction in valve thromboembolism, paravavular leaks, endocarditis and myocardial

infarctions. While the early major PREs following TAVI increased by 33% to 0.16. This was owing to the increase in valve thromboembolism and paravavular leaks. The probability of early minor PREs meanwhile increased for AVR and TAVI patients by 73% and 46% respectively. This was attributable to the increase in major vascular events and major bleeding reported.

Meanwhile, for medically managed patients evidence from PARTNER Cohort B was incorporated into the model to inform the treatment pathway. In the original model expert opinion was relied upon and a 30 day mortality rate of 0.00 was used. In the revised model for high risk operable patients this mortality rate is increased to 0.04. Also, the revised model includes the likelihood of balloon valvuloplasty in the short run (0.83).

In the long-term model the likelihood of late fatal PREs decreased for AVR and TAVI patients by 55% to 0.01 and 45% to 0.12 respectively. While late major PREs decreased by 35% for AVR patient and increased by 5% for TAVI patients to 0.11 and 0.18 respectively. This is explained by the reduction in paravavular leaks and endocarditis for AVR patients and the increase in paravavular leaks for TAVI patients. With respect to the probability of late strokes a differentiation was made between AVR and TAVI where the probabilities applied were 0.02 and 0.03 respectively.

With regard to cost parameters, the revised model included the probability of requiring a balloon valvuloplasty for 83% of medically managed patients in the short term and 50% in the persistent AS/failed valve replacement state in the long run. As described in Section 6.2, PARTNER Cohort A provided information on length of stay for AVR and TAVI patients which were incorporated into the in-hospital costs. There was a 20% increase in length of stay for AVR patients, with a 25% increase in time spent in higher dependence units. For TAVI patients there was a 38% increase in overall length of stay with a 50% increase in time spent in the intensive care unit. These revisions increased the overall cost of in hospital care by 75% for AVR patients and more than doubled the cost for TAVI patients. The costs of long term care per state were also revised which increased the cost of the persistent AS/failed replacement valve state following AVR of 9% and following TAVI by 10%. While the cost of the functioning valve replacement state increased by just 2% for AVR patients and remained constant for TAVI patients at £1,541. These changes in costs were explained by the 47% increase in annual hospitalisations associated with the persistent AS/failed valve for AVR patients to 0.78 and 34% increase for TAVI patients

bringing the probability of hospitalisations to 0.71. While, for AVR patients in the functioning valve replacement state there was a less than 1% decrease in hospitalisations at a probability of 0.07, while there was a 28% decrease in annual hospitalisations for TAVI patients in the functioning valve replacement state (0.05).

Revising the utilities per state resulted in a 2% increase in utility associated with having AS/persistent AS to 0.55. This reflects the difference between high risk operable and inoperable patients. The utility associated with the functioning valve replacement state following AVR decreased in the revised model by 3% to 0.75. While the utility associated with this state for TAVI patients increased by 1% to 0.78. This provided for differentiation between TAVI and AVR technologies.

So incorporating the PARTNER Cohort A evidence into the model provided revised parameters to represent the best currently available data. Specifically, the PARTNER Cohort A evidence provided evidence on early and late PREs following TAVI which had previously been scarce, as well as updating AVR evidence. This generally reduced the probabilities of mortality and major PREs associated with AVR and increased PREs associated with TAVI. Revising the model to incorporate evidence from PARTNER ensured that the current understanding of TAVI and its alternatives were reflected in the model. This provided the opportunity to differentiate between patient types, as previously common transition probabilities, costs and utilities were used for patients regardless of whether they were considered operable or inoperable. It also captured the heterogeneity between treatment types more explicitly than the original model, where relative risk parameters had to be employed owing to scarce data.

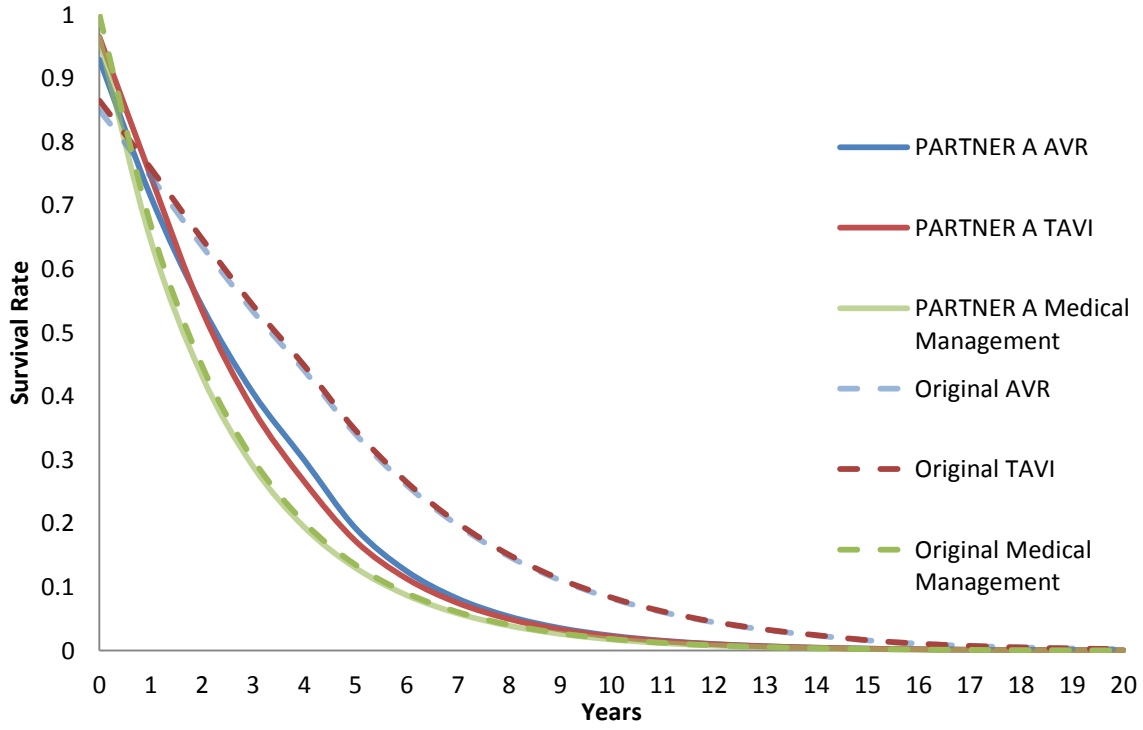
Cost Effectiveness Results

The revised cost effectiveness results demonstrated that AVR extends life and improves quality of life in the longer term for those patients who otherwise would not receive a valve replacement. Meanwhile, TAVI does not extend life or improve quality of life compared with patients who could receive an AVR. The average life years gained in the PARTNER Cohort A model was 3.44 for patients receiving TAVI, 3.49 for patients receiving AVR and 2.96 for patients receiving medical management. This represents a decrease compared to the original model (4.73 following TAVI, 4.65 following AVR and 3.05 following medical management) which is explained by the increase in mortality in year 1 of the

Markov model and higher PREs. The latter resulted in more patients entering the persistent AS/failed valve replacement state which has a higher mortality rate than the functioning valve replacement state. Figure 6.8 presents the survival estimates from each model for comparative purposes, illustrating that the revised model has much steeper survival than the original model. This is explained by the higher one year mortality estimates for each state in the Markov model as informed by the PARTNER evidence. In addition, there is a significant difference between TAVI and AVR, with AVR offering greater survival until year 13. The difference in medical management is marginal in the revised model compared to the original.

In the analysis of the revised model, incorporating PARTNER Cohort A evidence, the costs associated with TAVI were estimated to be just 16% higher than suggested by the original model while the QALYs produced were 28% less. Similarly, the costs associated with AVR based on the revised analysis incorporating the PARTNER trial evidence were higher (11%) than the values produced by the original model, while the QALYs were 23% less than value in the original model. These differences were explained by longer length of stay, the inclusion of repeat TAVI, higher rates of strokes and PREs which increase costs and have a disutility associated with them.

Figure 6.8 Survival Curve Comparison: High Risk Operable Patients



Chapter 4 presented the results of the original cost effectiveness analysis for high risk operable patients using data from published literature. Where the model demonstrated that despite the uncertainties surrounding the incremental costs and benefits there is very little uncertainty regarding the cost effectiveness of TAVI over the range usually considered cost effective (£20,000-£30,000 per QALY) with an ICER of £85,982 QALY. At a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective is 98%, while the probability that TAVI is cost effective is 2% and the probability that medical management is cost effective is 0%.

When the model was revised to include the best data available, including data from PARTNER Cohort A, the results changed but the conclusion with respect to cost effectiveness does not, in fact the potential cost effectiveness of TAVI deteriorates. As TAVI is more expensive and offers fewer benefits than AVR it is dominated. At a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective was 98.7%, while the probability that TAVI is cost effective was 0.2% and the probability that medical management is cost effective was 1.1%. Table 6.6 presents the costs, QALYs and ICERs for both versions of the model.

When comparing AVR with TAVI the different versions of the model report different results, but neither recommends TAVI. As discussed in Section 6.4 and 6.5, there is some uncertainty about the existence and extent of differences in effectiveness and costs. The ICE planes comparing TAVI and AVR produced in the original and updated revised models are compared in Figure 6.9. Here the points in Figure 6.9a represent the additional costs and benefits for the original model, while the points on Figure 6.9b represent additional costs and benefits for the revised, PARTNER Cohort A, model for comparative purposes. Comparing Figure 6.9 a and b it is visible that the uncertainty has shifted. Uncertainty regarding the existence of differences in QALYs still exists but the extent to which it exists has changed.

This is illustrated in the change in the 95% confidence interval surrounding the incremental QALYs. In the original model the incremental QALYs ranged from -0.21 to +0.41 (95% confidence interval was –0.08 to 0.21) this has shifted and now ranges from -0.89 to +0.67 (95% confidence interval is -0.53 to 0.30). There is still little uncertainty regarding the existence of difference in costs, with TAVI being more expensive, confirmed by the range and 95% confidence interval around the incremental costs. In the original model the

incremental costs ranged from £1,705 to £9,756 (95% confidence interval was £3,141 to £7,337). In the revised model with PARTNER Cohort A evidence this changed to -£5,123 to £20,560 (95% confidence interval is £540 to £12,363).

This shift is explained by the replacement strategy employed when updating with PARTNER evidence in the revised analysis. As outlined in Section 6.3.2, to incorporate the best evidence in the model the previous estimates from the literature employed in Chapter 4 were replaced with evidence from PARTNER where available. The results clearly indicate that the original model underestimated the uncertainty in costs and effects for TAVI.

Comparing the CEAC from the revised analysis with PARTNER Cohort A evidence with that produced from the original analysis demonstrates that the decision uncertainty in the original model is reduced, with the probability that TAVI is cost effective compared with AVR and medical management (at a ceiling ratio of £30,000 per QALY) being 2% in the original and 0.2% in revised model. Figure 6.10 presents the two CEACs side by side.

Figure 6.9 Incremental Cost Effectiveness Plane Comparison: High Risk Operable Patients

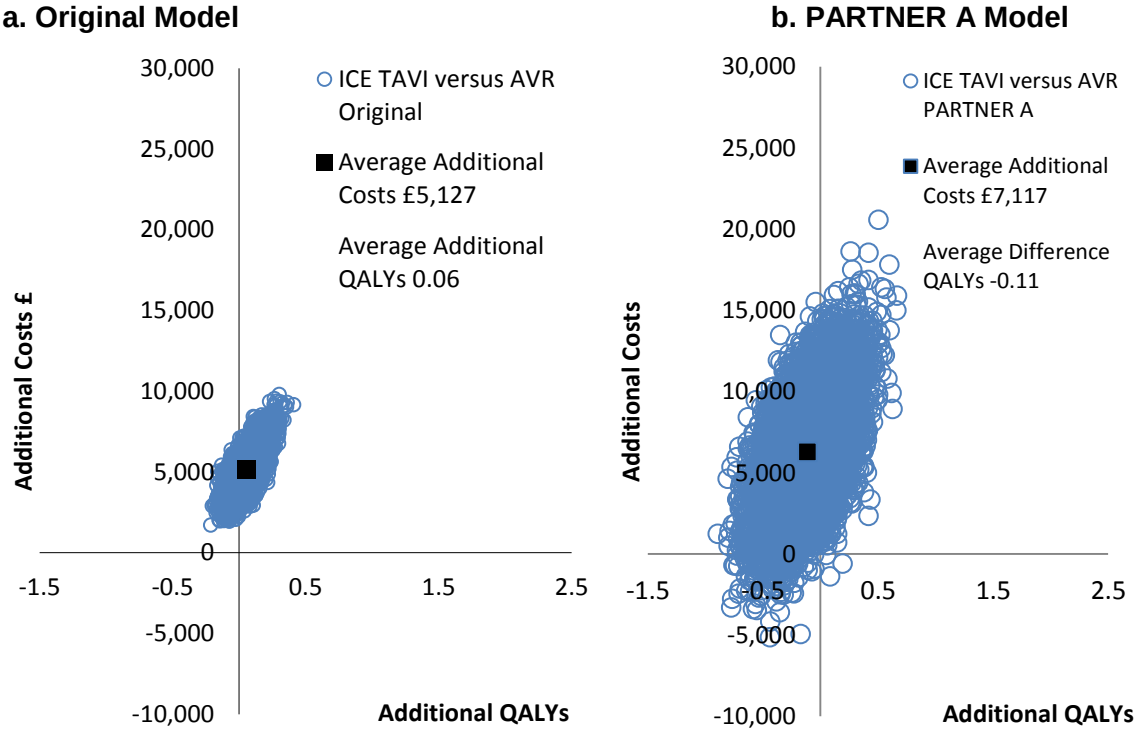
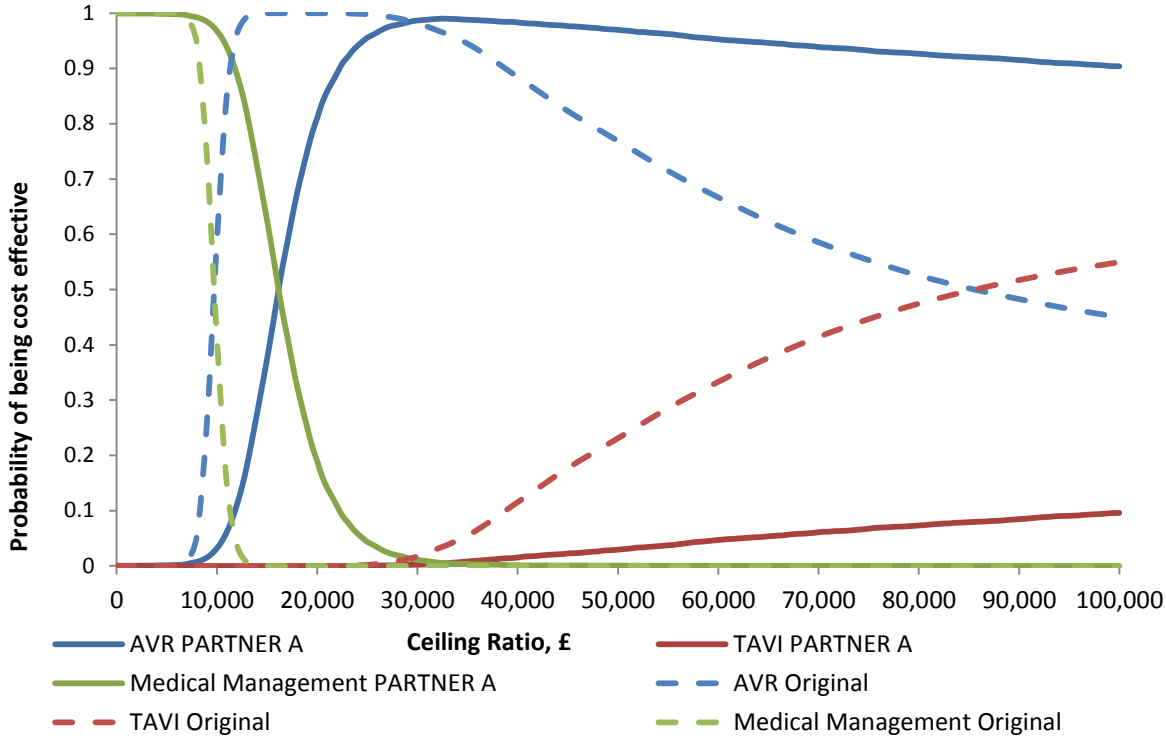


Table 6.6 Cost Effectiveness Results Comparison PARTNER A and Original Model: High Risk Operable Patients

	AVR			TAVI			Medical Management			ICER AVR VS. TAVI £/QALY	ICER AVR VS. MEDICAL MANAGEMENT £/QALY
	Costs (£)	QALYs	LYs	Costs (£)	QALY	LYs	Costs (£)	QALY	LYs		
ORIGINAL*	26,698	2.84	4.65	31,854	2.90	4.73	13,920	1.53	3.05	85,982	9,721
PARTNER A‡	29,695	2.20	3.49	36,813	2.09	3.44	19,012	1.54	2.96	TAVI Dominated	16,118

*Presented in Chapter 4 ‡Presented in Section 6.4

Figure 6.10 Cost Effectiveness Acceptability Curve Comparison: High Risk Operable Patients



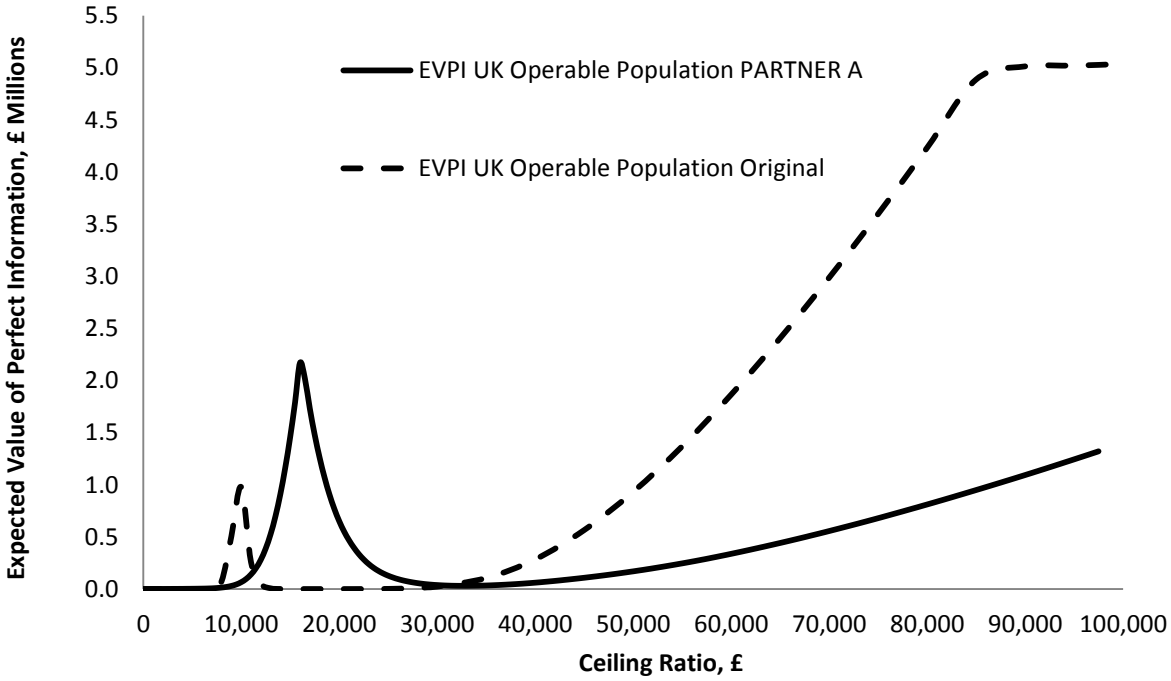
With respect to AVR versus medical management, both the original model and the PARTNER A model found that AVR is more expensive and more effective than medical management. Also, the estimated ICERs from both iterations were less than £20,000/QALY indicating AVR is cost effective compared to medical management for high risk operable patients. As demonstrated on the CEAC (Figure 6.10) there is little uncertainty surrounding this decision, with the probability that AVR being cost effective at a ceiling ratio of £30,000 being approximately 98% in both cases.

Value of Information

The VOI analysis estimated that the pEVPI, in deciding between AVR, TAVI and medical management, using PARTNER evidence over the range usually considered cost-effective ranges from £37,948 to £651,917 for the high risk operable population (2,250 (SHTG, 2009)) in the UK over one year. Figure 6.11 presents the pEVPI for the original model and revised model using PARTNER Cohort A evidence side by side for comparative purposes. As illustrated here, the additional evidence, provided from the PARTNER Cohort A trial, increased decision uncertainty in the region considered cost effective. However, as the

ceiling ratio increases the pEVPI in the revised model is less than the original model. So modest uncertainty remains and there is little potential value in collecting further evidence on the costs and effects of TAVI compared to medical management given the PARTNER evidence.

Figure 6.11 Expected Value of Perfect Information Comparison: High Risk Operable Population



6.7 COMPARISON WITH OTHER COST EFFECTIVENESS ANALYSES

As discussed in the case of high risk inoperable patients in Chapter 5, TAVI is a growing area with significant vested interests from patients, clinicians, decision makers and manufacturers. It is unsurprising then that others have also examined the cost effectiveness analysis of TAVI. While the cost effectiveness of TAVI for inoperable patients has received considerable attention to date, the cost effectiveness of TAVI for operable patients has got somewhat less attention. This may be attributable to trend in evidence

generation for novel medical devices, whereby attention is focused on the higher risk patients where most benefit is to be gained. It also may be owing to the discouraging results from the PARTNER trial which found no significant improvement between TAVI and AVR patients.

The economic evaluation of TAVI performed and published by the Belgian Health Care Knowledge Centre (Neyt et al., 2011) (discussed in Chapter 5) also included an analysis of TAVI compared to AVR. Similar to the analysis in this thesis, Neyt et al. (2011) found that for high risk operable patients the additional benefits of TAVI were outweighed by the additional costs compared to AVR. This study employed a mix of evidence from PARTNER Cohort A and Belgian resource data and estimated an ICER of €749,416/QALY (equivalent to £654,690 on date of publication[12] (OANDA, 2011)) for the baseline model. This decreased to €455,461/QALY when the cost of the TAVI device is reduced by €10,000 (£8,736). A second scenario analysis is used to assess the impact of setting the incremental benefit between AVR and TAVI to 0.10. In this scenario, the ICER decreases to approximately €205,000/QALY. Thus, even in the sensitivity analysis performed TAVI remains more expensive and only marginally more effective than AVR, so TAVI cannot be considered cost effective.

The unpublished NIHR HTA study, funded by the NHS in the UK (referred to in Chapter 5), also included a cost effectiveness analysis of high risk operable patients. Preliminary (unpublished) results demonstrate that they employed PARTNER Cohort B data and survival analysis techniques to estimate the cost effectiveness of TAVI compared to AVR for operable patients (PARTNER Cohort A evidence was not available at the time of analysis) (Orlando, 2011). The report found that given the higher cost and fewer benefits of TAVI compared to AVR, that TAVI was dominated by AVR. This result is similar to that found by this study. However, the analysis conducted in this study employs more recent and suitable evidence and also conducted a VOI.

[12] Converted as per Euro – GBP exchange rate on 22nd September 2011 (date of publication) (OANDA, 2011)

6.8 DISCUSSION

Transcatheter Aortic Valve Implantation (TAVI) offers a novel treatment option for patients suffering from severe Aortic Stenosis (AS). Publication of the PARTNER trial, with 12 month follow-up, offered the eagerly awaited one year outcomes for operable patients. Previously, TAVI had not been demonstrated to be appropriate for high risk operable patients, attention had focused on inoperable patients where most was to be gained as these patients were currently receiving little treatment benefit. Here, employing the DAM in an iterative manner, the cost effectiveness of TAVI for operable patients is re-assessed. Whereby, PARTNER data, reflecting the best available data, is incorporated into the model to investigate the suitability of TAVI for high risk operable patients.

Incorporating the PARTNER Cohort A results into the TAVI model afforded the opportunity to generate revised costs and effects for TAVI compared to AVR and medical management. The analysis revealed that TAVI was dominated by AVR when treating high risk operable patients, as it was more expensive and offered fewer benefits than AVR. The conclusion reached from these results is similar to that of the original model for the same group where it was also found that TAVI could not be considered cost effective compared to AVR. In the analysis of the revised model, the costs associated with TAVI were estimated to be slightly higher than suggested by the original model, while the QALYs produced were marginally less than those of the original model. Similarly, the costs associated with AVR based on the revised analysis incorporating the PARTNER Cohort A trial evidence were higher than the values produced by the original model and the QALYs were less. Comparing the results of the original model with the revised model suggests that the original model overstated the mortality associated with TAVI. In addition, the probability of PREs (including major stroke) identified in the PARTNER Cohort A evidence was greater than that used in the original model. The VOI analysis for the revised model, with PARTNER Cohort A evidence, suggests there is little value in collecting further evidence for high risk operable patients given current information.

Despite the shortcomings of the data, the DAM employed offers an insight into the longer term benefits of TAVI amongst high risk operable patients by extrapolating the data for 20 years. Such results offer decision makers an indication of the potential for further evidence in making coverage and access decisions regarding TAVI for severe stenosis patients deemed operable as the evidence base evolves. While using this additional evidence TAVI

remains not cost effective for high risk operable patients, some commentators, such as Schaff (2011), have argued this is owing to the early devices used and early experience of the centres studied. It is proposed that if further evidence were collected it may demonstrate better stroke rates and incidence of PREs which would improve health outcomes and subsequently improve the cost effectiveness of TAVI compared to AVR.

As demonstrated throughout this thesis, TAVI is a promising technology for patients with severe AS. While there appears to be two distinctive markets for the technology, operable and inoperable patients, there may be opportunities to exchange information between models/patient groups. For example, evidence from PARTNER B was exchangeable across the patient types for updating the medical management treatment in the model.

Owing to the characteristics and life stage of TAVI its' evidence base is still evolving. Since the release of PARTNER evidence, longer term evidence from external sources for example, PARTNER, the registries employed in Chapter 4 and the UK TAVI registry are beginning to emerge in the literature. This information is incorporated into model for inoperable and operable patients in the next chapter.

CHAPTER 7 WHERE NOW WITH TAVI?

7.1 INTRODUCTION

As indicated previously, Transcatheter Aortic Valve Implantation (TAVI) is a novel medical device technology with an evolving evidence base. This presents a challenge in estimating cost effectiveness in a demanding health care environment, owing to the complex characteristics of medical devices, where resources are scarce and coverage decisions are required alongside the generation of evidence. Consequently, an iterative framework for economic evaluations is advocated whereby the cost effectiveness of the technology is reviewed following developments in the evidence base. This ensures that advances in the evidence base, owing to incremental innovations, movements along the learning curve etc., are incorporated into decision making to reflect current understanding of the technology and disease.

Since the publication of the early results from the first clinical trial (PARTNER), other European Registries have released evidence on longer term TAVI outcomes amongst inoperable patients. Similarly, longer-term results for operable patients have been released from the PARTNER trial and short term results from the UK TAVI Registry. This provides the opportunity to re-assess the cost effectiveness of TAVI for each patient group and to ascertain if there is any value in collecting further evidence, given the evidence available. This ensures that decisions regarding TAVI can be based on the best available evidence. The decision analytical model (DAM) employed in Chapter 4, and updated in Chapters 5 and 6, is employed again in this chapter to re-consider the cost effectiveness of TAVI for both inoperable and operable patients in light of the evolving evidence (i.e. the adoption and priority setting decisions).

7.2 EVOLVING EVIDENCE FOR INOPERABLE TAVI PATIENTS

Inoperable patients are those for whom AVR is not considered suitable, as such only TAVI or medical management are viable treatment options. Since publication of the PARTNER Cohort B results (presented in Chapter 5) longer-term TAVI results for inoperable patients have been published from European TAVI Registries (Walther et al., 2012, Bleiziffer et al., 2012) and Cohort B of the PARTNER trial (Makkar et al., 2012). These results provide evidence on the longer term procedure related events (PREs) (i.e. beyond year one) as well as evidence on mortality rates for years two and three for inoperable patients.

Specifically, Bleiziffer et al. (2012) reported evidence from 580 patients, who received TAVI at the German Heart Centre in Munich, recorded in a registry which began in 2007. Follow up outcomes were available for 227 inoperable patients. Here it was reported that 30 day survival was 88.5%, one year survival was 74.5% and two year survival was 64.4%. Meanwhile, the probability of paravavular leaks remained constant between years one and two at 0.08 and the probability of stroke in year two was estimated at 0.04 which was higher than year 1 (0.01). The probability of bleeding also increased between years one and two (0.19 versus 0.26). This increased risk of bleeding was highlighted in Bleiziffer et al. (2012) and the authors suggest that the results indicate bleedings may be a persistent problem following the TAVI procedure.

Makkar et al. (2012) reported two year follow up outcomes from the 21 centres in the PARTNER Trial (Cohort B). All-cause mortality at the end of year two was 43.3% for TAVI patients and 65% for standard therapy (i.e. medical management) patients. The overall risk of stroke following TAVI between years 1 and 2 was found to be 0.03, while risk of bleeding was 0.07. Makkar et al. (2012) also provided evidence on the likelihood of patients requiring a late balloon valvuloplasty following TAVI (2%) and medical management (3%).

Walther et al. (2012) reported results for 299 inoperable patients collected between February 2006 and January 2010 from the European Registries. Overall, survival amongst these patients was 91% at 30 days; 73% at one year; 68% at year two and 58% at year three. It was reported that 10.7% of patients had one or more perioperative complications. However, this data was presented at an aggregate level and the type of events and number

of each event occurring could not be extracted from the evidence presented. Thus, Walther et al. (2012) informs mortality estimates only in this re-analysis.

These longer-term outcomes, extracted from Bleiziffer et al. (2012), Makkar et al. (2012) and Walther et al. (2012) are reported in Table 7.1. Here the number of events occurring (α) the total number at risk (n) and the number of events that did not occur ($n-\alpha=\beta$) are reported. To estimate the probability of an event occurring, the number of events occurring is divided by the number at risk (α/n). For example, Bleiziffer et al. (2012) report four incidences of stroke in year two. A total of 89 patients could have had a stroke in this time period, which gives a probability of 0.045 (4/89).

7.2.1 Incorporating Longer-Term Results into the Decision Analytical Model for High Risk Inoperable Patients

The longer-term results, on TAVI reported in Makkar et al. (2012), Walther et al. (2012) and Bleiziffer et al. (2012), provide evidence on outcomes for TAVI patients beyond one year. This evidence was not previously available so assumptions were employed in the model to extrapolate out for the remaining 19 years of the model. The additional evidence therefore can be employed to update the evidence in the PARTNER B model. An "updating" strategy is employed here, as opposed to the "replacement" strategy adopted in Chapter 5. Whereby, the evidence from Makkar et al. (2012), Walther et al. (2012) and Bleiziffer et al. (2012) are combined with the PARTNER B evidence. This strategy is considered optimal as Makkar et al. (2012), Walther et al. (2012) and Bleiziffer et al. (2012) provide longer term data which updates the transition probabilities. Evidence prior to PARTNER was immature and based on very early experiences with the device, as such the evidence provided by PARTNER was the best available at the time and replaced previous evidence. Here employing early PARTNER Cohort B (from (Leon et al., 2010)) and updating with Makkar et al. (2012), Walther et al. (2012) and Bleiziffer et al. (2012) ensures the best data available at the time is employed in the model. This synthesis of data, thus not relying on a single trial, is in line with the recommendations on iterative frameworks for economic evaluations and avoids partial or biased assessments (Sculpher et al., 2006).

Table 7.1 Mortality and Procedural Related Event Evidence - Makkar et al (2012), Walther et al. (2012) and Bleiziffer et al. (2012)

Paper - Parameter	α	β	n	Prob
Bleiziffer et al (2012)				
Mortality				
30 Day All-Cause Mortality	27	200	227	0.12
1 Year All-Cause Mortality	59	168	227	0.26
2 Year All-Cause Mortality	82	145	227	0.36
Procedure Related Events				
30 Day Stroke	10	193	203	0.05
30 Day Major Paravavular Leak	22	181	203	0.11
30 Day Major Bleeding	20	183	203	0.10
1 Year Major Paravavular Leak	9	107	116	0.08
1 Year Stroke	1	115	116	0.01
1 Year Major Bleeding	22	94	116	0.19
2 Year Major Paravavular Leak	7	82	89	0.08
2 Year Stroke	4	85	89	0.04
2 Year Major Bleeding	23	66	89	0.26
Makkar et al (2012)				
Mortality				
2 Year All-Cause Mortality – TAVI	73	95	168	0.43
2 Year All-Cause Mortality – Medical Management	117	62	179	0.65
Late Procedures				
Late Balloon Valvuloplasty Year 1 – TAVI	2	90	92	0.02
Late Balloon Valvuloplasty Year 2 – TAVI	2	90	92	0.02
Late Balloon Valvuloplasty Year 2 – Medical Management	2	60	62	0.03
Procedure Related Events – TAVI				
2 Year Stroke	3	89	92	0.03
2 Year Myocardial Infraction	1	91	92	0.01
2 Year Endocarditis	1	91	92	0.01
2 Year Major Bleeding	6	86	92	0.07
2 Year Pacemaker	2	90	92	0.02
2 Year Rehospitalisation	10	82	92	0.11
Walther et al (2012)				
Mortality				
30 Day All-Cause Mortality	24	243	267	0.09
1 Year All-Cause Mortality	72	195	267	0.27
2 Year All-Cause Mortality	85	182	267	0.32

n indicates the number of patients at risk; α indicates the number of events occurring; β the number of events that did not occur (n- α); probability is α /n. Note α and n were extracted from the literature and β and the probability of the event occurring were calculated by the author.

Box 7.1 provides an example of how PARTNER Cohort B evidence was updated using the aforementioned late results from the trial and European Registries. The pooling process employed here is equivalent to a fixed effects meta-analysis, involving the assumption that information is exchangeable and the baseline parameters being measured are identical. PARTNER Cohort B reported 30 incidences of early major bleeding; this corresponds with $\alpha_{\text{PARTNER B}}$ i.e. the number of events reported occurring in PARTNER Cohort B. There were 168 in the sample (denoted $n_{\text{PARTNER B}}$). Bleiziffer et al. (2012) reported 20 incidences of major bleeding, which is $\alpha_{\text{Bleiziffer}}$. The number of events which could have occurred was 203 ($n_{\text{Bleiziffer}}$). To update the transition probability the α ($\alpha_{\text{PARTNER B}}$ and $\alpha_{\text{Bleiziffer}}$) and n ($n_{\text{PARTNER B}}$ and $n_{\text{Bleiziffer}}$) are summed to estimate the revised probability. This is calculated as follows: $\alpha = 30 + 20 = 50$; $n = 168+203 = 371$; $\alpha/n = 50/371 = 0.13$. This process is repeated for late major bleeding, major paravavular leaks and strokes in the short and long term (1 year and 2 year) and incorporates evidence from Makkar et al. (2012) for procedure related events (PREs) beyond one year (presented in Table 7.1). These PREs beyond one year updated with evidence from Makkar et al. (2012) were endocarditis, stroke, myocardial infarction, repeat hospitalisations, major bleeding and new pacemaker.

Box 7.1 Example of Updating PARTNER A Evidence

Early Major Bleeding TAVI	**α**	**β**	**n**	**Probability**
PARTNER B	30	138	168	0.18
Bleiziffer	20	183	203	0.10
PARTNER B + Bleiziffer	50	321	371	0.13

The revised probabilities are shown in Table 7.2. Inclusion of evidence from Bleiziffer et al. (2012) resulted in the probability of stroke within 30 days remaining constant at 0.05. Major PREs after 30 days (early) following TAVI decreased from 0.18 to 0.16. This was owing to the reduction in major paravavular leaks from 0.14 to 0.12 following updating with Bleiziffer et al. (2012). Early minor PREs following TAVI also decreased when the transition probabilities were updated from 0.58 to 0.54. This was owing to the reduction in major bleeding (0.04) following updating. The transition probabilities in the first cycle of

the Markov Model were also revised as a result of evidence from Bleiziffer et al. (2012). The probability of fatal PREs in year one decreased from 0.58 to 0.54. The likelihood of major PREs in year one also decreased from 0.20 to 0.16. This was owing to the decrease in major paravavular leaks (0.13 to 0.10). However, late minor PREs within one year increased from 0.19 to 0.24, this was owing to the increase in major bleeding (0.08 to 0.14).

In previous iterations of the model, the probability of late PREs employed for cycle one of the Markov model were applied for the duration of the model. Publication of longer-term results in Bleiziffer et al. (2012) and Makkar et al. (2012), afforded the opportunity to update late PREs beyond one year. This resulted in an increase in major PREs following TAVI from 0.20 to 0.21 for year two onwards. This increase was owing to a rise in the number of strokes observed. Similarly, the likelihood of minor PREs beyond one year increased from 0.19 to 0.29. This was owing to the increase in major bleeding (0.08 to 0.19).

Thus, the inclusion of additional data for TAVI decreased the likelihood of PREs in the short term component of the model (first 30 days) and decreased the likelihood of PREs in the first cycle of the Markov model. The additional data on longer term outcomes increased the likelihood of PREs following TAVI after year one. The main contributors to these increases are increased strokes and bleedings. According to Walther et al. (2012) and Bleiziffer et al. (2012), while this occurs to a minority of patients it appears to be a persistent problem following the TAVI procedure.

As per previous iterations of the model, the uncertainty surrounding each of the parameters was incorporated into the model through the assignment of probability distributions. The PARTNER B evidence combined with Makkar et al. (2012) and Bleiziffer et al. (2012) results, identified the total number of patients and the number for whom events occurred; this information was used to specify a beta distribution for each probability (Table 7.2). All of the transition probabilities provided on Table 7.2 represent absolute risk for each arm of the model, TAVI and medical management.

Table 7.2 Revised Transition Probabilities

	Dist	Prob (95% CI)	α	β	n
All-Cause Mortality 30 Days TAVI	Beta	**0.09 (0.07-0.11)**	59	603	662
Probability Of Major Stroke TAVI*	Beta	**0.05 (0.03-0.09)**	19	352	371
Early Major PRE TAVI					
Valve Thromboembolism	beta	0.01	1	167	168
Major Paravavular Leak*	beta	0.12	45	326	371
Endocarditis	beta	0.00	0	168	168
Cardiac Tamponade	beta	0.03	6	162	168
Myocardial Infarction	beta	0.00	0	168	168
		0.16 (0.12-0.21)			
Early Minor PRE TAVI					
Access Site Events	beta	0.04	7	161	168
Vascular Events	beta	0.15	26	142	168
Pacemaker Implantation	beta	0.04	6	162	168
Major Vascular Event	beta	0.17	29	139	168
Major Bleeding*	beta	0.14	50	321	371
		0.54 (0.43-0.63)			
Late Fatal PREs TAVI Year 1*	beta	**0.22 (0.17-0.27)**	51	183	234
Late Major PRE TAVI Year 1					
Valve Thromboembolism	beta	0.00	0	118	118
Major Paravavular Leak*	beta	0.10	24	210	234
Endocarditis	beta	0.02	2	116	118
Cardiac Tamponade	beta	0.01	1	117	118
Stroke	beta	0.03	6	228	234
Myocardial Infarction	beta	0.01	1	117	118
		0.16 (0.11-0.22)			
Late Minor PREs TAVI Year 1					
Repeat Hospitalisations	beta	0.06	7	112	118
Major Vascular Complications	beta	0.01	1	117	118
Minor Vascular Complications	beta	0.02	2	116	118
Major Bleeding *	beta	0.14	32	202	234
New Pacemaker	beta	0.02	2	116	118
		0.24 (0.17-0.31)			
Late Major PRE TAVI Year 2					
Valve Thromboembolism	beta	0.00	0	84	84
Major Paravavular Leak*	beta	0.13	22	151	173
Endocarditis^	beta	0.02	3	173	176
Cardiac Tamponade	beta	0.01	1	83	84
Stroke *^	beta	0.05	12	253	265
Myocardial Infarction^	beta	0.01	2	174	176

Table 7.2 Continued

	Dist	Prob (95% CI)	α	β	n
		0.21 (0.15-0.28)			
Late Minor PREs TAVI Year 2					
Repeat Hospitalisations ^	beta	0.10	17	159	176
Major Vascular Complications	beta	0.01	1	83	84
Minor Vascular Complications	beta	0.02	2	82	84
Major Bleeding *^	beta	0.15	39	226	265
New Pacemaker^	beta	0.02	4	172	176
		0.29 (0.23-0.38)			

* Indicates where updated by Bleiziffer et al (2012) ^ Indicates where updated by Makkar et al. (2012) The remaining values are maintained as per Table 5.1-5.2 in Chapter 5.

Cost Parameters

For the cost analysis, the values of the following resources were estimated: TAVI device; TAVI and medical management procedures; length of stay; hospitalisations and other costs incurred with PREs. Neither Makkar et al. (2012), Bleiziffer et al. (2012) nor Walther et al. (2012) provided additional information on the cost of the TAVI procedure or length of stay, so the estimates from Chapter 5 were maintained. The state costs were also maintained (cost for the functioning valve replacement state of £1,578 and £8,163 for the persistent AS/failed valve replacement state).

With respect to the cost of PRES, these are estimated as previously with a weight assigned to each event and the unit cost. The weights, which are a proportion of each event occurring, are updated with the revised probabilities. The costs of early minor and major PREs were £319 and £651 respectively. The cost of late major and minor PREs in year one were £1,306 and £2,641 respectively. The cost of late major and minor PREs for year two onwards were £1,551 and £3,143 respectively. Normal distributions were applied to cost of treating PREs as per previous versions of the model.

Quality of Life Parameters

As per the original model presented in Chapter 4, QALYs were also derived for each health state adjusting for the condition, the procedure and PREs. As with the costs, the

impact on utility associated with the PREs were adjusted to account for the revised probabilities of events occurring. The utility of minor and major early PREs were 0.03 and 0.04 respectively. The utility of minor and major PREs after one year were 0.02 and 0.04. And the utility of minor and major PREs for two years and beyond were 0.02 and 0.04.

Makkar et al. (2012) provided updated NYHA classifications following TAVI and medical management in year two. This provided updated utilities for the functioning valve replacement and failed valve replacement states in year two and beyond, for TAVI and medical management respectively. The expected utility following a TAVI procedure was 0.75 and following medical management was 0.65 in year two (Table 7.3). Makkar et al (2012) did not provide sufficient detail to differentiate between TAVI patients in the functioning and persistent AS/failed valve replacement states as per the Markov Model developed for this model, so 0.75 was applied to patients in both states from year 2 onwards, (previously, this was 0.63). However, utility for patients in the persistent AS/failed valve replacement states is reduced by a utility hit associated with major PREs. Normal distributions were applied to the utility hits associated with the PREs, while a Dirichlet distribution was applied to the proportion of patients per NYHA class, used to estimate the utility per state.

Table 7.3 Utilities by NYHA Class For TAVI Decision Analytical Model Updated with Longer Term Outcomes

NYHA Class	Distribution	Utility*	Proportion¶	Utility (95% CI)
Utility Functioning Valve Replacement TAVI Year 2^				
I	Dirichlet	0.82	0.45	0.37
II	Dirichlet	0.72	0.43	0.31
III	Dirichlet	0.59	0.10	0.06
IV	Dirichlet	0.51	0.02	0.01
			1.00	**0.75 (0.73-0.76)**
Utility of Failed Valve Replacement Medical Management Year 2				
I	Dirichlet	0.82	0.10	0.08
II	Dirichlet	0.72	0.32	0.23
III	Dirichlet	0.59	0.48	0.28
IV	Dirichlet	0.51	0.10	0.05
			1.00	**0.65 (0.62-0.67)**

*(Maliwa et al., 2003) ¶(Makkar et al., 2012) ^ A common utility is applied for TAVI patients in functioning and persistent AS/Failed valve replacement states in year two onwards as it was not possible to ascertain the proportion of patients per state in the Markov Model developed here. However these utilities are differentiated by the utility reduction for each PRE in the Persistent AS/failed valve replacement state.

7.2.2 Analysis – Inoperable Patients

A similar analysis to those employed in Chapters 4 and 5 was undertaken here for inoperable patients, using the UK NHS perspective. A Monte Carlo simulation with 10,000 iterations was used to propagate the uncertainty in the individual model parameters, reflected by the probability distributions assigned, through the model. This produces a distribution of expected costs and expected QALYs associated with each procedure. The mean values of these distributions are used to calculate the incremental cost effectiveness ratio (ICER) in terms of the expected incremental costs associated with TAVI compared to medical management per incremental QALY gained. The uncertainty associated with the incremental costs and incremental QALYs are presented through incremental cost effectiveness (ICE) planes. The uncertainty associated with the cost effectiveness of TAVI compared to medical management is presented in terms of a cost effectiveness acceptability curve (CEAC). These facilitate the re-assessment of the adoption decision. Following this, the research priority setting decision is re-considered using a Bayesian VOI analysis is performed to estimate expected value of perfect information (EVPI).

7.3 COST EFFECTIVENESS RE- ANALYSIS INOPERABLE PATIENTS

The cost effectiveness of TAVI versus medical management was estimated for inoperable patients based on a mix of evidence from the PARTNER trial, Cohort B early (Leon et al., 2010) and late (Makkar et al., 2012) as well as European Registries (Bleiziffer et al., 2012, Walther et al., 2012). The results indicate a 40% reduction in absolute risk in terms of all-cause mortality at the end of year one between TAVI and medical management, which decreases to 23% at the end of year two. These mortality estimates for years one, two and three, correspond to observed mortality from the PARTNER trial (Makkar et al., 2012) and European Registry (Bleiziffer et al., 2012, Walther et al., 2012). This is illustrated by the survival estimates on Figure 7.1. TAVI also offers significantly greater quality of life benefits compared with medical management as per the PARTNER results, with an 18% increase in quality of life per person compared to medical management in year two. The differences in quality of life for TAVI compared with medical management are shown on Figure 7.2.

Figure 7.1 Survival Estimates for TAVI and Medical Management

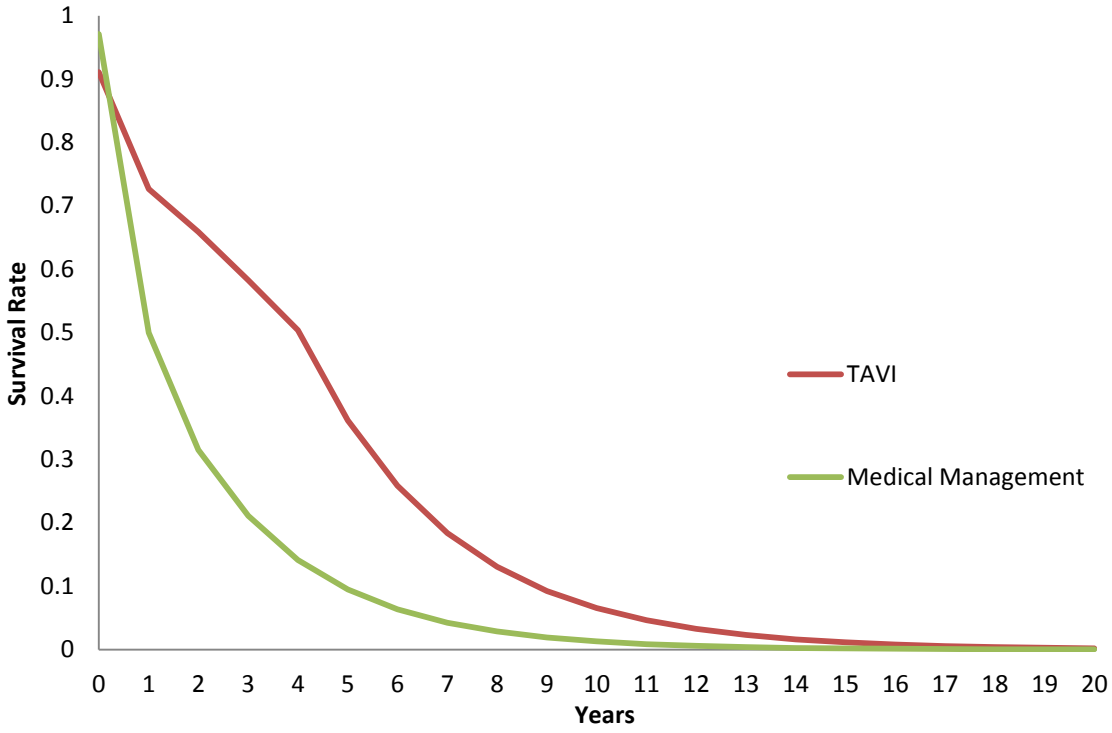
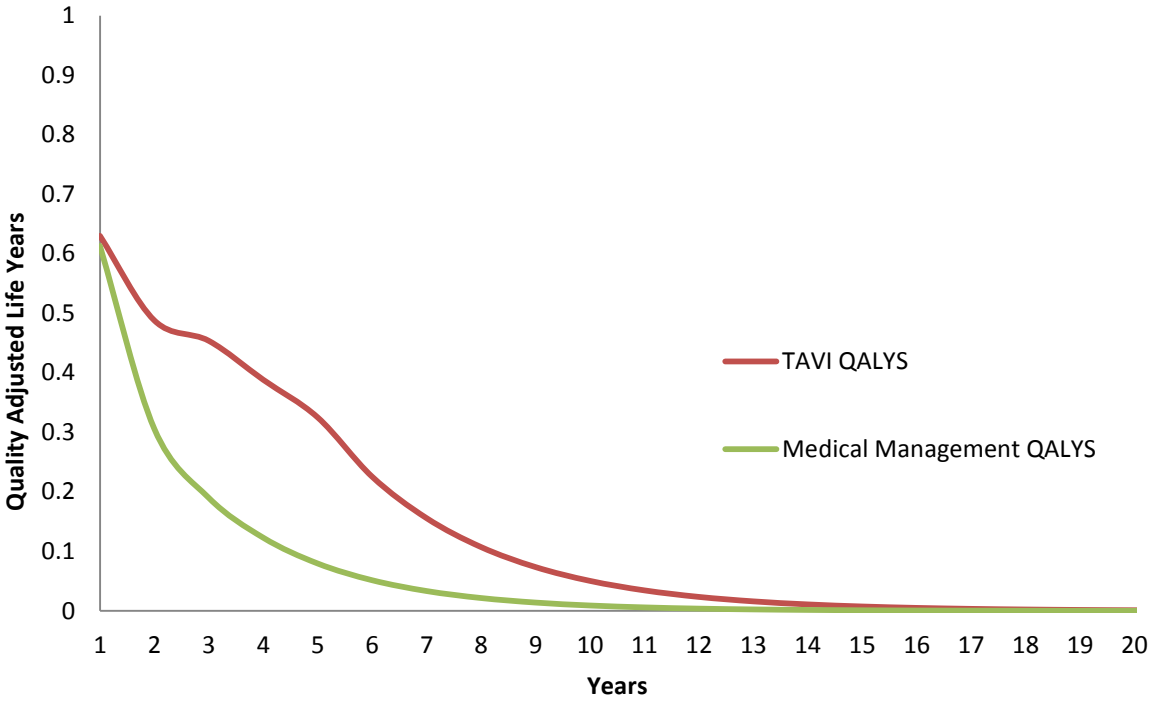


Figure 7.2 Quality of Life Estimates for TAVI and Medical Management



7.3.1 Deterministic Cost Effectiveness Results

The deterministic cost effectiveness results (Table 7.4) were estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. The results illustrate that for inoperable patients TAVI is both more costly (£29,797) and more effective (1.55 QALYS) than medical management. The ICER is estimated as £19,259 per QALY gained, which is below the level usually considered cost effective (£20,000-£30,000 per QALY (Rawlins et al., 2009)).

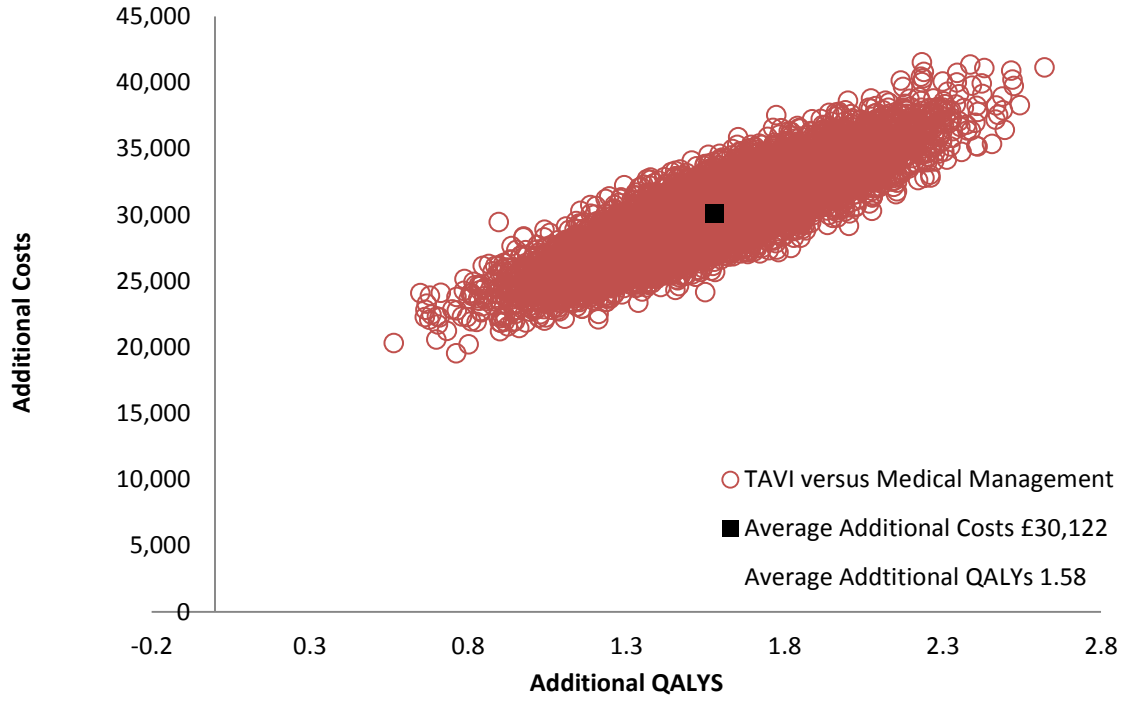
7.3.2 Probabilistic Cost Effectiveness Results

A Monte Carlo simulation with 10,000 iterations was run to propagate the uncertainty represented by the assigned probability distributions into the model. This produced a distribution of expected costs and QALYs for TAVI and medical management. The mean values of these distributions are used to calculate the incremental cost effectiveness ratio (ICER). The mean cost and QALY are presented in Table 7.4. Here it is illustrated that for inoperable patients TAVI is both more costly (£30,121) and more effective (1.58 QALYs) than medical management. The incremental costs from the Monte Carlo simulation ranged from £19,532 to £41,521. While the incremental benefit ranged from 0.56 to 2.62 QALYs (95% confidence intervals reported in Table 7.4). The probabilistic ICER is estimated as £19,078 per QALY gained, which is below the level usually considered cost effective (£20,000-£30,000 per QALY (Rawlins et al., 2009)). So given the developed evidence base TAVI can now be considered cost effective compared to medical management for inoperable patients.

The incremental cost effectiveness (ICE) plane (Figure 7.3) illustrates the existence and extent of the uncertainty surrounding the incremental effect and incremental cost (these are the red points plotted on Figure 7.3). In this case, there is no uncertainty surrounding the existence of benefit for TAVI (over medical management) with TAVI being more effective. There is however, some uncertainty surrounding the extent of the differences in effects. Furthermore, there is no uncertainty with respect to the existence of differences in costs, with TAVI being more expensive than medical management: this is driven by the cost of the TAVI device. However, there is some uncertainty surrounding the extent of the

differences in cost. This (and the extent of uncertainty in differences in effects) is potentially driven by uncertainties surrounding the probability of PREs.

Figure 7.3 Incremental Cost Effectiveness Plane: Inoperable Patients – TAVI versus Medical Management



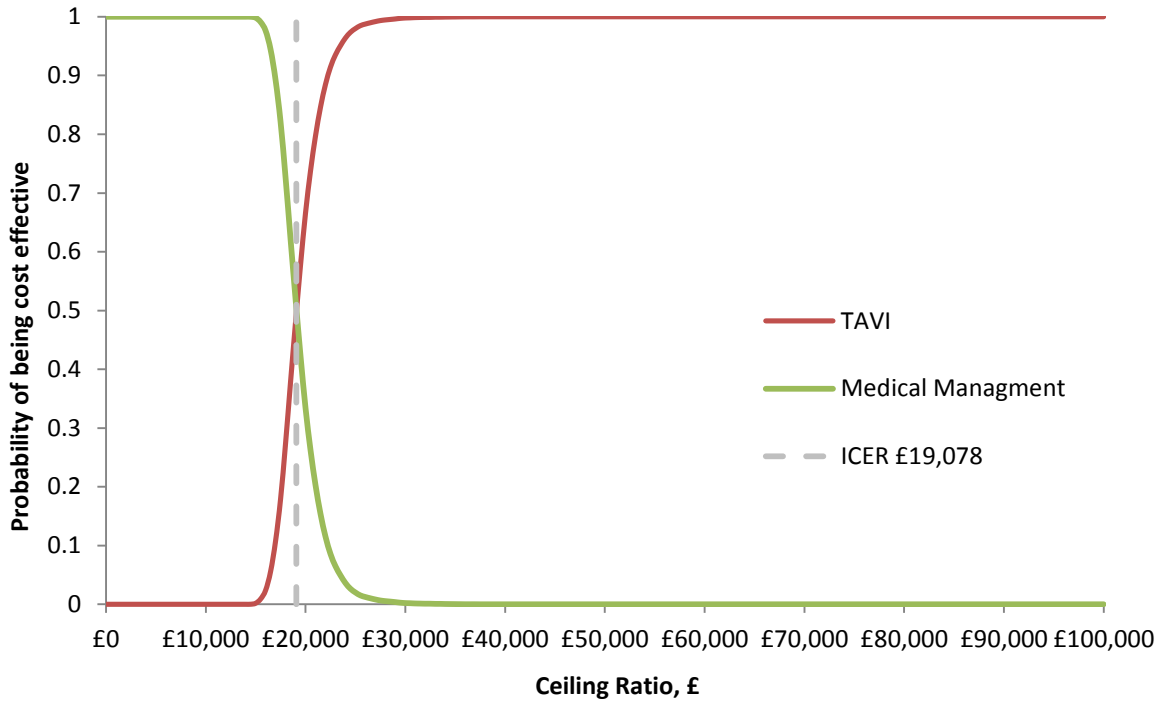
The cost effectiveness acceptability curve (CEAC) (Figure 7.4) presents the uncertainty surrounding the cost effectiveness of each treatment. Here the uncertainty identified in the incremental costs and incremental effects individually does not translate into decision uncertainty regarding the cost effectiveness of TAVI over the range usually considered cost effective. At a ceiling ratio of £30,000 per QALY the probability that TAVI is cost effective is 100% while the probability that medical management is cost effective is 0%. Indicating there is no decision uncertainty at this willingness to pay threshold. Whereas, at a ceiling ratio of £20,000 per QALY the probability that TAVI is cost effective is 67% while the probability that medical management is cost effective is 33%. Thus, the willingness to pay threshold employed can make a big difference to the decision uncertainty, however in this case it does not affect the adoption decision.

Table 7.4 Cost Effectiveness Results: Inoperable patients – TAVI versus Medical Management

	LYS	Costs (£)	Δ Costs £	QALY	Δ QALY	ICER £/QALY
Deterministic Results						
Medical Management	2.43	11,195		1.46		
TAVI	4.63	40,992	29,797	3.00	1.55	19,259
Probabilistic Results						
Medical Management	2.44	11,307		1.47		
	(1.98-3.01)	(8,461-14,702)		(1.21-1.77)		
TAVI	4.71	41,428	30,121	3.05	1.58	19,078
	(3.93-5.63)	(36,727-46,822)	(24,546-36,076)	(2.59-3.56)	(1.05-2.15)	

Value in parenthesis indicates 95% confidence interval.

Figure 7.4 Cost Effectiveness Acceptability Curve: Inoperable Patients – TAVI versus Medical Management



7.3.3 Value of Information Analysis

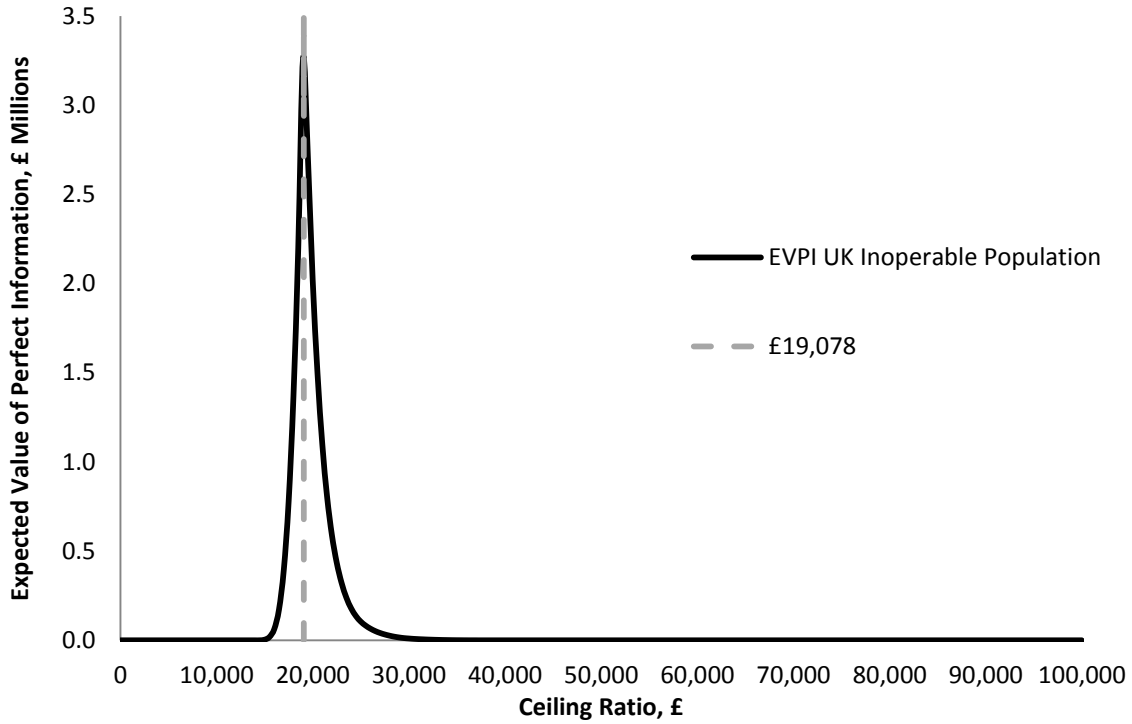
The potential value of undertaking further research is estimated by determining the value of eliminating all the uncertainties within the model (i.e. the EVPI). The per patient EVPI when deciding between TAVI and medical management, over the range usually considered cost effective (£20,000 - £30,000 per QALY (Rawlins et al., 2009)) ranges from £4 to £736 per high risk patient, for one year.

A one year lifetime is chosen to reflect the evolving evidence base and early life cycle stage of the technology, as beyond one year evidence may no longer represent the best evidence available. This is owing to incremental innovations and movements along the device-clinician learning curve.

Given the public good characteristics of information the EVPI for the population (pEVPI) can be estimated also. Over a one year lifetime for the technology, the pEVPI for the inoperable population in the UK (2,250 (SHTG, 2009)) at £30,000/QALY is £10,065 (Figure 7.5). This pEVPI estimates provide a maximum value for the return on further research, indicating there is very little value in collecting further information on per patient

basis here. The pEVPI reaches an inflection point at a ceiling ratio equal to the ICER £19,078 QALY. This corresponds to the CEAC (Figure 7.4) where at £19,078/QALY the decision is most uncertain. Here the probability that TAVI is cost effective is 0.48 and probability that Medical Management is cost effective is 0.52. Beyond this ceiling ratio the optimal treatment changes and TAVI is more likely to be cost effective compared with medical management. As only two technologies are under consideration here (TAVI and medical management) this inflection point is also the maximum pEVPI. However, as indicated in the CEAC discussion, the ceiling ratio chosen, to represent willingness to pay, influences the results. For example, if a ceiling ratio of £20,000/QALY is chosen instead, the pEVPI is over £2 million, which would indicate there is value in collecting additional information.

Figure 7.5 Expected Value of Perfect Information: UK Inoperable Population



7.3.4 Comparison of Original and PARTNER B Models with Revised Model Incorporating Longer-Term Outcomes for Inoperable Patients

Model Inputs

As outlined above, the additional evidence published by Makkar et al. (2012), Bleiziffer et al. (2012) and Walther et al. (2012) provided the opportunity to update the PARTNER trial evidence for inoperable patients. This updating ensured the best available data was employed in the re-analyses of the cost effectiveness of TAVI compared with medical management for this patient group. The updating resulted in no structural changes to the model but provided revised estimates for mortality within 30 days from all causes; early stroke; early major and minor PREs; major and minor PREs within one year and evidence on PREs beyond one year. Mortality from all causes with 30 days increased from the PARTNER B model (0.09 versus 0.07). The probability of having a stroke within 30 days remained constant at 0.05. While the probability of early major and minor PREs were both reduced by 0.02. This was owing to the reduction in major paravavular leaks and major bleeding. The probability of fatal PREs in year one was also reduced to 0.22 (from 0.23). While the probability of late major PREs in year one was reduced by 0.04 to 0.20. This is owing to the reduction in major paravavular leaks and strokes. The probability of late minor PREs in year one increased by 0.04 owing to the increase in major bleeding. In previous versions of the model the probabilities of late PREs experienced in year one were applied for subsequent years. Makkar et al. (2012), Bleiziffer et al. (2012) and Walther et al. (2012), presented data on PREs beyond one year and provided the opportunity to update the evidence for PREs in year two. As a result the probability of late major PREs increased by 0.01, owing to the increase in the probability of stroke. The probability of minor PREs beyond one year increased by 0.10, due to the high occurrence of major bleeding observed in the updated evidence (See Appendix VII).

Cost Effectiveness Results

When the model is populated with the revised estimates and cost effectiveness is re-examined, as discussed above, TAVI is found to extend life and improve quality of life. The average life years gained in the updated PARTNER B model for patients receiving TAVI was 4.71. This is a significant increase on the PARTNER B model (2.55) and the

original model (3.05). This increase is due to the longer term mortality evidence provided by Makkar et al. (2012), Bleiziffer et al. (2012) and Walther et al. (2012) which increased the 30 day mortality rate and decreased the 1 year and 2 year mortality rates significantly. Evidence from Makkar et al. (2012) also provided long term evidence on mortality following medical management. Here the average life years gained increased to 2.44 from 2.24.

In the re-analysis of the model, for inoperable patients, the costs associated with TAVI were estimated to be greater (£12,799; 145%) than suggested by the PARTNER B model. The QALYs produced in the re-analysed model were greater (1.43; 188%) than suggested by the PARTNER B model. These differences are explained by the revised probability of PREs and stroke associated with TAVI and the greater life expectancy for TAVI patients. Similarly, there is only a 7% difference between the costs of medical management from the re-analysis compared with the PARTNER B analysis. This is because the updated evidence provided little additional information on medically management patients. However, the QALYs were increased (0.28; 123%) owing to the additional evidence provided by Makkar et al. (2012) on NYHA classification and mortality.

Results from the original, PARTNER B and updated PARTNER B models indicated that TAVI is more costly and more effective compared with medical management for inoperable patients. The incremental costs in the updated PARTNER B model were 183% greater and the incremental QALYs were over three times greater than the PARTNER B model (presented in Chapter 5). In the PARTNER B model the ICER (£37,390) was outside the range usually considered acceptable but in the updated PARTNER B model the ICER was below the range usually considered acceptable (£19,078). Table 7.5 presents a comparison of the results from the three versions of the model.

The ICE plane compares the additional costs and benefits of TAVI over medical management. As discussed in Section 7.3.2, there was no uncertainty surrounding the existence of benefit and cost differences for TAVI over medical management with TAVI being more effective and more expensive. There was however some uncertainty surrounding the extent of the differences in effects and costs. Comparing the ICE planes, Figure 7.6a represents the incremental costs and QALYS for the original model; Figure 7.6b the PARTNER B model, and Figure 7.6c the updated PARTNER B model. Here it is illustrated that the uncertainty surrounding the extent of differences in QALYs and costs

particularly has shifted and increased. This shift to greater incremental costs and QALYs is explained by the reduction in mortality following TAVI; patients are surviving longer and incurring greater costs. The change between the versions of the models is also attributable to the evidence employed and how it is incorporated. In this updated PARTNER B model the evidence employed in Chapter 5 was updated rather than replaced as was the case in moving from the original model to that presented in Chapter 5 (PARTNER B).

Comparing the CEACs from the updated PARTNER B analysis with the PARTNER B model and the original analysis demonstrates that the decision uncertainty is considerably reduced as the evidence base develops. The probability that TAVI is cost effective compared with medical management (at a ceiling ratio of £30,000 per QALY) was 86% in the original model; this decreased when the evidence was replaced to 18% in the PARTNER B model and increases to 100% in the updated PARTNER B model. Figure 7.7a-c presents the three CEACs side by side, to illustrate the changes in decision uncertainty as the cost effectiveness of TAVI for inoperable patients is re-examined.

Thus, the original model the PARTNER B Model and the updated PARTNER B Model all suggest that TAVI is more costly and more effective compared with medical management in treating inoperable high risk AS patients.

Value of Information Analysis

The VOI analysis estimated that the pEVPI between TAVI and medical management for inoperable patients (2,750 (SHTG, 2009)), in the updated PARTNER B model at £30,000/QALY is £10,065 over one year. Overall this is lower than that estimated in the PARTNER B model which was £756,649 at £30,000/QALY for the UK inoperable population over one year. The pEVPI from the re-analysis of PARTNER B is also lower overall compared to the original analysis. Figure 7.8 presents the EVPI for the original model, PARTNER B model and updated PARTNER B model side by side for comparative purposes.

Table 7.5 Cost Effectiveness Results Comparison Updated PARTNER B, PARTNER B and Original Model: Inoperable Patients

	TAVI			Medical Management					
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYGs	Δ Costs	Δ QALYs	ICER
ORIGINAL*	28,353	2.18	3.48	13,942	1.53	3.06	14,441	0.65	22,108
PARTNER B‡	28,629	1.62	2.54	12,176	1.19	2.24	16,453	0.43	37,390
UPDATED -PARTNER B†	41,428	3.05	4.71	11,307	1.47	2.44	30,122	1.58	19,078

*Presented in Chapter 4 ‡ Presented in Chapter 5 † Presented in Section 7.3.2

Figure 7.6 Incremental Cost Effectiveness Plane Comparison: Inoperable Patients- Original, PARTNER B and Updated PARTNER B Models

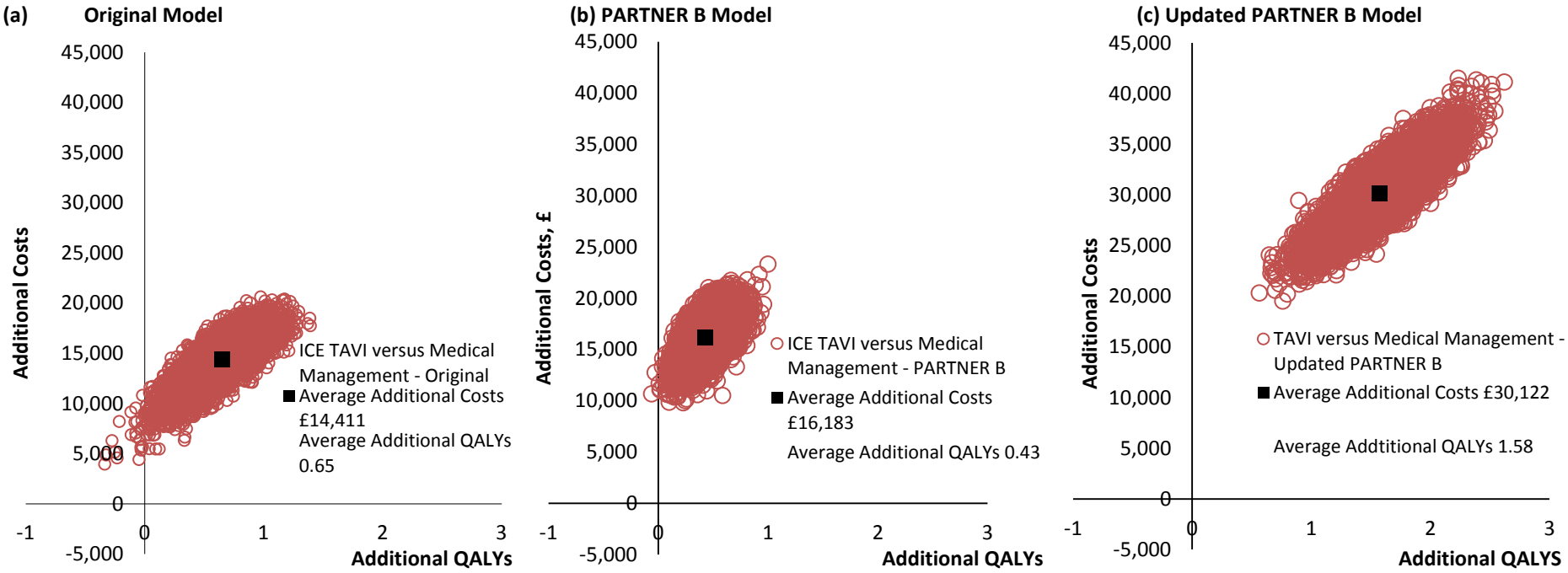
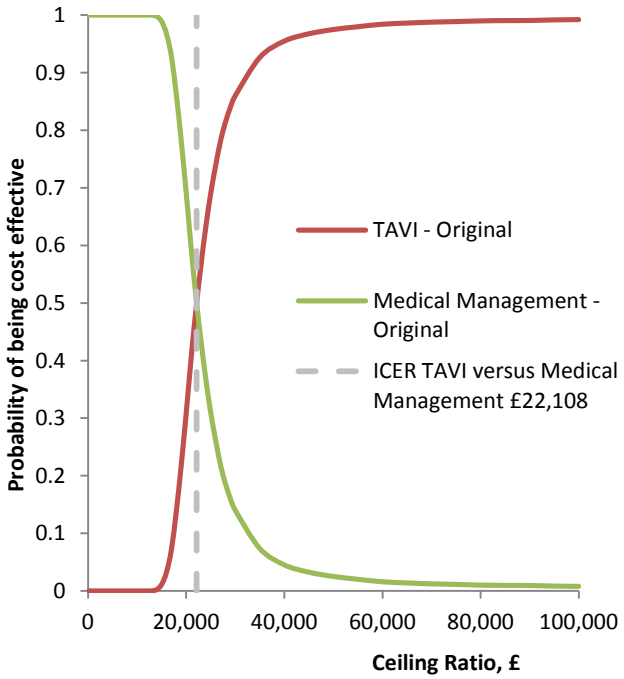
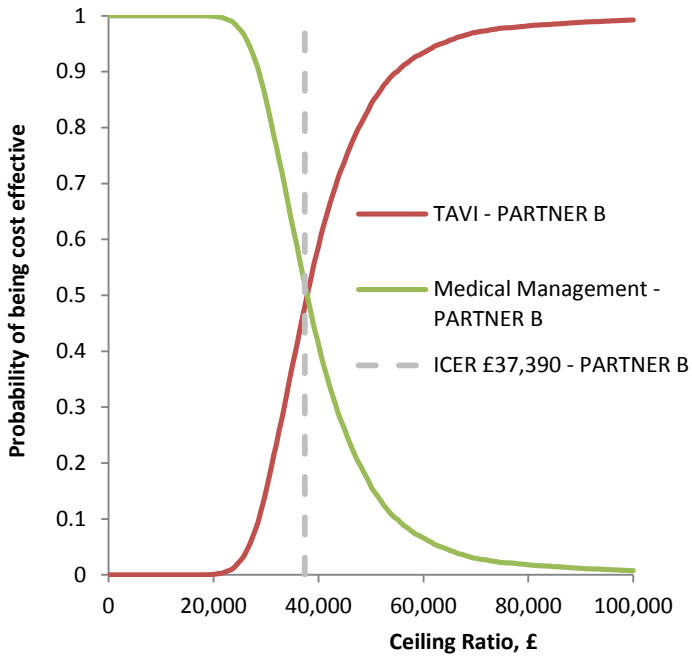


Figure 7.7 Cost Effectiveness Acceptability Curve: Inoperable Patients Comparison - Original, PARTNER B and Updated PARTNER B Models

(a) Original Model



(b) PARTNER B Model



(c) Updated PARTNER B Model

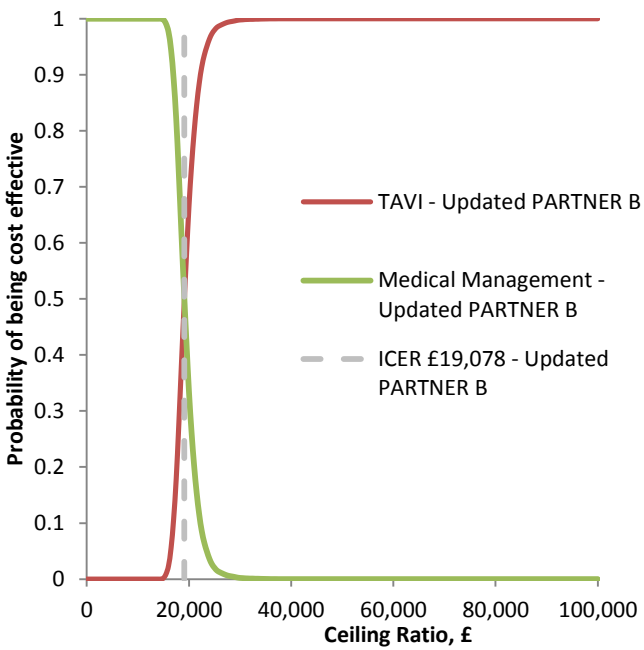
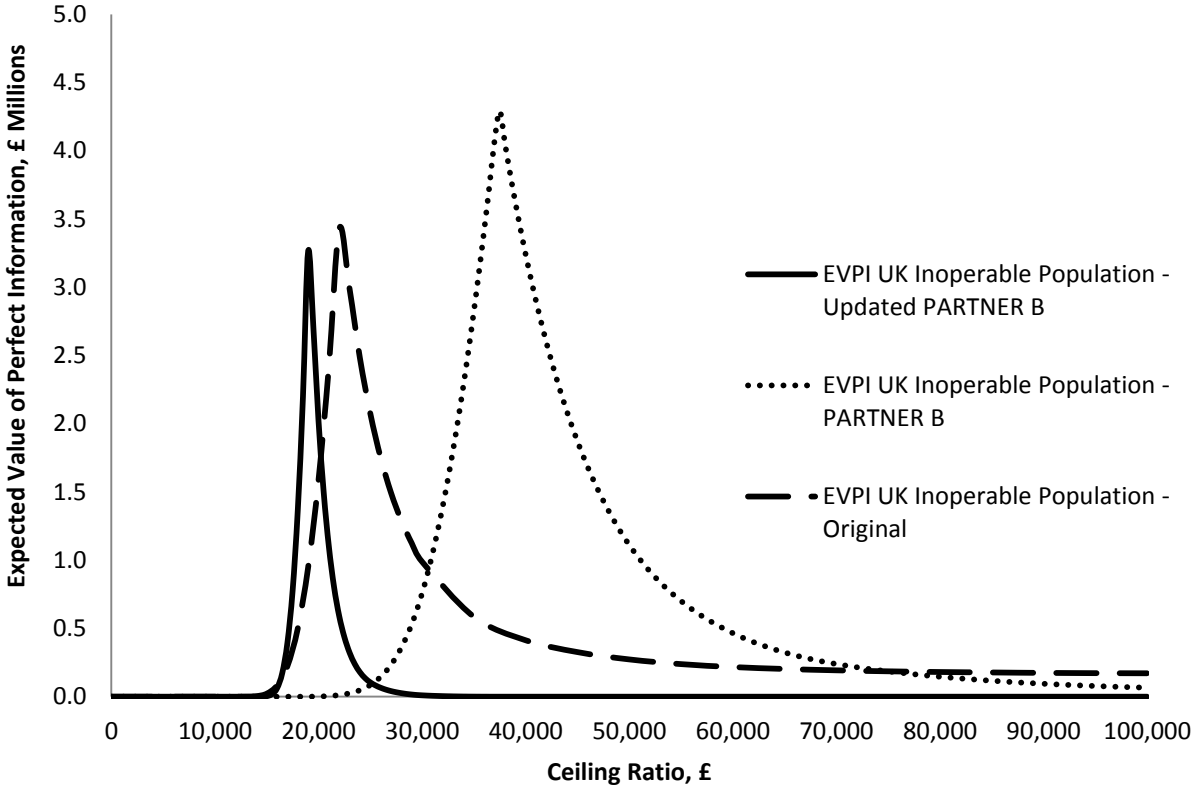


Figure 7.8 Expected Value of Perfect Information Comparison: Inoperable Patients - Original, PARTNER B and Updated PARTNER B Models



7.4 WHERE NOW FOR TAVI WITH INOPERABLE PATIENTS?

The decision analytical model constructed at the outset of this thesis has been employed in an iterative manner to handle the developing and evolving nature of TAVI's evidence base. This ensures the best available evidence was employed at each stage in considering the cost effectiveness of TAVI compared with medical management for high risk inoperable patients. Initially, evidence from early registries, expert opinion and experiences from AVR were employed. In this original analysis, it was demonstrated that TAVI was cost effective with an ICER equal to £22,603/QALY which is within the level usually considered cost effective (£20,000-£30,000/QALY). This initial analysis demonstrated there was value in collecting additional evidence. Following the publication of the results from the first trial (PARTNER B) for inoperable patients the model was updated. The initial evidence was replaced by trial evidence where available. Here the ICER was equal to £37,390/QALY for TAVI compared to medical management. This resulted in TAVI not

being considered cost effective and increasing the uncertainty surrounding the incremental costs and QALYs and adoption decision. The VOI analysis suggested that the value in collecting further information remained. The pEVPI at a threshold of £30,000/QALY was £756,649 for the UK inoperable population over one year. At this time there was much speculation about the likelihood of improved TAVI outcomes in the long-term, as new generations of devices were becoming available and centres were becoming more experienced (Schaff, 2011, Webb and Cribier, 2011). A scenario analysis tested the impact of such assumptions on the cost effectiveness of TAVI (in Chapter 5). The scenario analysis found if the incidence of all PREs following TAVI were reduced by 25%, TAVI could be considered cost effective compared to medical management for high risk, inoperable patients with an ICER of £23,642/QALY.

Subsequently, late outcomes from early registries and the PARTNER trial emerged in spring 2012. This evidence was employed to update the PARTNER B evidence so as to include the best available data. (Evidence revealed reductions in PREs in the initial 30 day and one year period, though they were less than the 25% suggested in the scenario analysis.) The re-analysis, presented in this Chapter, demonstrated that TAVI could be considered cost effective for inoperable patients given current evidence (ICER = £19,078/ QALY). The revised VOI analysis demonstrated there was very little value in commissioning additional research for this patient group (at £30,000/QALY the EVPI for the population is £10,065). However, as the evidence base is still evolving, continued collection of data on TAVI outcomes, using existing means, is advisable. Thus, updating the model with evidence, as it became available, reduced the decision uncertainty surrounding the cost effectiveness of TAVI amongst inoperable patients compared with medical management.

Concurrent to the release of these late TAVI outcomes, national health policies on access to TAVI were being revised. In late 2011, the Food and Drug Administration (FDA) approved TAVI for treating inoperable patients with severe AS in the US (Cadet, 2011). While in England and Wales, the National Institute of Clinical Excellence (NICE) Interventional Procedure Guidance (Number 421, 2012) recently approved the use of TAVI for inoperable patients provided patient/procedure details are entered into the UK Central Cardiac Audit Database (UK TAVI Registry) (NICE, 2012). While in Scotland, the Scottish Health Technologies Group (SHTG) advice statement (Number 005/11) issued prior to the release of the additional evidence does not currently recommend TAVI for

routine treatment of patients with AS (SHTG, 2011). The Scottish Government have though committed to reviewing this position (Scottish, 2012).

This recent NICE guidance on TAVI provides an efficient and unambiguous process for collecting further evidence at a low marginal cost, relative to the costs of commissioning a new clinical trial, for this patient group in the UK. This data collection strategy may be considered a form of Access with Evidence Development (AED). Whereby, access to TAVI has been granted for inoperable patients, with clear instructions for further evidence collection. This data collection arrangement is formal in nature and offers a means to overcome the issues associated with further collection once access is granted. Griffin et al. (2011) identified a negative relationship between further evidence collection and granting access to a technology. Whereby, once access is granted to a technology the likelihood of collecting further evidence decreases. As outlined in Chapter 2, the obstacles to the success of AED schemes are grounded in the complexities surrounding the structures put in place for funding, administration (including reporting), access to the technology and incentives to comply.

The UK TAVI Registry, referred to in the NICE Guidance, is populated with data from the Central Cardiac Audit Database (CCAD). This has been a functioning registry since 2007, recording all TAVI procedures performed in the UK (Ludmann, 2010). As the registry is already in existence the physical structure and resources are already in place. This encourages continued data collection, thereby reducing common complexities associated with collecting evidence after access is granted in a number of ways. Firstly, as the database has existed since 2007 data entry is routine, this reduces the start-up costs and administration burden, making reporting straightforward. Secondly, as the requirement for reporting evidence is incorporated into the NICE Guidance, compliance is enforceable by the Care Guidance Commission (NICE, 2010). Thirdly, evidence published to date from the Registry has contributed to developing the TAVI evidence base which may have contributed to the guidance revision at national level. (To date only aggregate early outcomes from the Registry have been published (Moat et al., 2011) these were not suitable for inclusion in this re-analysis). Finally, the guidance document clearly and legally identifies who has access to the technology. So as the guidance and data collection process is already in place, the traditional problems associated with collecting evidence after access is granted are reduced. Continual collection of evidence, via the UK TAVI Registry, as per the NICE guidance, ensures that up to date evidence will be available to

inform any future decisions regarding TAVI in this patient group, as advocated by the continuous iterative framework conceptualised in Chapter 2.

While continued collection of the data currently included in the UK TAVI Registry is useful, expansion of the parameters in the UK TAVI Registry would be desirable. Currently, the Registry collects evidence on conversions, mortality, stroke and other procedure related events within the first 30 days. Mortality after one year is also recorded. The EVSI calculations, in Chapter 5, demonstrated that expanding the registry to include late procedure related events, resource consumption and quality of life parameters (listed in Appendix VI) has a positive net benefit. Such an expansion would enhance the UK TAVI Registry in informing future economic evaluations of TAVI, in line with the continuous iterative framework proposed in Chapter 2.

7.5 EVOLVING EVIDENCE FOR OPERABLE TAVI PATIENTS

Operable patients are patients with high operative mortality for whom AVR is considered suitable. Here the treatment decision is between AVR and TAVI. In Chapters 4 and 6, medical management was included as a possible treatment for operable patients. However, it was repeatedly demonstrated to be less effective than AVR and TAVI and therefore it is excluded in the re-analysis presented here as patients would not be randomised to an inferior treatment.

Since the publication of early PARTNER Cohort A results, longer-term evidence has also emerged for high risk operable patients on TAVI and AVR. This includes evidence on late procedure related events (PREs) and late mortality for TAVI and AVR from PARTNER Cohort A (Kodali et al., 2012) and late mortality outcomes following TAVI from the UK TAVI Registry (Moat et al., 2011). The emergence of this additional evidence affords the opportunity to re-analyse the cost effectiveness of TAVI compared to AVR for operable patients.

Moat et al. (2011) reported on 870 TAVI procedures conducted in 25 centres in England and Wales between January 2007 and the end of December 2009. The logistical EuroScore of the patients averaged at 18.5% and ranged from 11.7 to 27.9. This range indicates the majority of these patients would have been considered operable, according to the model assumptions in this thesis, i.e. AVR was feasible, and so are included in this re-analysis of TAVI compared to AVR. The results reported in Moat et al. (2011) (Table 7.6) show that 62 patients died within 30 days, 186 within one year and 229 within two years. Six patients converted from TAVI to AVR, while seven patients required a second procedure. With respect to PREs, 35 patients had a stroke (and survived) in hospital; 55 patients had vascular complications and 11 patients suffered a myocardial infarction and 141 patients required pacemaker insertion.

Table 7.6 Mortality and Procedure Related Events Reported in Moat et al. (2011) for TAVI Patients

Event	α	β	n	Probability
Stroke	35	829	864	0.04
Myocardial Infarction	11	853	864	0.01
Conversion to AVR	6	844	850	0.01
Major Vascular Complications	55	814	869	0.06
Repeat procedure	7	863	870	0.01
Pacemaker	141	726	867	0.16
Died within 30 days all causes	62	808	870	0.07
Died within 1 year	186	684	870	0.21
Died within 2 years	229	641	870	0.26

Source: Moat et al (2011). Note α and n were extracted from the literature and β and the probability of the event occurring were calculated by the author.

In addition to the registry data, Kodali et al. (2012) published longer term results from the PARTNER Cohort A trial detailing PREs beyond one year and mortality beyond one year. All-cause mortality for year two following AVR was estimated at 33% and following TAVI was 33 %. With respect to major PREs in year two following AVR, two cases of major paravavular leaks, five late strokes and two myocardial infarctions were reported. With respect to minor PREs in year two following AVR, Kodali et al. (2012) reported nine repeat hospitalisations, six major bleeding and three pacemakers implantations. Two years after a TAVI procedure, one case of endocarditis and six late strokes were reported. Also, the following minor PREs are TAVI in year two were reported: 15 repeat hospitalisations, one major vascular event, eight major bleeding events and two pacemaker implantations. These results were extracted from Kodali et al. (2012) and were employed to estimate probabilities of each event occurring, shown in Table 7.7. These probabilities are estimated as the proportion of events that occurred (α) from those that could have occurred (n). For example, following AVR in year two 16 (α) incidences of valve thromboembolism were reported. A total of 235 (n) patients could have had a valve thromboembolism, which gives a probability of 0.07 (α/n = 16/235).

Table 7.7 Mortality and Procedure Related Events Beyond One Year Reported in Kodali et al. (2012) for TAVI and AVR Patients

	α	β	n	Probability
Major Late PREs Year 2 AVR				
Major Paravavular Leak	2	233	235	0.01
Endocarditis	0	235	235	0.00
Stroke	5	230	235	0.02
Myocardial Infarction	2	233	235	0.01
Major Late PREs Year 2 TAVI				
Major Paravavular Leak	16	247	263	0.06
Endocarditis	1	262	263	0.00
Stroke	6	257	263	0.02
Myocardial Infarction	0	263	263	0.00
Minor Late PREs Year 2 AVR				
Repeat Hospitalisations	9	226	235	0.04
Major Vascular Complications	0	236	236	0.00
Minor Vascular Complications	0	237	237	0.00
Major Bleeding	6	232	238	0.03
New Pacemaker	3	236	239	0.01
Minor Late PREs Year 2 TAVI				
Repeat Hospitalisations	15	248	263	0.06
Major Vascular Complications	1	263	264	0.00
Minor Vascular Complications	0	265	265	0.00
Major Bleeding	8	258	266	0.03
New Pacemaker	2	265	267	0.01
Fatal PREs Year 2 AVR	16	219	235	0.07
Fatal PREs Year 2 TAVI	5	258	263	0.02
All-Cause Mortality Year 2 AVR	115	236	351	0.33
All-Cause Mortality Year 2 TAVI	116	232	348	0.33

Source Kodali et al. (2012). Note α and n were extracted from the literature and β and the probability of the event occurring were calculated by the author.

7.5.1 Incorporating Longer-Term Results into the Decision Analytical Model for Operable Patients

These longer-term published results from PARTNER Cohort A and the UK TAVI Registry are used to update the PARTNER Cohort A model presented in Chapter 6. Here an "updating" strategy is employed as opposed to a "replacement" strategy, as Kodali et al. (2012) and Moat et al. (2011) provided data which complements and updates the transition probabilities, i.e. early TAVI transition probabilities (Moat et al., 2011) and late PREs for

AVR and TAVI (Kodali et al., 2012). Updating the PARTNER Cohort A data (employed in Chapter 6) ensures that the best, available data is employed in the model to re-assess the cost effectiveness of TAVI for operable patients compared to AVR. A pooling process is employed here equivalent to a fixed effects meta-analysis, involving the assumption that information is exchangeable and the baseline parameters being measured are identical. As outlined in Section 7.2, synthesising evidence from a variety of sources avoids the risk of biased assessment which can occur when relying on a single source (Sculpher et al., 2006).

As per Section 7.2, the new evidence presented above was combined with the existing evidence to give revised transition probabilities. For example, (Box 7.2) PARTNER Cohort A reported 19 major strokes following TAVI within the first 30 days ($\alpha_{\text{PARTNER A}} = 19$) from a total of 312 patients ($n_{\text{PARTNER A}} = 312$). Subsequently, Moat et al. (2011) reported 35 cases of stroke within the first 30 days ($\alpha_{\text{Moat}} = 35$) and a total of 864 strokes could have occurred ($n_{\text{Moat}} = 864$). To update the transition probability the α ($\alpha_{\text{PARTNER A}}$ and α_{Moat}) and n ($n_{\text{PARTNER A}}$ and n_{Moat}) are summed to estimate the proportion of events occurring. This was calculated as follows 19+35=54; 312+864=1153; 54/1153=0.05. This was repeated for conversions from TAVI to AVR; repeat TAVI and death within 30 days following TAVI; PREs in short term for TAVI and year 2 for AVR and TAVI. The revised estimates are shown in Table 7.8.

Box 7.2 Example of Updating PARTNER A Evidence

Early Stroke	**α**	**β**	**n**	**Probability**
PARTNER A	19	311	312	0.05
Moat	35	829	864	0.04
PARTNER A + Moat	54	1099	1153	0.05

Table 7.8 Revised Transition Probabilities

Transition Probability	Dist	Probability 95% CI	α	β	n
30 Day All-Cause Mortality TAVI*	Beta	0.07 (0.06-0.09)	62	808	870
30 Day Stroke From TAVI*	Beta	0.05 (0.04-0.06)	54	1099	1153
Conversion To AVR*	Beta	0.01 (0.01-0.02)	15	1179	1194
Repeat TAVI*	Beta	0.01 (0.01-0.02)	14	110	1174
Early Major PREs TAVI					
Valve Thromboembolism	Beta	0.03	9	321	330
Major Paravavular Leak	Beta	0.11	35	295	330
Endocarditis	Beta	0.00	0	330	330
Cardiac Tamponade	Beta	0.03	10	320	330
Myocardial Infarction*****	Beta	0.01	11	1172	1183
		0.17 (0.13-0.22)			
Early Minor PREs TAVI					
Access Site Events	Beta	0.06	20	310	330
Vascular Events	Beta	0.06	21	309	330
Pacemaker Implantation*****	Beta	0.15	154	902	1056
Major Vascular Event*****	Beta	0.08	93	1051	1144
Major Bleeding	Beta	0.10	32	298	330
		0.45 (0.40-0.51)			
Late Major PREs – Year 2 -AVR					
Valve Thromboembolism^	Beta	0.05	12	223	235
Major Paravavular Leak†	Beta	0.01	2	233	235
Endocarditis†	Beta	0.00	0	235	235
Cardiac Tamponade’	Beta	0.01	2	233	235
Stroke †	Beta	0.02	5	230	235
Myocardial Infarction†	Beta	0.01	2	233	235
		0.10 (0.06-0.14)			
Late Major PREs – Year 2 – TAVI					

Table 7.8 Continued

Transition Probability	Dist	Probability 95% CI	α	β	n
Valve Thromboembolism^	Beta	0.06	17	246	263
Major Paravavular Leak†	Beta	0.06	16	247	263
Endocarditis†	Beta	0.00	1	262	263
Cardiac Tamponade'	Beta	0.01	3	260	263
Stroke †	Beta	0.02	6	257	263
Myocardial Infarction†	Beta	0.00	0	263	263
		0.16 (0.12-0.21)			
Late Minor PREs – Year 2 – AVR					
Repeat Hospitalisations†	Beta	0.04	9	226	235
Major Vascular Complications†	Beta	0.00	0	235	235
Minor Vascular Complications‡	Beta	0.00	0	235	235
Major Bleeding†	Beta	0.03	6	229	235
New Pacemaker†	Beta	0.01	3	232	235
		0.08 (0.05-0.12)			
Late Minor PREs – Year 2 – TAVI					
Repeat Hospitalisations†	Beta	0.06	15	248	263
Major Vascular Complications	Beta	0.00	1	262	263
Minor Vascular Complications‡	Beta	0.00	0	263	263
Major Bleeding†	Beta	0.03	8	255	263
New Pacemaker†	Beta	0.01	2	261	263
		0.10 (0.06-0.14)			
Year 2 Fatal PREs AVR	Beta	0.07 (0.04-0.10)	16	219	235
Year 2 Fatal PREs TAVI	Beta	0.08 (0.05-0.11)	20	243	263

‡Set to 0 as "major vascular complications" includes all vascular complications ^as per year one 'as per literature (original model) see Table 5.3 *updated to include Moat et al. (2011) † Updated to include Kodali et al. (2012). The remainder of the parameters are maintained from Tables 6.1-2 in Chapter 6.

Updating the transition probabilities estimated, using evidence from PARTNER Cohort A with Moat et al. (2011) (early TAVI transition probabilities) and Kodali et al. (2012) (late

PREs following TAVI and AVR), decreased the probability of converting from TAVI to AVR (0.03 to 0.01). The probability of requiring a repeat TAVI procedure was also reduced (0.02 to 0.01). The 30 day all-cause mortality following TAVI increased from 0.04 to 0.07 following the updating with Moat et al. (2011). Major strokes within 30 days following TAVI decreased from 0.06 to 0.05. The additional evidence from Moat et al. (2011) also increased early major PREs following TAVI from 0.16 to 0.17. This is attributable to the increase in myocardial infarctions. The probability of early minor PREs following TAVI also increased from 0.38 to 0.45. This is owing to the increase in pacemakers and major vascular events.

As outlined above, incorporating evidence from Kodali et al. (2012) afforded the opportunity to differentiate between late PREs occurring during year one and beyond year one. This reduced the likelihood of late fatal PREs following AVR in year two, which decreased from 0.10 to 0.07. Also, the probability of late major and minor PREs following AVR in year two decreased from 0.11 to 0.10 and 0.22 to 0.08 respectively. The decrease in minor PREs is explained by the reduction in hospitalisations and major bleeding observed.

With respect to patients who receive TAVI, the probability of late fatal PREs in year two decreased from 0.12 to 0.08. The probability of late major PREs in year two following TAVI also decreased from 0.18 to 0.16. This decrease is explained by the reduction in strokes observed. The probability of late minor PREs in year two following TAVI also decreased from 0.28 to 0.10. This decrease is owing to the reduction in hospitalisations, vascular complications, bleedings and pacemaker insertions observed compared to year one.

As per previous iterations of the model, the uncertainty surrounding each of the parameters was incorporated into the model through the assignment of probability distributions. Combining results from PARTNER A with Moat et al. (2011) and Kodali et al. (2012) identified the total number of patients and the number for whom events occurred (Table 7.8). All of the transition probabilities provided on Table 7.8 represent absolute risk for each arm of the model, AVR and TAVI.

Cost Parameters

For the cost analysis the value of the following resources were estimated: AVR and TAVI devices, procedures, length of stay, hospitalisations and other costs incurred with PREs. Neither Moat et al. (2011) nor Kodali et al. (2012) provided additional information on the cost of the procedures, length of stay or unit costs of PREs. Therefore, the annual state costs and the procedural costs from Chapter 6 were maintained. The PRE costs are estimated as previously with a weight assigned to each event multiplied by the unit cost. The unit costs from Chapter 6 were maintained but the weights are updated with the revised probabilities. The PREs cost associated with AVR were estimated as follows. The cost of early minor PREs was £781 and early major PREs were £1,055. The cost of minor PREs were £2,341 and major PREs were £2,707 in year one. In year two onwards, the cost of minor PREs were £2,559 and major PREs were £3,164. The PRE cost associated with TAVI were estimated as follows. The costs of early minor PREs were £440 and early major PREs were £1,766. The cost of minor PREs were £2,594 and major PREs were £2,700 in year one. In year two onwards the cost of minor PREs was £2,412 and major PREs were £2,160. Normal distributions were applied to the cost of treating PREs. The costs are discounted at the recommended 3.5%.

Quality of Life Parameters

As per the original model presented in Chapter 4, QALYs were also derived for each health state adjusting for the condition, the procedure and PREs. As with the costs, the impact on utility associated with the PREs were adjusted to account for the revised probabilities of events occurring. The utility from minor early, 1 year and 2 year PREs following AVR was 0.02. While the utility associated with major early, 1 year and 2 year PREs following AVR was 0.04. The utility associated with minor early, 1 year and 2 year PREs following TAVI were 0.03, 0.02 and 0.02 respectively. While the utility associated with major early, 1 year and 2 year PREs following TAVI was 0.04. Moat et al. (2011) and Kodali et al. (2012) provided no additional information on NYHA classification of patients in each state either, so the utility of functioning valve replacement and failed valve replacement as per Chapter 6 were maintained. Normal distributions were applied to the utility hits associated with the PREs, while Dirichlet distributions were applied to the disutility associated with each NYHA classification. The QALYs are discounted at the recommended 3.5%.

7.5.2 Analysis – Operable Patients

An analysis similar to that employed in Chapter 4 and 6 is applied here for operable patients, with a UK NHS perspective. A Monte Carlo simulation with 10,000 iterations is used to propagate the uncertainty in the individual model parameters, reflected by the probability distributions assigned, through the model. This produces a distribution of expected costs and expected QALYs associated with each procedure. The mean values of these distributions are used to calculate the incremental cost effectiveness ratio (ICER) in terms of the expected incremental costs associated with TAVI compared to AVR per incremental QALY gained. The uncertainty associated with the incremental costs and incremental QALYs are presented through incremental cost effectiveness (ICE) planes. The uncertainty associated with the cost effectiveness of TAVI compared to AVR is presented in terms of a cost effectiveness acceptability curve (CEAC). Following this a number of scenario analyses were performed. After which a Bayesian VOI analysis is performed to estimate the value of collecting further evidence (using expected value of perfect information (EVPI)) and optimal data collection strategy using expected value of perfect information about parameters (EVPPI) and expected value of sample information (EVSI).

7.6 COST EFFECTIVENESS RE-ANALYSIS OPERABLE PATIENTS

The cost effectiveness of TAVI compared with AVR was estimated for operable patients based on a mix of early and late evidence from Cohort A of the PARTNER trial (Smith et al., 2011, Kodali et al., 2012) and the UK TAVI registry (Moat et al., 2011). The results indicate a 3% reduction in absolute risk in terms of all-cause mortality at the end of year one between TAVI and AVR which increases to 5% at the end of year two. This is illustrated on Figure 7.9. These mortality estimates correspond to the average mortality rates reported in the literature (Smith et al., 2011, Moat et al., 2011, Kodali et al., 2012). TAVI also offers significantly greater quality of life than AVR, with a 2% increase in quality of life compared to AVR in year 1 (Figure 7.10).

7.6.1 Deterministic Cost Effectiveness Results

The deterministic cost effectiveness results (Table 7.9) were estimated using the point estimates for the transition probabilities, costs and utilities presented in the previous section. The results illustrate that for operable patients TAVI is both more costly (£9,836) and more effective (0.02 QALYs) than AVR. The ICER is estimated as £472,903 per QALY gained, which is above the level usually considered cost effective (£20,000-£30,000 per QALY) (Rawlins et al., 2009).

Table 7.9 Cost Effectiveness Results: Operable Patients – TAVI versus AVR

	LYs (95% CI)	Costs (£) (95% CI)	Δ Costs (95% CI)	QALYs (95% CI)	Δ QALYs (95% CI)	ICER £/ QALY (95% CI)
Deterministic Results						
AVR	4.88	34,037		2.99		
TAVI	5.04	43,873	9,836	3.01	0.02	472,903
Probabilistic Results						
AVR	4.91	34,147		3.02		
	(4.43-5.45)	(29,920-38,540)		(2.75-3.29)		
TAVI	5.08	44,069	9,922	3.03	0.02	605,756
	(4.67-5.61)	(40,412-48,212)	(6,099-13,361)	(2.81-3.28)	(-0.25-0.28)	

7.6.2 Probabilistic Cost Effectiveness Results

Using the probability distributions assigned, a Monte Carlo simulation with 10,000 iterations produced the mean costs and QALYs (Table 7.9). Here it is illustrated that for operable patients TAVI is both more costly (£9,922) and more effective (0.01 QALYs) than AVR. The incremental costs from the Monte Carlo simulation ranged from £1,320 to £17,285. While the incremental benefit ranged from -0.60 to 0.50 QALYs (95% confidence intervals reported in Table 7.9). The probabilistic ICER is estimated as £605,756 per QALY gained, which is well above the level usually considered cost effective (£20,000-£30,000 per QALY (Rawlins et al., 2009)). Thus, given the developed evidence base TAVI still cannot be considered cost effective compared to AVR for operable patients**.**

Figure 7.9 Survival Estimates for TAVI and AVR

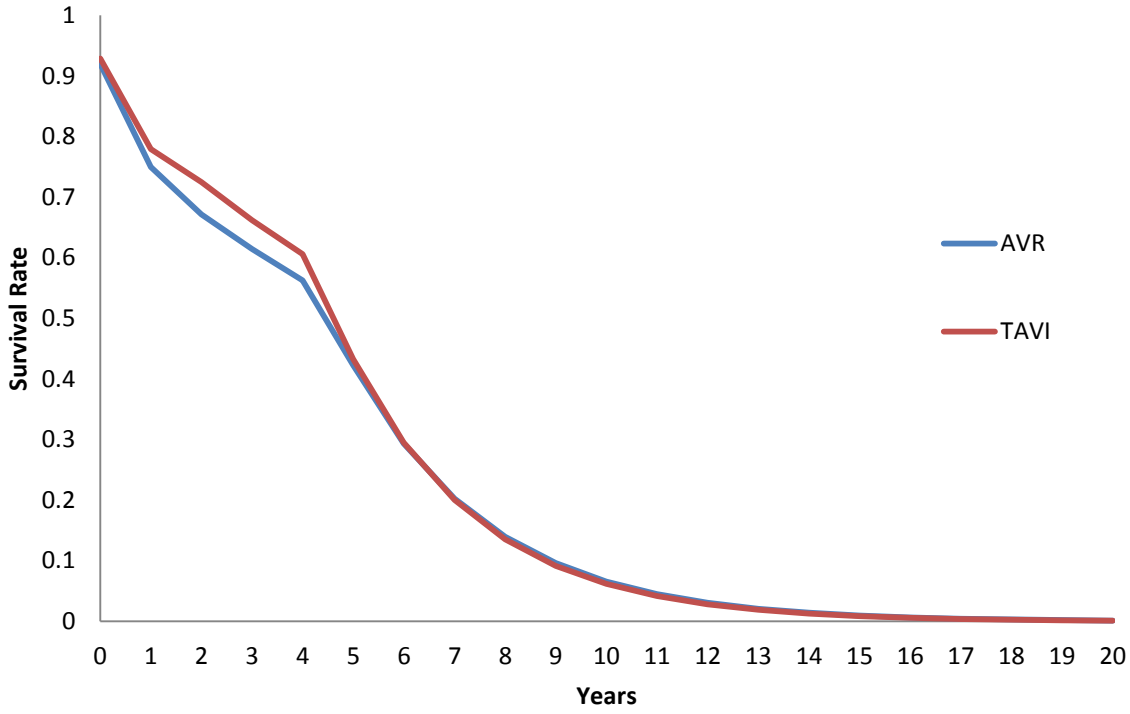
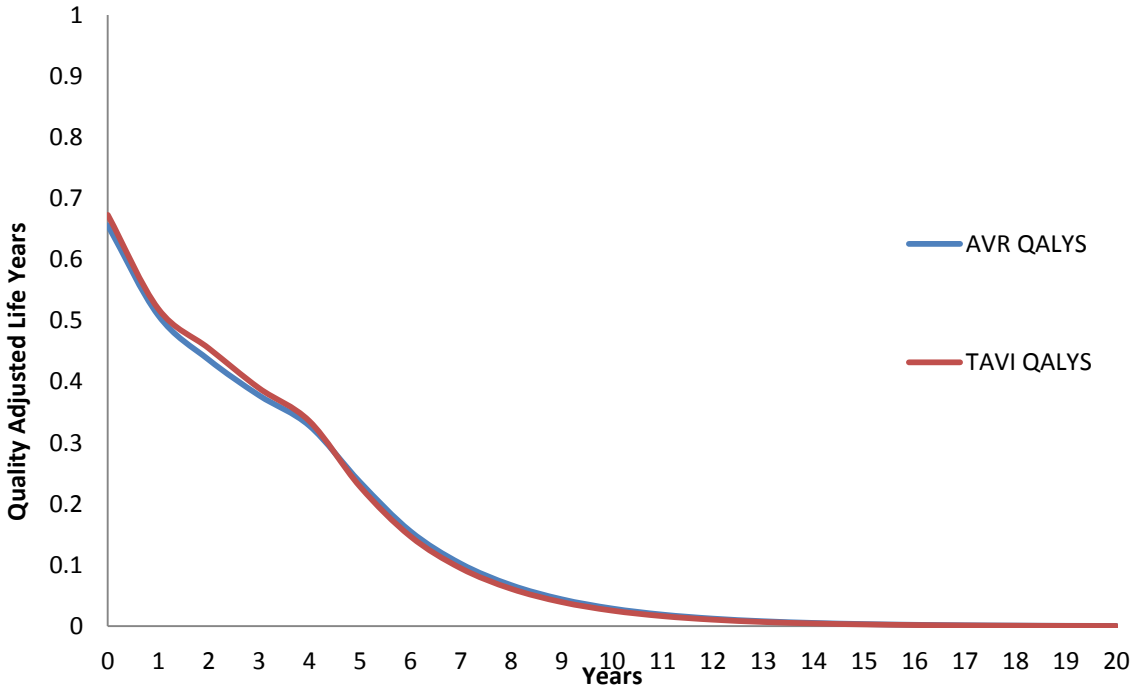


Figure 7.10 Quality of Life Estimates for TAVI and AVR



The ICE plane (Figure 7.11) illustrates the existence and extent of the uncertainty surrounding the incremental effect and incremental cost (these are the blue points plotted on Figure 7.11). There is considerable uncertainty surrounding the existence and extent of benefit for TAVI over AVR. However, there is little uncertainty surrounding the extent of differences in costs, TAVI is more expensive than AVR. Furthermore, there is considerable uncertainty with respect to the extent of differences in costs, between TAVI and AVR. This is driven by uncertainties surrounding the probability of PREs.

The CEAC (Figure 7.12) represents the decision uncertainty surrounding the cost effectiveness of each treatment. The uncertainty identified in the incremental costs and incremental effects individually does not translate into decision uncertainty regarding the cost effectiveness of TAVI over the range usually considered cost effective. At a ceiling ratio of £30,000 per QALY the probability that AVR is cost effective is 99% while the probability that TAVI is cost effective is 1%. Indicating there is little decision uncertainty.

Figure 7.11 Incremental Cost Effectiveness Plane: Operable Patients – TAVI versus AVR

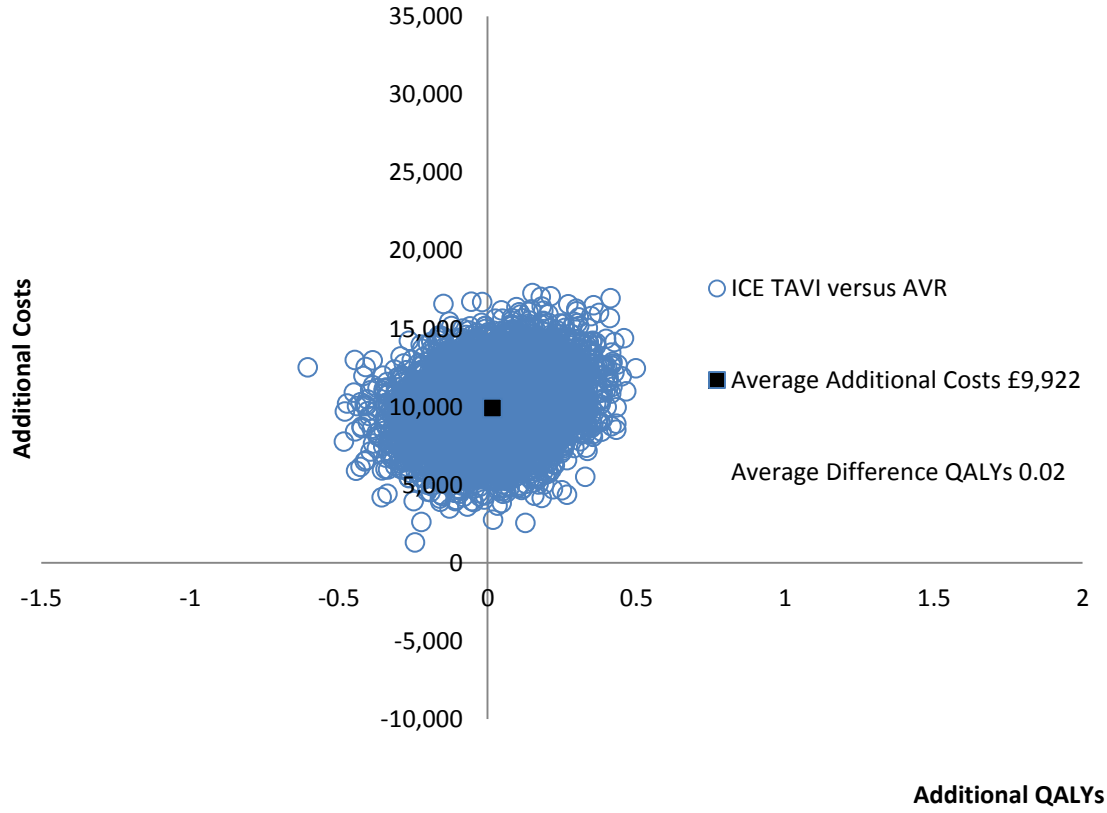
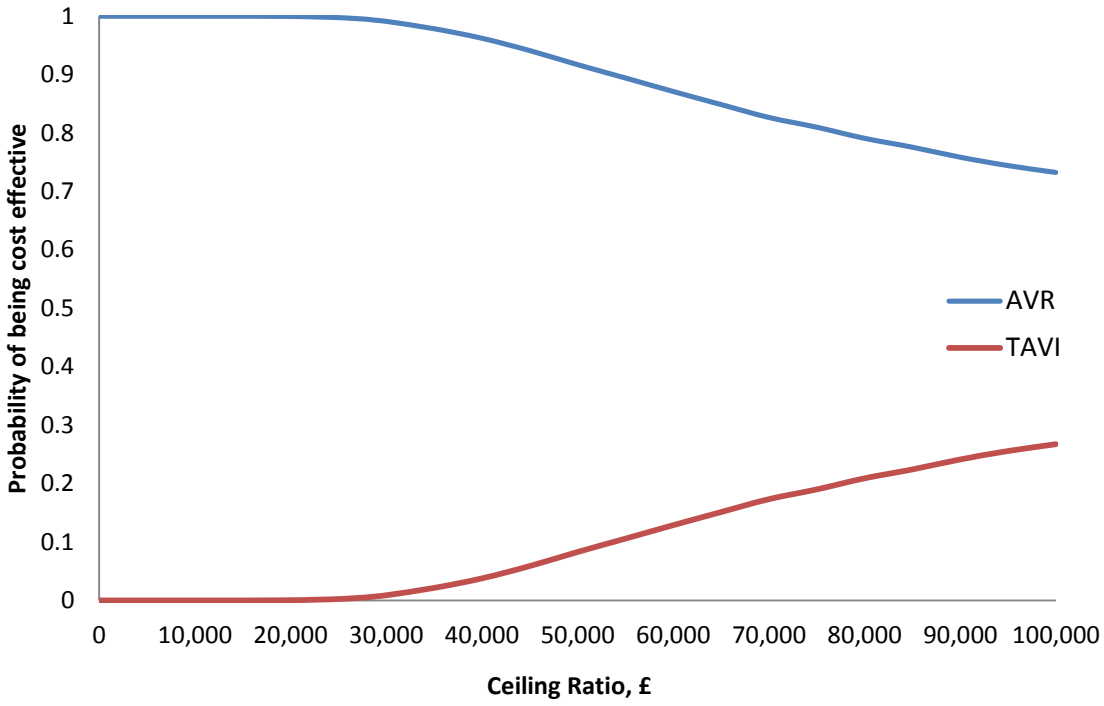


Figure 7.12 Cost Effectiveness Acceptability Curve: Operable Patients – TAVI versus AVR

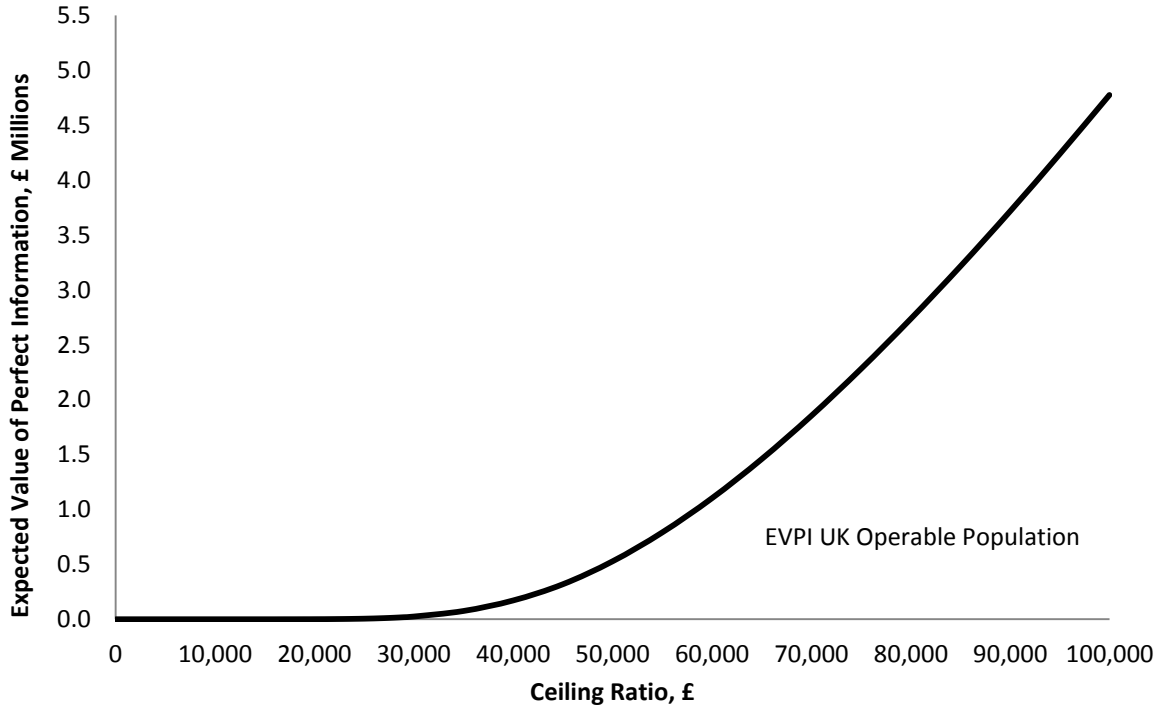


7.6.3 Value of Information Analysis

The potential value of undertaking further research is estimated by determining the value of eliminating all the uncertainties within the model (i.e. the EVPI). The per patient EVPI when deciding between TAVI and AVR, over the range usually considered cost effective (£20,000 - £30,000 per QALY) (Rawlins et al., 2009), ranges from £0 to £11 per operable patient, for one year. A one year lifetime is chosen to reflect the evolving evidence base and early life cycle stage of the technology, as beyond one year evidence may no long represent the best evidence available. These estimates provide a maximum value for the return on further research, indicating there is very little value in collecting further information here.

Given the public good characteristics of information the EVPI for the population (pEVPI) can be estimated also. Over a one year lifetime for the technology, the pEVPI for the operable population in the UK (2,250 (SHTG, 2009)) ranges from £563 to £24,375, over the range usually considered cost effective (Figure 7.13).

Figure 7.13 Expected Value of Perfect Information: UK Operable Population



7.6.4 Comparison of Original and PARTNER A Model with Revised Model Incorporating Longer-Term Outcomes for Operable Patients

Model Inputs

As outlined above, the additional evidence from the UK TAVI Registry (Moat et al., 2011) and late outcomes from PARTNER Cohort A (Kodali et al., 2012) provided the opportunity to update the early PARTNER Cohort A trial evidence on operable patients, employed in Chapter 6 (PARTNER A model). This updating ensured the best available data was employed in re-analysing the cost effectiveness of TAVI compared with AVR for this patient group. The updating resulted in no structural changes to the model but did provided revised estimates for mortality within 30 days from all causes; early stroke; early major and minor PREs follow TAVI and major and minor PREs following AVR and TAVI in year two.

Updating these transition probabilities increased the 30 day all-cause mortality following TAVI from that in the PARTNER A model (0.07 versus 0.04). However, the probability of

stroke within 30 days remained constant at 0.05. The probability of early major PREs following TAVI was reduced by 0.01, while the probability of early minor PREs following TAVI decreased from 0.45 to 0.33. This was owing to the increase in pacemaker insertions. While late PREs in year one remained unchanged, late PREs beyond one year were updated for AVR and TAVI. The probability of late major PREs following AVR decreased by 0.01 the probability of late minor PREs decreased by 0.10. This was owing to the decrease in hospitalisations, vascular complications and bleedings observed. Meanwhile, the probability of major PREs in year two following TAVI was reduced by 0.02 owing to the reduction in strokes. While the probability of minor PREs beyond one year following TAVI also decreased by 0.18. This was explained by the reduction in major bleeding, vascular events and pacemakers insertions observed in the updated evidence (See Appendix VII).

Cost Effectiveness Results

When the model is populated with the revised estimates and the cost effectiveness is re-examined, TAVI was found to extend life and improve quality of life. The average life years gained in the updated PARTNER A model for patients receiving TAVI was 5.08. This is a significant increase on the PARTNER A model (3.44) and the original model (4.75). This increase was owing to the longer term mortality evidence provided by Kodali et al. (2012) which suggested an increased 30 day mortality rate and decreased mortality rates for 1 year and 2 year. For patients receiving AVR the updated PARTNER A model reveals 4.91 life years gained. This is also greater than the PARTNER A model (3.49) and the original model (4.63).

In the re-analysis of the model, for operable patients, the costs associated with TAVI were estimated to be greater (£7,256; 20%) than suggested by the PARTNER A model. The QALYs produced in the re-analysis were also greater (0.94; 45%) than those from the PARTNER A model. These differences can be explained by the revised probability of PREs and stroke associated with TAVI and the greater life expectancy for TAVI patients. Meanwhile, the costs associated with AVR were estimated to be greater than suggested by the PARTNER A model (£4,452; 15%) as were the QALYs produced (0.82; 37%). These differences can be explained by the revised probability of PREs and stroke associated with TAVI and the greater life expectancy for AVR patients.

Results from the original, PARTNER A and updated PARTNER A models indicated that TAVI is more costly than AVR. The original model and updated PARTNER A models found that TAVI was marginally more effective compared with AVR for operable patients. However, the PARTNER A model found that TAVI was less effective than AVR for operable patients. The incremental costs in the updated PARTNER A model were 39% greater and the incremental QALYs were 109% greater than the PARTNER A model. In the PARTNER A model TAVI was dominated by AVR, but in the updated PARTNER A model TAVI is not dominated but the ICER is above the range usually considered acceptable (£605,756). Table 7.10 presents a comparison of the results from the three versions of the model.

Thus, the original model employing data from published literature and the updated PARTNER A Model (with longer term evidence from the PARTNER trial), suggest that TAVI is more costly and slightly more effective compared with AVR in treating operable, high risk AS patients. However, the incremental benefit is not enough to offset the additional costs, so TAVI cannot be considered cost effective, given current evidence.

The ICE plane compares the additional costs and benefits of TAVI over AVR. As discussed in Section 7.6.2, there is considerable uncertainty surrounding the existence and extent of differences in QALYs for TAVI over AVR in the updated PARTNER A model. Meanwhile, there is no uncertainty surrounding the difference in costs, with TAVI being more expensive, there is some uncertainty surrounding the extent of this uncertainty. Comparing the ICE planes, Figure 7.14a represents the incremental costs and QALYs for the original model; Figure 7.14b the PARTNER A model, and Figure 7.14c the updated PARTNER A model. Here it is illustrated that the uncertainty surrounding the extent of differences in QALYs and costs particularly has decreased when the evidence is updated. Comparing the updated PARTNER A model to the PARTNER A model it is evident that with the developed evidence base uncertainty surrounding the costs and effects persist but it has reduced. In the PARTNER A model the average incremental costs were £6,277 (range: -£5,126 to £20,560) and average incremental QALYs were -0.11 (range: -0.89 to 0.66). In the updated PARTNER A model the average incremental costs are £9,922 (range: £1,320 to £17,285) and average incremental QALYs are 0.02 (range: -0.60 to 0.50). This shift and reduction in uncertainty is explained by the updated evidence employed in the model which demonstrated a mortality advantage for TAVI and revised the incidence of PREs.

Comparing the CEAC from the updated PARTNER A model with the PARTNER A and original models demonstrates that there is little decision uncertainty. The probability that TAVI is cost effective compared with AVR (at a ceiling ratio of £30,000 per QALY) was 2% in the original model; this decreased significantly when the evidence was replaced to 0.2% in the PARTNER A model and increased to 1% in the updated PARTNER A model. Figure 7.15a-c presents the three CEACs side by side, to illustrate the changes in decision uncertainty as the cost effectiveness of TAVI for operable patients is re-examined.

Table 7.10 Cost Effectiveness Results Comparison Updated PARTNER A, PARTNER A and Original Model: Operable Patients

	AVR			TAVI					ICER
	Costs (£)	QALYs	LYs	Costs (£)	QALYs	LYs	Δ Costs	Δ QALYs	£/QALY
ORIGINAL*	26,698	2.84	4.65	31,854	2.90	4.73	5,157	0.06	85,982
PARTNER A‡	29,695	2.20	3.49	36,813	2.09	3.44	7,118	-0.11	TAVI Dominated
Updated PARTNER A	34,147	3.02	4.91	44,069	3.03	5.08	9,922	0.02	605,756

*Presented in Chapter 4 ‡ Presented in Chapter 6 † Presented in Section 7.6.2

Figure 7.14 Incremental Cost Effectiveness Plane Comparison: Operable Patients: Original, PARTNER A and Updated PARTNER A Model

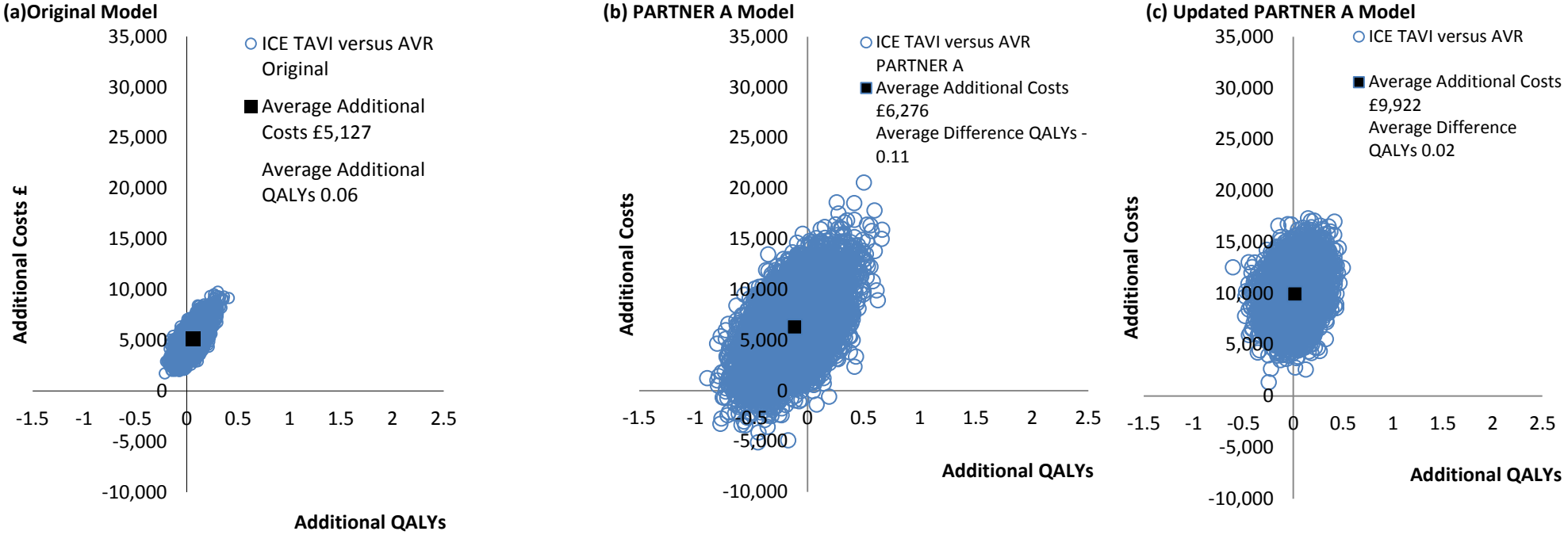
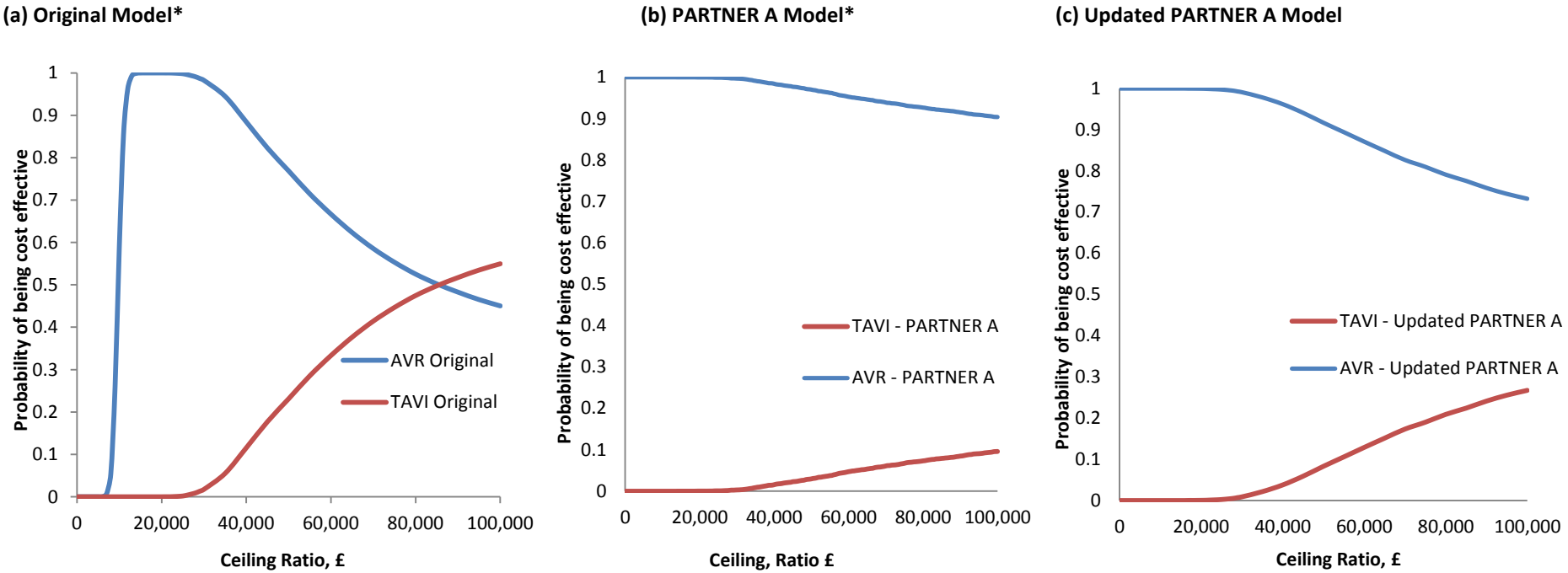


Figure 7.15 Cost Effectiveness Acceptability Curve Comparison: Operable Patients: Original, PARTNER A and Updated PARTNER A Model

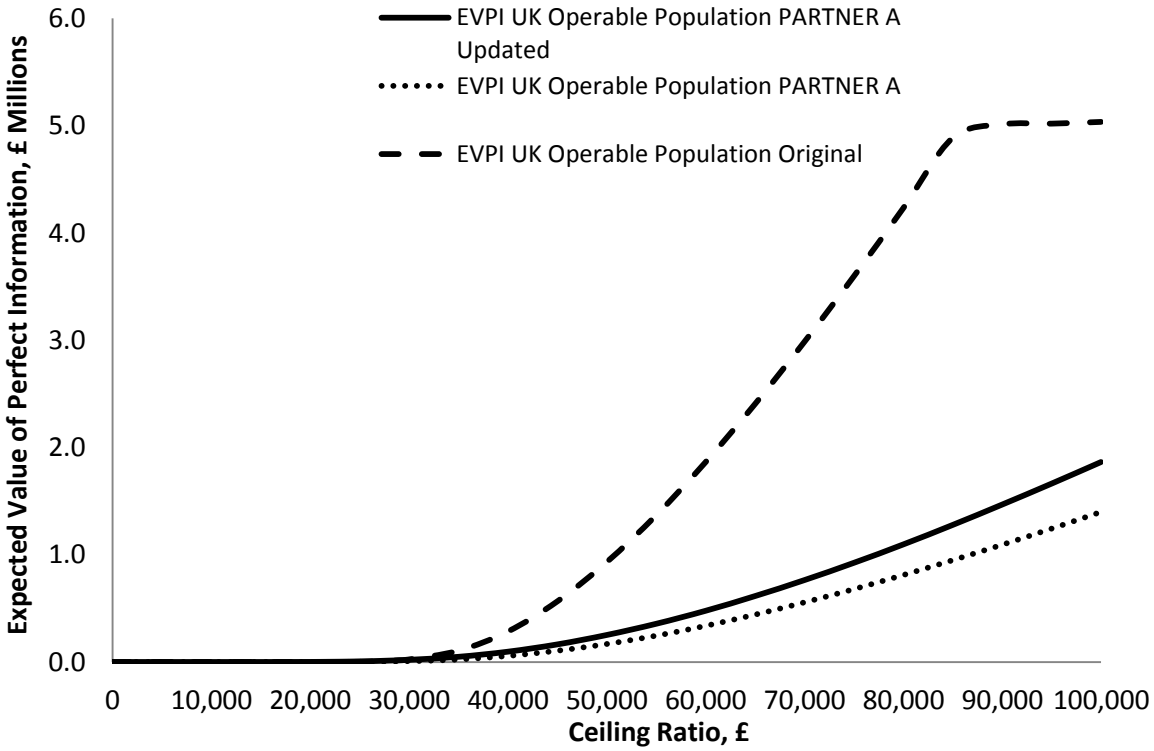


* Figures 7.15a and b differ to Figures 4.9, 6.6 and 6.10 as Medical Management is excluded from the analysis in Chapter 7.

Value of Information Analysis

The VOI analysis estimated that the pEVPI between TAVI and AVR for operable patients (2,250 (SHTG, 2009)), in the updated PARTNER A model, over the range usually considered cost-effective ranged from £0 to £23,433 over one year. This was lower than that estimated in the PARTNER A model which ranged from £37,948 to £651,917 for the same population. Which was lower than that originally estimated using data from the literature which ranged from £5,252 to £501,513 for the same population[13]. Figure 7.16 presents the pEVPI for the original, PARTNER A and updated PARTNER A models side by side for comparative purposes. As illustrated here, the additional evidence reduced the pEVPI. While some uncertainty remains there is little value in collecting further evidence on the costs and effects of TAVI compared with AVR at the national accepted ceiling ratio levels.

Figure 7.16 Expected Value of Perfect Information Comparison: Inoperable Patients - Original, PARTNER A and Updated PARTNER A Models [13]



[13] Here EVPI is considered for the decision between TAVI and AVR only. Previous EVPI analyses presented in Figures 4.16 and 6.12, considered TAVI, AVR and Medical Management simultaneously.

7.7 WHERE NOW FOR TAVI WITH OPERABLE PATIENTS?

When longer-term results for TAVI and AVR are incorporated into the model for operable patients, TAVI cannot be considered cost effective compared with AVR. There is little decision uncertainty and little value in collecting further evidence. A limitation of the re-analysis lies in the source of the additional evidence. Firstly, Moat et al. (2011) only provided evidence on PREs following TAVI in the short run from the UK TAVI Registry. Secondly, the longer term evidence presented in Kodali et al. (2012) is from the PARTNER Cohort A trial. As outlined previously (Chapter 6), commentators, such as Schaff (2011), on the advances in TAVI have indicated that results such as those produced by the PARTNER trial and earlier registries, may not be as conclusive in considering the future for TAVI as anticipated. These trials used early generations of the device and were conducted in centres with early experience in delivering the procedure (Smith et al., 2011). Over time the devices are being modified and enhanced, which should reduce risk of injury and complications (Smith et al., 2011, Webb and Cribier, 2011). Simultaneously, centres are becoming more proficient and efficient at delivering TAVI (Smith et al., 2011). Thus, the rate of complications, including stroke and other PREs, are expected to fall. These are because of incremental innovations and movements along the learning curve, which are common with medical device technologies (explained Section 1.2.1). In addition, there has been speculation that the current price of TAVI may be revised downwards as newer generations of device become available; more competitors enter the market; research and development costs are recouped or alternatively some cost-sharing scheme is established (Drummond et al., 2009, Sorenson et al., 2011).

To examine the potential impact of these changes on the cost effectiveness of TAVI a number of scenario analyses were performed and are presented here concerning the cost of the TAVI device, risk of stroke and PREs.

7.7.1 Scenario Analysis 1: Cost of TAVI

The current cost of TAVI is very high (six times the cost of the AVR device) and is expected to decline. To investigate these claims two scenario analyses (SA) were performed here (results summarised in Table 7.11).

Firstly, a scenario is considered whereby the initial cost of TAVI (including device, procedure and length of stay costs) is set equivalent to the initial cost of AVR (£18,988). This represents the possibility of the cost of the TAVI device being offset by the other procedure costs (Scenario 1.1). The analysis revealed that even with this reduction in the initial cost of TAVI it remains more expensive (£7,166; 20%) and marginally more effective (0.01; <1%) compared with AVR. This is owing to the high incidence of PREs with TAVI. The ICER is calculated as £551,323/QALY which is significantly above the acceptable ceiling ratio so TAVI cannot be considered cost effective compared to AVR. The probabilistic sensitivity analysis (PSA) revealed that at a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective is only 5%, while the probability that AVR is cost effective is 95% (Figure 7.17). Here the pEVPI for the operable UK population (2,250 (SHTG, 2009)) at £30,000/QALY is estimated at £163,103 for one year (Figure 7.18). This indicates in such a scenario, there is only some value in collecting additional information.

Secondly, a threshold analysis was performed to identify the price that the TAVI device would have to be for the ICER to be equal to £30,000/QALY in a deterministic model (Scenario 1.2). The threshold analysis revealed that holding all else constant, the price of the TAVI device would have to be lowered by 75% to £3,050, for it to be considered cost effective compared to AVR (i.e. ICER = £30,000). A PSA revealed that at this price at a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective in this scenario would be 48% while the probability that AVR is cost effective is 52% (Figure 7.17). Here the pEVPI for the operable UK population (2,250 (SHTG, 2009)) at £30,000/QALY is estimated at £3,357,524 for one year (Figure 7.18). This suggests that if such a scenario were to happen, there would be value in collecting additional information.

Table 7.11 Cost Effectiveness Results: Operable Patients – Scenario Analysis

Scenario	AVR		TAVI		ICER
	Costs £	QALYs	Costs £	QALYs	£/QALY
1.1 Equivalent Procedure Costs	34,140	3.02	41,306	3.03	551,323
1.2 Goal Seek: £30,000*	34,010	2.99	34,634	3.01	30,000
2.1 Equivalent Stroke Rates	34,171	3.02	43,561	3.02	456,867
2.2 33% Reduction in Early Major PREs TAVI	34,180	3.02	41,994	3.09	111,021
2.3 Equivalent Early, 1& 2 Year Major PREs	34,168	3.02	39,366	3.14	42,985

*Deterministic Result

Figure 7.17 Scenario Analyses 1 Cost of TAVI: Cost Effectiveness Acceptability Curve: Operable Patients – TAVI vs. AVR

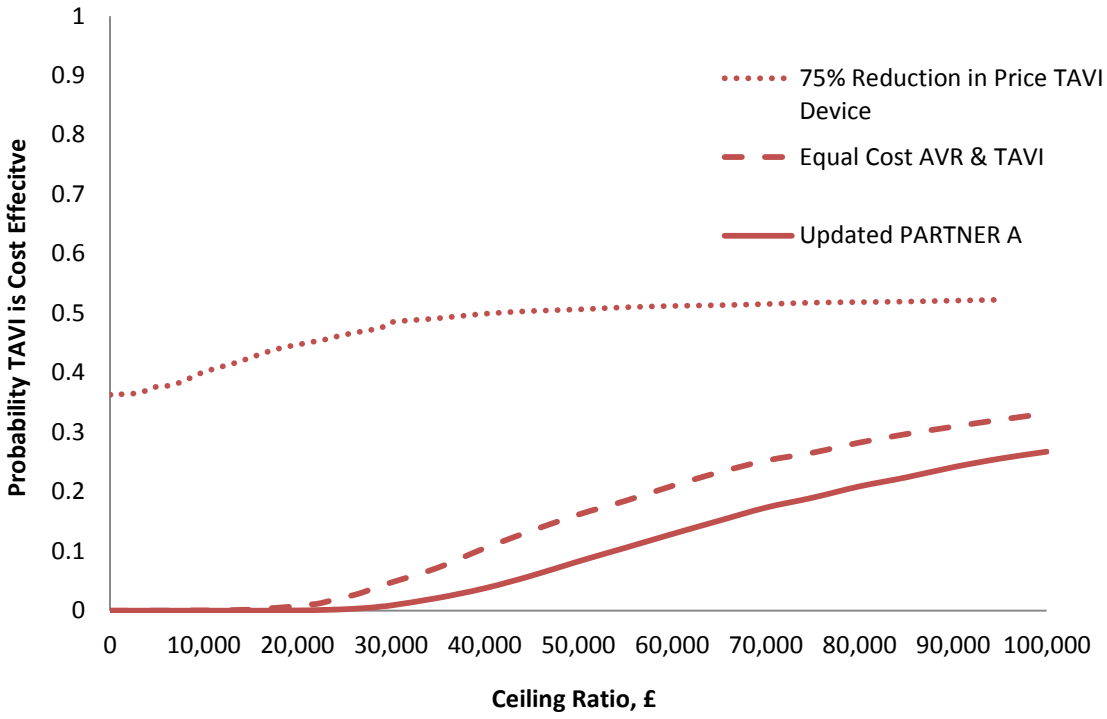
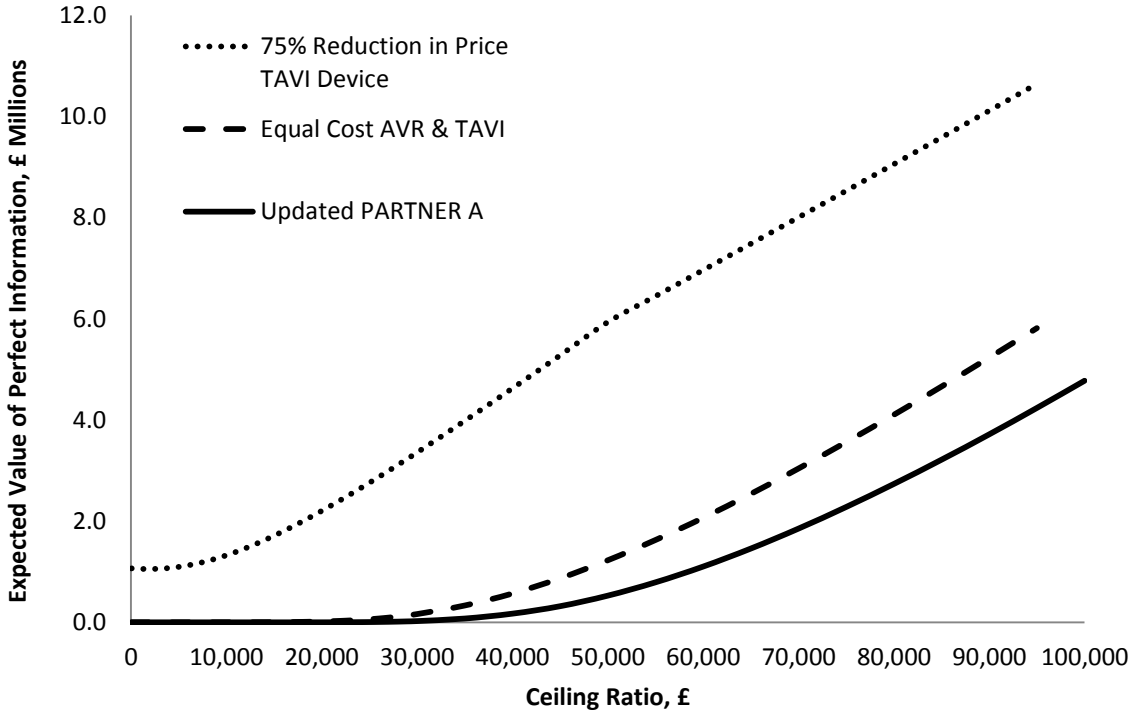


Figure 7.18 Scenario Analyses 1 Cost of TAVI: Expected Value of Perfect Information: UK Operable Population -



7.7.2 Scenario Analysis 2: Stroke Rate and Procedure Related Events

Using sensitivity analyses, the cost effectiveness analysis of TAVI produced here examines what if the stroke rate and early major PREs were reduced for these patients upon receiving TAVI through three different scenarios (results summarised in Table 7.11), compared to the baseline results employing best, currently available data.

Firstly, a scenario analysis was performed whereby early major stroke (within 30 days) following TAVI was set equivalent to the stroke rate following AVR (0.03) (Scenario 2.1). The probabilistic sensitivity analysis (PSA) revealed for this scenario TAVI is more expensive (£9,390; 22%) and generates 0.02 additional QALYs compared with AVR. The ICER is calculated as £456,867, which is significantly greater than the range usually considered cost effective, so TAVI cannot be considered cost effective compared to AVR. At a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective is only 2% while the probability that AVR is cost effective is 98% (Figure 7.19). The pEVPI for the operable UK population (2,250 (SHTG, 2009)) at £30,000/QALY is estimated at £77,694

for one year (Figure 7.20). This indicates that at such scenarios, there would be little value in collecting additional information.

Figure 7.19 Scenario Analysis 2 Stroke & Procedure Related Events: Cost Effectiveness Acceptability Curve: Operable Patients - TAVI versus AVR

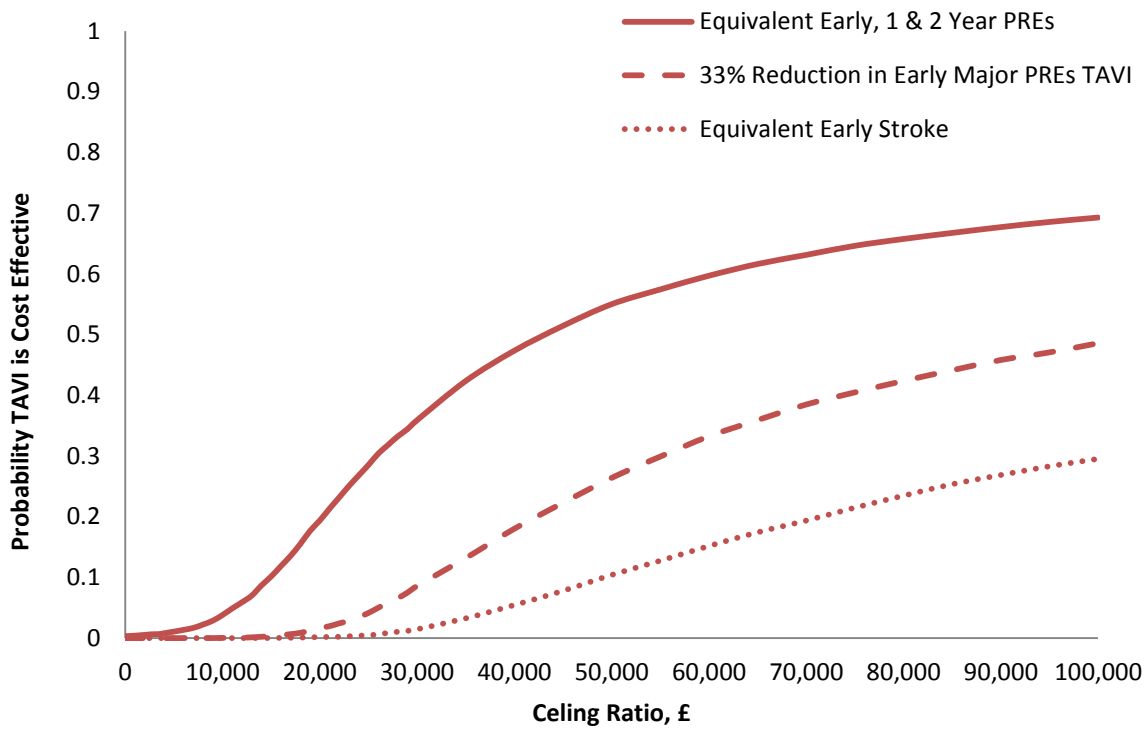
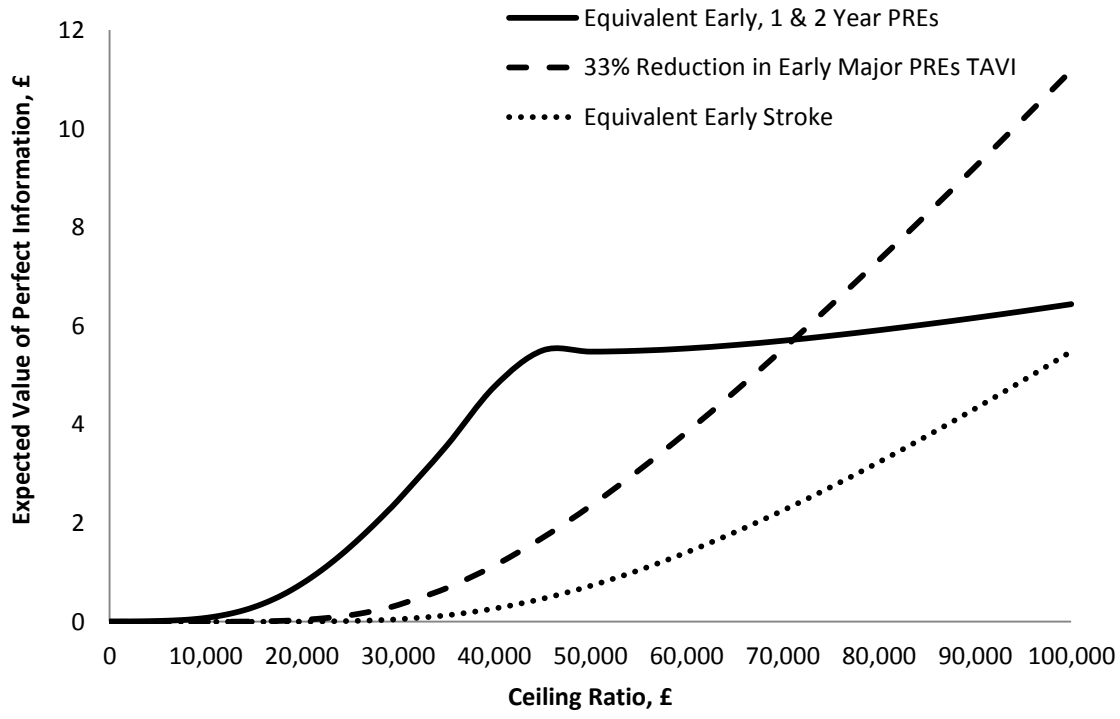


Figure 7.20 Scenario Analysis 2 Stroke & Procedure Related Events: Expected Value of Perfect Information: UK Operable Population -



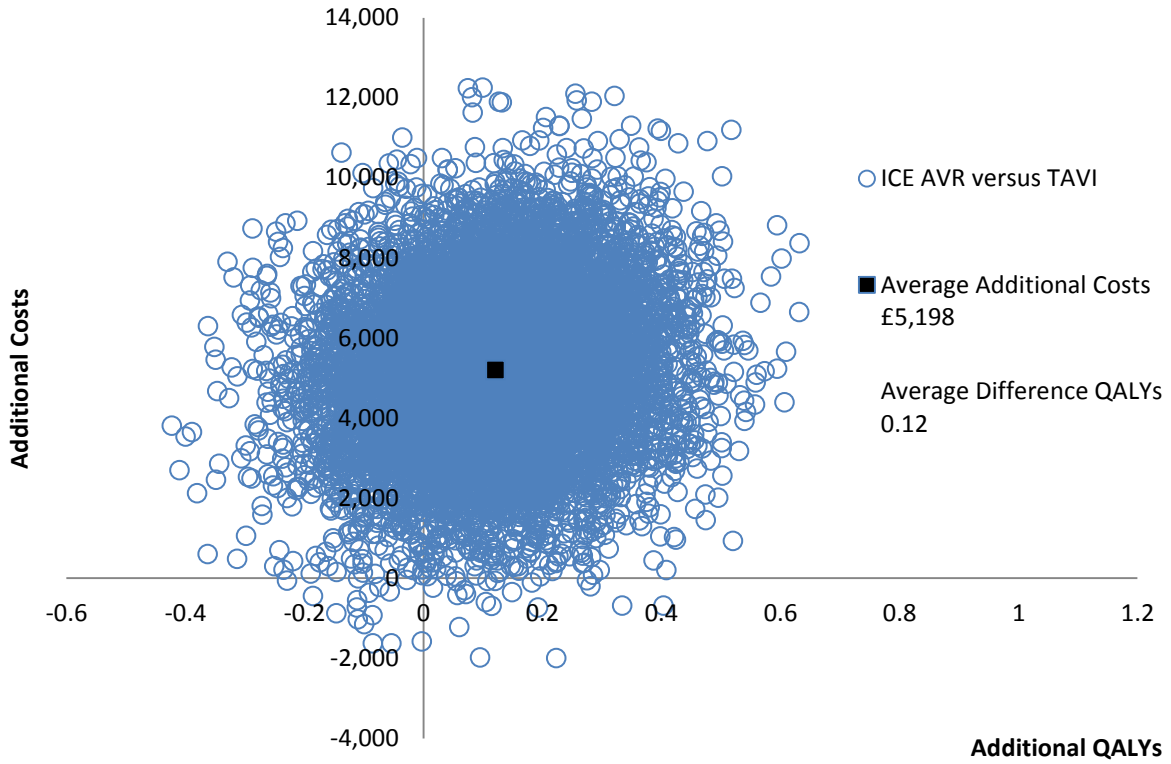
Secondly, a scenario analysis was performed whereby all early major PREs following TAVI were reduced to a third of those reported (in Section 7.6) (Scenario 2.2). (A reduction of a third was selected based on expert opinion (Toff, 2011).) The PSA revealed for this scenario TAVI is more expensive (£7,814; 23%) and generates more QALYs (0.07; 2%) than AVR. Here the ICER is estimated to be £111,021/QALY which is outside the range usually considered cost effective. At a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective is only 9% while the probability that AVR is cost effective is 91% (Figure 7.19). Here the pEVPI for the operable UK population (2,250 (SHTG, 2009)) at £30,000/QALY is estimated at £340,447 for one year (Figure 7.20). Indicating that in this scenario there is some value in collecting further information.

Thirdly, a scenario analysis was performed whereby the early, 1 year and 2 year major PREs following TAVI were reduced and set equivalent to those associated with the AVR procedure (Scenario 2.3). In this analysis, TAVI remained more expensive (£5,198; 15%) owing to the cost of the TAVI procedure etc. but generated more QALYs (0.12; 4%) than AVR. The ICER associated with TAVI is estimated at £42,985, which is marginally above the level generally considered cost effective in the UK. Thus, even with equivalent PREs to AVR, TAVI is still not cost effective amongst these patients, suggesting that the TAVI device is too expensive. If the price of the TAVI device fell and PREs improved then it may be considered cost effective.

The ICE plane (Figure 7.21) shows that in this scenario, uncertainty remains in both the existence and extent of the differences in costs and QALYs. This translates to an increase in the decision uncertainty (compared to the updated PARTNER A model). At a ceiling ratio of £30,000/QALY, the probability that TAVI is cost effective is 36% while the probability that AVR is cost effective is 64% (Figure 7.19).

This increase in the decision uncertainty leads to an increase in the maximum potential worth of further evidence concerning the relative effectiveness and associated costs of TAVI. The pEVPI is estimated to be £2.5 million for the UK operative population at a £30,000/QALY ceiling ratio (Figure 7.20). Given the substantial pEVPI here it was considered appropriate to undertake further calculations of VOI on parameters and sample information for this scenario analysis.

Figure 7.21 Scenario Analysis 2.3: Incremental Cost Effectiveness Plane: Operable Patients – TAVI versus AVR



7.8 COLLECTING FURTHER EVIDENCE – BAYESIAN VALUE OF INFORMATION ANALYSIS FOR OPERABLE PATIENTS

Operable patients account for approximately 45% of the potential UK TAVI market (2,250 patients (SHTG, 2009)). However, given current evidence TAVI cannot be considered cost effective for operable patients compared to AVR. It is worth noticing that the iterative cost effectiveness analyses performed in this thesis are heavily reliant on the PARTNER A trial results for operable patients. While this trial was a major contribution to the TAVI evidence base (being the first randomised controlled trial), it has limitations and its usefulness has been subject to criticism regarding it use of early devices in centres with early experience.

The NICE Guidance document revised in March 2012 (IPG421) states that for patients with AS, who are considered operable and do not pose a high risk, TAVI may only be used

in the context of research (NICE, 2012). This recommendation is owing to inadequate evidence, which is a signal that the TAVI evidence base is still evolving and further evidence is required to demonstrate TAVI's cost effectiveness. However, the EVPI estimates on the updated PARTNER A model (pEVPI is £24,375 at £30,000/QALY, Section 7.6) demonstrate there is little value in collecting further information based on currently, available data. It is anticipated however, that if new evidence (non-PARTNER) were to become available it may demonstrate improved TAVI outcomes amongst operable patients. The effect of such improvements was analysed in the previous section through scenario analyses which indicated that with improved TAVI outcomes the likelihood of TAVI being considered cost effective improves and there would be value in collecting further information. In which case, a sensible strategy may be to wait for additional evidence to emerge from other jurisdictions.

Alternatively, primary data could be collected using a specific UK clinical trial or utilising and expanding the existing UK TAVI Registry. Using the expected net benefits estimated in the scenario analysis (2.3 in Section 7.7), where the probability of major PREs following 30 days, one year and two year were set equivalent to those following AVR, a further Bayesian VOI analysis is performed and presented here. This examines on which parameters future evidence is most valuable, using Expected Value of Partial Perfect Information (EVPPI) and how this future evidence should be collected, using Expected Value of Sample Information (EVSI), in the context of the scenario analysis.

The EVPPI analysis indicates the maximum potential value associated with further data collection for specific parameters and/or groups of parameters. It estimates the value of eliminating the uncertainty surrounding those parameters under consideration, providing a maximum value that society would be willing to invest in further research concerning those parameters. While the EVSI estimates the value of a reduction in uncertainty associated with the collection of specific information based on a particular research design. (These techniques were described in detail in Chapter 2.)

As outlined above, additional evidence can be collected via trials or registries. It is anticipated that both of these methods would have the power to collect additional information short term transition probabilities; long term transition probabilities; resources consumed and quality of life/utility information for patients. Whereby, the trial would collect this evidence for both procedures and the registry would only collect this for TAVI.

This expectation is informed by what is currently collected in the UK TAVI registry (as per Ludmann (2010)) and what was collected in the PARTNER trial (see Appendix VI). These parameters are grouped into eight groups as shown in Table 7.12.

Table 7.12 Parameter Groups for a Potential Clinical Trial and Registry for Operable Patients

1 Short Term Outcomes	**2 Short & Long Term Outcomes**	**3 Quality of Life**	**4 Resources**
Major PRE AVR	Major PRE AVR	Utility Fn TAVI	Total LOS AVR
Major PRE TAVI	Major PRE TAVI	Utility persistent AS TAVI	Total LOS TAVI
Minor PRE AVR	Minor PRE AVR	Utility Fn AVR	Post discharge AVR
Minor PRE TAVI	Minor PRE TAVI	Utility persistent AS AVR	Post discharge TAVI
Converting to AVR	Converting to AVR		Cost functioning AVR
Converting to MM	Converting to MM		Cost functioning TAVI
Converting to TAVI	Converting to TAVI		Cost persistent AS AVR
Repeat TAVI	Repeat TAVI		Cost persistent AS TAVI
Major stroke AVR	Major stroke AVR		
Major stroke TAVI	Major stroke TAVI		
Death 30 days AVR	Death 30 days AVR		
Death 30 days TAVI	Death 30 days TAVI		
	late pre TAVI fatal yr 1		
	late pre AVR fatal yr 2		
	Late PRE TAVI		
	Late PRE AVR		
	Late minor PRE TAVI		
	Late minor PRE AVR		
	Late PRE TAVI yr 2		
	Late PRE AVR yr 2		
	Late minor PRE TAVI yr 2		
	Late minor PRE AVR y2		
	Late fatal PRE AVR y2		
	Late fatal PRE TAVI yr2		
	Relative risk of mortality AS		
	Death AS – TAVI		
	Death AS – post 1 year		

5 Short Term Outcomes – TAVI Only	**6 Short & Long Term Outcomes – TAVI Only**	**7 Quality of Life – TAVI Only**	**8 Resources– TAVI Only**
Major PRE TAVI	Major PRE TAVI	Utility Fn TAVI	Total LOS TAVI
Minor PRE TAVI	Minor PRE TAVI	Utility persistent AS TAVI	Post discharge TAVI
Converting to AVR	Converting to MM		Cost functioning TAVI
Converting to MM	Repeat TAVI		Cost persistent AS TAVI
Repeat TAVI	Major stroke TAVI		
Major stroke TAVI	Death 30 days TAVI		
Death 30 days TAVI	Late pre TAVI fatal yr 1		
	Late PRE TAVI		
	Late minor PRE TAVI		
	Late PRE TAVI yr 2		
	Late minor PRE TAVI yr 2		
	Late fatal PRE TAVI yr2		
	Relative risk of mortality AS		
	Death AS – TAVI		
	Death AS – post 1 year		

7.8.1 Clinical Trial

An application for a funded UK TAVI clinical trial was made to the NHS HTA committee and subsequently appealed and reapplied for in 2011 (NIHR, 2010) and was accepted in spring 2012 (NICE, 2012). The application was for a prospective, multi-centre, pragmatic, randomised control trial comparing TAVI with AVR amongst operable patients with severe symptomatic aortic stenosis. Data would be collected in specialist hospitals deemed to have an active cardiac surgical and TAVI programme which had performed at least 30 prior TAVI procedures. At the time of the proposal this included 20 centres around the UK. The target patient population was those with severe, symptomatic AS who have been referred for surgery. Patients would be 80 years or over, with one or more factors indicating high operable risk. The suggested sample size (as set out in the 2011 application) was 808 patients. The estimated fixed costs were £2,250,000 and variable costs were estimated to be £15,000 per patient[14] (Toff, 2012). The proposal identified that data would be collected over nine years, with five year minimum follow up. Examining the trial application it was apparent that the data collected would provide additional information on short and long term probabilities, utilities, resources and long term mortality. A list of the parameters such a clinical trial could provide information on is provided in Appendix VI.

Expected Value of Perfect Parameter Information

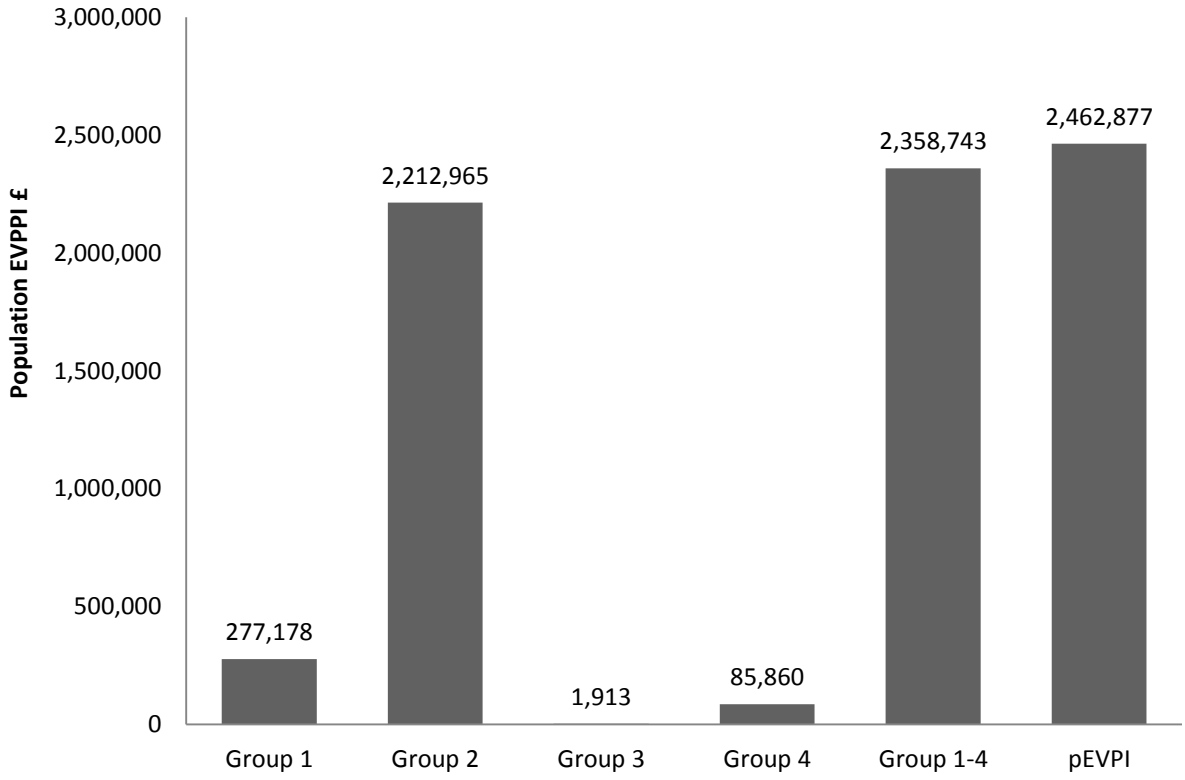
If a clinical trial, such as that described above was to be used to collect additional information it could potentially collect information on short and long term transition probabilities; mortality rates; resources and utilities for TAVI and AVR respectively. Thus, four groups of parameters (groups 1-4, Table 7.12) were considered individually and simultaneously in estimating the EVPPI, to indicate the maximum potential value associated with further data collection on those parameters.

Figure 7.22 illustrates the population EVPPI for these groupings at a ceiling ratio of £30,000/QALY. The results of the EVPPI analysis indicates that if further data collection was to provide evidence on group 2 individually, the short and long term events and mortality parameters following TAVI and AVR, would be worth a maximum of £2.21

[14] Cost estimates are based on consultation with experts from the proposed UK TAVI trial (Toff, 2012)

million for the UK population, at a ceiling ratio of £30,000/QALY. At this ceiling ratio there is no value in collecting evidence on short term probability, resource or quality of life parameters in isolation. While collecting additional evidence on the four groups simultaneously, would be worth a maximum of £2.36 million for the UK population, at £30,000/QALY. The population EVPI at £30,000/QALY is shown here also for comparison.

Figure 7.22 Expected Value of Perfect Parameter Information: UK Population – at Ceiling Ratio of £30,000/QALY (Clinical Trial)

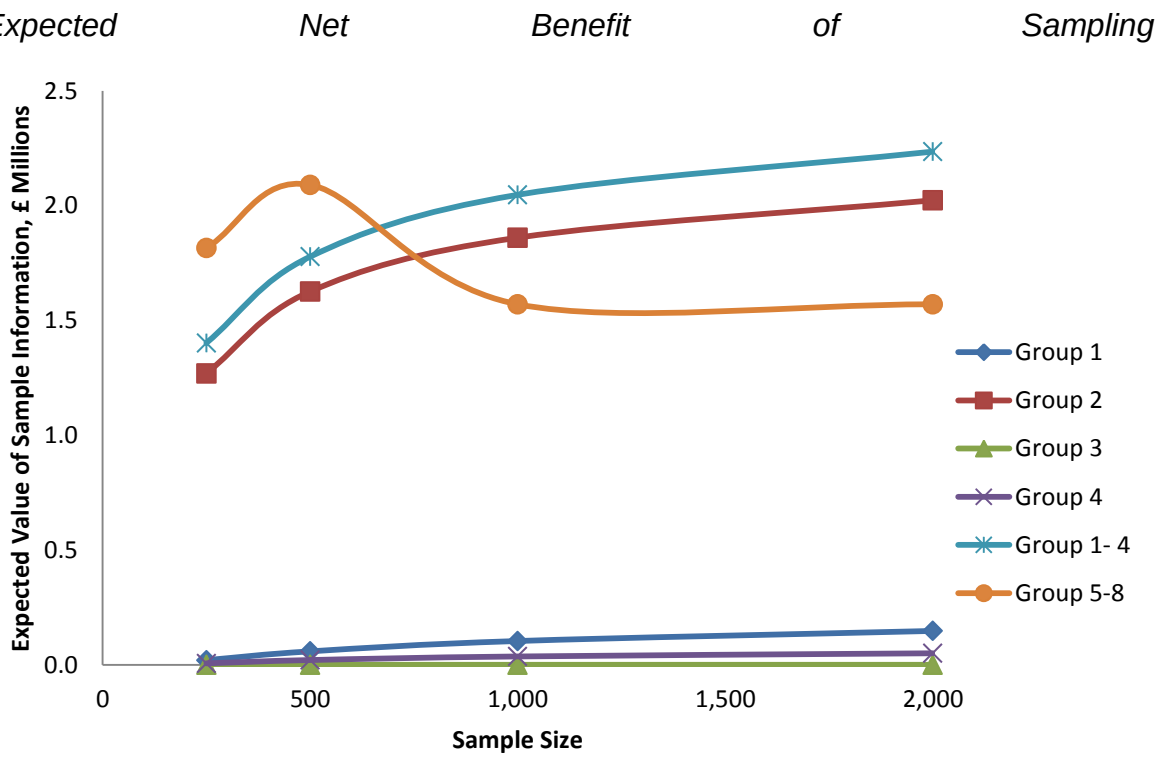


Expected Value of Sample Information

EVSI is calculated for groups 1-4 individually and simultaneously (illustrated as the blue line, series five on Figure 2.23), representing the clinical trial, for a variety of sample sizes: 250; 500; 1000 and 2000 (summarised in Table 7.13). The results indicate that with a sample size of 250 patients the EVSI for the trial is £1.40 million (at a ceiling ratio of £30,000/QALY) for the UK population for one year. If the sample size increases to 500 patients, the EVSI increases to £1.78 million for the UK population for one year at £30,000/QALY. Increasing the sample size to 1,000 patients increases the EVSI for the

trial to £2.05 million for the UK population for one year at £30,000/QALY. Finally, with a sample size of 2,000 patients the EVSI for the trial is £2.23 million for the UK population for one year at £30,000/QALY.

Figure 7.23 Expected Value of Sample Information: Operable Patients

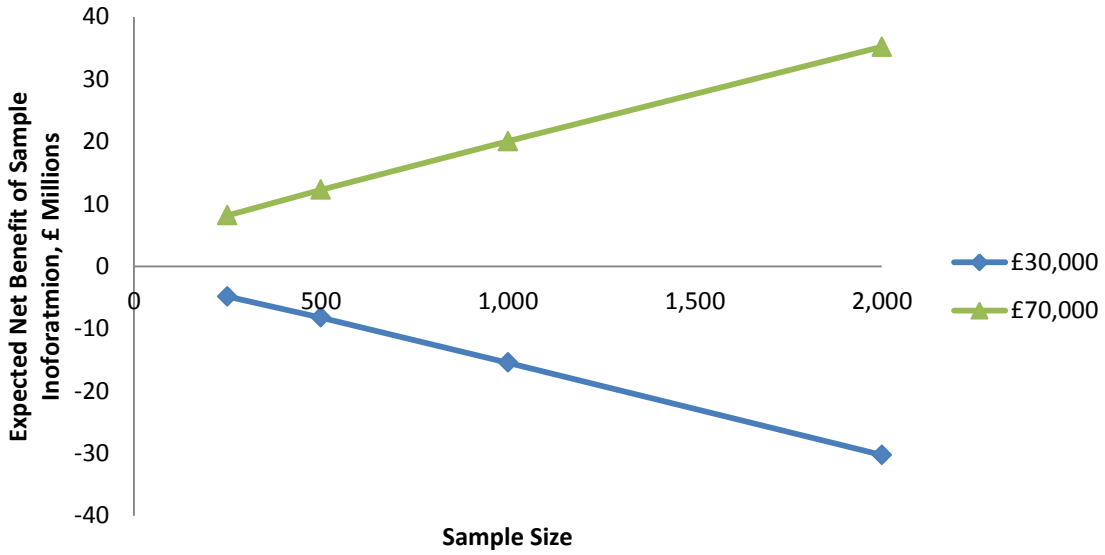


As discussed in Chapter 5, in the context of Figure 5.10, the EVSI analysis employed here (Figure 7.23) is also subject to limitations. It was not computationally feasible to increase the number of iterations employed, owing to computing constraints. Methodological developments in meta-models etc. over time should reduce the practical challenges associated with implementing EVSI.

The expected costs for a UK TAVI trial for operable patients were estimated using the same estimates considered in Chapter 5 (Toff, 2012). Fixed costs are estimated to be £2.25 million and variable costs are estimated to be £15,000 per patient. These expected costs can be compared to the expected benefit of the trial (measured by EVSI) to estimate the expected net benefit of sampling (ENBS).

For example, the expected value (EVSI) for a trial with 2,000 patients is £2.2 million (at £30,000/QALY). The expected cost of this trial is £32.5 million (estimated using fixed cost of £2.25 million and variable costs £30 million (£15,000 * 2,000 patients)). As the expected costs are greater than the EVSI, the ENBS is negative, indicating that a trial of this size and magnitude cannot be considered cost effective. This is repeated for different sample sizes. The ENBS results indicate that at a ceiling ratio of £30,000/QALY, across the four sample sizes, the ENBS for the trial is negative. Thus, the trial cannot be considered cost effective at the £30,000/QALY ceiling ratio (used to estimate EVSI). However, if the nationally accepted ceiling ratio was increased to £70,000 per QALY, the ENBS across the sample sizes is positive, indicating the trial would be viable, as demonstrated on Figure 7.24.

Figure 7.24 Expected Net Benefit of Sampling: Clinical Trial - Operable Patients



Using the expected costs estimated above, an approximation for how long the information from the trial would have to be relevant for to recoup the costs can be estimated. This is calculated by dividing the expected trial cost by the EVSI. For example, a trial with sample size of 250 patients is estimated to cost £6.25 million (based on the fixed and variable costs from above). A trial capable of collecting information on all parameters in groups 1-4 with this sample size has an EVSI of £1.4 million. Thus, to recoup the costs of the trial, the

information collected from it would need to be relevant for approximately four and a half years. Similarly for a trial with 2,000 patients, the expected costs are £32.5 million (including NHS service cost) and the EVSI is £2.2 million. Thus, to recoup the costs of the trial the information collected from it would need to be relevant for 14.5 years. These results are summarised in Table 7.13. Given the nature of novel medical devices like TAVI, information from trials like that proposed here are unlikely to yield information relevant for such long periods.

Table 7.13 Expected Value of Sample Information: Clinical Trial - Operable Patients

Sample Size	EVSI @ £30,000/QALY Groups 1-5	Cost of Trial* £ Millions			
		6.25 (n=250)	10.0 (n=500)	17.5 (n=1,000)	32.5 (n=2,000)
		Years to Recoup Costs			
250	1,401,705	4.46			
500	1,777,388		5.63		
1,000	2,046,758			8.55	
2,000	2,234,948				14.54

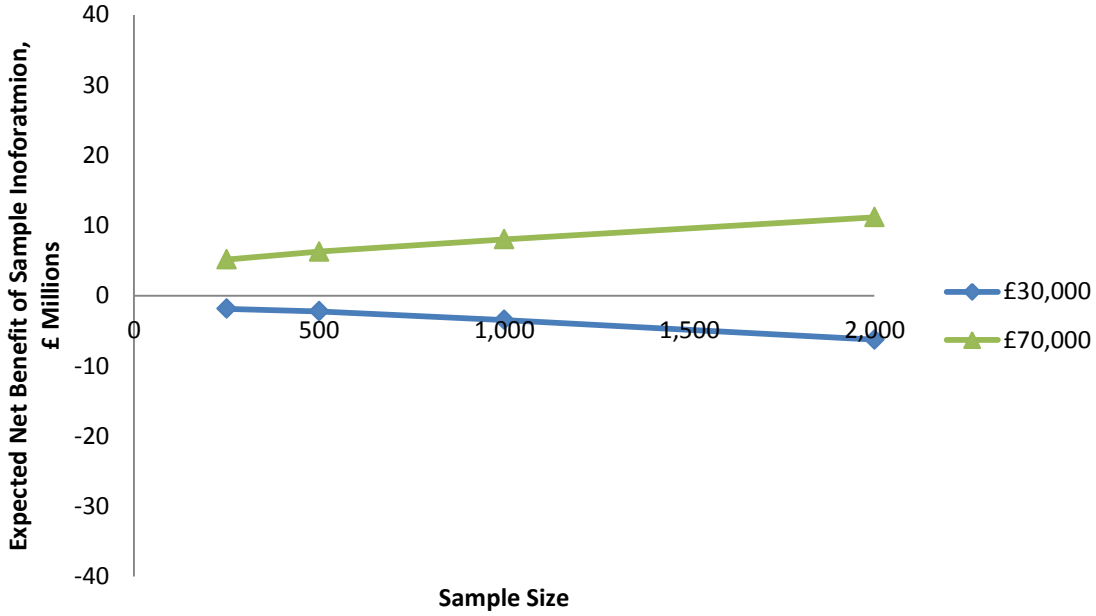
*Costs are based on fixed costs £2.25 million and variable costs of £15,000 per patient as per expert opinion (Jones, 1995).

Given the disincentives which persist for collecting additional evidence for medical devices and the attention TAVI has attracted, it is possible that such a trial may receive sponsorship from one or more device manufactures (as was the case previously for the PARTNER trial which was funded by Edwards LifeSciences). This could reduce the variable costs of the trial by up to £12,000 (assuming the sponsor covers the cost of the TAVI device). ENBS of the TAVI trial with fixed costs remaining at £2.25 million and variable costs reducing to £3,000 per patient revised the ENBS as follows (the sample design remains the same as above).

At a ceiling ratio of £30,000/QALY, across the four sample sizes the ENBS remains negative, even for the sponsored trial. However, if the nationally accepted ceiling ratio was increased to £70,000/QALY, a trial with sample size of 2,000 would have the highest net benefit, with an ENBS of £11.2 million. These ENBS results are presented on Figure 7.25.

This indicates that at the current range of nationally accepted ceiling ratio, i.e. what society is willing to pay for an extra QALY, even sponsorship trial there a clinical trial of this magnitude at the current expected costs is not economically viable.

Figure 7.25 Expected Net Benefit of Sample Information: Sponsored Clinical Trial - Operable Patients



7.8.2 Registry

An alternative to an expensive clinical trial would be to expand the existing UK TAVI Registry (Ludmann, 2010) to collect additional evidence. As per NICE guidelines, details on all TAVI procedures performed in the UK are recorded through the Central Cardiac Audit Database (CCAD) (Ludmann, 2010). From this database the UK TAVI Registry has developed through collaboration between the BSCIS and STCTS[15], Department of Health and Special Commissioners and Health Technology Assessment and NICE. Appendix VI shows the evidence currently being collected in the UK TAVI Registry and what additional evidence could be collected through a registry. It is anticipated that an extension of the UK TAVI Registry could collect additional evidence on the following types of parameters associated with the TAVI procedure: (1) short term probabilities, (2) short and long term

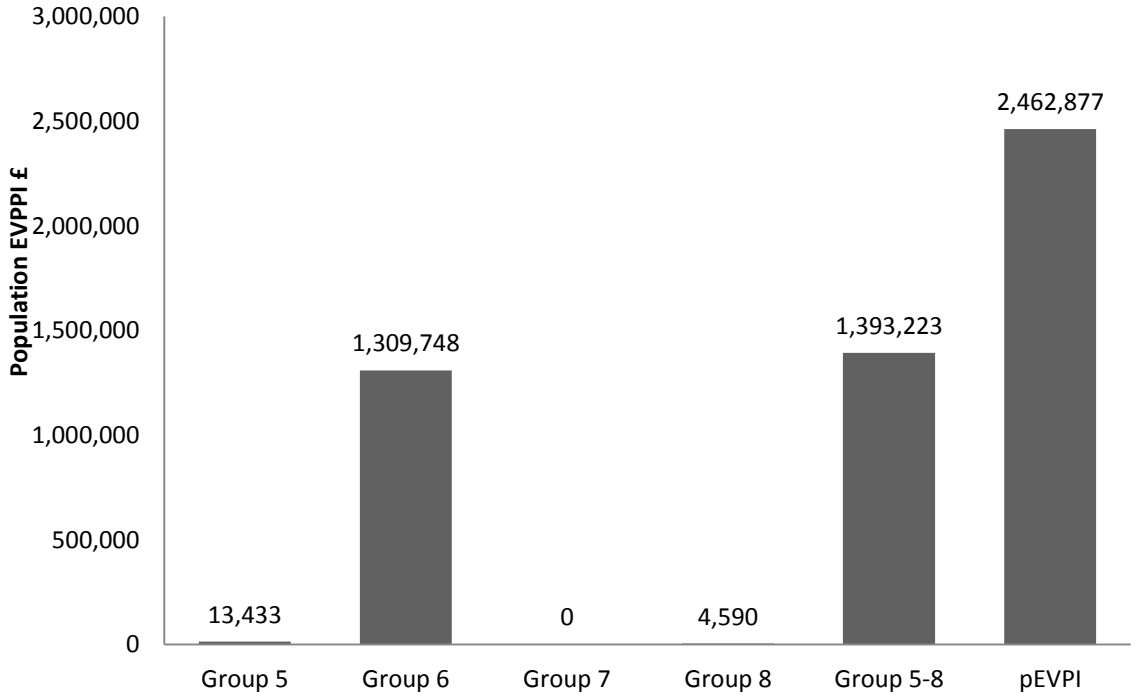
[15] British Cardiovascular Intervention Society (BCIS), Society of Cardiothoracic Surgeons (SCTS)

probabilities (including long term mortality), (3) utility and, (4) resources consumed. These correspond to parameter groups (5-8) listed in Table 7.12.

Expected Value of Perfect Parameter Information

An EVPPI analysis illustrates the maximum potential worth of collecting data on TAVI for each of the groupings through an expanded UK TAVI Registry. Data collected on group 6 individually, short and long term probabilities parameters for TAVI, would be worth a maximum of £1.31 million for the UK population, at a £30,000/QALY. At this threshold there is little value in collecting evidence on any of the remaining groups of parameters (5, 7 or 8) in isolation. However, if further data was collected on all the parameters contained in groups 5-8 simultaneously, it would be worth a maximum of £1.39 million for the UK population, at a ceiling ratio of £30,000/QALY. Figure 7.26 illustrates the population EVPPI for each grouping for a range of values of cost effectiveness thresholds. The population EVPI is also shown here for comparison at £30,000/QALY.

Figure 7.26 Expected Value of Perfect Parameter Information: UK Operable Population – at Ceiling Ratio of £30,000/QALY (Registry)



Expected Value of Sample Information

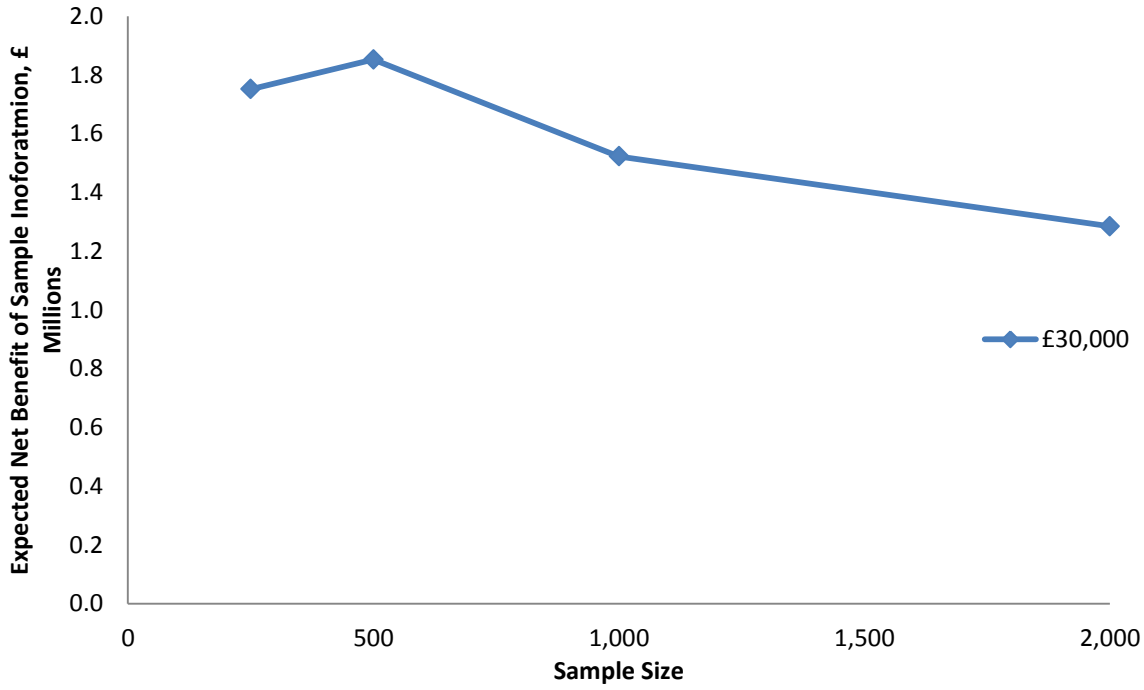
Using the same groups of parameters as per the EVPPI calculations the EVSI was estimated for a variety of sample sizes: 250, 500, 1,000 and 2,000. Firstly, with a sample size of 250 patients the EVSI analysis revealed that collecting data on all parameters within groups 5-8 simultaneously was worth £1.86 million (at a ceiling ratio of £30,000/QALY) for the UK population for one year. Secondly, with a sample size of 500 patients the EVSI, when collecting data on all parameters in groups 5-8 simultaneously, was worth £1.98 million for the UK population for one year at £30,000/QALY. Thirdly, with a sample size of 1,000 patients the EVSI, when collecting data on all parameters in groups 5-8 simultaneously, was £1.67 million for the UK population for one year at £30,000/QALY. Finally, with a sample size of 2,000 patients the EVSI, when collecting data on all parameters within groups 5-8 simultaneously, was £1.49 million for the UK population for one year at £30,000/QALY. These are illustrated as the orange line on Figure 7.23.

Expected Net Benefit of Sampling

Following consultation with experts (Cunningham, 2012) the fixed costs of a registry were estimated at £100,000 and variable costs were estimated as £50 per patient for operable patients. These expected costs were compared to the expected benefit of the trial (measured by EVSI) to estimate the expected net benefit of sampling (ENBS). The ENBS is estimated for four sample sizes, ranging from 250 to 2,000 (Figure 7.27).

For example, the expected value (EVSI) for a trial with 2,000 patients is £1.49 million. The expected cost of this trial is £200,000 (estimated using fixed cost of £100,000 and variable costs £100,000 (£50 * 2,000 patients)). As the expected costs are less than the EVSI (at £30,000/QALY ceiling ratio), the ENBS is positive, indicating that a registry of this size and magnitude can be considered cost effective.

Figure 7.27 Expected Net Benefit of Sampling: Registry - Operable Patients



7.8.3 The Future for TAVI for Operable Patients

This thesis applied an iterative approach to using a decision analytical model to handle the developing and evolving nature of TAVI's evidence base, in assessing the cost effectiveness of TAVI for operable patients. From the analysis it is evident that the challenges associated with medical devices persist for this patient group. These include evolving evidence owing to incremental innovations, movements along the learning curve etc. Also, as this group is lower risk than inoperable patients, the benefits to be gained from TAVI are less than those for inoperable patients. This can discourage evidence generation amongst this patient group. In addition, given that approval has been granted for TAVI amongst inoperable patients, there is a risk that the disincentives for further research in this patient group will remain.

The Bayesian Value of Information (VOI) analysis performed here using the results of the scenario analysis demonstrated there would be value in collecting further evidence on short and long term transition probabilities, resources and quality of life parameters for TAVI and AVR in the context of Scenario 2.3, Section 7.7. As for how this evidence should be collected, the EVPPI demonstrates that at a ceiling ratio of £30,000/QALY, there is value

in collecting this information on AVR and TAVI via a clinical trial or on TAVI only via a registry, in the context of Scenario 2.3 from Section 7.7.

However, evidence collection is not cheap. Using the estimates of expected costs (based on expert opinion (Cunningham, 2012, Toff, 2012)) and the EVSI estimates, the expected net benefit of sampling (ENBS) for a clinical trial (sponsored and unsponsored) and registry were calculated. The results indicated that for a clinical trial (even with sponsorship) the costs exceed the benefits at a ceiling ratio for £30,000/QALY, so it cannot be considered cost effective. Meanwhile, at a ceiling ratio of £30,000/QALY, a registry could be considered cost effective.

Nevertheless, uncertainties persist for this patient group and the UK TAVI Trial is going ahead as indicated in the most recent NICE guidance (Number 421, 2012) (NICE, 2012). This recommends that TAVI is only performed on operable patients in the context of research ("only in research"). Whereby, they encourage clinicians to report all procedures in the forthcoming UK TAVI Trial and the UK Central Cardiac Audit Database (i.e. the UK TAVI Registry). Thus, a form of Access with Evidence Development is being initiated.

The analysis presented in Section 7.6 suggested there was no value in collecting further information and the analysis based on the scenario analysis. Also, a clinical trial could not be supported, owing to the negative ENBS, Nevertheless, a chief shortcoming of the evidence surrounding novel medical devices, like TAVI, is the lack of evidence on their long term performance. One reason for this is the lack of requirements for evidence, which in turns creates disincentives for research. In particular, there are disincentives for research on medium to low risk patients where the gains are less than those for high risk patients.

A publically funded trial, like the UK TAVI Trial, endeavours to overcome these disincentives and to ensure evidence is collected before the device becomes part of routine clinical practice. It also avoids genericization by considering all devices and given the lengthy timeframe for the trial (approximately nine years) incremental innovations and movements along the learning curve should be captured. Also, it is anticipated that the trial will overcome some of the persistent challenges facing TAVI, owing to its medical device characteristics, the current evidence base and the stage it is at in its lifecycle. Thus, the UK TAVI Trial provides an opportunity to capture the advances in the evidence base since PARTNER. Another advantage of the proposed trial lies in its positioning within the NICE

guidance. Recommending "only in research" provides a means of collecting evidence in a pragmatic trial setting which should align the trial findings more closely to those expected in clinical practice. Such a recommendation is in line with Access with Evidence Development strategies which aim to grant coverage (albeit on a limited basis) while collecting additional evidence in a clinical practice setting. The additional evidence generated can be used to inform future adoption and research priority setting decisions, in line with the continuous iterative framework conceptualised in Chapter 2.

7.9 WHERE NOW WITH TAVI FOR ALL PATIENTS?

In this Chapter a third iteration of the TAVI model for operable and inoperable patients was performed to re-address the adoption and research priority setting decisions. Using evidence of late outcomes from the PARTNER trial and subsequent outcomes from European registries, the decision analytical model was updated and the cost effectiveness and VOI analyses were re-assessed for inoperable and operable patients respectively.

The results revealed that TAVI can be considered cost effective for treating inoperable patients compared to medical management. This supports the latest NICE guidance which recommends the use of TAVI for inoperable patients. The additional NICE recommendation that all details of the aforementioned procedures are entered into the UK Central Cardiac Audit Database for the UK TAVI Registry is welcomed, despite the low pEVPI at a ceiling ratio of £30,000/QALY, it has low collection costs. The continual collection of evidence ensures that up to date evidence on TAVI for inoperable patients is available to inform any future decisions regarding TAVI in the patient group, as per the continuous iterative framework.

In contrast, , the results of the analysis presented here suggest that TAVI still cannot be considered cost effective for treating operable patients compared to AVR and there is no value in collecting further information. It is suspected that in this patient group uncertainties and immature evidence remain. One explanation is owing to the persisting reliance on PARTNER outcomes. Despite the findings of this study, the latest NICE guidance advocates the collection of additional information via the forthcoming UK TAVI Trial and the UK TAVI Registry. While not cost effective this formal evidence collection

will add to the evidence base and its deployment via clinical practice is in line with Access with Evidence Development which is noteworthy. However, the expected costs of collecting information via a trial, even if sponsored, are high. Even under the scenario analysis presented here an expanded registry is more cost effective than a trial and the results of this analysis suggest such additional information will have little impact on the cost effectiveness results of analysis.

Having conducted an iterative economic evaluation of TAVI, focus now turns to the lessons learned from the case study and the recommendations for future economic evaluations of expensive novel medical devices with evolving evidence, presented in Chapter 8.

CHAPTER 8 CHALLENGES, LESSONS AND RECOMMENDATIONS FOR ECONOMIC EVALUATIONS OF HEALTH TECHNOLOGIES WITH AN EVOLVING EVIDENCE BASE

8.1 INTRODUCTION

While the methods for economic evaluations (described in Chapter 2) are well established for all types of health technologies, most international guidelines for conducting them are developed in the context of drugs (Drummond et al., 2009, Drummond et al., 2008). The National Institute of Clinical Excellence's (NICE) appraisal programme, which is explicitly for medical devices, is one of the first of its kind (Sorenson et al., 2011). There is also considerable variability between how drugs and devices are regulated. These factors, along with some unique characteristics of medical devices (presented in Chapter 1), present challenges for conducting economic evaluations of them (Drummond et al., 2009, Taylor and Iglesias, 2009). Such challenges include the lack of formal processes for adoption, difficulties with conducting randomised control trials (RCTs), the learning curve and innovative nature of devices which result in evolving evidence, the suitability of genericization and changes in prices (explained in Section 1.2.1). While previous studies (for example, Sorenson (2011)) identified these challenges retrospectively, this case study of TAVI is the first to investigate the challenges and identify potential solutions while conducting an economic evaluation. These challenges do not mean that cost effective studies are impossible; rather that the full range of methods for conducting an economic evaluation (Chapter 2) should be utilised to overcome the challenges. In particular, the continuous iterative framework proposed in Chapter 2 can be implemented to handle these challenges.

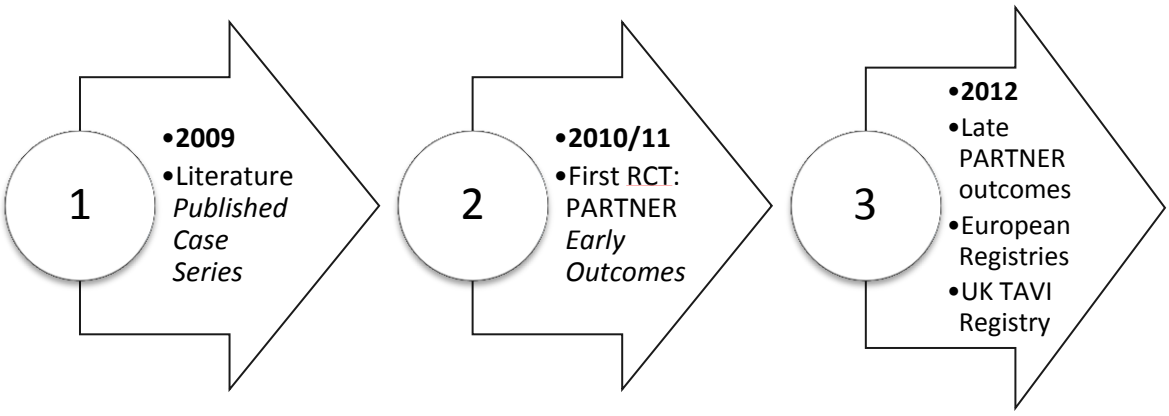
TAVI is employed in this thesis as a case study to investigate how economic evaluations of expensive, novel medical devices can be performed efficiently and informatively to advise adoption and research priority setting decisions as evidence develops using the continuous iterative framework proposed in Chapter 2. To investigate this, a decision analytical model

(DAM) is constructed and three iterations are performed for both operable and inoperable patients. While others have considered the cost effectiveness of TAVI for operable or inoperable patients amongst AS patients using PARTNER evidence (Neyt et al., 2011, Orlando, 2011, Reynolds et al., 2012, Watt et al., 2011) this is the first time an iterative framework is applied for both operable and inoperable patients. Also, the consideration of the Value of Information (VOI) for operable and inoperable patients is an important contribution of the thesis, as other studies only highlighted the need for further evidence qualitatively but did not formally quantify its value using Bayesian VOI. The results of the iterative economic evaluation and VOI are summarised below. Also, in conducting the evaluation characteristics of novel technologies like TAVI became apparent which provided challenges for the evaluation. These challenges are identified and reflected upon here, proposals for overcoming the challenges are considered and recommendations are made.

8.2 COST EFFECTIVENESS ANALYSIS AND VALUE OF INFORMATION ANALYSIS – TAVI

To investigate the cost effectiveness of TAVI in treating severe AS, the thesis considered two subgroups patients with severe AS: operable and inoperable patients (defined by risk). Operable patients were defined as those eligible to receive AVR, so the choice of treatment was between AVR, TAVI and medical management (depending on risk level). Inoperable patients were those considered unsuitable for AVR owing to high risk of operative mortality so the treatment choice was between TAVI and medical management. A DAM consisting of a decision tree and Markov model was constructed and populated for each group. To account for uncertainty, probability distributions were assigned to parameters and a Monte Carlo simulation was run for a probabilistic sensitivity analysis (PSA). Three iterations of the model were performed for both operable and inoperable patients (summarised on Figure 8.1). These iterations corresponded to evolutions in the evidence base: pre-trial evidence, evidence from the first randomised control trial (early outcomes), late trial and registry outcomes. The results for each subgroup are summarised below.

Figure 8.1 Evolutions in TAVI Evidence Base – Iterative Approach



8.2.1 Operable Patients

Low Risk Operable Patients

At the outset of the thesis two subgroups of operable patients were considered – high and low risk. Low risk operable patients were considered suitable for AVR or TAVI. In the original model (populated with published evidence from case series and early registries) they were assumed to have an operable mortality of 5%. The PSA produced mean costs and benefits (measured as quality adjusted life years (QALYs)) which demonstrated that TAVI was more expensive and more effective than AVR with uncertainty surrounding the extent of the incremental differences. The incremental cost effectiveness ratio (ICER) was estimated to be £147,617/QALY, which is outside the range usually considered cost effective (£20,000-£30,000/QALY). The cost effectiveness acceptability curve (CEAC) demonstrated that at a ceiling ratio of £30,000/QALY the probability that TAVI is cost effective was only 15%. Thus, TAVI could not be considered cost effective for this patient group. The expected value of perfect information for the population (pEVPI) at £30,000/QALY was £1.08 million indicating there is value in collecting further information for this patient group. However, neither cohort in the PARTNER Trial or subsequent published evidence considered low risk operable patients so the cost effectiveness of TAVI compared to AVR for these patients was not revisited explicitly within the thesis. Since 2007 all TAVI procedures performed in the UK are recorded in the UK TAVI Registry. Overtime, this may present some additional data for this patient group, facilitating a re-analysis.

High Risk Operable Patients

For high risk operable patients the treatment decision was between TAVI, AVR and medical management. The "original model" (populated with published evidence from case series and early registries) assumed an operative mortality of 15% and demonstrated that TAVI was more expensive and only marginally more effective than AVR, which was in turn more expensive and more effective than medical management. The ICER from the PSA comparing TAVI and AVR was £85,982/QALY which is outside the range usually considered cost effective. Meanwhile, the ICER comparing AVR and medical management was £9,721/QALY which is inside the range usually considered cost effective. Thus, comparing TAVI to AVR, TAVI cannot be considered cost effective and comparing AVR and medical management, AVR can be considered cost effective for this patient group. The CEAC demonstrated that at a ceiling ratio of £30,000/QALY the probability that AVR is cost effective was 98%, the probability that TAVI is cost effective is only 2% and the probability that medical management is cost effective was 0%. The pEVPI at £30,000/QALY was £23,433/QALY indicating there is very little value in commissioning additional research on this patient group.

Subsequent to the original analysis, the first TAVI randomised control trial (PARTNER), published results for high risk operable AVR versus TAVI (Cohort A). The results from Cohort A were employed to populate the TAVI and AVR arms of the DAM (replacing published literature employed in the original model) and evidence from Cohort B was used to populate the medical management arm (replacing published literature used in the original model) to reflect the best available data for a second iteration of the model ("PARTNER A"). This resulted in some structural changes to the model (described in Chapter 6). The results of the PSA indicated that TAVI was more costly and less effective than AVR. Thus, TAVI was dominated by AVR. The ICER for AVR compared to medical management was £16,276/QALY which is within the range usually considered cost effective. Thus, AVR could be considered cost effective compared to medical management for these patients. The CEAC demonstrated that at a ceiling ratio of £30,000/QALY the probability that AVR is cost effective is 98.7%, the probability TAVI is cost effective is 0.2% and the probability medical management is cost effective is 1.1%. The pEVPI at a ceiling ratio of £30,000/QALY was £651,917, indicating there was some value in commissioning further research for these patients.

After the initial publication of the PARTNER trial results, further external evidence became available for high risk operable patients (late results from PARTNER Cohort A and early results from the UK TAVI Registry). These were used to update the PARTNER Cohort A evidence from the second iteration and the cost effectiveness of TAVI compared to AVR was considered for a third time ("Updated PARTNER A"). The results from the original model and the model populated using PARTNER, both indicated that medical management was consistently outperformed by AVR. So where AVR was available it would be unethical to randomise patients to medical management. Thus, only AVR and TAVI were considered in this iteration. The PSA results, from updating the model with this evolved evidence and re-running the model, indicated that TAVI was more expensive and marginally more effective than AVR and the ICER was £605,756/QALY. So TAVI still cannot be considered cost effective compared to AVR. The CEAC demonstrated the probability of AVR being cost effective was 99% and TAVI was 1%. The pEVPI at a ceiling ratio of £30,000/QALY was £24,375, indicated there was very little value in commissioning further research.

However, owing to the nature of medical device technologies like TAVI there was much speculation that the TAVI outcomes would improve and/or the cost of TAVI would decrease over time. Scenario analyses were used to investigate these hypotheses. One scenario considered the impact on the ICER if the probability of early, year 1 and 2 major procedure related events (PREs) following TAVI were equivalent to those following AVR (informed by expert opinion (Toff, 2011)). Here the PSA produced an ICER of £42,985/QALY, which is marginally outside the range considered cost effective. The CEAC demonstrated the probability that TAVI was cost effective was 36% and the pEVPI was £2.5 million at a ceiling ratio of £30,000/QALY. Further VOI analyses demonstrated that further research should collect evidence on short and long term probability, resource and quality of life parameters. However, given the expected costs associated with collecting this evidence via a clinical trial for TAVI and AVR, a registry only collecting this evidence on TAVI is more suitable. Thus, should future research indicate improved TAVI outcomes, the cost effectiveness and value of collecting further information improves. Alternatively, the additional evidence simulated here using the scenario analysis, may be generated and collected externally from another jurisdiction for example.

8.2.2 Inoperable Patients

Inoperable patients with Aortic Stenosis are considered unsuitable for AVR owing to high operative mortality risk and co-morbidities. The treatment options available to these patients were TAVI and medical management. The first iteration of the model was populated using published literature on early case series, registries, expert opinion and experience with AVR ("Original"), owing to scarce evidence on TAVI. The operative mortality risk assumed for this patient group was 20%. The PSA estimates revealed an ICER of £23,603/QALY which was within the range usually considered cost effective. The CEAC demonstrated the probability that TAVI is cost effective was 86% and medical management was 17%. The pEVPI was £1.3 million at a ceiling ratio of £30,000/QALY. These results indicated that TAVI could be considered cost effective and there was value in collecting further information.

While the original analysis did indicate value in collecting additional evidence, the results from PARTNER trial for Cohort B were published a short time later. This additional evidence was used to replace the original point estimates in the TAVI and medical management arm where available for a second iteration of the model ("PARTNER B"). The PSA results indicated an ICER of £37,390/QALY which is outside the range considered cost effective. The CEAC demonstrated the probability of TAVI being cost effective as 18%. The pEVPI was £756,649/QALY, indicating there is still some value in collecting further information. The expected value of perfect information around parameters (EVPPI) and the expected value of sample information (EVSI) demonstrated the optimal research design for collecting this additional information should include the collection of evidence on short and long term probability, resources and quality of life parameters via a registry.

Sometime later (2012) further external evidence was published (late outcomes from PARTNER and early and late outcomes from European registries). The PARTNER Cohort B data employed in the previous iteration was updated with this new evidence facilitating a third iteration of the model ("Updated PARTNER B"). The PSA results indicated an ICER £19,078/QALY, so TAVI could now be considered cost effective. The CEAC demonstrated there was no decision uncertainty surrounding the cost effectiveness results (probability that TAVI was cost effective was 100%). The pEVPI at £30,000/QALY was just £10,065, indicating there was little value in commissioning research. However, given the low marginal costs, continued collection of evidence via the UK TAVI Registry (as per

NICE guidelines) is recommended and is in line with the continuous iterative framework proposed in Chapter 2.

8.3 OVERCOMING THE CHALLENGES FOR ECONOMIC EVALUATIONS FOR HEALTH TECHNOLOGIES WITH EVOLVING EVIDENCE

8.3.1 Evidence Requirements, Licensing Procedures, Diffusion & the Learning Curve

The evidence requirements for licensing medical devices is less demanding that that for drug technologies. In addition, as licensing occurs close to the point of market entry there is rapid clinical uptake as soon as a device is available and so it quickly becomes part of clinical practice, which can even happen prior to RCTs reporting. For example, the PARTNER trial only reported 30 day and one year outcomes in November 2010 and March 2011 respectively. However, the first TAVI device achieved a CE Mark in 2007 (Edwards SAPIEN valve) and by 2009 4,498 procedures had been performed worldwide. In March 2010, the next generation device, the Edwards SAPIEN XT valve and its two delivery systems, received a CE Mark (Eggebrecht and Thielmann, 2010) and in December of that year Medtronic's CoreValve system received the CE Mark (Medtronic, 2010). During 2010, the number of TAVI procedures performed in the UK increased to 14,599. This increased further to 18,372 in 2011 (Wood, 2012).

Also, when medical devices are diffused and become part of clinical practice there is interaction between the device and practitioners which influences the learning curve and increases uncertainty around the parameters. These evolutions can be captured in the evolutions of the evidence base, which are incorporated in the various iterations by updating and re-analysing the model.

An advantage of this rapid approval process however is the resulting increase in competition, which may reduce prices. The effects of such price reductions are captured using scenario analyses performed in Chapters 4, 5 and 7.

8.3.2 Difficulties with Randomised Control Trials (RCT)

Despite TAVI being available since 2002 when this evaluation began in 2009 only short term evidence on TAVI from small case series and early registries were available. The studies that were available had small sample sizes ranging from 1 to 86, were mainly single centre studies and were not randomised. Thus, in populating the initial model no "gold standard", i.e. randomised evidence, was available and immature evidence had to be employed along with AVR experience and expert opinion. To address this challenge Bayesian decision analytical modelling (DAM) was employed, as recommended by Taylor and Iglesias (2009). Such a framework facilitated evidence synthesis and extrapolation across patient groups and time frames. So for example, where evidence is provided for up to one year but a twenty year lifecycle is assumed, the estimates for year one were employed over twenty years. To account for uncertainty in parameters, owing to the source of the initial estimates and the extrapolation, probability distributions were assigned. A probabilistic sensitivity analysis (PSA) (described in Chapter 2) was used to propagate this uncertainty through the model using a Monte Carlo simulation, which provided distributions of expected outcomes (costs and QALYs). The mean values of these distributions provided estimates of the expected cost effectiveness of the device, given the uncertainty. These were used to estimate the ICER, incremental costs and effects and to estimate decision uncertainty.

Also, an analysis of the distributions from the PSA provided estimates of the potential worth of collecting further evidence. This Bayesian VOI analysis provided a means of determining what additional information would be necessary to reduce or eliminate uncertainty in the model, by estimating the population Expected Value of Perfect Information (pEVPI). This was useful in determining if further research was required and what the optimal research design was, in the absence of formal evidence requirements. Optimal research design was initially informed by the expected value of perfect information about parameters (EVPPI), which indicates on which parameters additional information would be most valuable and the expected value of sample information (EVSI). The latter was compared to the expected costs of sampling, to determine the expected net benefit of different study designs.

In addition, there is a tendency for early studies to focus on higher risk patients as the chance of demonstrating benefits are greatest amongst those patients. These data are often then used as "generic" and are "genericized" or applied to the other patient groups in the

initial model. In the case study presented here, evidence was limited in the original model. So by varying assumptions and structural parameters in the model the differing operative mortality risks and treatment options for each group could be considered. For example, an operative mortality risk of 5% was assumed for low risk operable patients, while 20% was assumed for high risk inoperable patients. Also, only the TAVI and medical management arms were considered suitable for high risk inoperable patients, while all three were suitable for high risk operable patients. As the evidence base evolved, evidence specific to patient groups became available so different point estimates could be incorporated to account for heterogeneity between patient groups reflecting the best available data for that time. Also, to account for heterogeneity between different patient groups, in this thesis individual analysis of sub-groups were considered. The DAM was populated with evidence associated with each particular risk group and a PSA was undertaken per sub group to estimate cost effectiveness and the value of collecting further information for each group.

8.3.3 Incremental Innovation

As illustrated in the summary of results above, the cost effectiveness of TAVI was examined three times in response to evolving evidence. This evolving evidence was linked to incremental changes or innovations in the TAVI device over time. Unlike drugs, where phase III trials are undertaken when clinical results are robust, devices undergo frequent modifications which impact efficiency and end points overtime. These evolutions are in response to clinical evidence and practice and may result in reduced procedure length, reduction in the number failures etc. Consequently, there is rarely a "steady-state" period where RCTs for devices could be undertaken without being obsolete upon reporting (Drummond et al., 2009, Taylor and Iglesias, 2009) as was suggested to be case with PARTNER by Schaff (2011) and Webb and Criber et al. (2011) .

To address the challenge of incremental innovations in this thesis, an iterative framework for the economic evaluation and DAM was applied. This provided a means of re-assessing the cost effectiveness or adoption decision for the technology as the evidence base evolved. Whereby, as there was an innovation, which updated the evidence, the transition probabilities and probabilistic distributions were revised, updating the evidence base and the decision uncertainty was re-assessed. The PSA was then re-run and the results were re-examined. In the TAVI case study, employed in this thesis, three iterations were

performed in line with significant evolutions in the evidence base (Figure 8.1). The first iteration included pre-trial evidence. The second iteration was performed upon publication of results from the first RCT for TAVI, PARTNER trial. The third iteration was performed upon publication of the first late outcomes on TAVI and publication of more recent European Registries. This was done for both operable and inoperable patient groups. For each iteration, the model structure was examined to ensure it reflected understanding of the procedure and disease at that time, in line with the continuous iterative framework. The second iteration, incorporating PARTNER evidence, resulted in some structure changes to the model, so as to reflect practice at that time. Also, scenario analyses were employed to forecast the effect of future evolutions in the evidence base. Then all newly available evidence was incorporated, the adoption and research priority setting decisions were re-considered.

8.3.4 Genericization and Class Affect

As outlined above, owing to lenient evidence requirements for the approval of devices, there is a disincentive for manufacturers to produce evidence of effectiveness after introduction to the market. Consequently, there may be unequal evidence available between device brands. This can result in evidence only being available for one brand and modellers having little choice but to genericize or extrapolate across brands. In the TAVI case study, as the Edwards devices received CE Marks before Medtronic devices (2007 and March 2010 (Eggebrecht and Thielmann, 2010) versus December 2010 (Medtronic, 2010)) there was less evidence available on the Medtronic devices, preventing a Medtronic only analysis. Thus, the results were genericized across brands. That is to say, all evidence available, irrespective of the brand was included. Thus, the model included all devices, and any additional uncertainty presented by this was handled when accounting for uncertainty through the PSA.

8.3.5 Pricing

The incremental innovations, undemanding evidence requirements and procurement procedures for medical devices can influence prices also; owing to increased competition

etc. To consider changes in device prices, different pricing scenarios were considered through sensitivity analyses in Chapters 4, 5 and 7.

Thus, employing an iterative Bayesian framework for economic evaluations, including decision analytical modelling, PSA and VOI analysis permits the modeller to capture the uncertainties resulting from the challenges discussed above. This enabled this economic evaluation of a novel expensive medical device with evolving evidence, to be just as useful as those for drugs in informing adoption and research priority setting decisions. A further means of addressing the challenges and utilising economic evaluations of devices to their full capacity is to consider implementing Access with Evidence Development schemes. This can facilitate balancing access demands and ensuring further evidence is collected promptly.

8.4 ACCESS WITH EVIDENCE DEVELOPMENT SCHEMES FOR HEALTH TECHNOLOGIES WITH EVOLVING EVIDENCE

8.4.1 Access with Evidence Development Schemes

As described in Chapter 2, Access with Evidence Development (AED) schemes are considered as a way to balance tensions between evidence requirements/standards and providing access to emerging innovative technologies. Such schemes grant limited or temporary coverage for a specific period during which additional evidence on risks, costs and effectiveness can be collected for a sample of the population. As indicated to be worthwhile using results of the VOI analysis (Pearson et al., 2006, Tunis and Chalkidou, 2007, Tunis and Pearson, 2006, Turner et al., 2010). As discussed in Chapter 2, there are different ways of organising AED schemes. For example, in the US they tend to be implemented via Medicare, whereby reimbursement for new technologies is only granted if patients enrol in relevant randomised control trials (RCTs) (Taylor and Iglesias, 2009). However, in the UK they tend to operate like a real-world RCTs or RCTs in practice whereby coverage is granted "only in research". Regardless of implementation type, AED schemes provide a means of considering the issues and resulting challenges associated with novel technologies, such as the learning curve and incremental innovations, while

simultaneously considering clinical and cost effectiveness of the device (Taylor and Iglesias, 2009).

Trueman et al. (2010) propose criteria to identify when AED schemes are most useful and valuable. Firstly, according to the authors, where a technology is meeting a high clinical need (previously unmet) and delivering improvements in outcomes, AED schemes are appropriate. Secondly, promising health technologies often have the potential to deliver clinical improvements compared to standard practice and have logical and theoretically valid value propositions. While some demonstration of efficacy and safety are necessary for CE Marks and equivalent, evidence of these improvements and justification for the value proposition may be outstanding. Thirdly, these ambiguities can suggest there is uncertainty surrounding clinical and cost effectiveness which are resolvable via the collection of additional data. Bayesian VOI analysis can be used to determine the value of generating this additional information. If it is demonstrated that additional data will reduce these uncertainties, then further information should be collected, provided it can be done at a reasonable cost. AED schemes can overcome the lack of motivation often present when it comes to collecting this additional information and incentivise it. However, care needs to be taken that AED schemes do not become an op out for earlier evidence generation, for which incentives are already low.

Fourthly, data collection via an AED scheme may be more appropriate than traditional coverage tools where there is uncertainty remaining around clinical and cost effectiveness. Traditionally, coverage was considered a dichotomous decision: yes or no. However, if coverage is granted ("yes") there is little incentive to continue research. Fifthly, as outlined above, coverage may be awarded to medical devices with persistent uncertainty owing to the characteristics of devices. In particular, there may be little or no evidence on long term effectiveness. Granting coverage therefore based on small, non-randomised trials/observational data which is extrapolated between patient groups and device brands can impact patient safety. This can occur if evidence informing decisions (adoption and research priority setting) is not being updated as there are movements along the learning curve, incremental innovations and long term patient experiences are not followed up and reported on. Alternatively, if coverage is not awarded device manufacturers can wait for others to conduct the research and be free-riders. Or if the decision is never revisited patients are denied access to potentially lifesaving technologies. Finally, AED is a more dynamic means of coverage compared with conventional tools, whereby coverage is

granted to sub-groups for a pre-specified period, agreed by stakeholders, during which time the agreed evidence is collected. As mentioned above, AED can incentivise the collection of further evidence, without which there may be little motivation to collect the additional evidence. This facilitates an iterative re-assessment of the coverage decision using relevant evidence as it becomes available. These six criteria are summarised in Box 8.1.

Box 8.1 Criteria for Access with Evidence Development Schemes

1. High unmet clinical need; significant improvements in outcomes outstanding.
2. Value proposition for the technology is logical and theoretically valid, but evidence to support this is lacking.
3. Data collection is the best solution to resolve the uncertainty.
4. Traditional coverage tools are inappropriate to resolve the clinical or cost effectiveness uncertainty.
5. The primary concern is uncertainty surrounding clinical or cost-effectiveness outcomes (not just financial/budgetary impact).
6. Stakeholders agree that the evidence development is achievable in a timely manner.

8.4.2 Access with Evidence Development– Suitable for TAVI?

Using the criteria above (summarised in Box 8.1), the feasibility and suitability of AED schemes for expensive novel health technologies, characterised by uncertainty and evolving evidence, can be examined. The TAVI case study presented here can be used to investigate this. Firstly, given the nature of the device and initial evidence used to gain CE Marks and equivalents, it was demonstrated that TAVI has the potential to improve clinical outcomes relative to AVR and is theoretically valid. Traditionally, AVR was the standard treatment for severe AS, where the aortic valve was replaced with invasive surgery. Those with very high operative risk were considered inoperable and they received medical management. This provides transient relief and does not prolong survival. TAVI offers an alternative for these inoperable patients providing them with a valve replacement while avoiding the risks associated with surgery. TAVI also provides an alternative for operable patients wishing to avoid the invasive procedure and longer recovery times.

Secondly, using a Bayesian framework for investigating cost effectiveness, including the DAM and PSA, persistent uncertainty surrounding the cost effectiveness of TAVI was investigated and shown to be constant in the first iteration, the original model. Here there was considerable uncertainty surrounding the cost effectiveness of TAVI compared to AVR for operable patients. This uncertainty persisted in the second and third iterations when the model was updated to incorporate trial and registry evidence.

Thirdly, when the short term trial evidence was updated, with longer term trial outcomes and registry evidence for operable and inoperable patients for the third iteration, decision uncertainty and uncertainty surrounding the incremental costs and effects was reduced. For example, with inoperable patients the probability that TAVI is cost effective at £30,000/QALY ceiling ratio was 18% in iteration two and this increased to 100% in iteration three. This demonstrates how incorporating additional evidence into the DAM via an iterative framework can reduce uncertainties. For the other patient group, operable patients, uncertainty persists. Updating the PARTNER A model only increased the likelihood of TAVI being cost effective from 0.2% to 1%.

Fourthly, Bayesian VOI techniques such as EVPI, EVPPI and EVSI were employed to determine the value of collecting further evidence to reduce the persistent uncertainty. In the second iteration for inoperable patients it was shown that there was value in collecting additional information. Here the EVPPI illustrated that further evidence on short and long term probability, resource and quality of life parameters are most valuable. When further evidence became available, from an external source, the model was updated forming the third iteration. Similarly, for operable patients the EVPI demonstrated there was potential value in collecting further information, particularly if outcomes improved. For medical devices, like TAVI, after CE marks etc. are granted and the devices become part of practice in some areas the demands for access increase, even if there outstanding information requirements. In such cases, AED schemes are superior to tradition coverage rules as they offer a means of balancing access and demand, while generating further evidence.

Fifthly, despite the lack of influence on what additional evidence was generated, the cost effectiveness analysis here demonstrated that after the third iteration TAVI could be considered cost effective compared to medical management for inoperable patients. Meanwhile, even after three iterations decision uncertainty persists and TAVI cannot be

considered cost effective compared to AVR for operable patients. In this instance, conventional coverage tools (dichotomous yes or no) are not suitable. Given the persisting uncertainties a "yes" is highly unlikely, while an outright "no" has significant opportunity losses for those who could benefit from TAVI. Had an AED scheme for TAVI been developed earlier there could have been more control over the parameters informed by the evolving evidence. This may have reduced decision uncertainty and uncertainties surrounding costs and effects, particularly for operable patients, even further. As outlined previously, PARTNER is still heavily relied upon, as it is the only published RCT, despite being for one brand of the device and including early experiences of the device.

Finally, for TAVI there has been considerable stakeholder involvement in generating further evidence, peripheral to this thesis. The first RCT, the PARTNER Trial, was initiated and funded by one of the TAVI manufacturers, Edwards LifeSciences. This demonstrated the manufactures commitment to research and generating further evidence. Also, clinicians and the health service in the UK demonstrated their commitment to generating further research with the establishment and continuation of the UK TAVI Registry and the forthcoming UK TAVI Trial.

In the past, there has been a varied success rate for AED schemes, as discussed in Chapter 2. This variation is due to the scheme characteristics, for example the type of data to be collected; the timeframe identified; the population chosen; who is funding the scheme etc. So when designing AED schemes access delays, which may produce disincentives for further innovations, and dichotomous outcomes, need to be avoided. In addition, good use should be made of patient sub-groups. For example, opportunities for exchangeability of evidence between patient sub-groups, as well as between jurisdictions, should be sought (Trueman et al., 2010).

Examining the case study presented here using the proposed criteria for AED, it appears that TAVI is in theory a suitable candidate. Had an AED scheme been formally considered upon CE approval in 2007 or 2010, the current RCT (PARTNER) may have been designed more efficiently, informed by VOI analysis. This may have reduced the costs associated with further research, avoiding the costs of additional trials like the upcoming UK TAVI Trial which this analysis could not consider to be cost effective). It also could have reduced the time taken for NICE and other decision makers to decide on the suitability of TAVI for

treating AS, or it would have at least formalised a time line for the re-assessment of the decision. Both of these may have reduced decision uncertainty and reduced access delays.

Nevertheless, an AED scheme was not employed and ad hoc and uncoordinated evidence has been generated to date. One could argue therefore that the costs of collecting additional evidence have been higher than would have been the case if an AED scheme has been employed earlier. Also, uncertainties persist so more evidence is still required and further collection is due to commence, for example the UK TAVI Trial. Such trials increase costs and time spent on generating evidence by first movers, which further incentivises free riders given the current regulatory environment.

Nevertheless, it is not too late, given the persisting uncertainties and expected incremental innovations further evidence is due to be collected on operable patients. The decision by NICE to only recommend the use of TAVI amongst operable patients with special arrangements for clinical governance, consent and data collection or research via the UK TAVI trial is welcomed (NICE, 2012). This form of AED attempts to balances access and data collection. Whereby, access is only granted for research or data collection purposes. This guarantees further evidence is collected and should ensure that the cost effectiveness of TAVI for these patients will be re-assessed. Furthermore, as access is conditional on evidence collection, it can be removed more easily if the need arises, than if full coverage had been granted.

8.5 LESSONS & RECOMMENDATIONS FOR HEALTH TECHNOLOGIES WITH EVOLVING EVIDENCE

8.5.1 Access with Evidence Development?

As mentioned above, it is not too late to implement an Access with Evidence Development scheme for TAVI, particularly amongst the operable patient population. Uncertainties, the incremental nature of medical devices and movements along the learning curve persist indicating that that further information is useful. The VOI analysis presented in Chapter 7 illustrated that a registry is more cost effective than a UK trial for generating additional evidence. Specifically, an expansion of the current UK TAVI Registry to collect

information on short and long term probability of events and mortality, resource consumption and quality of life of operable AS would be valuable. The VOI analysis in the scenario analysis (Section 7.8) indicates that a registry with 500 patients is optimal (yields highest ENBS) (Figure 7.27). This would mean that access would be limited to just over 20% of the population (total operable population in the UK is 2,250 per annum). Once this detailed evidence on TAVI outcomes are collected the decision analytical model could be re-examined to consider the cost effectiveness of TAVI. Patient selection could be informed by the existing measures in the NICE Guidance document (Number 421, 2012). Employing the continuous iterative framework, conceptualised in Chapter 2, ensures that AED (and other Performance Based Risk Sharing Agreements) are considered each time there is a model iteration after the adoption and research priority setting decisions have been considered.

8.5.2 Alternatives to UK Trials and Registries

Despite the indication that clinical trials may not be cost effective from the analysis presented here, there is an apparent preference for clinical trials over registries, as demonstrated in the case of TAVI in the UK. Given this preference, a feasible and potentially cost effective option may be to use global trials (Eckermann and Willan, 2009). As illustrated in this thesis, employing results from the PARTNER trial, using transferable evidence from trials conducted in other jurisdictions is beneficial and feasible in the continuous iterative framework conceptualised in Chapter 2. Considering external evidence is useful as new technologies, like TAVI, are generally released simultaneously across jurisdictions. For example, CE marks are applicable across Europe. Thus, provision and evidence collection decisions regarding such technologies are not unique to one health care system. Each health system generating its own economic evaluation, decision analytical model and evidence can be inefficient and impossible in some cases, owing to lack of resources, infrastructure and experience. In addition, data collection is time consuming and expensive and all too often results are released in an untimely fashion (Claxton et al., 2005). Therefore, a common evidence base could be useful to inform such coverage and research priority setting decisions.

In light of these concerns, organisations such as the European Network for Health Technology Assessments (EUnetHTA) promote international collaboration such as global

trials/ registries and information exchange. This can improve resource allocation; co-ordination of data collection and provision decisions; reduce duplication and thus improve the integration of HTA into policy decisions across Europe (EUnetHTA, 2011).

Collaboration is feasible owing to the nature of information as a public good (ISPOR, 2011, Garrison, 2010). As indicated in Chapter 2, information is considered a public good as it displays the two necessary principles: non-rivalry and non-excludability (Stiglitz, 1999). Non-rivalrous consumption means that consumption of a good by one individual does not detract from another. Non-excludability suggests it is impossible to exclude anyone from consuming a good, again for information this would mean it cannot be provided privately (Stiglitz, 1999). The public good nature of information therefore suggests that information should not be provided on a private basis. This has important implications for the generation of further research on novel technologies like TAVI, where multi-location projects are beginning to emerge with European clinical trials and registries like SURTAVI[16] from Medtronic and registries such as the European Advanced Registry[17] and the Source Sapien Registry[18] (Simmonds, 2011, Piazza et al., 2010, Kappetein, 2011, Thomas, 2010, Thomas et al., 2011). This should maximise the quantity and quality of timely data available and promote the efficient use of resources.

However, efforts must be taken to ensure "free rider" issues do not result which may cause market failure (Eckermann and Willan, 2009). "Free rider" issues in this situation, refer to where decision makers in a jurisdiction wait for others to bear the costs of commissioning a trial which is used to inform decisions in the former. Market failure in this situation can occur when all jurisdictions wait for another to conduct the research and the research never gets completed.

An optimal solution is to have global trials, where patients are selected across jurisdictions and fixed costs are shared amongst participating bodies. Such global trials aim to overcome issues faced by local decision makers, such as reducing the need for meta-analysis and associated problems of differences in protocols and treatments. Global trials endeavour to avoid delaying adoption decisions, whereby evidence is being generated in a timely

[16] SURTAVI Trial European Medtronic sponsored randomised controlled trial. Data collection was due to being in 2010/11 employing 1,000-2,000 patients (Simmonds, 2011, Kappetein, 2011).
[17] The European Advanced Registry employs approx. 1,000 patients across 50 sites in Europe and expects to release results in 2016 (Piazza et al., 2010, Thomas, 2010).
[18] SOURCE Sapien Registry has 1,038 patients enrolled and collects data from 32 sites (Thomas et al. 2011).

fashion. However, it needs to be the case that the new technology is only available through the trial in each jurisdiction. Overall, global trials can improve the expected net benefit of sampling (ENBS) relative to local trials when evidence is freely transferrable, as single trials underestimate the global value of trial information. Also, having more than one trial spreads costs and increases the homogeneity of evidence (Eckermann and Willan, 2009).

8.5.3 Future for Economic Evaluations of Medical Devices

This thesis demonstrates that employing economic evaluation methods such as decision modelling, PSA and VOI analysis in a continuous iterative manner for medical devices is feasible, despite their challenging characteristics. Just one case study was employed in this thesis examining the suitability of the continuous iterative framework for novel expensive medical devices characterised by evolving evidence and uncertainty. To test its suitability further, more case studies should be considered.

These future case studies should formally consider the employment of Access with Evidence Development schemes earlier and more formally in the iterative framework. However, for that to work decision makers and the environment in which they operate need to adapt to the characteristics of medical devices when considering them. The current lenient evidence requirements for licensing and market access discourage research and create incentives for manufacturers to be "free-riders". It also means that medical devices become part of clinical practice soon after licenses are granted, even those with persisting uncertainties. The aforementioned criteria need to be revised in the interest of patient safety, equity in access and to maintain standards in decision making, which economic evaluations inform. In addition, decision makers should formally recognise the unique characteristics of medical devices and promote the use of iterative economic evaluations when assessing them.

Also, these future case studies could examine the hypothesis that global trials are optimal for collecting additional evidence for novel expensive technologies compared to single country trials.

8.6 LIMITATIONS

8.6.1 Limitations of Proposed Framework

Despite the merits of using flexible Bayesian methods within the continuous iterative framework for economic evaluations to overcome the challenges posed by novel technologies and the promise of AED schemes there are some limitations.

Firstly, implementing a truly continuous iterative approach is challenging. It is highly resource intensive owing to the frequent updates and re-analyses required. Also, such methods warrant significant stakeholder involvement to inform the interval between iterations. This involvement however may be difficult to maintain over the course of the iterations. Iterative approaches to economic evaluations are also not conducive to academic publication. Owing to long lead and review times. For example, by the time a journal submission is returned with comments the iteration can be obsolete owing to movements along the learning curve and incremental innovations which lead to an evolution in the evidence base. This was experienced with this case study. When the original iteration was finalised the RCT data became available. These iterations for inoperable patients were written up as one paper and submitted to a leading health economics journal in April 2011. Comments from the editor and reviewers were received in September 2011 and the paper was returned in December 2011. After which a "revise and resubmit" decision was received in March 2012. The suggested revisions were made and in addition the results of the third iteration had to be included to ensure the paper was current as of submission in April 2012. Owing to these amendments the paper had to be considered for another review and notice of acceptance was only granted in August 2012. This lengthy process can provide a disincentive for iterative evaluations.

Secondly, the VOI employed in the analysis are promising but given their dependence on PSA uptake of them is slow and they are not yet routine in informing policy decisions. Thus, their potential is underestimated owing to inexperience and lack of understanding in decision making arenas.

Thirdly, in conducting this case study the non-rivalry of information and information as a public good come into question. Access to the UK TAVI registry was limited to what was published in late 2011 by Moat et al. (2011). Unfortunately, that publication only provided early outcomes aggregated for all patient risk groups. Had this registry data been available

earlier and in a more detailed form, it could have informed the analysis further. This brings into question the public nature of information and thus the usefulness of publically funded research for informing iterative economic evaluations such as that considered in this thesis.

8.6.2 Limitations of Thesis

It is acknowledged that more formal Bayesian techniques (described in Chapter 2) could have been employed in the model when updating the evidence between iterations. For example, in iteration two the early evidence from published case series and expert opinions could have been used as priors and updated with the PARTNER evidence. However, as discussed in Chapter 5 it was assumed in the model that the accumulated empirical evidence from the PARTNER trial dominated this early evidence and expert opinion. However, given that experience with TAVI from the experts was minimal and restricted to published case series etc. evidence from the PARTNER trial superseded experts opinion. This is in line with the view that expert opinion can become irrelevant in the presence of large RCTs; where it is considered that the accumulated empirical evidence dominates the expert opinion (NICE, 2004). In future iterations of the model, more formal Bayesian methods could be employed, as employed for relevant parameters in iteration three. It is also recognised that more formal elicitation methods could have been employed for eliciting expert opinion. However, given that results from the PARTENR trial were imminent, the additional cost of formally eliciting the information was considered to outweigh the additional benefit. This was especially true for variables on which there was no existing evidence at the time of eliciting expert opinion.

The original iteration of the model included several relative risk parameters which were used to model the difference between TAVI and AVR (see Table 4.4). As indicated in Chapter 4, these relative risk parameters were informed by expert opinion (who had little experience with the technology at the time), which became obsolete upon the publication of the first RCT. These relative risks were then replaced with absolute risks for the parameters considered (the rationale for the replacement strategy is discussed in Chapter 5). Alternatively, the relative risks between treatment options could have be estimated and then superimposed onto baseline probabilities (based on population characteristics etc.)(Philips et al., 2006). This is considered to be particularly useful where results are not generalizable to the population under investigation (Palmer et al., 2002). In the case of TAVI however, differences in expected health outcomes between the trial region and the UK were unknown. In addition, PARTNER A and B represent two different patient risk

groups (operable versus inoperable), this baseline risk impacted on procedure related events, quality of life and mortality. If further information were available on differences between patient risk groups and between jurisdictions then relative risks could have been employed. However, in the absence of this information the impact of using relative instead of absolute risk was minimal.

As described in Chapter 2, EVSI is a useful measure for informing the research priority setting decision. However, the analysis here demonstrated that employing EVSI has practical challenges, owing to its high computational costs. It is anticipated that in the future meta methods and other Bayesian methods which are currently being developed to reduce the computational expenses associated with EVSI will be accessible to health economists. These should reduce the practical challenges associated with estimating EVSI.

Finally, to assess uncertainty surrounding the model assumptions, a sensitivity analysis was employed in Chapter 7 to consider various scenarios, as is commonly done in HTAs. While sensitivity analyses are a straightforward means of assessing the implications of different assumptions they only give a partial expression of uncertainty. Conducting a complete analysis would require consideration of parameter uncertainty for each possible combination of structural assumptions in principle, however in practice this is a complex process. An alternative method is model averaging. Here, the results from different models are combined to provide a single set of averaged results. Each set of results are given a weight, reflecting their appropriateness (Jackson et al., 2010, Briggs et al., 2012, Jackson et al., 2011). While this method does incorporate information from various models it is computationally burdensome.

8.7 CONCLUSIONS

Using Transcatheter Aortic Valve Implantation (TAVI) as a case study this thesis has demonstrated how informative and efficient economic evaluations of novel expensive medical device technologies, with evolving evidence, can be conducted. This is the first such evaluation where a formal iterative framework is applied to an economic evaluation of a medical device using decision analytical modelling, probabilistic sensitivity analysis

with Monte Carlo simulations and a Bayesian VOI analysis for patient subgroups simultaneously.

Using these methods the iterative evaluation concluded that TAVI can be considered cost effective for inoperable patients compared with medical management. While there is little value in commissioning new research for continued data collection for this group, the continued collection of evidence via the UK TAVI trial as indicated in the NICE guidelines is welcomed. This continual collection of evidence ensures that up to date evidence is available to inform any future decisions regarding TAVI in this patient group (in an AED type fashion) as advocated in the continuous iterative framework. For inoperable patients, the iterative model could not conclude that TAVI is cost effective compared to AVR. However, should further evidence demonstrate improved outcomes, it would improve the cost effective position of TAVI for these patients. The Bayesian VOI, in the scenario analysis, indicates that further information on short and long term probability, resource and quality of life parameters is most valuable and a cost effective research design of collecting such information is a registry.

Applying the TAVI case study afforded the opportunity to examine the challenges of under taking a cost effectiveness analysis for such complex medical device technologies. These challenges were identified and overcome by employing the continuous iterative framework, as discussed above. This demonstrates that economic evaluations do not have to be static one-off activities. In fact, owing to the characteristics of medical devices (learning curve, incremental innovations etc.) economic evaluations of this kind should be continuous. Their evolving evidence should be incorporated into the decision making process so as to re-address their cost effectiveness on an iterative basis. Using these methods this thesis also demonstrates how optimal study designs can be created for such technologies. Further to this, the thesis examined how the economic evaluation results and study designs can be incorporated into emerging policies for generating further information like Access with Evidence Development schemes through the proposed continuous iterative framework.

APPENDICES

I TAVI STEERING GROUP MEMBERS

Table I.a TAVI Steering Group Members

Name	Role
Prof Colin Berry	Professor of Cardiology and Imaging
Ms Pascale Brasseur	Medtronic
Prof Andrew Briggs	Health Economist
Ms Carole Cohen	Edwards LifeSciences
Mr Hussein El-Shafei	Cardiac Surgeon
Dr Elisabeth Fenwick	Health Economist
Ms Fiona MacDonald	Cardiac Services – Service Improvement Manager
Ms Clare McGrath	Senior Director HTA Policy, Europe/ROWD
Dr Malcolm John Metcalfe	Cardiologist
Ms Aileen Murphy	Health Economist
Dr Keith Olroyd	Cardiologist
Mr Renzo Pessotto	Cardiac Surgeon
Dr Karen Richie	Lead Health Services Researcher, Quality Improvement Scotland
Mr Fraser Sutherland	Cardiac and Transplant Surgeon
Dr Neil Uren	Cardiologist
Mr Derek Yuille	Director of Finance, NHS Ayrshire & Arran

II LITERATURE REVIEW

Table II.a Literature Review: Clinical Effectiveness of TAVI

The literature search for evidence on TAVI began with the published review conducted by Vahanian et al (2008). Each of the publications reported by Vahanian et al (2008) were sourced and reviewed by the author. After which a literature search was conducted between April and May 2009 using PubMed and Google Scholar.

Search Terms:

1. percutaneous heart valve implantation
2. percutaneous
3. Aortic stenosis
4. percutaneous aortic valve implantation
5. transapical
6. aortic valve replacement
7. minimally invasive
8. aortic bioprosthesis
9. novel
10. severe aortic stenosis
11. older patients
12. implant
13. elderly
14. management
15. Transcatheter
16. insertion

Exclusion criteria:

- pre- 2002

Date of Search:

- April – May 2009

RESULTS

Search Strategy	Included/ Reason for Excluding
1: Google Scholar	
(Cribier et al., 2004)	✓
(Cribier et al., 2006)	✓
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Bauer et al., 2004)	Mismatch/insufficient evidence provided for model
(Webb et al., 2006)	✓
(Lichtenstein et al., 2006)	✓
(Grube et al., 2006)	✓
(Webb et al., 2007)	✓
(Walther et al., 2007)	✓
2 + 6: Google Scholar	
(Grube et al., 2007)	✓
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Webb et al., 2007)	✓
(Grube et al., 2008)	Results included in (Grube et al., 2006) & (Grube et al., 2007)

Table II.a Continued

Search Strategy	Included/ Reason for Excluding
2 + 6: Google Scholar (continued)	
(Grube et al., 2006)	✓
(Moss et al., 2008)	Mismatch/insufficient evidence provided for model
(Lichtenstein et al., 2006)	✓
2 + 3: Google Scholar	
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Grube et al., 2007)	✓
(Webb et al., 2007)	✓
(Webb et al., 2006)	✓
(Cribier et al., 2004)	✓
(Cribier et al., 2006)	✓
(Grube et al., 2006)	✓
(Lichtenstein et al., 2006)	✓
(Hanzel et al., 2005)	✓
(Bauer et al., 2004)	Mismatch/insufficient evidence provided for model
4: Google Scholar	
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Grube et al., 2008)	Results included in (Grube et al., 2006) and (Grube et al., 2007)
(Webb et al., 2006)	✓
(Grube et al., 2006)	✓
(Wenaweser et al., 2007)	Mismatch/insufficient evidence provided for model
(Lutter et al., 2002)	Reports results for animals not humans
2+6: Pubmed	
(Sack et al., 2005)	✓
5+6+7: Google Scholar	
(Walther et al., 2007)	✓
(Walther et al., 2008)	✓
(Lichtenstein et al., 2006)	✓
(Ye et al., 2007)	Included in (Ye et al., 2009)
(Ye et al., 2009)	✓
4+9: Pubmed	
(Berry et al., 2007)	✓
8+2+12: Google Scholar	
(Grube et al., 2006)	✓
(Lichtenstein et al., 2006)	✓
(Cribier et al., 2004)	✓
(Lutter et al., 2002)	Reports results for animals not humans
10+13+2: Google Scholar	
(Grube et al., 2007)	✓
(Webb et al., 2007)	✓
(Cribier et al., 2006)	✓
(Grube et al., 2006)	✓
(Webb et al., 2006)	✓
(Grube et al., 2008)	Results included in (Grube et al., 2006) and (Grube et al., 2007)
10+11+8: Google Scholar	
(Piazza et al., 2008a)	Mismatch/insufficient evidence provided for model

Table II.a Continued

Search Strategy	Included/ Reason for Excluding
(Grube et al., 2007)	✓
(Marcheix et al., 2007)	✓
(Wenaweser et al., 2007)	Mismatch/insufficient evidence provided for model
(Cribier et al., 2004)	✓
10+13+2+14: Google Scholar	
(Webb et al., 2007)	✓
(Descoutures et al., 2008)	✓
(Cribier et al., 2006)	✓
(Webb et al., 2006)	✓
15: Google Scholar	
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Piazza et al., 2008a)	Mismatch/insufficient evidence provided for model
(Ye et al., 2007)	Included in (Ye et al., 2009)
(Webb et al., 2007)	✓
(Lichtenstein et al., 2006)	✓
15 + 16: Google Scholar	
(Cribier et al., 2002b)	Included in (Cribier et al., 2004)
(Svensson et al., 2008)	✓
(Webb et al., 2007)	✓
(Piazza et al., 2008a)	Mismatch/insufficient evidence provided for model
(Walther et al., 2007)	✓

Table II.b Literature Review: Clinical Effectiveness of AVR

Search Terms:

1. aortic stenosis
2. bioprosthesis
3. aortic valve replacement
4. older
5. early and long term results
6. surgery
7. severely symptomatic
8. UK
9. valve-related complications
10. elderly
11. aortic valves

Exclusion criteria:

- studies published pre 1990
- balloon valvuloplasty
- Single sex studies
- studies with < 50 patients
- stented/stents
- allograft
- full text not available

Date of Search:

- April – May 2009

RESULTS

Search Strategy	Included/ Reason for Excluding
1+2: Google Scholar	
(Rosenhek et al., 2000)	Mismatch/insufficient evidence provided for model
(Pereira et al., 2002)	Mismatch/insufficient evidence provided for model
(Tasca et al., 2003)	Mismatch/insufficient evidence provided for model
(Aupart et al., 2006)	✓
3+4+5: Google Scholar	
(Gehlot et al., 1996)	✓
(Asimakopoulos et al., 1997)	Mismatch/insufficient evidence provided for model
(Melby et al., 2007)	✓
1+6+7+8: Google Scholar	
(Gilbert et al., 1999)	✓
(Collinson et al., 1999)	Sample size insufficient
(Urso et al., 2007)	Mismatch/insufficient evidence provided for model
(Kojodjojo et al., 2008)	Mismatch/insufficient evidence provided for model
9+10+11: Google Scholar	
(Sidhu et al., 2001)	Mismatch/insufficient evidence provided for model
(Milano et al., 1998)	✓
(Otto et al., 1999)	Mismatch/insufficient evidence provided for model
2+12+13: Google Scholar	
(Eichinger et al., 2008)	✓
(Poirier et al., 1998)	Mismatch/insufficient evidence provided for model
(Corbineau et al., 2001)	Mismatch/insufficient evidence provided for model
(Conrad Pelletier et al., 1995)	Mismatch/insufficient evidence provided for model

Table II.c Literature Review: Economic Evaluation/Cost Effectiveness TAVI

Search Terms:

1. Economic evaluation
2. Cost effectiveness analysis
3. Economic analysis
4. cost analysis
5. TAVI
6. PAVR
7. Transcatheter aortic valve implantation
8. Percutaneous heart valve implantation
9. Percutaneous aortic valve implantation
10. Percutaneous aortic valve replacement

Exclusion criteria:

- None

Date of Search:

- April – May 2009

Search Strategy:

- 1+5; 1+6; 1+7; 1+8; 1+9; 1+10.
- 2+5; 2+6; 2+7; 2+8; 2+9; 2+10.
- 3+5; 3+6; 3+7; 3+8; 3+9; 3+10.
- 4+5; 4+6; 4+7; 4+8; 4+9; 4+10.

Google Scholar
Google
PubMed

RESULTS

- (Van Brabandt and Neyt, 2008)
- (Bazian, 2008)

III PROCEDURE RELATED EVENTS

Table III.a Definition of Procedure Related Events

Event	Definition	Source
Stroke	Sudden diminution or loss of consciousness, sensation, and voluntary motion caused by rupture or obstruction (as by a clot) of a blood vessel of the brain.	(MedlinePlus, 2011)
Thromboembolism	The blocking of a blood vessel by a particle that has broken away from a blood clot at its site of formation.	(MedlinePlus, 2011)
Paravalvular Leak	Paravalvular leak refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue as a result of a lack of appropriate sealing. The majority of paravavular leaks are crescent, oval or roundish-shaped and their track can be parallel, perpendicular or serpiginous.	(Smolka, 2010)
Endocarditis	Endocarditis is inflammation of the inside lining of the heart chambers and heart valves (endocardium).	(Levy, 2010)
Cardiac tamponade	Cardiac tamponade is compression of the heart. It can occur when blood or fluid builds up in the space between the myocardium (heart muscle) and the pericardium (outer covering sac of the heart).	(Health, 2010a)
Myocardial infarction	A myocardial infarction is when blood vessels that supply blood to the heart are blocked, preventing enough oxygen from getting to the heart. The heart muscle dies or becomes permanently damaged.	(Health, 2010b)
Pacemaker	A pacemaker is a device that sends small electrical impulses to the heart muscle to maintain a suitable heart rate or to stimulate the lower chambers of the heart (ventricles). A pacemaker may also be used to treat fainting spells (syncope), congestive heart failure and hypertrophic cardiomyopathy.	(Clinic, 2011)

IV MODEL INVESTIGATIONS

Table IV.a Descriptive Statistics for Input Parameters

PARAMETERS	LARGE N Mean Probability	SMALL N* Mean Probability	MID-POINT
Major disabling stroke	0.031	0.031	0.031
Probability of Converting to AVR	0.038	0.057	0.048
Major valve related complications – TAVI			
Valve thromboembolism	0.000	0.000	0.000
Major paravavular leak	0.038	0.063	0.050
Endocarditis	0.000	0.000	0.000
Cardiac tamponade	0.020	0.057	0.039
Myocardial infarction	0.029	0.046	0.038
Major valve related complications –AVR			
Valve thromboembolism	0.010	0.010	0.010
Major paravavular leak	0.003	0.006	0.005
Endocarditis	0.005	0.005	0.005
Cardiac tamponade	0.000	0.000	0.000
Myocardial infarction	0.000	0.000	0.000
Minor valve related complications – TAVI			
Access site events	0.011	0.059	0.035
Vascular Events	0.047	0.138	0.093
Pacemaker implantation	0.062	0.062	0.062
Minor valve related complications –AVR			
Access site events	0.009	0.037	0.023
Vascular Events	0.012	0.027	0.020
Pacemaker implantation	0.052	0.059	0.056
Probability late procedure related event			
Hospitalisations	0.056	0.056	0.056
Valve thromboembolism	0.065	0.068	0.067
Major paravavular leak	0.006	0.016	0.011
Endocarditis	0.024	0.024	0.024
Cardiac tamponade	0.000	0.000	0.000
Fatal Procedure related event	0.218	0.223	0.221

Table IV.b Descriptive Statistics from Probabilistic Sensitivity Analysis Large v's Small Sample Size, 1,000 Simulations

	Small v's Large (1)	Difference	Small v's Large (2)	Difference
rmajor_vre	>	-0.06	>	-0.05
rminor_vre_CVR	>	-0.18	>	-0.17
rminor_vre_TAVI	>	-0.23	>	-0.22
pconverting_to_CVR	>	-0.02	>	-0.02
Pmajorstroke	<	0.00	<	0.00
RRomTAVI	>	-0.10	>	-0.09
Rrmajorcomplications_TAVI	>	-0.01	>	-0.01
Excess_Stroke_Risk	>	0.00	<	0.02
Platevre	>	-0.01	>	-0.01
Rrvre_TAVI	<	0.20	<	0.12
Platefatalvre	>	0.00	>	0.00
rrsmrAS	<	0.01	<	0.05
pdeath_AS	>	-0.01	>	0.00
Cmajorstroke	<	15.52	<	7.53
TAVIprocedure	<	88.64	<	24.91
LOSTAVI	>	-105.34	>	-53.41
PostdischargeTAVI	<	8.42	>	8.99
CVRprocedure	<	16.77	>	22.03
LOSCVR	>	-110.10	<	-119.68
PostdischargeTAVI	<	30.40	>	-76.85
cminorvreCVR	<	-502.02	<	-455.82
cminorvreTAVI	<	1462.56	<	1547.56
Costlatevre	>	156.90	<	157.73
cfv_AS	<	1.54	>	-17.99
Cfn	>	1.74	<	-5.91
Relative cost of procedure	<	0.02	<	0.00
Relative cost of hospital stay	<	0.00	<	0.00
Relative cost of post-discharge care	>	0.00	<	0.00
uAS	<	0.00	>	0.00
Umajorvre	>	0.00	>	0.00
uminorvreCVR	>	-0.01	>	-0.01
uminorvreTAVI	<	0.01	<	0.01
Ufv_AS	<	0.00	>	0.00
uFnVR	<	0.00	<	0.00
distuility_late_vre	>	0.00	<	0.00

Difference refers to the difference in the ranges between the NL model and the NS model. Those highlighted in red indicate the unexpected.

Table IV.c Descriptive Statistics from Probabilistic Sensitivity Analysis Large v's Small Sample Size, 10,000 Simulations

	Small v's Large (1)	Difference	Small v's Large (2)	% Difference
rmajor_vre	>	0.07	>	-0.19
rminor_vre_CVR	>	0.05	>	-0.17
rminor_vre_TAVI	>	0.11	>	-0.37
pconverting_to_CVR	>	0.04	>	-0.09
Pmajorstroke	>	0.01	>	-0.07
RRomTAVI	>	0.16	>	-1.35
Rrmajorcomplications_TAVI	>	0.17	>	-1.51
Excess_Stroke_Risk	>	0.18	>	-1.50
Platevre	>	0.02	>	-0.21
Rrvre_TAVI	>	0.57	>	-2.57
Platefatalvre	>	0.04	>	-0.33
rrsmrAS	>	0.60	<	-3.20
pdeath_AS	>	0.08	<	-0.57
Cmajorstroke	>	163.98	>	-806.68
TAVIprocedure	>	602.85	<	-4324.63
LOSTAVI	>	905.37	>	-5639.95
PostdischargeTAVI	>	152.07	<	-940.32
CVRprocedure	>	483.53	<	-5067.48
LOSCVR	>	1415.13	>	-9992.57
PostdischargeTAVI	>	745.98	<	-5344.16
cminorvreCVR	>	679.639	<	-4265.245
cminorvreTAVI	>	163.058	<	-2850.144
Costlatevre	>	341.761	<	-3240.710
cfv_AS	>	347.456	<	-8551.169
Cfn	>	218.034	<	-2157.136
Relative cost of procedure	>	0.129	<	-1.100
Relative cost of hospital stay	>	0.089	<	-0.770
Relative cost of post-discharge care	>	0.027	<	-0.240
uAS	>	0.012	<	-0.571
Umajorvre	>	0.008	>	-0.053
uminorvreCVR	>	0.006	>	-0.046
uminorvreTAVI	>	0.002	<	-0.034
Ufv_AS	>	0.012	<	-0.571
uFnVR	>	0.023	>	-0.839
distuility_late_vre	>	0.006	<	-0.048

% Difference refers to the difference in the ranges between the NL model and the NS model. Those highlighted in red indicate where the percentage difference is greater than 10%.

Table IV.d Summary of ANOVA Results (High Risk Operable Patient Group)

Summary of Proportion Sum of Squares	Large N 1	Large N 2	Small N 1	Small N 2
Incremental QALYs AVR vs. TAVI	rrvreTAVI	rrvreTAVI	rrvreTAVI	rrvreTAVI
Incremental Costs AVR vs. TAVI	rrvreTAVI ----------	rrvreTAVI ----------	rrvreTAVI ----------	rrvreTAVI Pdeath_AS
Incremental QALYs TAVI vs. Medical Management	rrvre_TAVI rrsmras pdeath_as	rrvre_TAVI rrsmras pdeath_as	rrvre_TAVI rrsmras pdeath_as	rrvreTAVI ---------- Pdeath_as
Incremental Costs TAVI vs. Medical Management	rrvre_TAVI pdeath_as ----------	rrvre_TAVI pdeath_as ----------	rrvre_TAVI pdeath_as ----------	rrvre_TAVI pdeath_as Rrsmras
Incremental QALYs AVR vs. Medical Management	rrsmras pdeath_as	rrsmras pdeath_as	rrsmras pdeath_as	Rrsmras pdeath_as
Incremental Costs AVR vs. Medical Management	rrsmras pdeath_as	rrsmras pdeath_as	rrsmras pdeath_as	Rrsmras pdeath_as

Parameters listed are those who representation > or = to 10%
N = sample size

Table IV.e Correlation Coefficients: Costs and Effects

		AVR: Costs & Effects	TAVI: Costs & Effects	Medical Management: Costs & Effects
Low Risk Operable	Large N 1	0.579	0.851	0.985
	Large N 2	0.582	0.847	0.985
	Small N 1	0.594	0.849	0.985
	Small N2	0.601	0.853	0.985
High Risk Operable	Large N 1	0.628	0.824	0.985
	Large N 2	0.627	0.822	0.985
	Small N 1	0.632	0.829	0.985
	Small N2	0.627	0.822	0.985
High Risk Inoperable	Large N 1	0.667	0.806	0.985
	Large N 2	0.671	0.804	0.985
	Small N 1	0.667	0.806	0.985
	Small N2	0.662	0.812	0.985

N = sample size

Table IV.f ANOVA Costs, QALYS and Life Years Gained per Patient Group and Model: Summary of Proportion Sum of Squares

	Large N 1	Prop. SS	Large N 2	Prop. SS	Small N 1	Prop. SS	Small N 2	Prop. SS
AVR Costs	platefatalvre	0.025	platefatalvre	0.025	platefatalvre	0.023	platefatalvre	0.023
	RrsmrAS	0.193	rrsmrAS	0.196	rrsmrAS	0.149	rrsmrAS	0.149
	pdeath_AS	0.679	pdeath_AS	0.676	pdeath_AS	0.733	pdeath_AS	0.733
	cfv_AS	0.028	cfv_AS	0.029	cfv_AS	0.027	cfv_AS	0.029
	Cfn	0.038	cfn	0.039	cfn	0.031	cfn	0.030
	Residual	0.026	residual	0.025	residual	0.028	residual	0.028
AVR QALYs					rfailed	0.066	rfailed	0.068
	Platevre	0.091	platevre	0.093	platevre	0.096	platevre	0.094
	rrsmrAS	0.595	rrsmrAS	0.599	rrsmrAS	0.491	rrsmrAS	0.488
	pdeath_AS	0.215	pdeath_AS	0.210	pdeath_AS	0.260	pdeath_AS	0.261
	uFnVR	0.061	uFnVR	0.058	uFnVR	0.054	uFnVR	0.052
	residual	0.015	residual	0.016	residual	0.017	residual	0.020
TAVI Costs	Rrvre_TAVI	0.728	Rrvre_TAVI	0.738	Rrvre_TAVI	0.712	Rrvre_TAVI	0.706
	pdeath_AS	0.172	pdeath_AS	0.162	pdeath_AS	0.195	pdeath_AS	0.199
	rrsmrAS	0.049	rrsmrAS	0.048	rrsmrAS	0.039		
	residual	0.019	residual	0.020	residual	0.021	residual	0.022

Prop. SS = Proportion Sum of Squares

Parameters listed are those who represent > or = to 10%

V PARTNER TRIAL

Table V.a PARTNER Inclusion and Exclusion Criteria

Inclusion Criteria

1. Senile degenerative aortic valve stenosis with echocardiography derived criteria: mean gradient >40 mm Hg or jet velocity > 4.0 m/s or an aortic valve area (AVA) of < 0.8 cm^2 (or AVA index< 0.5 cm^2/m^2).
2. Symptomatic due to aortic valve stenosis as demonstrated by NYHA Functional Class ≥ II.
3. The subject or the subject's legal representative was informed of the nature of the study, agreed to its provisions and provided written informed consent as approved by the Institutional Review Board of the respective clinical site.
4. The subject and the treating physician agreed that the subject would return for all required post procedure follow-up visits.
5. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agreed that medical factors precluding operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeded the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity exceeded 50%. The surgeons' consult notes should specify medical or anatomic factors leading to that conclusion and included should be a printout of the STS score calculation to further identify the risks in these patients.

Exclusion Criteria

1. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment (defined as Q wave MI, or non-Q wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin level elevation (WHO definition).
2. Aortic valve was a congenital unicuspid or congenital bicuspid valve, or was non-calcified.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).
5. Pre-existing prosthetic heart valve in any position, prosthetic ring, severe mitral annular calcification, or severe (greater than 3+) mitral regurgitation
6. Blood dyscrasias as defined: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 mg%), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.
7. Untreated clinically significant coronary artery disease requiring revascularization.
8. Hemodynamic instability requiring inotropic therapy or mechanical hemodynamic support devices.
9. Need for emergency surgery for any reason.
10. Hypertrophic cardiomyopathy with or without obstruction.
11. Severe ventricular dysfunction with LVEF < 20%.
12. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
13. Active peptic ulcer or upper gastro-intestinal bleeding within the prior 3 months.
14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated.
15. Native aortic annulus size < 18mm or > 25mm as measured by echocardiogram.
16. Recent (within 6 months) cerebrovascular accident or transient ischemic attack.
17. Renal insufficiency (creatinine > 3.0mg/dL) and/or end stage renal disease requiring chronic dialysis.
18. Life expectancy < 12 months due to non-cardiac co-morbid conditions.

Table V.a Continued

19. Significant abdominal or thoracic aorta disease, including aneurysm (defined as maximal luminal diameter 5cm or greater), marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated), narrowing of the abdominal aorta (especially with calcification and surface irregularities), or severe "unfolding" and tortuosity of the thoracic aorta
20. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe calcification, severe tortuosity or vessels size diameter < 7 mm for 22F sheath or < 8mm for 24F sheath
21. Currently participating in an investigational drug or another device study.
22. Active bacterial endocarditis or other active infections.
23. Bulky calcified aortic valve leaflets in close proximity to coronary ostia.

Source: Table 1, Leon et al. (2010)

Table V.b PARTNER Cohort B Clinical Outcomes at 30 day days and 1 year

Outcome		TAVI		Standard Therapy		P Value	TAVI		Standard Therapy		P Value
		n	%	N	%		n	%	N	%	
Death	From any cause	9	5	5	2.8	0.41	55	30.7	89	49.7	<0.001
	From cardiovascular cause	8	4.5	3	1.7	0.22	35	19.6	75	41.9	<0.001
Repeat Hospitalisation§		10	5.6	18	10.1	0.17	40	22.3	79	44.1	<0.001
Death from any cause or repeat hospitalisation§		19	10.6	22	12.3	0.74	76	42.5	126	70.4	<0.001
Stroke or TIA	All	12	6.7	3	1.7	0.03	19	10.6	8	4.5	0.04
	TIA	0	0	0	0	-	1	0.6	0	0	1
Stroke	Minor	3	1.7	1	0.6	0.62	4	2.2	1	0.6	0.37
	Major	0	5	2	1.1	0.06	14	7.8	7	3.9	0.18
Death from any cause or major stroke		15	8.4	7	3.9	0.12	59	33	90	50.3	0.001
Myocardial infarction	All	0		0		-	1	0.6	1	0.6	1
	Peripreocedural	0		0		-	0		0		-
Vascular Complications	All	55	30.7	9	5	<0.001	58	32.4	13	7.3	<0.001
	Major	29	16.2	2	1.1	<0.001	30	16.8	4	2.2	<0.001
Acute kidney injury											
Creatinine > 3mg/dl (265 γmol/litre) ¶		0		1	0.6	1	2	1.1	5	2.8	0.45
Renal-replacement therapy ‖		2	1.1	3	1.7	1	3	1.7	6	3.4	0.5
Major Bleeding		30	16.8	7	3.9	<0.001	40	22.3	20	11.2	0.007
Cardiac re-intervention											
	Balloon aortic valvuloplasty	1	0.6**	2	1.1	1	1	0.6	66	36.9††	<0.001
	Repeat TAVI‡‡	3	1.7	NA		-	3	1.7		NA	-
	Aortic-valve replacement	0		3	1.7	0.25	2	1.1**	17	9.5	<0.001
Endocarditis		0		0		-	2	1.1	1	0.6	0.31
New atrial fibrillation		1	0.6	2	1.1	1	1	0.6	3	1.7	0.62
New pacemaker		6	3.4	9	5	0.6	8	4.5	14	7.8	0.27

Source: Table 2, Leon et al. (2010)* NA denotes not applicable, TAVI transcatheter aortic-valve implantation, and TIA transient ischemic attack. † P values are for between-group comparisons of the frequency of the event at each time point. ‡ Deaths from unknown causes were assumed to be deaths from cardiovascular causes. § Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVI). ¶ Patients who received renal-replacement therapy were not included.‖ ‖ Patients who received renal-replacement therapy after randomization were included. ** One patient in the TAVI group did not receive TAVI (because of failed access) and subsequently underwent balloon aortic valvuloplasty, followed by aortic-valve replacement. †† A total of 30 patients underwent a repeat balloon aortic valvuloplasty after the index balloon aortic valvuloplasty procedure that had been performed in the first 30 days after randomization, and 36 patients underwent a first balloon aortic valvuloplasty more than 30 days after randomization. ‡‡ Three patients underwent a repeat TAVI within 24 hours after the index TAVI procedure; four patients in the standard-therapy group who underwent TAVI at a non-participating site outside the United States are not.

Table V.c PARTNER Cohort A Clinical Outcomes at 30 days and 1 year

Outcome	30 days			1 Year		
	TAVI (N = 348)	AVR (N = 351)	p-value	TAVI (N = 348)	AVR (N = 351)	p-value
All mortality – no. (%)	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
Cardiac mortality – no. (%)	11 (3.2)	10 (3.0)	0.9	47 (14.3)	40 (13.0)	0.63
Rehospitalisation – no. (%)	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or rehosp – no. (%)	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
MI – no. (%)	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Acute kidney inj* – no. (%)	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56
Vascular complications						
All – no. (%)	59 (17.0)	13 (3.8)	<0.01	62 (18.0)	16 (4.8)	<0.01
Major – no. (%)	38 (11.0)	11 (3.2)	<0.01	39 (11.3)	12 (3.5)	<0.01
Major bleeding – no. (%)	32 (9.3)	67 (19.5)	<0.01	49 (14.7)	85 (25.7)	<0.01
Endocarditis – no. (%)	0 (0.0)	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New AF – no. (%)	30 (8.6)	56 (16.0)	< 0.01	42 (12.1)	60 (17.1)	0.07
New PM – no. (%)	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68
All Stroke or TIA – no. (%)	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
TIA – no. (%)	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
All Stroke – no. (%)	16 (4.6)	8 (2.4)	0.12	20 (6.0)	10 (3.2)	0.08
Major Stroke – no. (%)	13 (3.8)	7 (2.1)	0.2	17 (5.1)	8 (2.4)	0.07
Minor Stroke – no. (%)	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Death/maj stroke – no. (%)	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68

Source: (Smith et al., 2011)

VI PARAMETERS FOR FURTHER EVIDENCE GENERATION

Table VI.a Proposed Parameters for Further Evidence Generation

Parameters	Potentially Provided in trial	Provided in Current Registry	Could be provided in a future registry
Events			
Probability of major procedure related events AVR	✓		
Probability of major procedure related events TAVI	✓	✓	✓
Probability of minor procedure related events AVR	✓		
Probability of minor procedure related events TAVI	✓	✓	✓
Probability of converting to_AVR	✓	✓	✓
Probability of converting to_noavr	✓	✓	✓
Probability of converting TAVI	✓		
Probability of repeat_TAVI	✓	✓	✓
Probability of major stroke_AVR	✓	¥	
Probability of major stroke_TAVI	✓		✓
Probability of death within 30 days_avr	✓		
Probability of death with 30days_Tavi	✓	✓	✓
Early Major PRE : TAVI			
Valve thromboembolism	✓	✓	✓
Major paravavular leak	✓	✓	✓
Endocarditis	✓	✓	✓
Cardiac tamponade	✓		✓
Myocardial infarction	✓	✓	✓
Early Minor PRE : TAVI			
Access site events	✓		✓
Vascular Events	✓		✓
Pacemaker implantation	✓	✓	✓
Major Vascular Event	✓		✓
Major Bleeding	✓	✓	✓
Late Major PRE : TAVI			
Valve thromboembolism	✓		✓
Major paravavular leak	✓		✓
Endocarditis	✓		✓
Cardiac tamponade	✓		✓
stroke	✓		✓
MI			
Late Minor PRE : TAVI			
repeat hospitalisations >30 days < 1 year	✓		✓
major vascular complications >30days < 1 year	✓		✓
minor vascular complications > 30 days < 1 year	✓		✓
major bleeding > 30 days < 1 year	✓		✓
new pacemaker > 30 days < 1 year	✓		✓
Early Major PRE : AVR			
Valve thromboembolism	✓		
Major paravavular leak	✓		
Endocarditis	✓		
Cardiac tamponade	✓		
Myocardial infarction	✓		
Early Minor PRE : AVR			
Access site events	✓		
Vascular Events	✓		
Pacemaker implantation	✓		
Major Vascular Event	✓		

Table VI.a Continued

Parameters	Trial Provided in trial?	Current Registry	Future Registry
Major Bleeding	✓		
Late Major PRE : AVR			
Valve thromboembolism	✓		
Major paravavular leak	✓		
Endocarditis	✓		
Cardiac tamponade	✓		
stroke	✓		
MI			
Late Minor PRE : AVR			
repeat hospitalisations >30 days < 1 year	✓		
major vascular complications >30days < 1 year	✓		
minor vascular complications > 30 days < 1 year	✓		
major bleeding > 30 days < 1 year	✓		
new pacemaker > 30 days < 1 year	✓		
Probability of fatal pre AVR	✓		
Probability of fatal pre TAVI	✓		✓
Probability of death natural causes AVR	✓		
Probability of death natural causes TAVI	✓		✓
Probability of death persistent AS AVR	✓		
Probability of death persistent AS TAVI	✓		✓
Resource Use			
Intensive Care Unit - LOS initial	✓		✓
High Dependency Unit - LOS initial	✓		✓
General Ward - LOS initial	✓		✓
probability of hospitalisations initial	✓		✓
Probability of cardiac rehab initial	✓		✓
Temporary Nursing home LOS initial	✓		✓
Annual probability of Hospitalisations - Functioning	✓		✓
Probability permanent nursing home care functioning	✓		✓
Routine Drug Therapy functioning TAVI	✓		✓
Annual probability of Hospitalisations - persistent AS	✓		✓
Probability permanent nursing home care - persistent	✓		✓
Routine Drug Therapy - persistent AS TAVI	✓		✓
Probability of late balloon TAVI	✓		✓
Annual probability of Hospitalisations - Functioning	✓		
Probability permanent nursing home care functioning	✓		
Routine Drug Therapy functioning AVR	✓		
Annual probability of Hospitalisations - persistent AS	✓		
Probability permanent nursing home care - persistent	✓		
Routine Drug Therapy - persistent AS AVR	✓		
Probability of late balloon TAVI	✓		
Quality of Life			
Utility of Aortic Stenosis - Baseline TAVI *	✓	✓	✓
Utility Functioning VR TAVI*	✓	✓	✓
Utility of Persistent AS TAVI*	✓	✓	✓
Utility of Aortic Stenosis - Baseline AVR*	✓		
Utility Functioning VR AVR*	✓		
Utility of Persistent AS AVR*	✓		
Utility of Aortic Stenosis - Baseline TAVI+	✓		✓
Utility Functioning VR TAVI+	✓		✓
Utility of Persistent AS TAVI+	✓		✓
Utility of Aortic Stenosis - Baseline AVR+	✓		
Utility Functioning VR AVR+	✓		
Utility of Persistent AS AVR+	✓		

* Proportion NYHA + EQ-5D ¥ doesn't distinguish between major and minor

VII TRANSITION PROBABILITIES COMPARISION

Table VII.a Transition Probabilities for the Five Versions of the Model

TRANSITION PROBABILITIES	*All Patient Groups*	*Inoperable*		*Operable*	
	Original Model	**PARTNER B**	**Updated PARTNER B**	**PARTNER A**	**Updated PARTNER A**
Short term - 0-30 days					
Converting TAVI to AVR	0.06 (0.03-0.09)	0.01 (0 - 0.02)	As per PARTNER B	0.03 (0.01-0.04)	0.01 (0.01-0.02)
Converting TAVI to medical management	-	0.02 (0.01-0.05)	As per PARTNER B	0.01 (0.00-0.03)	As per PARTNER A
Converting from AVR to TAVI	-	-	-	0.003 (0.00-0.12)	As per PARTNER A
Repeat TAVI procedure	-	0.02 (0-0.04)	0.02 (0-0.04)	0.02 (0.01-0.04)	0.01 (0.01-0.02)
Major stroke AVR	0.03 (0.02-0.05)	-	-	0.03 (0.01-0.05)	As per PARTNER A
Major stroke TAVI	0.03 (0.02-0.05)	0.05 (0.03-0.09)	0.05 (0.03-0.09)	0.06 (0.03-0.08)	0.05 (0.04-0.06)
Major PREs AVR	0.12 (0.09-0.17)	-	-	0.05 (0.02-0.07)	As per PARTNER A
Major PREs TAVI	0.12 (0.09-0.17)	0.18 (0.12-0.24)	0.16 (0.12-0.21)	0.16 (0.12-0.21)	0.17 (0.13-0.22)
Minor PREs AVR	0.19 (0.15-0.23)	-	-	0.33 (0.29-0.40)	As per PARTNER A
Minor PREs TAVI	0.24 (0.17-0.32)	0.58 (0.48-0.69)	0.54 (0.43-0.63)	0.38 (0.31-0.44)	0.45 (0.40-0.51)
Death 30 days all causes AVR	+	-	-	0.07 (0.04-0.10)	As per PARTNER A
Death 30 days all causes TAVI	+	0.07 (0.03-0.11)	0.09 (0.07-0.11)	0.04 (0.02-0.06)	0.07 (0.06-0.09)
AS persisting medical management	1	0.96 (0.93-0.99)	As per PARTNER B	As per PARTNER B	As per PARTNER B
Death medical management	-	0.04 (0.01-0.07)	As per PARTNER B	As per PARTNER B	As per PARTNER B
Balloon valvuloplasty (MM)	-	0.83 (0.76-0.88)	As per PARTNER B	As per PARTNER B	As per PARTNER B
Long term - post 30 days					
Fatal PRE AVR Year 1	0.22 (0.18-0.27)	-	-	0.10 (0.06-0.14)	As per PARTNER A
Fatal PRE TAVI Year 1	0.22 (0.18-0.27)	0.23 (0.15-0.31)	0.22 (0.17-0.27)	0.12 (0.08-0.17)	As per PARTNER A

Table VII.a Continued

TRANSITION PROBABILITIES	*All Patient Groups*	*Inoperable*		*Operable*	
	Original Model	**PARTNER B**	**Updated PARTNER B**	**PARTNER A**	**Updated PARTNER A**
Fatal PRE AVR Year 2					0.07 (0.04-010)
Fatal PRE TAVI Year 2	-	-	-	-	0.08 (0.05-0.11)
Major PRE AVR Year 1	0.17 (0.13-0.18)	-	-	0.11 (0.08-0.16)	As per PARTNER A
Major PRE TAVI Year 1	0.17 (0.13-0.18)	0.20 (0.13 -0.29)	0.16 (0.11-0.22)	0.18 (0.13-0.24)	As per PARTNER A
Major PRE TAVI Year 2	-	-	0.21 (0.15-0.28)	-	0.16 (0.12-0.21)
Major PRE AVR Year 2	-	-	-	-	0.10 (0.06-0.14)
Minor PRE TAVI Year 1	-	0.19 (0.12-0.27)	0.24 (0.17-0.31)	0.28 (0.22-0.35)	As per PARTNER A
Minor PRE AVR Year 1	-	-	-	0.22 (0.17-0.27)	As per PARTNER A
Minor PRE TAVI Year 2	-	-	0.29 (0.23 - 0.38)	-	0.10 (0.06-0.14)
Minor PRE AVR Year 2		-	-	-	0.08 (0.05-0.12)
Death from AS state AVR[¶]	0.33 (0.23-0.43)	-	-	0.18 (0.05-0.36)	As per PARTNER A
Death from AS state TAVI[¶]	0.33 (0.23-0.43)	0.60 (0.44-0.74)	As per PARTNER A	0.08 (0.03-0.15)	As per PARTNER A
Death from AS state - Medical Management[¶]	0.33 (0.23-0.43)	0.57 (0.49-0.65)	As per PARTNER A	0.33 (0.25-0.41)	As per Original Model
Death from AS state – post 1 year [¶]	-	0.33 (0.24-0.42)	As per PARTNER A	0.33 (0.24-0.42)	As per Original Model
Mortality from natural causes (mr)	†	As per Original	As per Original Model	As per Original Model	As per Original Model
Morality from natural causes - AVR	-	-	-	0.14 (0.10-0.18)	As per PARTNER A
Mortality from natural causes - TAVI	-	-	-	0.15 (0.10-0.19)	As per PARTNER A
Relative risk of death due to AS (rrsmrAS)	1.50 (0.95-2.24)	As per Original	As per Original Model	As per Original Model	As per Original Model
Mortality from persistent AS/ failed valve replacement	mr * smrAS	-	-	-	-
Balloon valvuloplasty	-	0.50 (0.41-0.58)	As per PARTNER A	As per PARTNER B	As per PARTNER B

Table VII.a Continued

TRANSITION PROBABILITIES	***All Patient Groups***	***Inoperable***		***Operable***	
	Original Model	**PARTNER B**	**Updated PARTNER B**	**PARTNER A**	**Updated PARTNER A**
Mortality from natural causes – TAVI (year 1)	-	0.14 (0.09-0.21)	As per PARTNER A	-	-

Source: Tables 4.4, 5.1, 6.1, 7.2 and 7.8

+ Low risk 5%; medium risk 15% and high risk 20%. † Standard life tables ¶(Legrand et al., 1991) - indicates not applicable

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