Modelling the cost-effectiveness of strategies to treat end-stage heart failure using discrete event simulation

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Certificate of original authorship

I, Sopany Saing declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, Health Economics, in the Faculty of Business at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualification at any other academic institution.

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Dissemination

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Abbreviations

ABM	Agent based modelling
ACT	Australian Capital Territory
AFT	accelerated failure time
AHF	advanced heart failure
AIC	Akaike's information criterion
AIHW	Australian Institute of Health and Welfare
ALOS	average length of stay
ANZCOTR	Australia and New Zealand Organ Transplant Registry
ANZOD	Australia and New Zealand Organ Donation
APDC	Admitted Patient Data Collection
AR-DRG	Australian Refined-Diagnosis Related Group
BIC	Bayesian information criterion
biVAD	biventricular assist device
BMI	body mass index
BTDB	British NHS Blood and Transplant Database
BTC	bridge to candidacy
BTR	bridge to recovery
BTT	bridge to transplant
C-Pulse	Extra-aortic counter pulsation device
CABG	coronary artery bypass grafting
CAV	cardiac allograft vasculopathy
CDRH	Center for Devices and Radiological Health
CHF	congestive heart failure
CRD	chronic renal dysfunction
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CF	continuous-flow
CI	confidence interval
CRT	Cardiac Resynchronisation Therapy
CUA	cost-utility analysis
DCD	Donated after Circulatory Death
DES	Discrete event simulation
DPMP	Deceased organ donors per million population
DT	Destination Therapy
ECMO	extra-corporeal membrane oxygenation
EDDC	Emergency Department Data Collection
ESHF	End-Stage Heart Failure
EQ-5D	European Quality of Life-5 Dimensions
FDA	US Food and Drug Administration
GDP	Gross Domestic Product
HHT	Heterotopic heart transplants
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	hazard ratio
HRQOL	health related quality of life

HTx	Heart Transplant
HTA	Health Technology Assessment
HVAD	HeartWare™ HVAD™ System
IABP	intra-aortic balloon pump
ICD	Implantable Cardioverter Defibrillator
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICER	Incremental Cost-Effectiveness Ratio
ICU	intensive care unit
IDCM	idiopathic dilated cardiomyopathy
IDMT	inotrope-dependent medical therapy
IMACS	International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IPD	Individual Patient Data
ISHLT	International Society for Heart & Lung Transplantation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
MCS	mechanical circulatory support
MedaMACS	Medical Arm of Mechanically Assisted Circulatory Support
MLWHFQ	Minnesota Living With Heart Failure Questionnaire
MM	Markov model
MSAC	Medical Services Advisory Committee
MVAD	HeartWare® Miniaturized Ventricular Assist Device (MVAD®)
n	number of observations
N	number of sample
N/A	Not Applicable
NHCDC	National Hospital Cost Data Collection
NICE	National Institute for Health and Care Excellence
NLG	Dutch Guilder
NS	not specified
NSW	New South Wales
NT	Northern Territory
NYHA	New York Heart Association
NZ	New Zealand
min	minimum
max	maximum
LVEF	left ventricular ejection fraction (%)
LTCS	long-term chronic support
LVAD	left ventricular assist device
LY	life year
LYG	life year gained
OHT	orthotopic heart transplant
OMM	Optimal Medical Management
PBAC	Pharmaceutical Benefits Advisory Committee
PF	pulsatile-flow
PH	proportional hazards

PMSI	Program for the Medicalisation of Information Systems
PPN	Project specific Person Number
PPP	purchasing power parity
PRA	panel reactive antibody
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
QALYG	Quality-adjusted life year gained
QLD	Queensland
QoL	quality of life
RCT	randomised controlled trial
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
RR	Relative Risk
RVAD	Right ventricular assist device
UK	United Kingdom
UNOS	United Network of Organ Sharing
USA	United States of America
SA	South Australia
SD	Standard deviation
SE	standard error
SG	standard gamble
SHTAC	Southampton Health Technology Assessment Centre
SIMULATE	System, Interactions, Multilevel, Understanding, Loops, Agents, Time, Emergence
SMDM	Society for Medical Decision Making
SRTR	Scientific Registry of Transplant Recipients
SVHS	St. Vincent's Hospital Sydney
TAH	total artificial heart
TAS	Tasmania
TTO	time trade-off
VAD	ventricular assist device
VAS	visual analogue scale
VIC	Victoria
VOI	Value of Information
WA	Western Australia
WL	waiting list
WTP	willingness to pay

Abstract

The cost of providing healthcare is increasing due to an ageing population and new technologies, hence the assessments of value for money are becoming more important. Health Technology Assessment (HTA) is an approach to estimate the cost-effectiveness of treatment strategies to assist in decision-making.

However, resource constraints are not usually explicitly considered in HTA. For example, if a patient requires a new drug, it is assumed that that resource is available immediately, without delay to the patient. Queues and waiting lists are commonplace in health care; for instance, patients in an emergency department waiting room or the waiting list for elective surgery. Not incorporating queuing theory into HTA is likely to be an issue if the consequences of delayed treatment significantly affect a patient's morbidity and mortality.

A case-study in end-stage heart failure is utilised to explore the restrictions faced by patients as they enter the heart transplant (HTx) waiting list due to the shortage of donor organs. Unique to organ donation is the matching process, whereby patients are matched to a donor heart based on blood type and weight rather than a simple first-come first-served basis. Additionally, artificial implantable devices, such as a left ventricular assist device, can buy patients more time on the waiting list or allow patients to become eligible for a HTx when used as a bridge to candidacy.

This thesis explicitly considers a resource constrained HTA by applying queuing theory using discrete event simulation (DES). A dynamic simulation modelling method, DES models queues representing the competition between patients for resources. This study used real-world data from an Australian transplanting hospital to inform the modelling. The results of a DES model with and without queuing are compared with a traditional cohort Markov model to explore the impact of the modelling methods on decision-making.

1 CHAPTER 1: INTRODUCTION – HEALTH TECHNOLOGY ASSESSMENT OF COMPLEX INTERVENTIONS WITH RESOURCE CONSTRAINTS

The cost of delivering health care continues to increase. New and potentially better health technologies are constantly being developed, providing better treatment options for patients. However, there is an opportunity cost of funding these technology compared to proven existing treatments and other health care services. Health Technology Assessment (HTA), which provides an estimate of the cost-effectiveness or 'value for money' of a treatment, is a widely accepted decision-making tool to inform the efficient allocation of health resources. Economic evaluations conducted as part of the HTA capture the relevant costs and benefits of alternative or competing interventions or policies.

A common feature of almost all economic evaluations is the assumption that the supply of the new health technology is unlimited, and that, as a consequence, the patient is able to access the treatment immediately if they meet appropriate criteria as set out by the supporting evidence and funding arrangement. This situation is analogous to the funding of a new pharmaceutical drug, in which the supply is unconstrained and patients do not compete with each other to access the new drug. However, for some health technologies it is unrealistic to assume unlimited availability, since in some cases demand for the new technology may exceed the available supply. A simple example of a supply-constrained resource is hospital beds. There are more patients than available beds, which leads to a greater reliance on day procedures, waiting lists for elective surgeries or triaging in emergency departments.

In health economics, we are concerned by how society allocates resources among alternative uses. Scarcity of resources provides a foundation of economic theory that focuses on what goods and services are produced, how we produce these goods and services, and who should receive them. Supply constraints and scarce resources are common in health care and take many forms. For example, there are a limited number of surgeons, operating theatres and intensive care beds, which limits the number of operations that can be performed per year. Similarly, there is a finite number of technicians and diagnostic medical equipment, which limits the number of patients that can be screened for early cancer. Access to expensive new drugs may also be limited to contain costs, restricting the supply of the drug to patients by imposing strict treatment criteria.

In this thesis, I will be focussing on the treatment of end-stage heart failure (ESHF), which is synonymous with long waiting periods for heart transplants and the restricted supply of suitable donor organs. As a result of the restricted supply of donors, a suite of treatment options have become

available to ESHF patient and have altered their life-expectancy and treatment costs. Two such technologies have the potential to change the heart transplant waiting list. The first is mechanical support devices, known as left ventricular assist devices (LVADs) or VADs (used interchangeably throughout the thesis). LVADs support a patient's cardiac function, enabling them to live at home and buying the patient more time while they wait for a suitable donor heart to become available. The second technology is ex vivo organ perfusion, which increases the pool of available donor hearts for patients. When modelling the treatments for ESHF, these two technologies help patients in different but similar ways. LVADs allow patients to remain on the waiting list for longer, whereas organ perfusion increases the supply of donor hearts. Together, they increase the likelihood of finding a suitable donor/recipient match. As a consequence, the waiting list (or patient queue) plays a pivotal role in understanding the impact on patient health due to delayed treatment.

When modelling health care interventions, the analyst usually adopts a pragmatic approach by only modelling the key features of the health problem, and simplifying the model where possible (or in the absence of data). Common modelling techniques include decision tree analysis and Markov modelling, which typically estimate the impact of a new intervention on a cohort of patients with common features. While these modelling approaches dominate the literature, neither explicitly considers the impact of restricting supply and waiting times, nor are they necessarily the best approaches when patient level data are available. Discrete event simulation (DES) is an alternative approach that allows for the use of individual-level data and explicitly incorporates queuing theory into the decision problem. So, a significant question is whether modelling techniques that explicitly incorporate complexities such as competition among patients reach a similar or different decision-making conclusion compared with modelling techniques that do not? This thesis explores the application of discrete event simulation in HTA using an ESHF case-study to assess the contribution of this technique in health care decision-making.

1.1 Research Question

The primary aim of this thesis is to estimate the cost-effectiveness of a resource-constrained intervention. To do this I will use queuing theory as applied in discrete event simulation (DES) and compare the use of DES with traditional cohort-based Markov modelling. Using a case study in ESHF, I model the impact of mechanical circulatory support devices on human donor heart replacement, using the different modelling techniques to evaluate the strengths and weakness of each approach. This study relies on a rich, linked dataset of individual patient data of costs and outcomes for patients with ESHF from the leading transplant centre in Australia (St Vincents Hospital Sydney). The case study was chosen due to the supply-constrained resources and heart transplant waiting list affected by queuing theory.

Research objectives:

1. To review guidance on the choice of modelling technique for health technology assessment with constrained resources and to conduct a review of the empirical comparison of cohort Markov and Discrete Event Simulation (DES) models .
2. To conduct a systematic review of the modelling methods in cost-effectiveness analyses for mechanical circulatory support compared to heart transplants (HTx) in end-stage heart failure (ESHF).
3. To estimate the clinical effectiveness and cost of different interventions to treat ESHF using hospital individual level patient data (St Vincent's Hospital Sydney).
4. To build a cohort Markov model to assess the cost-effectiveness of a range of policies to treat patients with ESHF.
5. To build a DES model to assess the cost-effectiveness of a range of policies to treat ESHF.
6. To compare and contrast the results of the two models, highlighting the strengths and weaknesses of each technique and to summarise the application of DES in health technology assessment.

Objectives 2, 3, 4 and 5 will be addressed over four empirical chapters.

1.2 Background

1.2.1 Health care funding

The funding of healthcare is complex and includes health interventions such as pharmaceuticals, medical devices and public health programs and services. The health care system in Australia is largely publicly funded by Medicare, a universal public health insurance scheme.(1) Therefore, essential healthcare is available to all Australians. Medicare is funded by the Australian federal government via taxation. Pharmaceuticals are reimbursed through the Pharmaceutical Benefits Scheme (PBS) and medical services are reimbursed through the Medicare Benefits Scheme (MBS). Both schemes are funded by the Australian Government, with the patient usually contributing directly via a co-payment.

There are inter-governmental agreements for public hospital funding between the Australian Government and state and territory governments for public hospital treatments. Private health insurance can cover part of the patient costs in hospitals as a 'private patient in a private hospital or private patient in a public hospital' or non-medical health services such as dental.(1) There are multiple purchasers in medical device reimbursement, including public hospitals, which are state/territory government-funded, and private hospitals, which are reimbursed via private health

insurance and federal government rebates. This has implications for the available services provided in a public compared to a private hospital setting. For instance, deceased organ transplants occur in public hospital settings only.

The national budget available for expenditure on health care is finite and takes up a significant proportion (>9% in 2016) of overall government expenditure.(2) As in most developed countries, the demand for health care is increasing due to an ageing population and improvements in new (usually more expensive) treatments. In 2016, Australia ranked 14th amongst OECD countries in terms of expenditure on health as a proportion of GDP, which is slightly above the OECD average.(2) Given the increasing cost pressure on the healthcare system, efficient allocation of resources is paramount and not all new health interventions can be funded.

The delivery and funding of health care in Australia and many other developed countries relies heavily on government involvement. This is largely because of market failures, such as the unpredictability of health, adverse selection of health insurance markets, externalities and asymmetric information between providers and consumers.(3) As a consequence of government involvement, funding decisions for new interventions are usually based on some notion of value for money (or cost-effectiveness). Economic evaluation is an evidence-based systematic methodology of applying welfare economics to identify the best intervention and generate recommendations about whether a particular state of the world is preferable to another.(4) In other words, it is about formally ranking, from better to worse, resource allocations and the associated policies from an economic perspective.(5)

1.2.2 Health Technology Assessment

Decision analysis by decision-making bodies aims to estimate the effectiveness, safety, value for money and budgetary impact of new health technologies. Specifically, the economic evaluation of health technologies is part of Health Technology Assessment (HTA). HTA is the systematic evaluation of properties, effects or other impacts of health technology.(6) The impacts of technologies can include technical properties, safety, efficacy, economic attributes or social, legal, ethical and/or political impacts.(6) A HTA process enables countries to evaluate the jurisdiction-specific impact of new technologies.

Australia was one of the first countries to introduce HTA processes in decision-making about pharmaceuticals, medical services and other health services interventions to inform adoption decisions of new technologies.(7) The Pharmaceutical Benefits Advisory Committee (PBAC) reviews the evidence to support pharmaceuticals being reimbursed on the Pharmaceutical Benefits Scheme. The implementation of HTA processes depends on the requirements and can be influenced by single-

payer vs multi-payers health sytems. For instance, Australia, the United Kingdom and Canada have single-payer health systems and have adopted HTA in decision-making.(8) In countries where there are multiple-payers, such as the United States, the role of HTA is much more diverse.

The purpose of HTA is to guide local jurisdiction decision-making on health technologies. Therefore, the evidence collected is usually fit for purpose and relevant to the population affected by the funding decision. Consequently, results of HTA analysis of a particular intervention are usually not applied to other jurisdictions due to differing health care systems and resource use implications. In the process of HTA, data collection may include primary data from randomised controlled trials (RCTs), synthesis methods such as systematic literature review and meta-analysis of studies. Secondary data sources, such as administrative data, may also be relied on during assessment of evidence. Other methods include economic analyses, which may include modelling; also embedded in economic analyses is budget impact analysis.(6)

1.2.3 Types of economic evaluation

Economic evaluations quantify the opportunity cost of alternative health care interventions or programmes. The concept of 'opportunity cost' is defined as 'the health benefits (life years saved, quality-adjusted life years (QALYs) gained) that could have been achieved had the money been spent on the next best alternative intervention or healthcare programme'.(9) Therefore, decision-makers are interested in whether an intervention is considered value for money. There is a demand for many different health technologies, and one dollar spent on any form of health care (e.g. a surgery for heart failure) means that one dollar is unavailable to spend on another form of health care (e.g medication for cancer).

Economic evaluation aims to determine the most efficient allocation of resources in the health system.(10) There are two main types of efficiency, demand-side allocative efficiency and supply-side technical efficiency. Allocative efficiency has two perspectives; on the output side this is 'whether limited resources are directed towards producing the correct mix of health care outputs, given the relative value attached to each'.(10) A payer (e.g. government) aims to see their financial contributions used to maximise health gain. Alternatively, on the input side this is 'whether an optimal mix of inputs is being used to produce its chosen outputs'.(10) If a provider (e.g. device manufacturer) produces treatments that are low value (i.e. high cost-effectiveness), then these inputs could be better used producing outputs with higher potential health gain. Allocative inefficiency can occur at all levels and 'may arise from inadequate priority-setting, faulty payment mechanisms, lack of clinical guidelines, incomplete performance reporting or simply inadequate governance of the system'.(10)

Conversely, technical efficiency is achieved when the number of inputs are minimised to produce a given level of output.

There are a number of approaches that can be used to determine value for money via the most efficient allocation of new interventions. Cost-effectiveness analysis (CEA) is the evaluation of the incremental effectiveness of an intervention versus an alternative use of funds (often current practice) compared to the incremental cost. In CEA, the unit of measurement of outcomes is a natural unit such as life years gained. This is distinct from cost-utility analysis (CUA), which explicitly measures effectiveness using quality-adjusted life years (QALYs), which can be described as taking an extra-welfarist approach (see below).(11) A QALY is an outcome measure and is a combination of survival and quality of life (QoL) or utility. QoL is a measure of morbidity and captures a benefit of technologies distinct from life extension. CUAs are a specific type of CEA that report cost per QALYs gained. Two other types of anaylsis can also be used. Cost-minimisation analysis (CMA) compares the cost of two treatments when the effectiveness of both treatments is demonstrated to be equivalent; hence, this analysis is used to find the lowest-cost alternative. Cost-benefit analysis (CBA) is widely used in economics but is less popular in health economics because it relies on the health benefit being explicitly converted to a monetary value.

1.2.3.1 Welfarism and extra-welfarism

To determine the value of improvement in health, welfare economics is based on the desirability of a particular policy, i.e. whether the policy is socially preferable to another based on some explicitly stated ethical criteria.(11) Welfare economics is typically divided into 'classical' and 'neo-classical' forms. These differ in how they are measured, with classical being cardinally measured (added across individuals and the social optimum reached when the maximum output is reached) and neo-classical being ordinally measured. Within the neo-classical approach there are two subdivisions, Paretian[1] and interpersonal comparisons. The welfarist approach is focussed on maximising utility[2] for the individual according to their own preferences.

In health economics, extra-welfarism is the normative basis for assessing social welfare.(12) A normative basis is distinct from a positive basis as it refers to the value derived from an intervention

[1] The Pareto principle is that 'any increase of utility for one individual that involved no utility loss for another was an improvement and an optimum was where no reallocation of resources could be made without reducing at least one person's utility (there might be many such optima, choice between which is impossible using only the Pareto criterion)'.(11)

[2] The concept of utility is described as 'a representation of an individual's preference ordering over bundles of goods or states of the world and, in welfarist economics, an individual moving to a preferred state of the world is an equivalent statement to an individual having a higher level of utility'.(11)

or policy rather than a fact that can be proved.(5) Extra-welfarism refers to health, rather than utility, as the most relevant outcome for conducting normative analysis in the health sector.(5) The second argument is the concept of need as opposed to demand, where need is the ability to benefit from health and demand is based on ability to pay and preferences for the particular service.

The extra-welfarist approach includes welfarism but differs in four distinct ways: (i) it permits the use of outcomes other than utility; (ii) it permits the use of sources of valuation other than the affected individuals; (iii) it permits the weighting of outcomes (whether utility or other) according to principles that need not be preference-based; and (iv) it permits interpersonal comparisons of well-being in a variety of dimensions, thus enabling movement beyond Paretian economics.(11) Accordingly, extra-welfarism transcends traditional welfare and includes characteristics such as whether patients are pain-free or able to choose.(11) In addition to health, other relevant factors include consumer choice, privacy and speed of service.(12) These intangible attributes may be relevant to the decision problem; for example, the alternative treatment may be invasive surgery, which may improve life expectancy but patients may fear the procedure. Therefore, a patient may prefer medication over surgery, despite the potential for improved health outcomes from the latter.

Taking an extra-welfarist view in health economic evaluation has led to the dominance of CUAs as QALYs are relied on as the single maximand. Despite this, there are criticisms of the sole use of QALYs in that the focus may be too narrow due to reliance on health-related quality of life (13, 14) and QALYs disadvantage those with the least potential to return to full health (such as the elderly and disabled). Therefore, even within the extra-welfarist view only health is maximised. Although a single maxim is unlikely to capture complete health maximisation, for the purposes of this thesis QALYs were measured as this is consistent with many published HTAs.[3]

1.2.3.2 Threshold value and willingness to pay

In HTA, the incremental cost and incremental benefit of two alternatives are summarised using an incremental cost-effectiveness ratio (ICER). This can be used to assess whether the intervention represents value for money, i.e. the 'extra effect is worth the extra cost'.(17) The ICER is calculated as the incremental cost of two health care interventions (A vs B) over the incremental benefit of those interventions. The equation is summarised as follows:

Eq1: $$ICER: (Cost_A – Cost_B)/ (Effect_A – Effect_B)$$

[3] In addition to QALYs, outcomes such as disability-adjusted life years (DALYs) (15) and healthy year equivalents (HYEs) (16) have been used in economic evaluation.

The resulting cost per QALY allows programmes of different sizes and varying opportunity costs to be compared on a single statistic.(10) Once an ICER is estimated, a decision is made on whether the intervention is considered good value for money. This is determined on the basis of a pre-defined threshold; if the ICER is below this threshold the intervention may be considered cost-effective, if the ICER exceeds this threshold, it may not be considered cost-effective.

The willingness to pay thresholds (WTP) have been used to inform how much society is willing to forgo for gains in health. Currently in Australia, there is no explicitly defined WTP threshold. The most recent estimates of the WTP threshold in Australia across all health care was $28,033 per QALY gained (range of $20,758 to $37,667 per QALY gained) using an opportunity cost approach based on 2011/2012 government health expenditure.(18) In a previous study, a retrospective analysis of past inferred ICERs from pharmaceutical reimbursement decisions produced an estimate between $42,000 and $76,000 (1998/1999 Australian dollars).(19) In another retrospective analysis of pharmaceutical reimbursement decisions from 1994 to 2004, the authors concluded that there was no evidence of a fixed public WTP threshold, but noted that characteristics of the clinical condition, perceived confidence in the evidence and total cost to government determined value for money.(20)

It was initially the World Health Organization that proposed the concept of a WTP threshold rather than one based on Gross Domestic Product so that different countries could have a common threshold adjusted for country wealth.(21) It is debated whether an explicit WTP threshold should exist, with proponents desiring a systematic means of decision-making while opponents suggest it could lead to uncontrolled growth in healthcare expenditure.(22) If set, the threshold value would still differ across countries, with high-income countries being able to accept higher thresholds.(22)

1.2.4 Why do we need disease models?

Disease models can assist funding decision by providing a framework for estimating the health impact and resource use of a new technology. A model is a simplified representation of reality that captures the essential properties and relationships of the alternative choices.(23) Models are developed for economic evaluation when direct experimentation is impractical or costly.(23) These models aim to appraise the value of a particular intervention for a disease. The UK National Institute for Health and Care Excellence (NICE) Guide to the method of technology appraisal (2013)(24) specifies situations when modelling is likely to be required. These include cases where:

1. all the relevant evidence is not contained in a single trial,
2. trial participants do not represent the typical patients likely to use the intervention within the specific country,

3. intermediate outcome measures are used rather than final outcome measures, such as health related quality of life (HRQOL) and survival,
4. trials do not include relevant comparators or relevant populations,
5. trial design includes crossover (treatment switching) that would not occur in clinical practice, or
6. costs and benefits of the technologies extend beyond the trial follow-up period.(24)

An extension of the typical disease-based intervention models can take a broader health system perspective and can be used to represent system behaviour. For example, an institution (e.g the UK National Health Service) may wish to evaluate clinical policy guidelines and a model can be useful in conceptualising the decision problem. A whole-of-disease life-cycle – through pre-diagnosis, screening, diagnosis, treatment and follow-up – can be modelled. A hospital may wish to explore clinically relevant policy changes and a model can be useful in illustrating how the decision may affect local resource use. This type of analysis will include downstream consequences of a policy change.

1.2.5 Does the economic modelling approach chosen matter in HTA?

There is an abundance of published guidance on which modelling method to use in what situation.(23, 25-28) Some modelling approaches are complex and there is generally a trade-off between simplicity and clinical validity.(29) The first decision is whether a cohort-level or individual-level model is necessary for the research question. In cohort-level models, an average patient approach is taken and patients flow throughout the model in unison. In contrast, in individual-level models, individuals flow throughout the model one at a time and the characteristics of each individual are unique (see Table 1-1). Individual level models can be useful when there is patient heterogeneity that affects the outcome of a patient receiving the intervention – for instance, the risk of adverse events from a procedure is higher as the patient gets older.

The next major attribute that guides model structure choice is whether there are interactions between patients. Brennan et al. (2006) argue that when interactions between patients are crucial to the decision problem, then only individual-level models can capture such complexity.(27) Infectious disease models often include interactions; for example, individuals can transmit disease to others so that the infected group increases exponentially. Interactions can include competition for resources resulting in waiting time for a treatment.

Table 1-1: A comparison of cohort-level vs. individual level models

Patient attribute	Cohort-level	Individual-level
Movement	In unison	Individual
Characteristic	Average population	Individual with correlations captured
Interaction between patients	Not captured	Interact/compete
Outputs	Average outputs, may cause statistical bias in estimates of the mean.	Can cope with a non-linear interaction between the risk and outcome

Source: (23, 27, 28)

1.2.6 Taxonomy of model structures

There are a number of economic modelling structure taxonomies available in HTA.(23, 27-29) For example, Brennan et al. (2006)(27) distinguish between two types of economic model structures, cohort-level (column A and B) and individual-level (column C and D) models(27) (see Table 1-2). The simplest model structure is a decision tree. This model structure is analysed via expected value for a cohort of patients with no interactions between patients. It has been acknowledged that 'decision trees and Markov cohort models are the most commonly used approaches in economic evaluation' (29) (rows 1 and 2). When interaction between patients is required to be modelled then system dynamics and discrete event simulation (DES) can be used (rows 3 and 4).

Table 1-2: A taxonomy of Model Structures for Economic Evaluation of Health Technologies

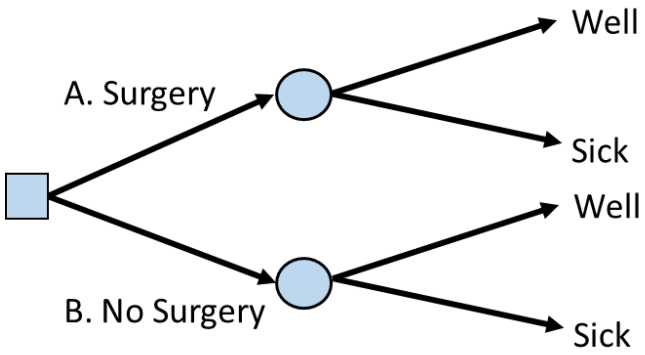
			A	B	C	D
			Cohort/aggregate level/counts		Individual level	
			Expected value, continuous state, deterministic	Markovian, discrete state, stochastic	Markovian, discrete state, individuals	Non-Markovian, discrete-state, individuals
1	No interaction allowed	Untimed	Decision tree rollback	Simulated decision tree	Individual sampling model: Simulated patient-level decision tree	
2		Timed	Markov model (evaluated deterministically)	Simulated Markov model	Individual sampling model: Simulated patients-level Markov model (variations as in quadrant below for patient level models with interaction)	
3	Interaction allowed	Discrete time	System dynamics (finite difference equations)	Discrete time Markov chain model	Discrete-time individual event history model	Discrete individual simulation
4		Continuous time	System dynamics (ordinary differential equations)	Continuous time Markov chain model	Continuous time individual event history model	Discrete event simulation

Source: adapted from Table 1, p.1297, Brennan 2006(27)

1.2.6.1 Decision trees

Decision trees are probably one of the most widely used models in economic evaluation.(8) Decision trees begin with a decision node that represents the decision problem – typically, which intervention is more cost-effective (A vs B) (see Figure 1-1). The effects of the alternatives are represented by possible pathways of branches ('chance nodes') with probabilities of particular events determined by 'branch probabilities'.(8) The criteria for the pathways are mutually exclusive and exhaustive, and each pathway would have a payoff of benefit or costs. Although widely used, there are two main limitations of decisions trees. Firstly, time is not explicitly defined in the model and, secondly, models can be complex when there are recurring events, such as in chronic health conditions.(8)

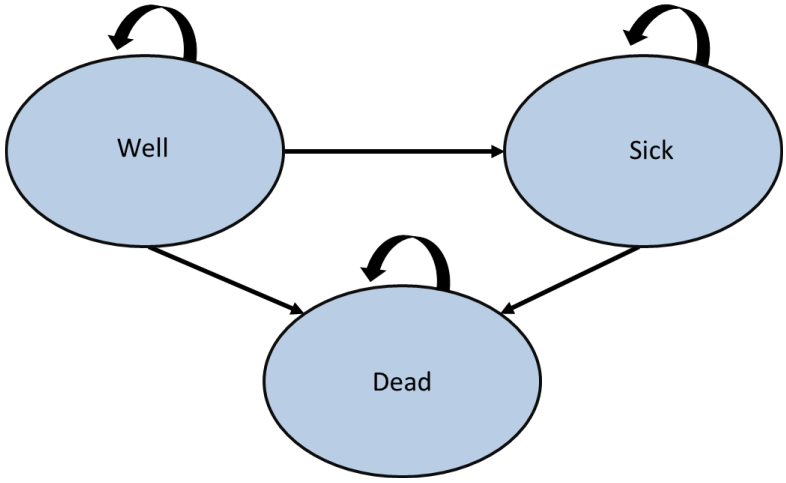
Figure 1-1: Example of Decision tree diagram



1.2.6.2 Markov models

Markov models are widely used and characterise events as 'health states' a patient can occupy at a point in time (Figure 1-2). Markov models address the limitations of decisions trees as time is explicitly incorporated into the model via discrete time periods, known as 'cycles'.(8) Patients transition between health states and can transition back to the same health state, which addresses the second decision tree limitation of recurrent health states. The speed at which patients move between health states is informed by transition probabilities. In a traditional Markov model, patients enter as a single cohort and expected value of costs and effects are those of the average patient.

Figure 1-2: Example of Markov model diagram



Time dependency can be handled in a Markov model via 'time-dependent transition probabilities', e.g. as a patient ages a higher probability of death is applied. However, there are limits to incorporating time dependence due to a core property of Markov models being the 'lack of memory' (a.k.a memoryless). Memoryless refers to the fact that the probability of moving to a state is contingent on the current state only, not on previous states or the time spent in the current state. This lack of memory or 'Markovian property' can be disadvantageous when there are conditions

where a patient's history will determine what happens next, e.g. relapse from disease based on previous relapse.[4]

1.2.6.3 Individual patient microsimulation

'Individual sampling' models or 'microsimulation' models address the limitiations of a cohort Markov model by estimating the costs and effects of a large number of simulated patients. The use of health states and discrete cycles from a Markov model is retained in microsimulation models.(8) A limitation of microsimulation models is that, in order to incorporate greater structural flexibility, individual patient data are required to inform the transition probabilities. Related to this greater flexibility, the simulations are computationally demanding. Another issue of microsimulation models is the reduced transparency, which makes them more challenging for reviewers to assess.

1.2.6.4 Discrete event simulation

A discrete event simulation (DES) model is a specific type of individual patient simulation model and does not use health states or discrete cycles. Rather, DES simulates the time until the next event for a particular simulated patient and time-varying event rates are incorporated into DES models for individual patients.(8) A core difference between microsimulation and DES is the explicit handling of resources and their resulting queues or competition for those resources; therefore, competition between patients for resources can be modelled.(30) If the resource is occupied, the patient has to wait for a resource to become available.(8)

1.2.6.5 Agent Based Modelling

Agent Based Modelling (ABM) is an individual-level dynamic simulation modelling method wherein agents are objects that are social and interact with each other. Agents are objects that are aware about their state (e.g. infected with a disease) and follow decision rules on how to communicate and interact with other agents or their simulated environment.(23) Agents and their environment can change, develop or evolve over time. The rules governing individual actions allow complex behaviours and this informs the understanding of the network. Specifically, in HTA ABM models have been used to model the impact of vaccines on the spread of infection.

1.2.6.6 System Dynamic Modelling

System Dynamics (SD) models traditionally characterise the populations in terms of subpopulations and how they relate to each other. Therefore, SD models the population in aggregate rather than at the individual level.(31) The core elements of SD are feedback, accumulation (stocks), rates (flows)

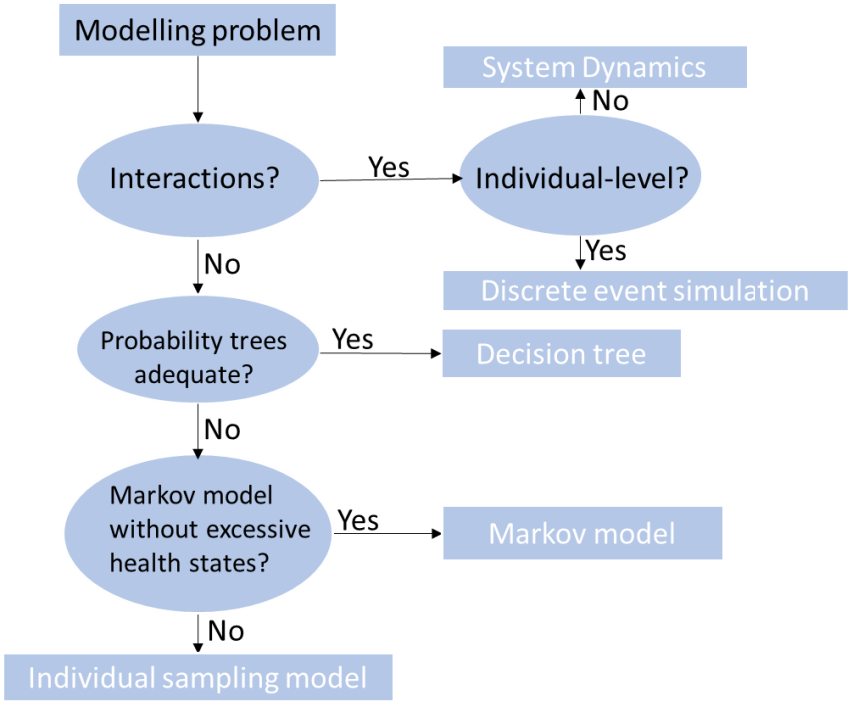
[4] However, this can be rectified through the use of tunnel states.

and time delays.(31) An example of stocks is accumulations of hospital beds, and the flow of patients in and out of stocks either drains or replenishes capacity. Feedback processes reflect nonlinearity so that an effect is not proportional to the cause.(31) Examples of the use of SD modelling in HTA are the spread of infectious diseases (such as HPV 16 infection)(32) and vaccination strategies (33),(34).

1.2.7 Choice of model structure

Barton et al. (2004)(28) present guidance for selecting a modelling approach in a flow-chart (Figure 1-3). The first consideration is whether the decision problem requires interactions between patients; if so, a SD or DES model may be useful and the choice between the two is based on whether individual-level modelling is required. If interactions between individuals are not essential, and the patient pathway cannot be adequately represented by probability trees, then a cohort Markov model is the preferred structure. However, if the use of a cohort Markov model would lead to excessive number of health states then an individual sampling model ('microsimulation') is the preferred option.

Figure 1-3: Flow-chart for selecting an appropriate model type



Note: Individual sampling model also known as microsimulation.
Source: adapted from Barton et al. (2004)(28).

A report by the International Society for Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making (ISPOR-SMDM) Task Force (35) provided recommendations for the appropriate application of state-transition models, a.k.a. Markov models. Specifically, '[i]f the decision problem can be represented with a manageable number of health states that incorporate all

characteristics relevant to the decision problem, including the relevant history, a cohort simulation should be chosen because of its transparency, efficiency, ease of debugging, and ability to conduct specific value of information analyses'.(35) This acknowledges additional considerations such as ease of use and understanding for modellers and reviewers in model choice. The report provided the recommendation that 'DES models should be used when the problem under study involves constrained or limited resources'.(35) Despite this recommendation, constrained environments or DES modelling are not usually considered in HTA.

1.3 Empirical comparisons of cohort Markov model vs. discrete event simulation models

There have been a number of empirical comparisons of economic modelling approaches in HTA. For the remainder of this thesis I have chosen to focus on the comparison of cohort-level Markov model to individual-level patient models that explicitly incorporate interactions and queuing, i.e. the comparison of cohort-level Markov models against DES.[5] There have been few empirical comparisons of a cohort Markov model and a DES model in HTA (36-41). A previous systematic literature review by Standfield et al. (2014) searched for empirical comparison of Markov models and DES models (42) published in electronic databases from inception (1947/1950) to 2012 and identified two empirical comparisons of pharmaceutical interventions (37, 39). Since then, two studies have compared screening strategies in breast cancer(40) and abdominal aortic aneurysm(41); another pharmaceutical intervention(36) and physiotherapy service(38). The six studies that empirically compared the results of a Markov model to a DES model are presented in Table 1-3.

Karnon et al. (2003) modelled breast cancer therapy using a Markov model and DES. The results of the Markov model were slightly lower for costs, QALYs and life years than the DES model; however, the resulting resource allocation decision would not have changed.(37) The authors concluded that although the DES model provided slightly more accurate results, which may provide the user with more confidence, there is a cost in that it requires more data and analysis time. DES may provide value in addition to typical metrics (cost per QALY) desired in HTA such as clinically relevant outputs. For instance, in a comparison of Markov model and DES in HIV by Simpson et al. (2009), the DES model had slightly better long-term (5-year) predictive validity compared to the 1-year time horizon, with the estimated CD4 and viral load count compared to actual clinical data more accurate than the

[5] Agent-based models (ABM) can incorporate interactions and are an extension of DES. The difference between the two is that in ABM the eligible population is defined at the start of the simulation; hence, ABMs are used to evaluate population-based vaccination programs with herd immunity. For the purposes of the literature search, DES models were compared to incorporate queuing theory.

Markov model.(39) Similarly, compared to DES the Markov model was not able to predict certain clinical attributes.

Neither Karnon et al. (2003)(37) nor Simpson et al. (2009)(39) used an example that modelled a capacity-constrained setting, where the added value of DES modelling may be greatest. Standfield et al. (2017)(38) compared a Markov model and DES (with and without dynamic queuing[6]) in orthopaedic physiotherapy(38). In this study, the authors modelled a capacity-constrained setting of a new orthopaedic physiotherapy-led screening clinic (OPSC) compared to usual care, which relied on medical specialists to assess new patients. It was hypothesised that OPSC would alleviate the waiting list for orthopaedic specialists compared to usual care. The DES with dynamic queuing model included patients' demand for orthopaedic services and the capacity of the clinic to deliver.(38) The DES with dynamic queuing model showed longer wait times due to the supply of services not being able to meet demand over the model period, compared to the fixed and shorter waiting time of the Markov model and DES without dynamic queuing. The DES with dynamic queuing produced an ICER with 95% CI above $0 per QALY gained, indicating higher cost and more benefits, whereas the Markov model produced a 95% CI that crossed $0 per QALY gained, indicating some ICERs were negative (lower cost and more benefits). Therefore, the DES model with dynamic queuing ($2,342 per QALY gained) produced a higher ICER compared to the Markov model ($495 per QALY gained), meaning the OPSC was less cost-effective when dynamic queuing was taken into account. Therefore, resource constraints and queuing theory (wait time for orthopaedic services) was an issue for the decision problem.

The use of a DES may provide different results to a Markov model when multiple alternatives are compared. Jahn et al. (2016) compared eight personalised medicine screening strategies in breast cancer using Adjuvant! Online (prognostic decision aid) with and without 21-gene assay (Oncotype DX (ODX))[7] (40). The eight strategies were NNN, NNY, NYY, NYN, YNN, YYN, YNY and YYY; a strategy of NNN meant no patients additionally tested with ODX, while YYY indicated low, intermediate and high risk score patients from Adjuvant! Online would then be tested with ODX. The authors identified that small differences in model outcomes of cost or QALYs led to different decision-making conclusions. For instance, in the Markov model the strategy NNN (patients would not be tested with ODX) is the baseline comparator, whereas in the DES model it is the dominated stategy and hence not used. In the Markov model, NYY (patients with Adjuvant! Online intermediate and high risk scores would be

[6] Dynamic queuing refers to the waiting time for services changing as the number of patients in the queue changes, so that demand for services and supply of services interact.

[7] The first letter indicates whether patients with low risk according to Adjuvant! Online were tested using ODX (Y = yes; N =no); the second and thrd for intermediate- and high-risk patients per Adjuvant! Online, respectively (e.g., NYN = patients with Adjuvant! Online intermediate risk would be tested with ODX).

tested with ODX) was compared to NNN, whereas NYY was compared to NNY (patients with Adjuvant! Online high risk scores would be tested with ODX) in the DES because NNN was dominated.

Overall, it appeared that the DES model and Markov model produce similar ICER results. An empirical comparison of three model structures in cholinesterase inhibitor therapy Alzheimer's disease in micro-simulation, Markov model, and Southampton Health Technology Assessment Centre (SHTAC) prediction model returned similar ICERs.(43) This was expected and the authors noted variability between models with the micro-simulation model returning the lowest ICERs as it utilised a 'more graded approach in estimating disease progression and the associated quality of life weights'.(43) Gustavsson et al. (2009) demonstrated that the model results were robust to model structure and this was similar to the studies included in the current purposive review.(43)

The purposive review identified two circumstances where the DES model produced a different conclusion to the Markov model. Firstly, different resource allocation decision were reported in Jahn et al. (2016)(40), where the dominated option differed between the model structures when multiple alternatives were compared, as small differences in model outcomes changed the dominated/non-dominated status. Secondly, Standfield et al. (2017)(38) considered a scenario of restricted supply of health services and reported a lower ICER range from the Markov model compared to the DES model (with dynamic queuing). The conclusion of OPSC being cost-effective did not change as the disutility associated with increased waiting time was low. This result would suggest that the overall impact on the QALY gained due to waiting longer for treatment was minimal. However, it is plausible that the difference between modelling techniques may be significant when comparing treatments that are restricted in supply with long waiting times and the impact (in terms of QALY loss) of not receiving timely treatment is high. A case-study in organ transplants and high-cost life-extending mechanical circulatory support satisfies the above criteria.

Table 1-3: Characteristics and results of the empirical comparison of MM and DES models

Population	Comparison	Software	Capacity constraint	ICER	Conclusion
Karnon (2003)(37) Early breast cancer, node positive, postmenopausal women aged under 65.	Tamoxifen and chemotherapy vs. tamoxifen alone	MM: Excel with risk analysis add-in ('Crystal Ball') DES: Simul8®	No.	Costs (year not reported Pounds) DES: T+C £9,146; T £7,115. MM: T+C £8,740; T £6,721 QALYs DES: T+C 12.14; T 11.56. MM: T+C 12.00; T 11.40 ICER Mean (2.5th and 95th percentile) DES: £3,483 (£452, Tamoxifen dominates); MM: £3,365 (£588. Tamoxifen dominates)	All outputs for DES model were higher than MM.
Simpson (2009)(39) HIV. Anti-retroviral-naïve, mean baseline CD4+T-cell count of 175 cells/mm^3	Lopinavir + ritonavir (lop/rit) vs atanazavir + ritonavir (atan)	DES: Arena®	No.	Costs (2007, $US) DES: lop/rit $340,022; atan $352,843. MM: lop/rit $310,194; atan $318,882 QALYs DES: lop/rit 12.40; atan 12.11. MM: lop/rit 10.55; atan 10.11 ICER DES: lop/rit dominant. MM: lop/rit dominant.	Both MM and DES models estimated a cost saving from lop/rit vs. atan/rit.
Jahn (2016)(40) Personalised cancer medicine in breast cancer	Adjuvant! Online (prognostic decision aid) + 21-gene assay (Oncotype DX (ODX)).	MM: TreeAge Pro DES: Arena®	No.	NNN, NNY, NYN, YNN, YYN, YNY, NYY, YYY[a] ICER (2012, $CAD) MM (probabilistic): NA, $90, D, $5,365, D, D, D, $30,863 MM (microsimulation: NA, $873, D, $4,443, D, D, D, $22,063 DES: D, NA, D, $6,380, D, D, D, $23,246	Small differences in model outcomes lead to different CE results. The strategy NNN is baseline comparator in the MM but is dominated in DES. The non-dominated NYY and YYY ICERs are relatively comparable. MM, NYY was compared to NNN, whereas NYY was compared to NNY in the DES because NNN was dominated.
Standfield (2017)(38) Orthopedic Physiotherapy (knee, shoulder, lumbar spine)	Orthopaedic physiotherapy screening clinic (OPSC) vs. Usual care (UC) – conservative management	MM: TreeAge Pro 2014 DES: Simul8©	Three DES models, DES-no-DQ, DES-CAL and DES-DQ.	Costs (2015, $AUD) MM: UC $1,292; OPSC $1,404. DES-no-DQ: UC $1,461; OPSC, $1,425. DES-CAL: UC $1,296; OPSC $1,403. DES-DQ: UC $1,009; OPSC $1,557. QALYs MM: UC 2.4; OPSC 2.6. DES-no-DQ: UC 2.4; OPSC, 2.6. DES-CAL: UC 2.4; OPSC 2.6. DES-DQ: UC 2.4; OPSC 2.8. ICER	All 4 models estimated that OPSC would be very cost-effective. DES-DQ resulted in the highest ICER. The article noted that patient disutility for waiting was low.

				MM: $495 (-$1,928 to $3,552); DES-no-DQ: -$165 OPSC dominates (-$3,638 to $3,042); DES-CAL: $482 (-$2,154 to $3,594); DES-DQ: $2,342 ($13 to $6,729)	
Degeling (2018)(36) Maintenance treatment in metastatic colorectal cancer	CAP-B vs. observation after 6 induction cycles of (CAPOX-B)	MM: TreeAge DES: AnyLogic	No.	Costs CAP-B vs. observation (2014, € Euros) DT-STM: 35,536 (CI: 19,945; 54,629); DES €30,053, (CI: 17,047; 46,132) QALYs DT-STM: 0.21 (CI: 0.015; 0.430); DES: 0.18 (CI: 0.006;0.374) ICER DT-STM: €172,443; DES: €168,383	Cost-effectiveness outcomes were comparable for the DT-STM and DES model. DES matched the original study KM curves slightly better.
Glover (2018)(41) Screening for abdominal aortic aneurysm in men aged 65 years and older	Screening vs. no screening	MM: Excel DES: R	No.	Incr Cost: MM: £65.58; DES: £62.86 Incr QALYs MM: 0.0017 ; DES: 0.0015 ICER (cost per LY gained) MM: £37,700; DES: £42,137	MM and DES results similar. DES was able to model time-varying surveillance intervals unlike the MM model. DES useful for policy-relevant protocol changes.

Note: DQ or dynamic queuing. Queuing times were generated dynamically as a function of the demand (e.g., patients requiring orthopaedic assessment) and the capacity of the service (e.g. availability of orthopaedic specialists).

a. The 1st letter indicates whether patients with low risk according to Adjuvant! Online were tested using ODX (Y = yes; N =no); the 2nd and 3rd for intermediate- and high-risk patients per Adjuvant! Online, respectively (e.g., NYN = patients with Adjuvant! Online intermediate risk would be tested with ODX).

Abbreviations: CAL, calibrated; CAP-B, capecitabine and bevacizumab; CAPOX-B, capecitabine, oxaliplatin, and bevacizumab; DES, discrete event simulation; DQ, dynamic queuing; KM, Kaplan-Meier; MM, Markov model; OPSC, Orthopaedic physiotherapy screening clinic.

1.4 Economic Framework - Queuing Theory and resource allocation

The choice of model structure should not change the decision-making conclusion; that is, a cohort and and individual-level model should produce an equivalent ICER if the models are specified correctly. A difference may occur, however, if there is non-linear relationships in the decision problem that is not captured in the model. Examples of such differences can include interaction between patients due to competition for limited resources. Queues occur frequently in health care due to excess of demand of a service and consequent shortage in supply. The competition can be manifested as a physical queue for a service, resulting in poorer outcomes and higher costs.

Waiting lists are essentially queues, and queuing theory and mathematical analysis are used to predict a queuing system. A queuing system consists of the population, nature of arrival, service time and mechanism, queuing behaviour and the queuing discipline.(44) Queuing theory explicitly acknowledges the resource availability in a given system. A patient waits for a resource, forming a queue, so there are delays in the health care provided. A typical type of queue ('queuing discipline') is the first-in-first-out (FIFO). This type of queuing system occurs in GP waiting rooms, where patients who have an earlier appointment time will see the GP first; if patients have the same appointment time, the patient who arrived first will see the GP next. Another, more complex queuing discipline is a prioritisation system, which considers level of medical need. This type of queuing system is often seen in emergency departments, where patients with the greatest need are treated first and patients with less urgent needs wait longer.(30)

This thesis is specifically interested in the modelling of complex interventions where resource constraints manifest as waiting lists and hence are analogous with queuing theory. The method chosen to model resource constraints is DES, which is a computer simulation technique traditionally used as an operational research method.(30) DES was first developed by Tocher et al. in the late 1950s for United Steel Companies (UK) for a simulation model of a steel plant.(45) Other applications of DES include supply and logistics, scheduling and finance.(30) The application of DES in the healthcare system, and specifically in HTA, has emerged over the last few decades. The method allows for the analysis of complex systems via virtual experimentation to assess the impact of interventions on health services. This method allows for competition between patients and the interaction (matching) between patients and donor organ characteristics to be modelled.

DES explicitly incorporates queuing theory where resources are limited, including physical spaces such as emergency rooms. That is, an emergency room will have patients waiting; the treating clinician(s) can only treat patients one at a time (known as capacity); and once a patient is treated and released a new patient is treated (known as utilisation). Typical applications of queuing theory in acute

care/community care health services are to model patient flows for planning purposes.(46) A review by Palmer et al. (2017) highlights the range of factors that influence patient flow, such as no-shows from patients, staffing constraints, health of patient arrivals and scheduling policy.(46) For example, DES was used to compare two organisational models of primary care to estimate the change in time to medical appointment and medical and nursing consultations.(47) The outcomes of interest in DES may be through-put or performance measures such as wait times, clinic overtime, staff utilisation ('occupied') and number of surgeries., e.g. acute care health services such as staffing. These outputs are often important to health care planners and managers at the local level, but are rarely considered by national level HTA agencies.

1.5 Conclusions

The cost of health care is ever-increasing and new therapies provide benefits to patients, but at a cost. This section has briefly described the rationale for conducting HTA so as to inform the efficient allocation of resources. Due to the limitations in collected clinical and economic data, economic modelling is relied on as part of HTA, and there are a number of economic modelling methods available for the analyst. When reviewing the results of a HTA, a decision-maker must ensure the appropriate modelling method is chosen. In a situation where individual patient data are available and a new technology is affected by limited resources, it may be appropriate to employ more complex modelling methods than the traditional cohort state-transition model.

Overall, the literature suggests that for a decision problem where a queue for a resource with restricted supply (e.g. any organ transplantation program) is important, individual-level models may be useful. Specifically, the waiting list is a type of interaction that should be modelled explicitly, and the exclusion of relevant interactions may lead to biased estimates. This is particularly true if a longer wait time has deleterious effects on the patients' health and/or healthcare system costs.

1.6 Overview of thesis structure

This thesis is divided into seven chapters.

Chapter 2 introduces the case study of end-stage heart failure. A summary of the organ donation matching process and heart transplant waiting lists trends in Australia is provided. The use of LVADs in Australia is explored with particular focus on their role as a bridge to transplant (BTT). An overview of the current funding of the treatment options is provided.

Chapter 3 consists of a systematic literature review of published cost-effectiveness studies of LVADs. Included in the review are published economic evaluations of the use of LVADs as destination therapy and as BTT. The chapter provides detailed descriptions of the model structure and whether wait time

for a heart transplant was incorporated into the model. Finally, a discussion of the ICER threshold for life-saving technologies within the framework of 'rule of rescue' is provided.

Chapter 4 begins with a review of the published RCTs and registries in LVADs and HTx. Limited RCT data of VADs in BTT results in use of observational data. This chapter includes the analysis of the individual patient registry data from St Vincent's Hospital Sydney (SVHS), including assessment of benefit, costs and time-to-event analyses. The analyses from Chapter 4 are assessed for use as model inputs and to inform the structure for the economic evaluations in Chapter 5 and 6.

Chapter 5 presents the Markov model comparing the cost-effectiveness of LVADs compared to a range of alternative policies to treat ESHF. The objective of this economic evaluation was two-fold: 1) to assess the cost-effectiveness of the current 'restricted LVAD supply' ESHF policy against the previous ESHF without LVADs and 2) to assess the cost-effectiveness of expanded availability of LVADs for patients with ESHF.

Chapter 6 presents the discrete event simulation model addressing the same decision problem as Chapter 5. The same data sources are used, with necessary statistical adjustments to implement as a DES. A description of the additional data sources required is included. In addition to the comparison against the Markov model (presented in Chapter 5), two DES models are compared, one with queuing and one without queuing.

Chapter 7 presents the major findings and discussion. A recommendation is provided on the most appropriate modelling method for this decision problem. The implications of this research on the broader HTA context and on funding of these technologies are discussed.

2 CHAPTER 2: CASE STUDY IN END-STAGE HEART FAILURE

2.1 ESHF symptoms and treatments

The incidence of end-stage heart failure (ESHF) is increasing due to the ageing population, increased prevalence of ischaemic heart disease, obesity and metabolic syndromes, and prolonged survival of patients with congestive heart failure (CHF).(48) CHF is characterised by the inability of the ventricle to fill with or eject blood, and patients experience periods of cyclical and progressive decline culminating in ESHF and hospitalisation.(49) One of the main symptoms of ESHF is dyspnoea (shortness of breath) and, in severe cases, dyspnoea at rest.(49) Prognosis of CHF can be informed by severity of symptoms, most commonly described using the New York Heart Association (NYHA) classification (Table 2-1), among other investigations. A patient with NYHA Class I status is the least severe, with NYHA Class IV being the most severe. Markers of impending mortality include advanced age, recurrent hospitalisation, NYHA Class IV symptoms, poor renal function and cardiac cachexia.(49)

Table 2-1: New York Heart Association (NYHA) grading system

Class	Description
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic left ventricle dysfunction).
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF)

Abbreviations: CHF, congestive heart failure
Source:(49)

Patients with symptomatic abnormal heart functionwarrant introduction of optimal medical management (OMM) including beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, aldosterone antagonists, a neprilysin inhibitor and possibly device therapy, including automatic implanted cardioverter defibrillator or cardiac resynchronisation therapy (CRT)(50) in line with Australian guidelines[8]. In the event that patients continue to have symptoms on medical therapy, the treatment algorithm is determined by whether the patient has surgically correctable disease. Surgical treatments such as valve repair aim to address different pathophysiological mechanisms in HF and can be elective or emergency.(21,43) Patients with NYHA Class IV symptoms on OMM may require hospitalisation for intensive intravenous therapy including diuretics and inotropes.

[8] The type of pharmacotherapy used will depend on if a patient has heart failure with reduced ejection fraction (HFREF) or heart failure with preserved ejection fraction (HFPEF).

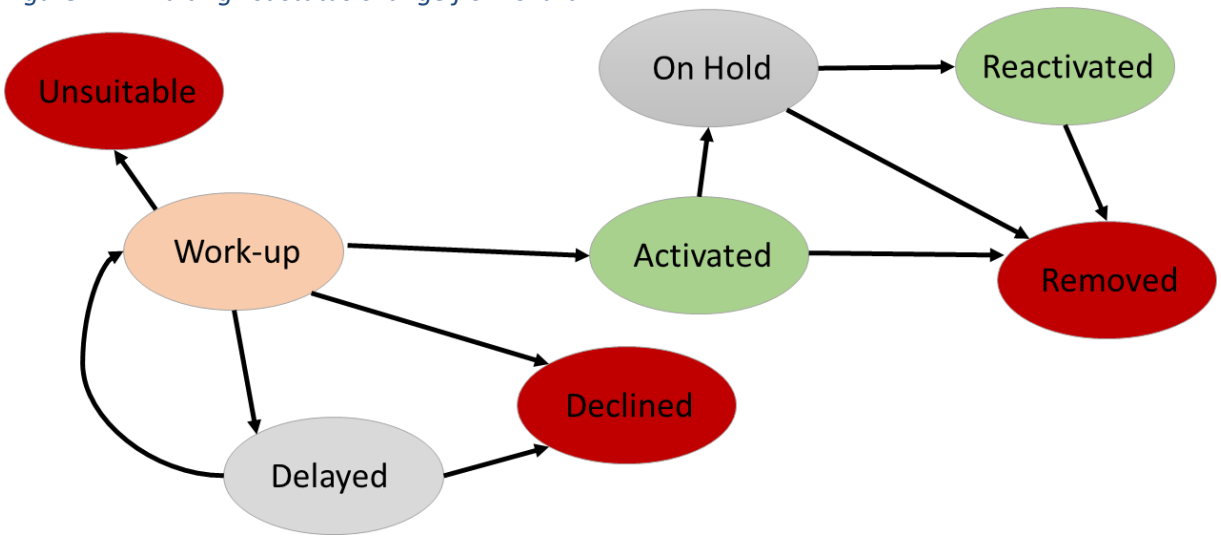
2.2 Heart transplant

For patients with ESHF a heart transplant (HTx) may be a viable treatment option. Recipients of a donor heart can expect to have good quality of life post-transplant and can generally go about their usual activities. Orthotopic heart transplants (OHT) are the most common type of HTx, where the recipient's diseased heart is removed and replaced with the donor heart. Patients are likely to remain in hospital for a couple of weeks, with regular medical review, with approximately 15-20 visits in the first 12 months post transplant with the transplant cardiologist. To avoid organ rejection, recipients are on life-long immunosuppression medication.

Since the first heart transplant performed in 1967 in South Africa, heart transplantation rates have grown worldwide. In Australia, the first HTx was performed at St Vincent's Hospital, Sydney (SVHS) in 1968, with the procedure performed more regularly since 1984. Over 1,000 patients have undergone heart transplantation at SVHS since the programme started. Patients can be offered a HTx if they have end-stage disease, have exhausted all alternative treatment options and there is an expected survival benefit, with a reasonable prospect of returning to an active lifestyle.(50) Patients listed for HTx, by definition, have severely impaired quality of life and have an estimated survival of less than 2 years without transplantion.(50) Some patients may not qualify for a HTx due to contraindications such as active malignancy, age greater than 70 years and complicated diabetes.(50)

At SVHS a patient is referred to the the Heart and Lung Clinic and worked-up or screened for eligibility for the HTx waiting list (Figure 2-1). Once work-up is complete and there is a contraindication for a transplant, the patient status is changed to 'unsuitable'; alternatively, the patient can 'decline'. Once accepted onto the waiting list, patients who receive a donor organ/left ventricular assist device (LVAD) or die are 'removed' from the waiting list. Occasionally a patient can be placed 'On-Hold' due to improving or deteriorating health. Once eligible again, the patient can be 'Reactivated' onto the waiting list or can be 'Removed'.

Figure 2-1: Waiting list status change flow-chart

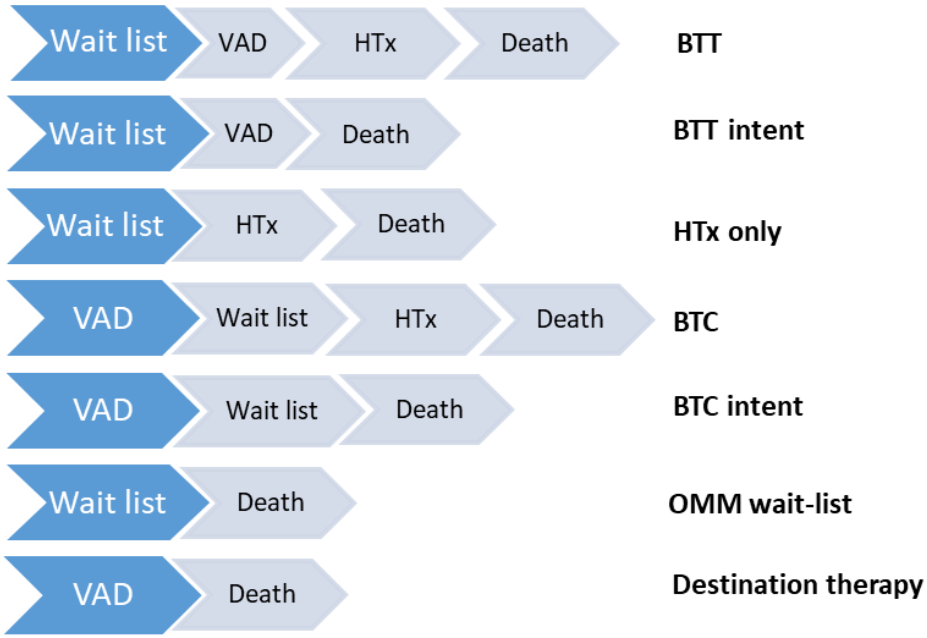


Source: Developed during the thesis.

2.2.1 Mechanical circulatory support

Mechanical circulatory support (MCS) devices are mechanical organ replacements used to support a patient's damaged ventricles. Mechanical support is provided while a patient awaits a HTx (bridge to transplant, BTT), as a bridge to candidacy (BTC) or an alternative to human organ transplantation (Destination Therapy, DT). Figure 2-2 illustrates the available potential pathways.

Figure 2-2: Examples of patient events in End-stage heart failure



Abbreviations: BTC, bridge to candidacy, BTT, bridge to transplant; HTx, heart transplant, OMM, optimal medical management; VAD, ventricular assist device.

MCS is divided into temporary emergency devices and long-term durable devices. Temporary life-saving devices such as intra-aortic balloon pumps (IABP) and extracorporeal membrane oxygenation (ECMO) may be used as a bridge to a more durable device. However, these devices have limited durability and are used for less than one month, unless there are exceptional circumstances. The IABP is a temporary acute MCS life-saving intervention aimed at increasing myocardial oxygen perfusion and cardiac output. The balloon is timed to inflate and deflate along with the cardiac cycle. Similarly, the use of ECMO is a supportive strategy for patients at high risk of death from respiratory failure and cardiogenic shock and uses an external blood pump and oxygenator. Percutaneous temporary LVADs are also used after cardiogenic shock until HTx or receiving a durable implanted MCS.

2.2.1.1 Ventricular assist devices

LVADs are durable mechanical pumps that replace the role of the damaged ventricle and restore normal blood flow. Patients typically have a VAD implanted in the left ventricle and may occasionally receive a biventricular assist device (biVAD) to support both the left and right ventricle. The pump connects the aorta and left ventricle and a driveline (percutaneous lead) connects the pump to the external system controller and battery pack. Regular check-ups are provided by a multidisciplinary team of cardiologist, nurses and allied health professionals.

The first-generation devices consisted of a pulsatile flow (PF) pump, while the second and third-generation devices utilise a continuous-flow (CF) pump. CF devices were introduced in 2004 and are now the main type of device implanted, superseding PF devices in the USA.(51) Since 2013, centrifugal CF devices have been used; however, axial CF devices remain more commonly implanted.[9] The second-generation devices have an axial pump (e.g. HeartMate II), while the third-generation devices have a centrifugal pump (e.g. HeartWare HVAD (52, 53) and HeartMate3,(54)). Acute LVAD complications include thromboembolism, right ventricle failure and haemorrhage, whilst long-term complications include infection and device malfunction.(52) Currently in Australia, only HeartMate3 pumps are available for commercial use.

Implantable medical devices such as LVADs are subject to incremental improvements.(55) CF second generation (axial pump) and third generation (centrifugal pump) devices have superseded first generation PF VADS.(53) Miniaturisation and change in pump type have resulted in markedly different survival curves for CF compared to PF devices. Efficacy is dependent on the surgeon as well as care by the patient e.g. maintenance of device and driveline site. Similarly, the increasing use of LVADs and

[9] The rotating element in centrifugal-flow pumps are spinning disks with blades that 'throw' fluid whilst in axial-flow pumps the rotating element are propellers in a pipe that 'push' fluid.

reported registry data by Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) have improved patient selection by providing data on risk factors for post-implantation adverse events and complications.(56) These improvements have resulted in the reduction of adverse events and device failure, and consequently hospitalisation costs.(57)

As mentioned above, the main indications for LVADs are; 1) bridge to transplant (BTT), 2) destination therapy (DT) and 3) bridge to candidacy (BTC). DT patients typically have worse prognostic characteristics due to older age or co-morbidities such as diabetes and prior coronary artery bypass grafting (CABG) than BTT patients.(58) In Australia, patients are mostly given a LVAD when they are listed on the transplantation waiting list (BTT). DT is approved, but not currently funded by the Federal governments. In BTC, LVADs are used in patients who are not eligible for HTx, but are supported with a LVAD until kidney function or nutritional status improves and they can subsequently be eligible for a donor organ.(53) LVAD intent strategies have been shown to be arbitrary as a LVAD may be intended as a BTT but the patient may die before a HTx, or remain for long periods on LVAD, as with DT.(58) In Australia the use of LVADs is inextricably linked to HTx.

Another form of MCS is the total artificial heart (TAH) which is used as bridge to HTx.(59) These patients need biventricular support and consequently an LVAD would not be adequate. The TAH differs from a biVAD (both left and right) in that it replaces both the ventricles and all cardiac valves. In Australia, the SynCardia TAH (SynCardia Systems, Inc., Tuscon, Arizona) has been implanted at SVHS since 2010.(53) TAHs are more burdensome than implantable biVADs as they are pneumatically powered (compressed air), resulting in a larger wound, and tubes connected to an external pneumatic pump. Survival outcomes are worse than isolated LVADs.

2.3 Organ donation policy

In Australia, donors must opt in to provide consent for their donation on the Organ Donor Register and the next of kin must also provide consent. Usually, donor hearts are from individuals that have died from brain death with otherwise healthy organs. Donors cannot be directed to a specific recipient, and enter into a rigorous and unbiased patient matching scheme.

2.3.1 HTx allocation algorithm

In Australia, the HTx waiting list are not nationally managed but are instead specific to each of the transplant units (see Table 2-2). There are four adult transplant units and one paediactric transplant unit in Australia and one adult transplant unit in New Zealand.

Table 2-2: Heart transplant units of donor hospitals

Jurisdiction of donor hospital	Location of heart transplant unit
NSW, ACT	NSW; St Vincent's Hospital, Sydney
VIC, TAS	VIC; The Alfred Hospital, Melbourne and The Royal Children's Hospital, Melbourne

QLD	QLD; The Prince Charles Hospital, Brisbane
WA	WA; Fiona Stanley Hospital, Perth
NZ	NZ; Auckland Public Hospital, Auckland

Source: (50)

The primary matching criterion is blood type compatibility, followed by size and weight compatibility and negative lymphocytotoxic crossmatch (see Table 2-3). The matching process identifies donors with the same blood type, a similar body size and weight and peak panel reactive antibodies (PRA). Guidelines allow recipients to receive a donor heart within 20% plus/minus the body weight, with undersizing of donor hearts avoided moreso than oversizing of donor hearts. It has been suggested that increasing the guidelines to 30% plus/minus body weight may increase the HTx donor pool.(60, 61) Currently, body weight is used as a proxy for donor heart size in matching recipients; however, the literature suggests that a more optimal size match metric may be predicted heart mass (62), and this has recently been introduced as the criterion in SVHS. The PRA is an immunologic test for the presence of circulating antibodies to a random panel of donor lymphocytes. These are antibodies to Human leukocyte Antigen A, B, and DR in the serum. High levels of PRA are associated with worse survival for patients; a score of 0% means that there are no cross-matched antibodies and therefore better outcomes.(63)

Table 2-3: Matching criteria for heart donation

1.ABO compatibility*	Except paediatric patients aged <12 months.
2.Size and weight compatibility	Recipient within plus or minus 20% of donor body weight. Greater variability in the donor: recipient weight ratio may be acceptable depending on the ages of the donor and recipient, especially in paediatric cases.
3.Negative lymphocytotoxic crossmatch*	Sensitised recipients for whom there are no other options may require transplantation in the setting of a positive T and B cell cross-match, followed by augmented immune suppression.
4.Urgent status**	Patients can be listed as 'urgent' on the waiting list if 'candidates are unsuitable for mechanical support or develop life-threatening complications while on support, and the patient's survival is estimated to be days or weeks if they do not receive a transplant'.(50) If a patient is placed on an urgent list, the Transplant Unit Director must notify other units in Australia and New Zealand. Re-notification to other units occurs at two-week intervals.
5.ABO identity	
6.Recipient waiting time	
7.Logistical considerations**	

Notes: * Items 1–2 are absolute requirements for adult patients. ** Logistical considerations include coordination with other donor retrieval teams, transport of surgical teams and donor organs, type of heart transplant operation (orthotopic, heterotopic, or domino) and number of transplants to be performed (usually heart and lung transplants are performed simultaneously in separate operating theatres) and the availability of intensive care unit beds.
Source: (50)

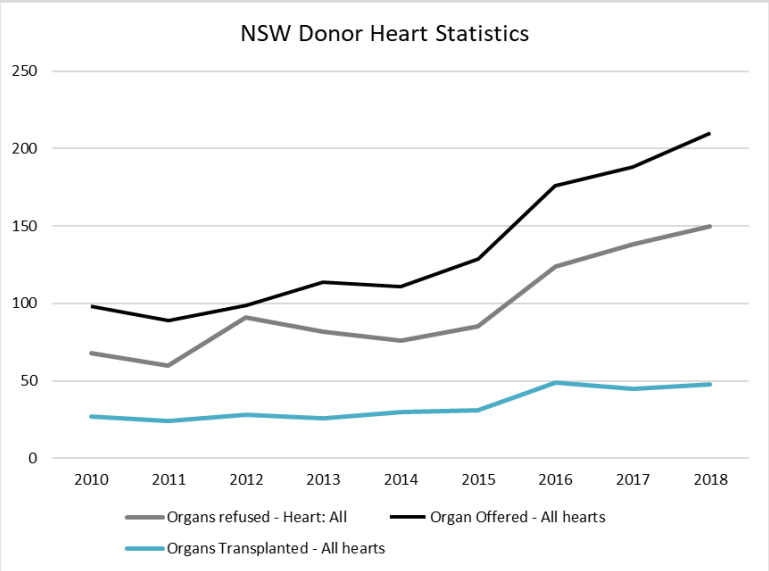
2.3.2 Donation rates in Australia

Organ donation rate is measured via the deceased organ donor per million population (dpmp). In 2017 Australia was ranked 16 globally and had a rate of 20.8 dpmp.(64) This was a dramatic improvement from 2013, when Australia ranked 20 in the world with 16.9 dpmp. For comparison, in 2017 Spain was

the leading country with organ donation rate of 47 dpmp (64), more than double the Australian rate. Spain has 19 transplant units, of which 2 exclusively transplant children, which demonstrates that the infrastructure in Spain supports transplant activity.(65) In contrast to Australia, Spain has a 'opt-out' system for deceased organ donation and the transplant program is nationally managed.

Donor shortage occurs because not all Transplant Unit requests for a donor heart are fulfilled. In 2016, 393 potential donor hearts in Australia were requested of which 94% (n=370) provided consent from next of kin via a family interview.(66) Of the donor hearts that are available (n=370), only 32% (n=125) were retrieved (n=124).(66) Decisions to accept donations are performed on an institutional basis. Between 2010 and 2018 in NSW, the main reason donor organs were refused was medical donor unsuitability (48%), followed by no suitable recipient (35%, e.g. weight), logistics (5%) and other (12%, e.g. expected ischaemic duration); see Figure 2-3.(67)

Figure 2-3: NSW Donor Heart Statistics



Source: SVHS, NSW Donor Heart Statistics(67)

2.3.3 Waiting time

There is variability in an individual's waiting time for a HTx. In Australia, the average wait time for a donor heart is around 6 months.(68) The mortality rate for patients on the waiting list increases the longer a patient has to wait for a donor heart.(69) The average wait time for the 117 heart recipients in 2017 was 164 days (SD±221; median 78; min 1 to max 1,043).(70) Some patients received a donor organ a day after they were accepted onto the wait list. Conversely, some patients waited over 4 years.

The average waiting time for a HTx differs by blood group.(70) Blood group is an important matching characteristic between donor organs and recipients. The wait time is reflective of the blood group; for instance, while blood group O is common, they are 'universal donors' resulting in those donor hearts

being used across all ABO blood groups. This results in a longer average wait time for O patients of 225 days (1984 to 2018).(70) However, patients with the blood type AB were waiting for a substantially shorter period of time of 112 days from 1984 to 2018, as they are 'universal recipients' and can receive donor hearts with blood type A, B, AB or O.(70)

2.3.4 Donation after circulatory death via Organ Care System (OCS)

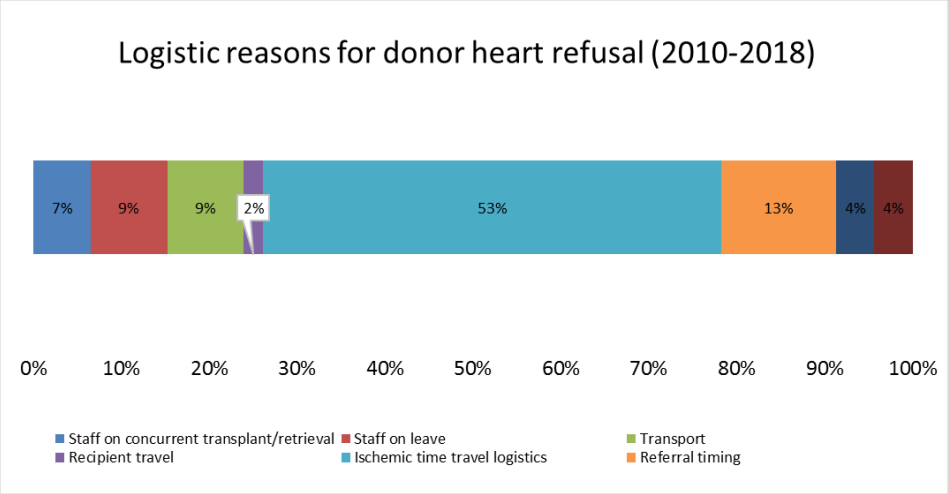
Traditionally, HTx relied solely on donation after brain death where a patient has complete loss of brain function. The retrieved heart was stopped (using 'cardioplegia') while it was still beating. The heart was then placed in ice to prolong viability. The duration of time on ice is known as the cold ischaemic time, and in 2018 the mean cold ischaemic time was 3.7 hours.(70) Very long cold ischaemic times (more than 6 hours) increases the risk of death after transplantation. However, an alternative to donation after brain death is donation after circulatory death (DCD). DCD is more common for kidney, liver and lung transplantation but has recently been performed for HTx.(71)

In Australia, SVHS introduced cardiac transplantation with DCD in 2014 and to date 39 transplants have been performed.(72) The device used for ex vivo preservation[10] is the transportable Organ Care System (OCS) (TransMedics; Andover, MA, USA), also known as 'Heart in a Box', which is used for both standard and marginal criteria donor hearts.(71) Based on an Australian case series report (n=3), outcomes of DCD were positive for patients.(71) A 1:1 RCT of standard donor hearts preserved with the OCS compared to standard cold storage demonstrated similar short-term outcomes.(73) However, it is unclear if outcomes for DCD will be the same as with the current donation policy of hearts from brain death recipients.

Accepting donor hearts after circulatory death and not just brain death increases the rate of recovery of donor hearts from the existing donor pool.(50) The potential change in policy for hearts from brain-dead donors and DCD has implications of narrowing the gap between the supply and demand. The OCS keeps organs viable for longer and allows donor hearts to be transported. Offered donor hearts can be refused for logistical reasons, and from 2010 to 2018 on average 2.2% (45/2,142) donor hearts were refused for logistical reasons. The main logistical reason for refusal was ischaemic travel time being too long (53%), followed by referral timing (13%) (Figure 2-4).

[10] Warm ischaemic time refers to the amount of time that an organ remains at body temperature after its blood supply has been stopped or reduced.

Figure 2-4: Reasons for donor heart refusal in NSW (2010-2018)



Abbreviations: OCS, physiological support and transportation for marginal donor hearts and lungs utilising a system known as the Organ Care SystemNote: Staff not available due to concurrent transplants or retrieval; Staff on leave; Transport = no flight available; Recipient travel = won't delay donor for recipient travel; Ischemic time travel logistics = long travel time; Referral timing = about to cross clamp or would not delay start time; Poor weather = fog or storms impacting travel.
Source: St Vincent's Hospital Sydney Heart/Lung Clinic(67)

2.3.5 Impact of growth in HTx on health services

It is apparent that donor activity is increasing over time due to the increasing donation rate per million. In addition to increased donation rates, innovation in DCD via the Organ Care System has the potential to grow the retrieved organs from the donor pool. The referral and assessment process for a transplant is also resource-consuming. At SVHS, it is estimated that for every one patient who proceeds to transplant, there are an additional 2 patients who are assessed but not progressed to the transplant waiting list. The median work-up time for hearts is 5.5 months from referral to listing.(64) In addition, organ retrieval has grown tremendously over the past few years. Retrieval activity is costly with unsuccessful retrievals or 'bailouts' making up around 20% of retrieval activity.

A heart transplant is a resource-intensive procedure including organ procurement and transplant. Consequently, there is a strain on existing resources including beds, surgeons and clinical staff. Having these resources being 'occupied' by transplant-related activities impacts on the ability to schedule other major cardiac surgery. Essentially, cardiac surgeries such as CABG are cancelled and later rescheduled due to transplant activities. For instance, at SVHS there were almost 80 CABG surgeries cancelled due to a HTx surgery in 2016-2018 [data on file].

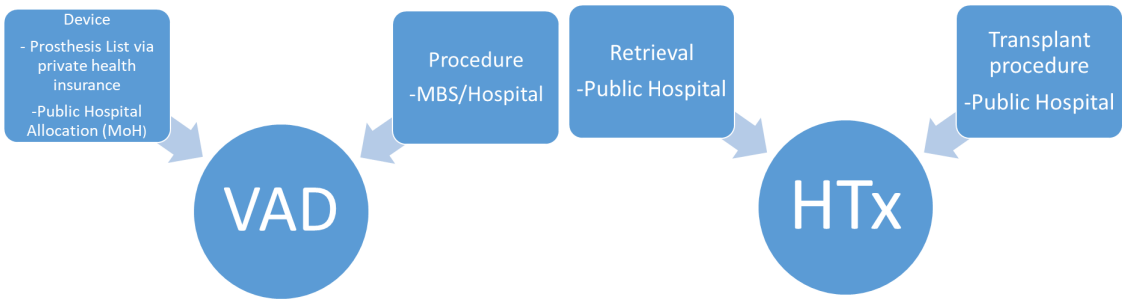
2.4 Funding of medical devices and HTx in Australia

The flow of funding within the Australian health care system is complex and includes both government and non-government sectors.(74) The Australian Government provides funds to the state and territory governments who, in turn, allocate these funds to health service providers such as public hospitals,

dental services and public health services. For public hospital care, in addition to the states and territories and funds from the Australian Government (via the National Health Funding Pool), public hospitals are also funded by out-of-pocket payments from individuals and private health insurers.

Before a medical device is publicly reimbursed it is evaluated for its clinical effectiveness and cost-effectiveness. Medical devices include a cost of the medical service in addition to the acquisition of the device. Through a rigorous HTA process, reimbursement of medical services is determined by the Medical Services Advisory Committee (MSAC). If recommended for subsidised funding, the procedure, device or consultation is listed on the the Australian Medical Benefits Schedule (MBS). Having a procedure listed on the MBS is a prerequisite for coverage by private health insurers for hospital procedures. The Australian Prosthesis List provides a list of medical procedures and devices that must be subsidised by private health insurers. A diagram of the sources of funding of LVADs and HTx in Australia is presented in Figure 2-5.

Figure 2-5: Funding of LVADs and HTx in Australia



Abbreviations: HTx, Heart Transplant; MBS, Medicate Benefits Schedule; MoH, Ministry of Health; VAD, Ventricular Assist Device.

At present, LVADs are funded for the four heart transplant centres in public hospitals that are state government-funded. The allocation of devices per hospital is determined on a local basis. For instance, in the SVHS, the current funding arrangement (with the NSW Ministry of Health) is limited to a maximum of 25 devices per year. (See 8.1.1 for a peer-reviewed published discussion paper on LVAD funding in Australia which highlights that widespread use of LVADs is limited due to the high cost, however, LVADs fulfil many of the eligibility criteria that support the funding of life-extending high-cost pharmaceuticals).(75) Broadly, the life-saving drugs programme (LSDP) consists of eight criteria including the disease being 1) rare; 2) identifiable; 3) reducing life-expectancy and that the medicine 4) increases life expectancy; 5) is clinically effective but not cost-effective; 6) is an unreasonable financial burden and 7) there are no other cost-effective medicines or 8) cost-effective non-drugs available.(75)

In Australia, HeartMate II (no longer used) and HeartWare LVADs are listed on the Prosthesis List.(76) The minimum benefit for the devices was $AUD95,000 in 2018 (76), representing the most expensive item on the Prosthesis List. The MBS reimburses the procedure of implanting a left or right (or bi)VAD contingent on the patient being on the HTx waiting list or being expected to be a suitable candidate.(77) Therefore, using LVADs for destination therapy is not currently reimbursed in Australia (53); see (Table 2-4).

Table 2-4: Reimbursement of VADs in Australia

Reimbursement criteria for insertion of a left and/or right ventricular assist device, for use 'as listed on the MBS':	*Intent strategy*	*Funding source*
(a) a bridge to cardiac transplantation in patients with refractory heart failure who are: (i) currently on a heart transplant waiting list, or	*BTT (listed)*	*Procedure funded by MBS or public hospital.* *Devices are allocated to hospitals which are State Government funded.* *Procedures are not performed in the private sector however, LVADs have been listed on the prosthesis list*
(ii) expected to be suitable candidates for cardiac transplantation following a period of support on the ventricular assist device; or	*BTC*	
(b) acute post cardiotomy support for failure to wean from cardiopulmonary transplantation; or	*Complications post heart-lung Tx*	
(c) cardio-respiratory support for acute cardiac failure which is likely to recover with short term support of less than 6 weeks	*BTR*	
not being a service associated with the use of a ventricular assist device as destination therapy in the management of patients with heart failure who are not expected to be suitable candidates for cardiac transplantation	*DT*	*Procedure not funded by MBS for DT*

Abbreviations: BTC, bridge to candidacy; BTR, bridge to recovery; BTT, bridge to transplant; DT, destination therapy; MBS, Medicare Benefits Schedule; Tx, transplant.
Source: (78) MBS item 38615 and 38618

2.5 LVADs as a bridge to heart transplant

In Australia, LVADs are intended for patients who are candidates or potential candidates for HTx. The Australian MBS Item Report[11] was searched for the LVAD items from 1993 to 2017. There are currently two items on the MBS that can be reimbursed for the procedure left or right VAD (MBS item 38615) and bi-VAD (MBS item 38618) for all device types.(77) For left or right VAD, between 1993 and 2017 15% of the 286 services were claimed in paediatric patients (defined as 0-14 years) (Figure 8-1). For biVADs, 14% of the 232 services over the same time period were claimed in paediatric patients. In children, the gender distribution was fairly even; however, for adults, three times as many male patients received VADs.

Most of the VAD implants have occurred in recent years and in 2016-2017 there were 32 VAD implants. The average number of implants from 2012 to 2017 was 29. In NSW, there are more single VADs implanted than BiVADs and from June 2013 to June 2018 there were on average 19 VAD implants. In Australia, Victoria provided the most VAD insertion services via the Alfred Hospital and The Royal Children's Hospital, followed by New South Wales via SVHS.

The allocations of LVADs at the four transplant units in Australia were obtained to determine current funding arrangements within the units. The split between provision of LVADs and HTx within a unit was also determined. For LVADs and HTx supply, the current allocation of LVAD supply and the proportion of services in the transplanting units is presented in Table 2-5. In NSW, around 50% of HTx

[11] http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp

candidates who were on the waiting list were supported with a LVAD. In contrast, in Victoria, there was a significant proportion of patients who were supported with a LVAD who were not on the waiting list. This situation is synonymous with an increase in use of LVADs policy scenario.

Table 2-5: Allocation of VADs at transplanting units in 2018

	LVAD cap (no. per year)	HTx n per year	VAD, n per year	Bridged HTx n (%)
NSW	<25	55	20	16 VAD out of 30 on waitlist = 53%
Victoria	30-35	35	25	6 VAD out of 11 on waitlist = 55% 19 VAD not on waitlist.
QLD	15-20	10	4	2 VAD out of 7 on waitlist = 29%
WA	10	2016 = 11 2017 = 9 2018 = 10	NR	2016 = 3 (27%) 2017 = 4 (44%) 2018 = 5 (50%)

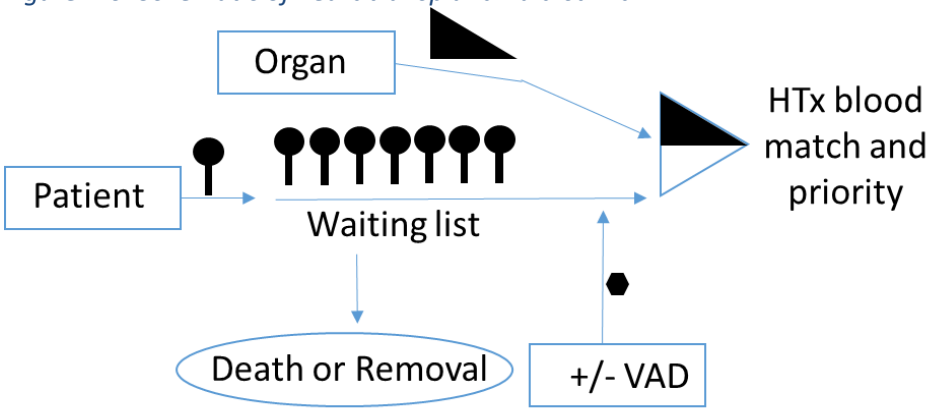
Abbreviations: HTx, heart transplant; NSW, New South Wales; QLD, Queensland; VAD, ventricular assist device; WA, Western Australia; Source: personal communication with Professor Christopher Hayward, St Vincent's Hospital Sydney.

Internationally, the use of LVADs in HTx eligible patients is similar. The UK Registry maintained by the National Health Service (NHS) Blood and Transplant reported outcomes of adults implanted with continuous-flow long-term bridging devices. The Annual Report listed the heart transplant listing status of adults with LVADs from the 6 centres, and between 2012 and 2016, 46% of LVAD recipients were already listed on the HTx wait list (BTT) and a further 19% were listed within the first year of implant (BTC).(79) Of the LVAD recipients, 13% either died or were explanted within a year without listing and the remaining 23% were alive and not listed within the year.(79) Similarly, the International Society for Heart and Lung Transplantation (ISHLT) reported the level of pre-transplant support for HTx recipients from 2009 to June 2015.(80) Half the patients were already hospitalised at the time of treatment and 38% were bridged with a LVAD, 3% with RVAD and 1% with TAH.(80)

2.6 Modelling ESHF using queuing theory and patient matching

Having discussed the HTx policy in Australia, I now focus on some of the considerations when modelling treatments for ESHF. As discussed, there are clearly significant resource constraints in the treatment options for ESHF, in the form of a limited number of donor hearts and the artificial funded supply cap for LVADs. In this case study, queuing theory is illustrated in ESHF patients listed on the HTx waiting list, which has a service time with mean wait of 6 months in Australia. While in the queue, patients' priority for a heart transplant can change based on the patient need and donor suitability via a matching process. Some patients can leave the queue altogether (Figure 2-6). The queuing discipline determines the order of patient treatment and, in this example, it is a combination of priority and matching (e.g. blood type). In addition to the queue for the donor heart, the use of mechanical pumps such as LVADs can also alter the waiting list processes of patients which may impact the cost-effectiveness of these interventions.

Figure 2-6: Schematic of heart transplant waitlist with VAD



Abbreviations: VAD, ventricular assist device

Incorporating queuing theory in the economic model can address two research questions.

1) What is the cost-effectiveness of using LVADs as a bridge to transplant compared to HTx only?
2) What is the cost-effectiveness of increasing the supply of donor hearts or LVADs, compared to HTx only?

2.6.1 Waiting time for a HTx

Patients are placed on a waiting list and compete for the same pool of donor hearts. The proposed model for ESHF would incorporate the wait time for a heart transplant for eligible patients. The matching process between the donor heart and the recipient, based on an independent criterion (blood type), makes it an ideal case study as this is not a typical first-in first-out (FIFO) queue. Changes to organ allocation policy are particularly interesting in that organs are known to be scarce resources and costly. Therefore, any changes to organ allocation policies impact the balance between allocative efficiency and equity.

2.6.2 Impact of organ replacement technology on wait time for HTx

The advent of mechanical organ replacement technologies and the potential impact this might have on the HTx waiting list has not yet been explored. However, an example in a similar setting can be found in the assessment of liver transplant allocation using a discrete event simulation model.(17) LVADs represent an alternative to heart transplant (HTx) and can substitute or delay the use of a HTx. However, the high cost associated with the implantation and maintenance of LVADs has limited their use in Australia. LVADs are limited by the number available to be transplanted within a hospital. This artificial supply cap influences the decision to implant a patient with a LVAD, meaning that that LVADs effectively become the de facto last treatment of choice. The implication is that patients who receive an LVAD are often less healthy than they would be without the restricted supply constraint.

2.6.3 Impact of queuing theory on model structure

In traditional Markov models, the healthcare services are delivered instantly so that the costs and effects occur at once. No patient has to wait for doctors, hospital beds, medical devices or donor hearts to become available so that essentially, all treatment options have unlimited availability (implicit in the transition probabilities). This approach, however, does not reflect reality. The decision problem for LVADs was applied to a checklist proposed by Brennan et al. (2006)(27) to determine the appropriate model structure (see Table 8-1). Based on this checklist, it was determined that an individual-level model – specifically, a DES model – would be a suitable option. The delay in receiving health care resources is the rationale for choosing a DES model structure when compared to the Markov model. This was due to the complexity of factors affecting survival, meaning the Markovian assumption[12] would not be ideal. Similarly, DES is the only method that can explicitly account for the interaction between patients in the form of restricted supply of donor hearts and LVADs.

2.7 Discussion

Due to improvements in the diagnosis and treatment of CHF, incidence of ESHF is increasing with the ageing population. ESHF continues to have a large impact on an individuals' and families' health and wellbeing. The treatment and management of CHF takes up considerable outpatient and inpatient health care resources and represents the most expensive disease resulting in medical hospitalisation. Therefore, the development of interventions that extend life and improve quality of life need to be prioritised. Given the current waiting list problem in Australia, any assessment of policies of introducing interventions should be assessed within the context of the HTx waiting list, as well as the cost constraints in the Australian economy.

2.7.1 HTx waitlist as a queue

There is a shortage of donor organs leading to a long wait time for some ESHF patients. Donor hearts are a constrained resource and HTx eligible patients are placed on a waiting list until a match becomes available. The decision problem is thus defined by the fact that patients do not immediately receive treatment and that there is a delay in the form of a queue. Another characteristic of this queue is that patients can leave the waiting list due to death, sickness or improvement in health.

Advances in technology in the donor organ procurement space, such as ex vivo preservation of hearts, will impact on the waiting list. The donor pool will increase as ex vivo presentation increases the quantity of viable donor hearts to be retrieved and implanted. There is potential that by increasing

[12] See footnote 4 above.

the availability of viable donor hearts, the wait-time for patients could be shortened. Naturally, another method to increase the donor pool would be to increase the donation rate.

2.7.2 LVADs as an organ replacement technology

LVADs can be a temporary or permanent alternative to a heart transplant and have affected the HTx waiting list. This is analogous to the use of dialysis in end-stage kidney failure. Patients who would otherwise die are able to survive until a donor kidney match becomes available. Consequently, the impact of these organ replacement technologies is that the potential eligible patient pool grows as patients who in the past would have died remain alive long enough to receive a donor heart. The funding of LVADs in Australia has also affected how they are used in treating ESHF. Given DT is unfunded, LVADs are only used as a bridging tool. The potential of LVADs in patients who are ineligible for a heart transplant has not been explored in Australia. Therefore, LVADs are typically used in the sickest of patients and are seen as a last resort.

2.7.3 Modelling ESHF

Economic evaluation of health technologies in ESHF when dealing with resource constraints can make modelling more challenging. There is an interaction between the patients and the potential donors. The availability of donor organs is driven by a range of factors including donation policy, donation rate and physical location of potential donor. The chance of a patient receiving a donor organ match is driven by the patient's health and the matching characteristics such as blood type, as well as physical location. These elements of the HTx waiting list are represented neatly in queuing theory. Therefore, a model that captures queuing theory is likely to realistically represent the waiting list.

Economic evaluation can be a useful tool in assessing the cost-effectiveness of various policy scenarios rather than typical single technology comparisons. It is apparent that donation policy and/or number of available donor organs will have a profound impact on a patients' waiting time, their health and the costs to society. Changes to the supply of donor organs will affect the waiting list, as will changes to the the supply of LVADs. Therefore, the modelling component of the thesis will reflect the suite of interventions available under various supply scenarios.

2.8 Conclusion

The HTx waiting list is subject to supply constraint issues as patients with ESHF are added to an existing queue to await a match. There is a supply constraint due to the number of organs being donated with appropriate consent, from an appropriate geographical location, and that are medically suitable and a match based on weight and blood type. All these factors affect the waiting time for a patient to receive a donor organ. The advent of mechanical circulatory supports such as LVADs has changed the

heart transplant waiting list as it buys ESHF patients time to remain on the waiting list rather than being removed. In addition, the use of LVADs as BTC can allow ESHF patients who may not have been eligible for a donor organ to be added to the waiting list. Similarly, the advent of 'Heart in a Box' has the potential to increase the available donor organs (i.e. supply) for patients on the waiting list.

The use of LVADs in Australia is inextricably linked to the HTx waiting list as its use in DT is not funded in Australia. This means in Australia LVADs are not intended to be long-term solutions and are seen only as bridging support for HTx. This has implications for the device's use, which is distinct from overseas experience. The lack of funding of DT LVADs may be related to the prohibitive cost.

The motivation for this thesis is to explicitly consider resource allocation decisions in HTA using this case study. The literature has identified that a waiting list would benefit from resource allocation consideration. An economic evaluation of the impact of LVADs on the HTx waiting list will estimate the cost-effectiveness of LVADs in Australia as a bridge to HTx. Similarly, assessing policy options such as the impact of LVADs and availability of donor organs may affect the HTx waiting list.

3 CHAPTER 3: REVIEW OF MODELLING METHODS USED IN COST-EFFECTIVENESS LITERATURE OF END-STAGE HEART FAILURE TREATMENTS

3.1 Introduction

Economic evaluation is the systematic assessment of the costs and benefits of an intervention or programme. Evaluating the cost-effectiveness of interventions is an important tool to inform decision-making about the allocative efficiency of funding new treatments. The aim of cost-effectiveness analysis (CEA) is to rank alternatives with respect to cost-effectiveness in order to determine the relative value for money. This chapter reviews the cost-effectiveness literature of the two main treatment options for patients with end-stage heart failure (ESHF). Hence, two systematic literature reviews were conducted: 1) a review on the cost-effectiveness of left ventricular assist devices (LVADs), and 2) a review on the cost-effectiveness of heart transplant (HTx).

HTx is the gold standard long-term treatment option for patients with ESHF. First introduced as an experimental procedure in the late 1960s, HTx has proven patient benefits in terms of survival and improved quality of life. A previous systematic literature review of solid organ transplantations (heart, kidneys, lung and liver) included cost-effectiveness studies from 2000 to 2010.(81) This review noted there were few economic evaluations of solid organ transplantations due to the lack of randomised controlled trials (RCTs), predominantly due to ethical reasons. Included studies failed to account for uneven samples in treatment groups or used unrealistic alternative treatment options.(81) The issue of sample selection is a confounding issue because variations in baseline characteristics between those who receive a donor organ and those who do not may result in different long-term outcomes. Furthermore, it can be challenging to determine the counterfactual of a HTx programme.

Developed in the 1990s, LVADs are implantable mechanical circulatory support (MCS) used to treat patients awaiting HTx. Motivated by the shortage of donor hearts, LVADs were initially developed as a bridge to transplant (BTT) for those patients eligible for a HTx. As the LVAD technology has improved, a second indication known as destination therapy (DT) is now available for patients who are ineligible for a HTx. Most patients receive an LVAD, but occasionally a patient may require a BiVAD (LVAD and right ventricular assist device (RVAD)). Most of the current literature compares LVADs to non-VAD strategies, such as optimal medical management (OMM) and HTx without LVAD bridging. The earlier pulsatile-flow (PF) devices are known as ‘first-generation’ devices and are now rarely implanted. Continuous-flow (CF) devices have superseded PF devices and are further distinguished by pump type: axial are ‘second generation’ and centrifugal are ‘third generation’.

There are several published systematic literature reviews of CEAs of LVADs, which are summarised in Table 3-1 (52, 82-90). Some of the reviews were conducted as part of national HTA submissions to assess public funding of LVADs. Published country-specific HTA reviews included the UK (52, 87, 88), Netherlands (85) and Canada.(84) The majority of the included studies were cost-effectiveness analyses (CEA or CUA); however some reviews included cost-minimisation analyses and costing studies.

Table 3-1: Summary of systematic literature reviews of economic evaluations of ventricular assist devices in end-stage heart failure

Systematic literature review	Indication	Included studies	Search year
Recent reviews			
Schmier et al. (2019)(89)†	BTT and DT	12 studies; 1 CEA, 11 CUA	2017
Seco et al. (2017)(82)	BTT	5 studies; 1 CEA, 4 CUA	2016
Nunes et al. (2016)(90)	BTT and DT	11 studies; 2 CEA, 9 CUA	2014
Hutchinson et al. (2008)(83)	BTT and DT	12 studies; 3 cost/cost summation, 6 CMA, 1 CEA, 2 CUA; 6 abstracts[a]	2004
Reviews as part of national HTA			
Canada: Health Quality Ontario et al. (2016)(84)	DT	3 studies; 3 CUA	2015
UK: Sutcliffe et al. (2013)(52)	BTT	1 study; 1 CUA	2012
Netherlands: Neyt et al. (2014)(85) Original report in Dutch(91)	DT	6 studies; 4 CUA and 2 health economic models (VOI or payment by results)	2012
UK: Sharples et al. (2006)(88)	BTT and LTCS	17 studies; 14 cost/cost summation, 1 CEA, 2 CUA; 7 abstracts[a]	2005
UK: Clegg et al. (2005)(87)	BTT, BTR and LTCS	19 studies; 10 CMA; 5 cost/cost summation; 2 CEA; 2 CUA	2002-2003

Note: Some systematic literature reviews included abstracts, these have been excluded in the current review due to insufficient information reportable in an abstract.
†Published during the development of this chapter
Abbreviations: BTR, bridge to recovery; BTT, bridge to transplant; CEA, cost-effectiveness analysis; CMA, cost-minimisation analysis; CUA, cost-utility analysis; DT, destination therapy; LTCS, long-term chronic support; UK, United Kingdom; VOI, value of information.

The most recent review, published by Schmier et al. (2019)(89), included the same studies as the two recent reviews published by Seco et al. (2017)(82) and Nunes et al (2016)(90) that were conducted in 2016 and 2014 respectively. Seco et al. (2017) reviewed the use of LVAD as BTT compared to non-bridged HTx. This study included five cost-effectiveness studies (92-96). The review published by Nunes et al. (2016), which also identified the same five CEA studies, was broader in scope and included cost-effectiveness studies of LVAD used for DT.(90)

The systematic literature review in this chapter builds on the existing reviews. The Patient, Intervention, Comparator and Outcome (PCIO) framework focuses on two groups of adult patients with ESHF. Those who receive a LVAD (compared to non-bridged HTx, another VAD or OMM) and those who receive a HTx with no VAD (compared to patients activated on the cardiac transplantation waiting list that receive OMM). The aim of the review was to inform subsequent chapters, in particular the structure of an economic evaluation of treatment modalities in ESHF from the Australian perspective (Chapter 5). In both reviews, published CEAs were analysed to determine the type of

modelling approach, how wait time was modelled for those listed on the cardiac transplantation waiting list and how long-term survival was estimated.

3.2 Methods

3.2.1 Search strategy (LVADs)

An updated literature review of economic evaluations was conducted to identify all new cost-effectiveness studies for LVADs for any indication (BTT and DT), including CUAs and CEAs (that report LYG). The search terms used were based on the review by Nunes et al. (2016)(90). The most recent review by Schmier et al. (2019)(89) was published during the development of this chapter. The databases searched included Ovid MEDLINE/Embase, EBSCO Host (CINAHL and EconLit), PubMed, Cochrane Library and the Tufts CEA Registry (Table 3-2). The search was restricted to articles published in English and the search terms are presented in Table 3-3 . The reference lists of the included studies were searched for other articles that matched the inclusion criteria ('pearling'). This was conducted from 2014 to June 2017 and the PubMed search was updated monthly until December 2020.

Table 3-2: Databases searched for economic evaluation literature review of VAD

Database	Dates searched	Search date	Results returned
Ovid MEDLINE	2014 – Current	27/06/2017	47
Ovid Embase	2014 – Current	27/06/2017	166
CINAHL via EBSCO Host	2014/01/01-2017/12/31	27/06/2017	71
EconLit via EBSCO Host	2014/01/01-2017/12/31	27/06/2017	
PubMed	2014/01/01 to 2017/06/27	27/06/2017[a]	207
Cochrane Database of Systematic Reviews	Jan 2014 - Current	28/06/2017	115
Database of Abstracts of Reviews of Effects	Jan 2014 - Current	28/06/2017	
Health Technology Assessment Database	Jan 2014 - Current	28/06/2017	
NHS Economic Evaluation Database	Jan 2014 - Current	28/06/2017	
Tufts Cost Effectiveness Analysis Registry	2014 onwards	28/06/2017	4

[a]Search updated monthly from June 2017 to December 2020.

Table 3-3: Search terms for economic literature review for VADs

Type	Terms (Medline)	Terms (PubMed/EBSCO host)	Terms Cochrane Database
Cost-effectiveness of VADs	• heart assist device/ • assisted circulation/ • ((ventric* or biventric* or heart or cardiac) adj assist*).mp. • (lvad* or lvas* or rvad* or bivad*).mp. • ((vad or vads) and (heart or cardiac)).mp. • (HeartMate or HeartWare).mp.	• heart assist device • assisted circulation • ((ventric* or biventric* or heart or cardiac) AND assist*) • (lvad* or lvas* or rvad* or bivad*) • (vad or vads) and (heart or cardiac) • (HeartMate or HeartWare)	• heart assist device • assisted circulation • ((ventric* or biventric* or heart or cardiac) and assist*):ti,ab,kw • (lvad* or lvas* or rvad* or bivad*):ti,ab,kw • (vad or vads) and (heart or cardiac):ti,ab,kw • (HeartMate or HeartWare):ti,ab,kw
Economic	• economic evaluation/ or 'cost benefit analysis'/ or 'cost effectiveness analysis'/ or 'cost utility analysis'/ • (cost adj2 (benefit* or effect* or utility or analys*)).mp. • (economic adj (evaluation* or analysis or analyses)).mp. • (cost* or economic*).ti.	• (economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') • (cost AND (benefit* or effect* or utility or analys*)) • (economic AND (evaluation* or analysis or analyses)) • TI (cost* or economic*)	• (economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') • (cost and (benefit* or effect* or utility or analys*)):ti,ab,kw • (economic and (evaluation* or analysis or analyses)):ti,ab,kw • (cost* or economic*):ti
Restrictions	• english or french or german or italian or portuguese or Spanish • human only	• Limiters Published Date: 20140101-20171231	• Online Publication Date from Jan 2014

Source: adapted from Nunes et al. (2016) and Sutcliffe et al. (2013)

The inclusion criteria were adapted from Nunes et al. (2016) and are presented in Appendix 3: Economic literature review for LVADs. Briefly, the study publication had to be a full manuscript with original data in a peer-reviewed journal. The population was the adult ESHF population with an indication for MCS in the form of an intracorporeal VAD. The comparator groups had to include OMM, HTx or another type of MCS. Excluded articles included conference abstracts/posters, letters to the editor, reviews and case studies. Studies of inappropriate indications/populations (e.g. paediatric patients) were also excluded. Temporary strategies for emergency rather than durable treatment options, such as extra-corporeal membrane oxygenation (ECMO), were not considered part of this review.

3.2.2 Search Strategy (HTx not bridged)

The search strategy for HTx-only versus OMM was similar to the strategy described in the previous section and was adapted from Sutcliffe et al. (2013)(52). The search strategy described by Nunes et al. (2016) was not used because it excluded economic evaluations for HTx without VAD as an intervention or comparator. The databases and search terms used from 2012 to October 2017 are presented in Appendix 4: Economic literature review for heart transplant.

The inclusion criteria of the search included all cost-effectiveness studies on HTx published as a full manuscript in a peer-reviewed journal and where the population was adults with ESHF. The other arm had to include medical management (or 'on wait list'). Only cost-effectiveness analyses or cost-utility

analyses were included. Conference abstracts, letters to the editor, reviews and case studies were excluded. Studies of inappropriate indications/populations (e.g. paediactric patients) were excluded.

3.2.3 Analysis

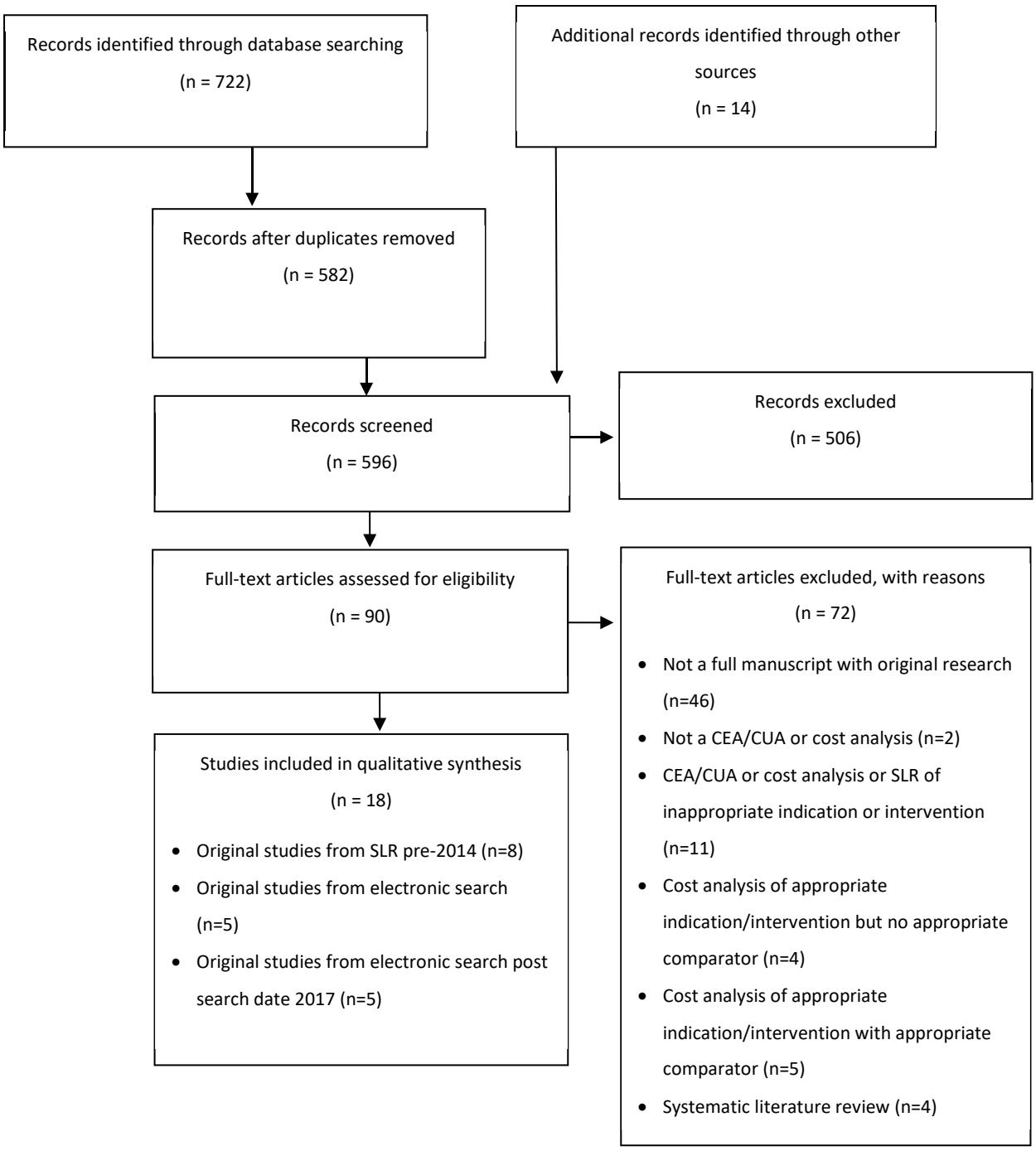
The following information was extracted from the included studies: publication year, device type (if applicable), comparator, source of clinical evidence, utilities and costs, model structure, health states, ICER as reported, country of analysis and discounting rate for costs and benefits. Special attention was focussed on if and how the wait time for HTx was addressed in the model if patients were HTx eligible. The ICERs from the included studies were inflated to 2018 values using the Australian Institute of Health and Welfare (AIHW) Health Index (74) and converted to Australian dollars using purchasing power parity (PPP).(97)

3.3 Results

3.3.1 Search results (LVAD)

The PRISMA Flow Diagram for the systematic literature review on LVADs is presented in Figure 3-1 (see Appendix 8.3.1. for details of the search results for the LVAD search). The current systematic literature review searched for papers published since 2014 to 2017 and identified five studies (95, 96, 98-100). The systematic literature review by Nunes et al. (2016) included 11 studies published prior to 2014 and the current analysis excluded CETQ (2000)(101) as no economic model was presented so that seven studies (92-94, 102-105) supplement the current updated review. One study (106) was taken from the systematic literature review from Health Quality Ontario via pearling. Five studies were identified after the electronic search conducted on June 2017 (107-111). In total, 18 original studies for the treatment of ESHF with LVADs met the inclusion criteria.

Figure 3-1: PRISMA Flow Diagram for economic evaluation of VAD literature review



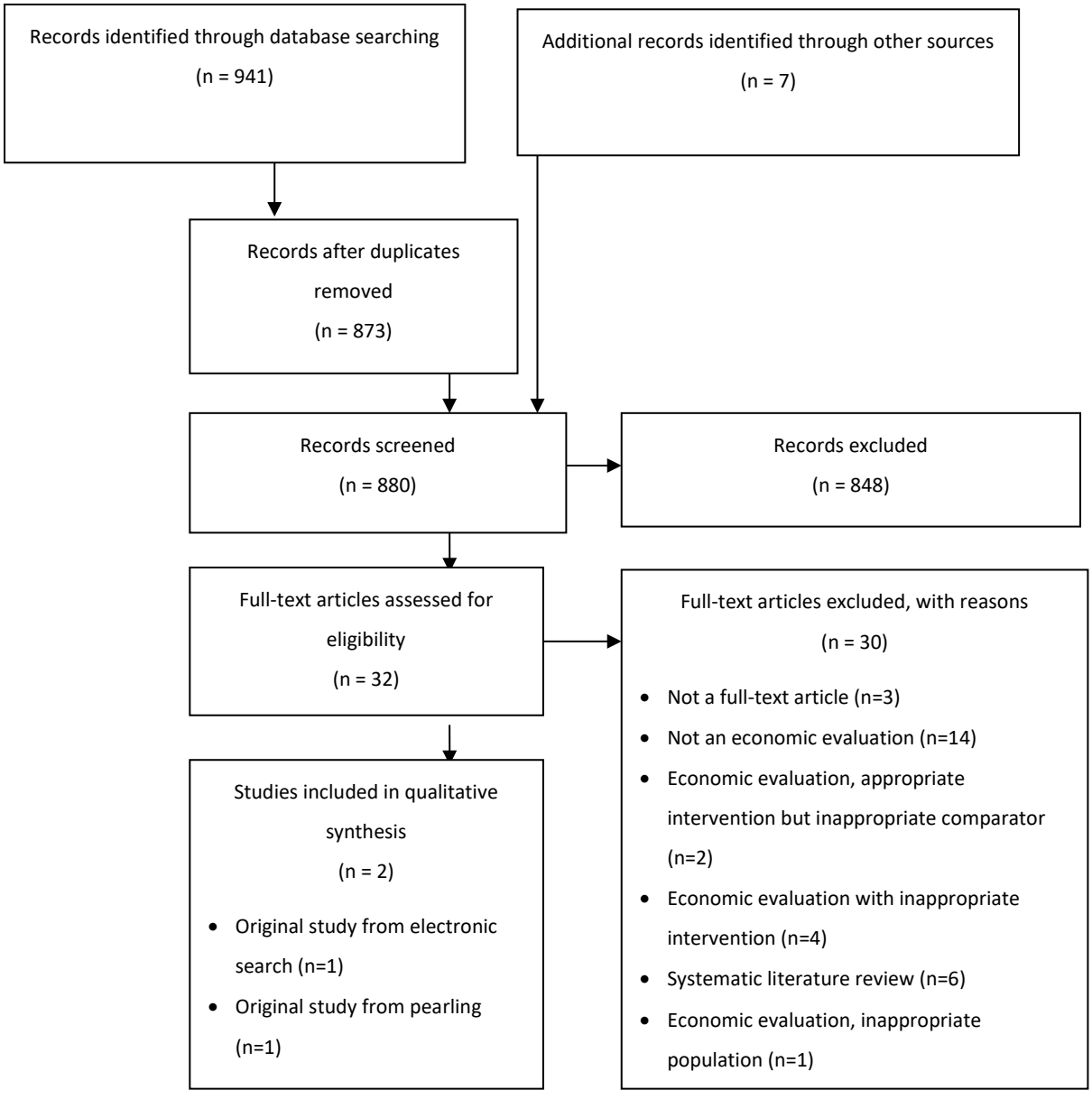
Abbreviations: CEA, cost-effectiveness analysis; CUA, cost-utility analysis; SLR, systematic literature review.
Source: (112)

3.3.2 Search results (HTx not bridged)

The search results from the updated systematic literature review of economic evaluations of HTx in adults are presented in Figure 3-2. The search included economic evaluations comparing HTx with OMM. Of the 880 screened articles (title and abstract review), 32 were included for a full-text review

after which 30 were excluded. Reasons for exclusion were: 1) not a full-text article, e.g. letter or conference abstract (n=3); 2) not an economic evaluation, e.g. cost analysis (n=14); 3) economic evaluation with appropriate intervention but inappropriate comparator, e.g. BTT vs HTx rather than HTx vs OMM (wait list) (n=2); 4) economic evaluation with inappropriate intervention, e.g. no HTx, VAD in HTx ineligible (n=4); 5) systematic literature review (n=6), and; 6) paediatric population (n=1).

Figure 3-2: PRISMA Flow Diagram for economic evaluation of HTx literature review



Source: (112)

An additional review (113) was identified via pearling; this article reviewed the economic evaluations and costing studies of heart failure therapies including medical (e.g. beta-blocker therapy), implantable cardioverter defibrillator, CRT, MCS (including VADs) (87, 92, 93, 102) and HTx (113). Four

studies from Rohde et al. (2013) were excluded from the literature review as they were a cost analysis (114), in paediatric population (115), a cost-benefit analysis (116) and review article (117). The analysis of Ouwens et al. (2003)(116) was based on van Hout et al. (1993)(118), which was a Dutch economic evaluation using heart transplant programme registry data.

3.3.3 Overview of included studies (LVADs)

The 18 economic evaluations of ESHF patients treated with LVADs are presented in Table 3-4. Overall, 10 studies considered LVAD when used as a BTT (92-95, 98, 100, 102, 108, 110, 111), 7 studies considered LVAD when used as DT (99, 103-107, 109, 110) and one study (96) considered LVAD for both BTT and DT and HTx compared to OMM. The pearling search from the systematic literature review also identified an older economic evaluation by van Hout et al. (1993), which was referenced by Ouwens et al. (2003)(116). The study by van Hout et al. (1993) evaluated the Dutch heart transplantation programme vs no programme (118). Two studies (98, 108) claimed to have combined BTT/DT population patients; for the purpose of the current review, as the model structures included a HTx health state, the corresponding analyses were categorised as BTT.

Table 3-4: Included economic evaluations - data extraction

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
BTT											
Clegg et al. (2006)(87, 102)	BTT	HeartMate LVAD, Jarvik Heart 2000 and MicroMed Debakey LVAD	OMM	Retrospective cohorts (Aaronson 2002; Massad 1996). Aaronson follow-up to 60 months, no extrapolation.	SG utilities, Moskowitz (1997)(103).	Hospitals/manufacturers.	'Decision analytic' Area under the curve analysis.	Alive, Dead.	BTT vs. OMM £65,252 (95% CI: £34,194 to 364,564) per QALYG. Currency: Pounds 2004.Time horizon: 5 year.	UK	Cost 6%; Benefit 1.5%
Sharples et al. (2006)(88, 92)	BTT	Heartmate VE, Thoratec	HTx (inotrope dependent and hypothetical worst-case scenario).	Observational data of UK patients with VADs, IDMT on HT wait list and received HT. UK Transplant registry post 12 months.	Primary data: EuroQoL EQ-5D during support.	Hospital costing data.	Discrete-time, semi-Markov, multistate model. Patients in UK program from 2002-2004.	VAD; HTx; Death	VAD vs. inotrope dependent: inotrope cheaper and greater survival (VAD is dominated); VAD vs. worst case scenario £49,384 (US$89,790) per QALYG. Currency: Pound 2004. Time horizon: lifetime (50 year).	UK	Cost 3.5%; Benefits 3.5%
Moreno et al. (2012)(93)	BTT	HeartMate II	OMM	Cohort study 7 years (Russo 2009), UNOS registry data (Lietz 2007). Uncontrolled trial (Pagani 2009)(119); (Moskowitz 1997) Registry of transplant.	As in Sharples (2006).	As in Sharples (2006).	Discrete-time, semi-Markov, multistate model, 100 hypothetical patients (UNOS 1A/1B), mean age 50 years.	BTT: VAD, HTx, death. OMM: OMM, HTx, death.	BTT vs. OMM: £258,922 (USD $414,275) per QALYG (6 month wait list), £178,829 (USD $286,126) per QALYG (12 month wait list), £133,860 (USD $214,176) per QALYG (18 month wait list). Currency: UK pounds, 2011. Time horizon: 7 year.	UK	Cost 3.5%; Benefit 3.5%

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
Alba et al. (2013)(94)	BTT	HeartMate II; HeartWare; DuraHeart.	HTx	Systematic review of cohort studies; large registries (UNOS, INTERMACS; UK National Database) with extrapolation.	N/A	Hospital costing data.	Markov model, simulated transplant cohort (UNOS).	HF waiting; HTx; VAD; Death and secondary model incorporating 6 states for post-HTx and post-VAD complications (rejection, cardiac allograft vasculopathy, chronic renal dysfunction, cancer, infection).	QALYs not estimated. High-risk: BTT vs. HT $84,964 per LYG. Medium-risk: BTT vs. HT $99,039 per LYG. Low-risk: BTT vs. HT $119,574 per LYG. Currency: $Canadian 2011. Time horizon: 20 year.	Canada	Cost 5%; Benefit 0%.
Clarke et al. (2014)(95)[52]	BTT and ATT.	HeartMate II; Jarvik Heart 2000 Flow Maker; MicroMed DeBakey VAD, Berlin Heart INCOR; Terumo DuraHeart LVAD; HeartWare HVAD.	OMM	British database (British Cardiothoracic Transplant Audit Group) with extrapolation.	Derived from health states based on NYHA classes.(120)	Hospital costing(103)g data.	Discrete-time, semi-Markov, multistate model, UK NHS BTBD.	Alive (on LVAD or OMM); alive (after HTx); dead.	BTT vs. OMM £53,527 (US$84,963) per QALYG. Currency: Pounds 2011. Time horizon: lifetime (50 year).	UK	Cost 3.5%; Benefit 3.5%
Pulikottil-Jacob et al. (2014)(100)	BTT	HeartWare (HW) third generation.	VAD (HeartMate II second generation).	British Cardiothoracic Transplant Audit Group. Extrapolation post-LVAD (20 months and 34 months) and post-HTx (7 years).	Health states based on NYHA.	Hospital costing data; Sharples et al. 2006.	Discrete-time, semi-Markov, multistate model. Individual patient data.	LVAD (HM II or HW); HTx; Dead.	BTT HW vs. BTT HM II: £23,530 per QALYG Currency: UK Pounds, 2012. Time horizon: 50 year.	UK	Cost 3.5%; Benefit 3.5%
Long et al. (2014)(96)	BTT	HeartMate II and other.	OMM and HTx	INTERMACS Registry, (Kirklin 2013) and ISHLT (Stehlik 2012). Extrapolation for post-VAD and post-HTx.	As in Sharples (2006) and Rogers (2012); Post (2001) SLR of utilities after stroke.	HeartMate II DT trial (Slaughter 2009); Nationwide Inpatient Sample (Mulloy 2013).	Health state-transition model. Simulated cohort of 20,000 patients.	OMM: Alive, death. LVAD DT: If perioperative survival - Alive, stroke, bleed, driveline infection, pump failure, death. HTx: waitlist, if perioperative survival (alive, organ rejection, CAV, renal	BTT vs. HTx: BTT dominated by immediate HTx; $226,300 per QALYG (5.6 months HT wait list) and $191,400 per QALYG (12 months wait list). Currency $US Dollars,	US	Cost 3%; Benefit 3%

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
								dysfunction, skin malignancy, lymphoma, death). LVAD BTT: If perioperative survival with LVAD health states from LVAD, if Alive and perioperative survival for HTx, HTx health states.	2012. Time horizon: lifetime.		
Baras Shreibati et al. (2017)(98)	DT ambulatory/ BTT.	Cost for VAD implanted 2009-2010. Effectiveness for VAD 2016.	OMM (non-inotrope dependent)	INTERMACS, MedaMACS; ISHLT (Lund 2015). Extrapolation beyond 3 years (post-VAD).	LVAD Grady (2014); Post (2001); Sanders (2005).	Medicare - fee-for-service of VAD patients (before and after implantation).	Decision Tree/Markov model, Medicare/INTERMACS/MedaMACS registry, mean age 61 years.	LVAD: perioperative death or survival, if perioperative survival: HTx, alive (with or without major stroke) and death. OMM: HTx, Alive (with or without major stroke), LVAD and Death. Event model from alive (with or without stroke) include all-cause readmission, stroke, pump replacement, HTx, alive and death.	Low-risk patients - DT vs. OMM $209,400 per QALYG and $597,400 per LYG. High risk patients - DT vs. OMM $171,000 per QALYG and $167,400 per LYG. Currency: $US 2016. Time horizon: lifetime.	US	Costs 3%; Benefits 3%
Tadmouri et al. (2017)(108)	BTT/DT	HeartMate II, Thoratec; Jarvik Heart 2000 Flow Maker and HeartWare HVAD.	OMM (no LVAD)	French hospital discharge database (PMSI).	Clarke 2014 and Sharples. 2006.	PMSI	Markov model PMSI, mean age 57 years.	LVAD: alive, HTx and Dead. No LVAD: alive and dead.	LVAD (BTT + DT) vs. no LVAD (OMM): ICER €123,109 per QALYG (deterministic). PSA ICER was €125 580 (€105 587-€150 314) per QALYG. Currency Euro 2017. Time horizon: Lifetime (20 year).	France	Costs 4%; Benefits 4%
Silvestry et al. (2020)(110)	BTT	HeartWare HVAD	OMM	BTT - ADVANCE and Continued Access Protocol (Slaughter 2013 Aaronson 2016). OMM - SHFM	As before.	CMS and Baras Shreibati 2017	Markov model, ADVANCE mean age 53 years	Alive and Dead	$69,768 per QALY gained. Currency $US 2017. Time horizon: lifetime.	US	Costs 3%; Benefits 3%
Mahr et al. (2020)(111)	BTT	HeartWare HVAD	OMM	LATERAL nonrandomised	As before and ADVANCE Continued	CMS and Baras	Markov model, LATERAL mean age 53 years	Alive and Dead	$64,632 per QALY gained. Currency $US 2018. Time horizon: lifetime	US	Costs 3%; Benefits 3%

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
				trial (McGee 2019)	Access Protocol (Slaughter et al. 2013, Aaronson et al. 2016)	Shreibati 2017					
DT											
TEC (2004)(105)	DT	HeartMate VE	OMM	US registry CDRH FDA, 2002; (Rose 2001(121)).	(Moskowitz 1997) with probability of NYHA I/I or III/IV status from Thoratec Registry.	Hospitals and literature (Oz 2003; Gelijns 1997). No indirect costs.	pseudo-Markov, REMATCH patients with extrapolation.	Alive, dead.	VAD vs. OMM: $802,674 per QALYG. Currency: US 2002. Time horizon: 3 year.	US	Cost 3%; Benefit 3%
Clegg et al. (2007)(87, 103)	DT	HeartMate LVAD, Jarvik 2000; and MicroMed Debakey LVADs.	OMM	RCT (Rose 2001) with extrapolation from 10 months.	Mapped MLWFQ to utilities.	Hospitals/manufacturers.	Pseudo-Markov, hypothetical cohort of 100 patients.	Alive, Dead.	DT vs OMM £170,616 (95% CI: £136,597 to 190,283) per QALYG. Currency: Pounds 2004. Time horizon: 5 year.	UK	Cost 6%; Benefit 1.5%
Rogers et al. (2012)(104)	DT	HeartMate II	OMM	2 RCTs of DT (Slaughter 2009; Rose 2001). Extrapolation of post-VAD from 24 months to 60 months.	Health states based on NYHA. TEC 2004 (OMM) and Slaughter 2009 (LVAD).	Hospital; Center for Medicaid and Medicare Services.	Markov model. Patients from REMATCH and HMII DT Trial with extrapolation.	Alive, Dead.	DT vs. OMM: $US198,184 per QALYG. Currency: US Dollars, 2009. Time horizon: 5 year.	US	Costs 3%; Benefits 3%
Neyt et al. (2013)(91, 106)	DT	Pulsatile flow from REMATCH trial) and HeartMate II.	OMM	2 RCTs of DT (Rose 2002 and Slaughter 2009). Extrapolation of OMM and VAD survival.	Moskowitz (1997)	Hospital costing data and national (Dutch) databases.	Markov model, hypothetical cohort of 1,000 patients, adjusted Dutch Life table.	Death; Hospitalisation; No event.	DT vs.OMM ICER €94,100 per LYG. DT vs. OMM €107,600 per QALYG. Currency: Euro 2011. Time horizon: lifetime.	Netherlands	Cost 4%; Benefit 1.5%
Long et al. (2014)(96)	DT	HeartMate II and other.	OMM and HTx	INTERMACS Registry, (Kirklin 2013) and ISHLT (Stehlik 2012).	As in Sharples (2006) and Rogers	HeartMate II DT trial (Slaughter 2009);	Health state-transition model. Simulated cohort of 20,000 patients.	OMM: Alive, death. LVAD DT: If perioperative survival - Alive, stroke, bleed, driveline	DT vs. OMM: $201,600 per QALYG; Currency $US Dollars, 2012. Time horizon: lifetime.	US	Cost 3%; Benefit 3%

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
				Extrapolation for post-VAD and post-HTx.	(2012); Post (2001) SLR of utilities after stroke.	Nationwide Inpatient Sample (Mulloy 2013).		infection, pump failure, death. HTx: waitlist, if perioperative survival (alive, organ rejection, CAV, renal dysfunction, skin malignancy, lymphoma, death). LVAD BTT: If perioperative survival with LVAD health states from LVAD, if Alive and perioperative survival for HTx, HTx health states.			
Takura et al. (2016)(99)	DT	DuraHeart and Evaheart	Percutaneous VAD Nipro VAD	3 Hospitals in Japan, Survival from literature(122, 123)	3 Hospitals in Japan, EQ-5D	Hospital costing data.	Markov model	VAD, death, adverse events	Implantable VAD vs. Extracorporeal VAD $303,104 (12 months) and $102,712 per QALYG (36 months). Currency: $US 2016. Time horizon: 1 year.	Japan	Costs 3%; Benefits 3%
Chew et al. (2017)(107)	DT	Pulsatile flow from REMATCH trial; HeartMate II.	OMM	2 RCTs of DT (Rose 2002 and Slaughter 2009). HR from DT applied to PF-LVADs.	INTERMACS (Kirklin 2011)	Hospital costing data.	Markov model, simulated cohort of DT patients.	Alive, dead.	DT-VAD vs. OMM $230,692 per QALYG. Currency $Canadian 2015. Time horizon: lifetime (2 years).	Canada	Cost 1.5%; Benefits 1.5%
Magnetta et al (2018)(109)	DT	CF 2012-2014	OMM	INTERMACS Registry (Kirklin 2015(56)) and RCT (Rose 2001(121))	Gohler (2009)(120) and Uzark 2012.(124)	Literature for VAD(125, 126) and for DMD(127)	Markov model, hypothetical cohort	DT: Death at implant, implant survival, VAD replacement, other readmission, alive (no readmission), and death. OMM: readmission, alive (no readmission) and death.	DT vs. OMM: $179,086 per QALYG. Currency: USD, 2016. Time horizon: 5 years.	US	Cost 3%; Benefit 3%
Silvestry et al. (2020)(110)	DT	HeartWare HVAD	OMM	DT – ENDURANCE Trial (Rogers 2017, Milano 2018) OMM - SHFM	As before.	CMS and Shreibati 2017	Markov model, ENDURANCE Supplement mean age 63 years	Alive and Dead	$102,587 per QALY gained. Currency $US 2017. Time horizon: lifetime.	US	Costs 3%; Benefits 3%

Reference	Indication	Device	Comparator	Source of clinical evidence	Source of utility	Source of costs	Economic model and modelled patients (if applicable)	Health states	ICER as reported	Country	Discounting
HTx only											
Van Hout et al. (1993)(118)	HTx	N/A	No programme	Dutch HTx programme (1984-1988) and Eurotransplant.	SG in patients.	Two hospitals, costing data and national (Dutch) databases.	Discrete-event simulation, 'Micro-simulation'.	'Treatment stage'. Programme (HTx): first screening, second/third screening, waiting-list, post-transplant. No programme (OMM): first screening, second/third screening, waiting-list.	HTx vs. OMM: NLG 57,650 (€26,160) per LYG and 71,900 (€32,627) per QALYG. Currency – Dutch Guilder (Euro). Time horizon: lifetime.	Netherlands	Costs 5%; Benefits 5%.
Long et al. (2014)(96)	HTx	N/A	OMM	INTERMACS Registry, (Kirklin 2013) and ISHLT (Stehlik 20120. Extrapolation for post-HTx.	As in Sharples (2006) and Rogers (2012).	Nationwide inpatient sample (Mulloy 2013)	Health state-transition model. Simulated cohort of 20,000 patients.	OMM: Alive or death. HTx: waitlist, perioperative survival (alive, organ rejection, CAV, renal dysfunction, skin malignancy, lymphoma, death.	HTx vs. OMM: $96,900 per QALYG (5.6 months wait list) and $97,300 per QALYG (12 months wait list). Currency $US Dollars, 2012. Time horizon: lifetime.	US	Costs 3%; Benefits 3%.

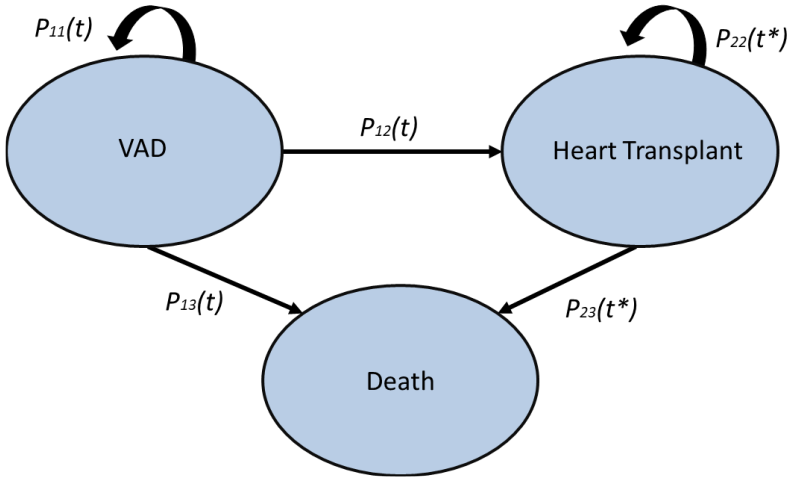
Abbreviations: ATT, Alternative to transplant; BTDB, British NHS Blood and Transplant Database; BTT, Bridge To Transplant; CAV, cardiac allograft vasculopathy; CDRH, Center for Devices and Radiological Health CMS, Centers for Medicare and Medicaid Services; DT, Destination Therapy; FDA, US Food and Drug Administration ; HR, hazard ratio; HTx, Heart Transplant; ICER, Incremental Cost-Effectiveness Ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support ; ISHLT, International Society for Heart & Lung Transplantation; MLWHFQ, Minnesota Living With Heart Failure Questionnaire; N/A, Not Applicable ; NLG, Dutch Guilder; NYHA, New York Heart Association; LY, life year; LYG, life year gained; LVAD, left ventricular assist device; OMM, Optimal Medical Management; PF, pulsatile-flow; PMSI, Program for the Medicalisation of Information Systems; PSA, probabilistic sensitivity analysis; QALY, Quality Adjusted Life Year; QALYG, quality-adjusted life year gained; RCT, randomised controlled trial; SG, standard gamble; SHFM, Seattle Heart Failure Model; UK, United Kingdom; UNOS, United Network of Organ Sharing ; US, United States; VAD, Ventricular Assist Device.
Note: First generation devices: Thoratec HeartMate VE; Novacor HeartMate LVAD. Second generation devices: Thoratec HeartMate II, Jarvik Heart 2000 Flow Maker, MicroMed DeBakey VAD. Third generation devices: HeartWare HVAD, Berlin Heart INCOR, Terumo DuraHeart LVAD.
XE Currency Converter from Dutch Guilder to Euro: 0.453780 (accessed 9 October 2018)

3.3.3.1 Model type, structure and nomenclature

The nomenclature used to describe the model types varied across the studies. The systematic literature review by Nunes et al. (2014), described the 10 included studies in the current review as 'Pseudo-Markov'.(90) A few studies (93, 95, 100) described a Markov state-transition model as 'discrete-time, semi-Markov model'. For the purpose of the current review the nomenclature as reported in the individual papers is used. Most studies (15/18) presented a cohort state-transition model or Markov model[13] Conversely, the BTT study by Clegg et al. (2006) presented a partitioned survival model and estimated survival via area under the curve analysis.(102) A discrete event simulation was used in the comparison of VADs to no VADs in van Hout et al. (1993)(118).

Five of the studies that considered LVAD as a BTT (92, 100, 95, 93, 108) utilised a similar 3-health state model structure (Figure 3-3). All patients started in the *'LVAD'* health state and either transitioned to the *'Heart Transplant'* health state, remained alive with a LVAD or died. From the *'Heart Transplant'* health state patients either remained alive or died. There were two BTT models that included additional health states to account for patients waiting for a HTx (94, 96) and corresponding complications for HTx and VAD (94, 98).

Figure 3-3: Typical BTT model structure: Sharples et al. (2006)

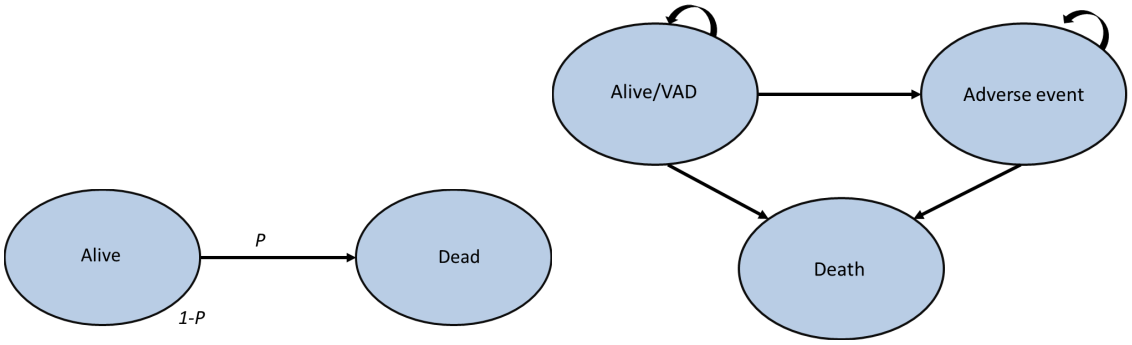


Abbreviations: VAD, ventricular assist device.
Notes: Semi-Markov discrete-time multistate model: P11(t), probability of a VAD patient surviving t months after VAD implant; P12(t), probability a VAD patient receives a HTx t months after VAD implant; P13(t), probability of a VAD patient dying t months after VAD implant, before HTx; P22(t*), probability of a transplant recipient surviving t* months after HTx; P23(t*), probability of a transplant recipient dying t* months HTx.
Source: adapted from(92)

[13] Here, the term 'Markov model' includes semi-Markov models using time-dependent transition probabilities.

Of the seven studies that considered LVAD for DT, five models comprised two health states of *'alive/survival post-VAD'* and *'death'* (103-105, 107, 110) (Figure 3-4). The remaining three studies included an additional *'hospitalisation/adverse event'* health state (106, 107, 109) and in addition, Magnetta et al. (2018)(109) included the health states *'death at implant'* and *'VAD replacement'*.

Figure 3-4: Typical DT model structure: Rogers et al. (2012) (104) and Neyt et al. (2013)



One study compared a number of different indications using separate model structures (96) (Table 3-5). Similar to Alba et al. (2014)(94), the authors included a HTx waitlist health state, the difference being with or without bridging due to the HTx only strategy. The same model structure of two health states *'Alive'* and *'Dead'* with five additional stroke related health states for severity via modified Rankin Scale was used by Silvestry et al. (2020)(110) and Mahr et al. (2020)(111); notably, heart transplants were not a distinct health state in the BTT indications for either model.

Table 3-5: Markov models with adverse event and waiting list health states

	Long 2014	**Magnetta 2018**	**Silvestry 2020**	**Long 2014**	**Long 2014**	**Alba 2013**	**Baras Shreibati 2016**	**Mahr 2020**
Health states	**DT**	**DT**	**DT and BTT**	**HTx**	**BTT**	**BTT**	**BTT**	**BTT**
Number	6	4	7	8	12	9	7	7
Alive/Perioperative survival	✓	✓	✓	✓	✓	✓	✓	✓
Dead/Perioperative death	✓	✓	✓	✓	✓	✓	✓	✓
Wait-list				✓	✓	✓		
HTx							✓	
All-cause/other readmission		✓					✓	
Stroke	✓		✓ (mRS 0-1 to 5)		✓		✓ (major and minor)	✓ (mRS 0-1 to 5)
GI bleed	✓				✓			
Driveline infection	✓				✓	✓		
Pump failure/replacement	✓	✓			✓		✓	
Organ rejection				✓	✓	✓		
Cardiac allograft vasculopathy				✓	✓	✓		
Renal dysfunction				✓	✓	✓		
Skin malignancy				✓	✓			
Lymphoma/cancer				✓	✓	✓		

Abbreviations: HTx, heart transplant, GI, gastrointestinal, mRS; modified Rankin Scale.

The study by van Hout et al. (1993) describes a modelling approach that used an unspecified 'micro-simulation programme'. The model included 'the interactions between the number of patients on the waiting list, survival probabilities, the number of donor organs and matching-criteria between donors and recipients'.(118) In their methods, the authors referenced a paper by Davies and Davies (1987)(128), which was explicitly described as a 'discrete-event simulation' conducted to plan services in kidney transplantation in Europe. Van Hout et al. (1993) do not present a figure of the model structure, and do not use the term health states but instead refer to 'treatment stage'. Therefore, although described as a microsimulation, it is likely the authors conducted a discrete event simulation.

The study by van Hout et al. (1993) included 346 patients referred to 2 centres between 1984 and 1988 and modelled survival of patients who did not receive transplantation (those on the waiting list) using pre-transplant patient data.(118) The study developed a simulation model using the annual number of patients referred to the transplant centres; pre-transplant duration distributions; the annual number of donor hearts; post-transplant survival; and costs. Survival and costs per patient per treatment stage were extrapolated by the non-parametric sum-limit method. Transplant-related and non-transplant-related costs were estimated for patients in the first screening (for heart transplant eligibility) or second or third screening. This reflects patient severity in the life-cycle of heart failure.

3.3.3.2 Comparator

The comparator to LVADs was usually HTx or OMM. Two studies (99, 100) compared the cost-effectiveness of LVADs to another LVADs. Most studies explored one indication for LVADs, that is, either BTT or DT. However, Long et al. (2014)(96) compared the cost-effectiveness of BTT and DT in a single model, with an additional comparison of HTx compared to OMM. Baras Shreibati et al. (2017)(98) evaluated the cost-effectiveness of VAD in DT within ambulatory patients who could potentially receive a HTx; therefore, the definition of DT is more in line with alternatives to transplant. Finally, Silvestry et al. (2020)(110) assumed the comparator was OMM in the separate analyses for BTT and DT indications, with the former allowing transplants to occur to patients.

The definition of OMM differed between studies. In Sharples et al. (2006)(92), OMM referred to patients with severe disease who are dependent on inotrope therapy and are hospital-bound. Conversely, in Baras Shreibati et al. (2017)(110) the comparator was non-inotrope dependent patients. Naturally, OMM would differ in DT studies compared to BTT studies as the former group is ineligible for a HTx. In Tadmouri et al. (2017) the comparator group 'was the same patients assuming that they will not receive an LVAD (no LVAD group), but only medical management and die probably in the 3 months'.(108) Consequently, medical management differed in resource use and expected survival amongst the studies.

3.3.3.3 Time horizon

Most studies used a lifetime horizon. Guidelines for state-transition modelling noted that common approaches for applying a lifetime horizon included modelling to 120 years or until 99.9% of the individuals are dead so that the time horizon 'should be sufficiently large to capture all health effects and costs relevant to the decision problem'.(129) The use of a lifetime horizon is therefore based on available data and extrapolation may be required. Seven of the included studies explicitly noted the use of a 'lifetime' horizon and adhered to best practice. The years in a lifetime horizon differed, e.g 20 years in Tadmouri et al. (2017)(108) and 50 years in Clarke et al. (95), with the former assuming patients aged 66-68 years and the latter assuming patients aged 42 years.

3.3.3.4 Evidence base for survival estimates

There are three RCTs for VADs as DT. These are the REMATCH trial (121), HeartMate II Destination Therapy Trial (130) and MOMENTUM trial (included BTT patients) (54). Recently the ENDURANCE trial (131) enrolled HTx eligible patients but compared VADs to VADs, rather than HTx or OMM, and was relied on in the recent DT analysis.(110) The REMATCH (121) and HeartMate II (130) were used to inform survival on VAD in the DT economic evaluations (103, 104, 106, 107). RCTs are generally preferred to observational studies due to improved internal validity of efficacy conclusions. The BTT CEAs rely on non-RCT sources for effectiveness estimates, including retrospective cohort studies and national registries (Table 3-6). Two studies (95, 100) relied on the British Cardiothoracic Transplant Audit Group Registry (BTDB).[14] Three of the BTT studies (94, 96, 98) and two DT studies (107, 109) relied on Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)[15] survival data for LVADs. The earlier studies (102, 92, 93) relied on retrospective cohorts.

[14] The United Kingdom (UK) National Health Service Cardiothoracic Transplant Audit began on 1 July, with MCS data collected from 2002 and from 1 April 2009 to 31 March 2019 including 1,372 patients.

[15] The Interagency Registry for Mechanically Assisted Circulatory Support is a database established in 2005 in North America and as of May 2020 had 25,087 patients enrolled (https://www.uab.edu/medicine/intermacs/).

Table 3-6: Type of data sources for clinical evidence

Study	VAD	HTx	OMM
BTT			
Clegg 2006	Retrospective cohort Aaronson et al. (2002)(132) (VAD n=66, OMM n=38, HTx subset of VAD/OMM)		
Sharples 2006	Retrospective cohort UK (n=70)		N/A
Moreno 2012	Uncontrolled trial Pagani et al. (2009)(119) (n=281)	Retrospective cohort Russo et al. (2009)(133) (n=10,668)	
Alba 2013	Registry INTERMACS(134) (n=1,221)	Registry ISHLT(135) (n=22,477)	N/A
Clarke 2014	Registry BTDB (VAD n=235, OMM n=307, HTx subset of VAD/OMM)		
Long 2014	Registry INTERMACS(134, 136) (n=6885)	Registry ISHLT(137) (n=24,021), 2003- 2010	N/A
Pulikottil-Jacob 2014	Registry BTDB (n=207 CF VAD, HW=82, HM II=125)		N/A
Baras Shreibati 2016†	Registry INTERMACS(56, 138) (n>2,000)	Registry ISHLT(139) (n=nr)	Registry MedaMACs(140) (n=144)
Tadmouri 2017†	Registry PMSI (n=508)		RCT REMATCH(121) (OMM=61)
Silvestry 2020	Uncontrolled trial ADVANCE + CAP (n=382)(141, 142)	Registry UNOS(143) (n=nr)	Survival calculator SHFM (n=1,125+9,942)(144)
Mahr 2020	Uncontrolled trial LATERAL (n=144)(145)	Registry ISHLT(146)	Survival calculator SHFM (n=1,125+9,942)(144)
DT			
TEC 2004	RCT REMATCH(121) (n=129, VAD=68; OMM=61)	N/A	RCT REMATCH (n=129, VAD=68; OMM=61)
Clegg 2007	As in TEC 2004	N/A	As in TEC 2004
Rogers 2012	RCT REMATCH(147) (n=129, VAD=68; OMM=61) RCT HeartMate II (n=200, CF-VAD=134, PF-VAD=66)	N/A	RCT REMATCH, indirect comparison REMATCH(121) and HeartMate II(130), PF-VAD common reference arm
Neyt 2013	As in Rogers et al. (2012)	N/A	As in Rogers et al. (2012)
Long 2014	As in Long 2014 BTT, however assumed 5% lower survival at 1 year for DT patients.	N/A	As in Rogers et al. (2012)(104, 121)
Takura 2016	Japan Hospital contributing to J-MACS from Nov 2010 to Oct 2012 (n=37, 30 CF and 7 percutaneous VAD)	N/A	N/A
Chew 2017	RCT as in Rogers et al. (2012)	N/A	RCT as in Rogers et al. (2012)
Magnetta 2018	INTERMACS CF-VAD in DT (n=3,243){Kirklin, 2015 #30}	N/A	RCT REMATCH (OMM=61)
Silvestry 2020	RCT ENDURANCE (131)Supplemental(148) (n=465)	N/A	Survival calculator SHFM (n=1,125+9,942)(144)

†LVAD population not split by BTT or DT, use same data for both.

Abbreviations: BTDB, British NHS Blood and Transplant Database; BTT, Bridge To Transplant; CAP, continued access program; CF, continuous-flow; DT, Destination Therapy; HTx, Heart Transplant; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support ; ISHLT, International Society for Heart & Lung Transplantation; MedaMACS; Medical Arm of Mechanically Assisted Circulatory Support; N/A, Not Applicable; OMM, Optimal Medical Management; PF, pulsatile-flow; PMSI, Program for the Medicalisation of Information Systems; RCT, randomised controlled trial; VAD, Ventricular Assist Device.

In ESHF, the highly regimented treatment modalities MCS and HTx are provided in the hospital setting. This results in useful registry data available such as INTERMACSs and national hospital databases, e.g. the British database (British Cardiothoracic Transplant Audit Group) or French Programme de Médicalisation des Systèmes d'Information (PMSI). The advantages of using registry data over RCT data include real-world applicability, larger cohort size and longer follow-up. Another benefit of the

registry data, such as the US United Network for Organ Sharing (UNOS), was the ability to draw out waiting list mortality and transplant probability, as done by Alba et al. (2013)(94).

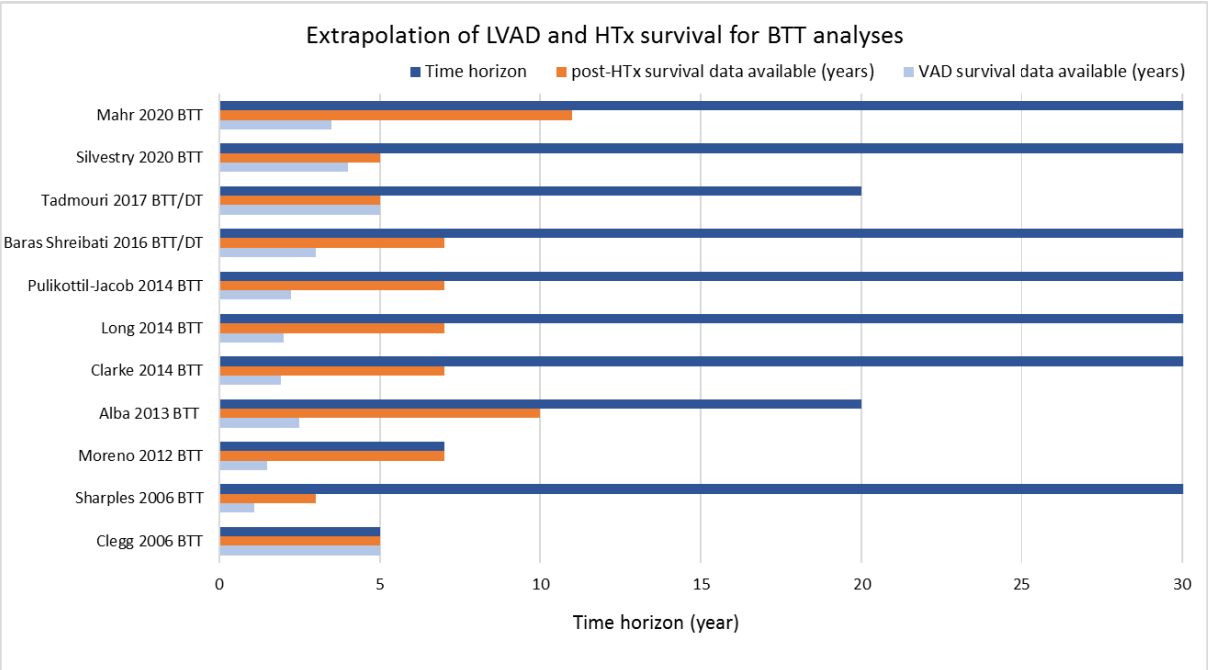
One of the challenges of using registry data was highlighted in Tadmouri et al. (2017)(108), who struggled to obtain the intent strategy of LVAD implants (BTT vs DT) from the PMSI registry in France and instead included all LVAD recipients in the analysis. This is significant as many studies that estimate the cost-effectiveness of LVADs focus on either BTT or DT models separately. Similarly, Baras Shreibati et al. (2016) combined populations of BTT and DT for LVADs rather than have them as separate arms of the economic evaluation as done in Long et al. (2014)(96). Given the prognostic differences between those eligible for a HTx and those who are not, combining these patients into the same analysis may over- or under-estimate the health outcomes and costs for patients.

3.3.3.5 Extrapolation of survival

Beyond the follow-up study period in the registries or trials, the authors extrapolated the mortality rates to project future survival post-HTx, post-VAD or OMM. The Markov models used time-dependent transition probabilities obtained via Kaplan-Meier (KM) survival curves. For BTT studies the issue of cross-over for patients who receive a LVAD but then receive a HTx was not explicitly addressed in any model. Once a patient received a transplant (regardless of bridging), their transition probabilities were taken from a post-HTx Kaplan Meier curve. Therefore, it is assumed that patients have the same rate of survival once transplanted regardless of whether they were bridged with a LVAD or not.(94, 100).

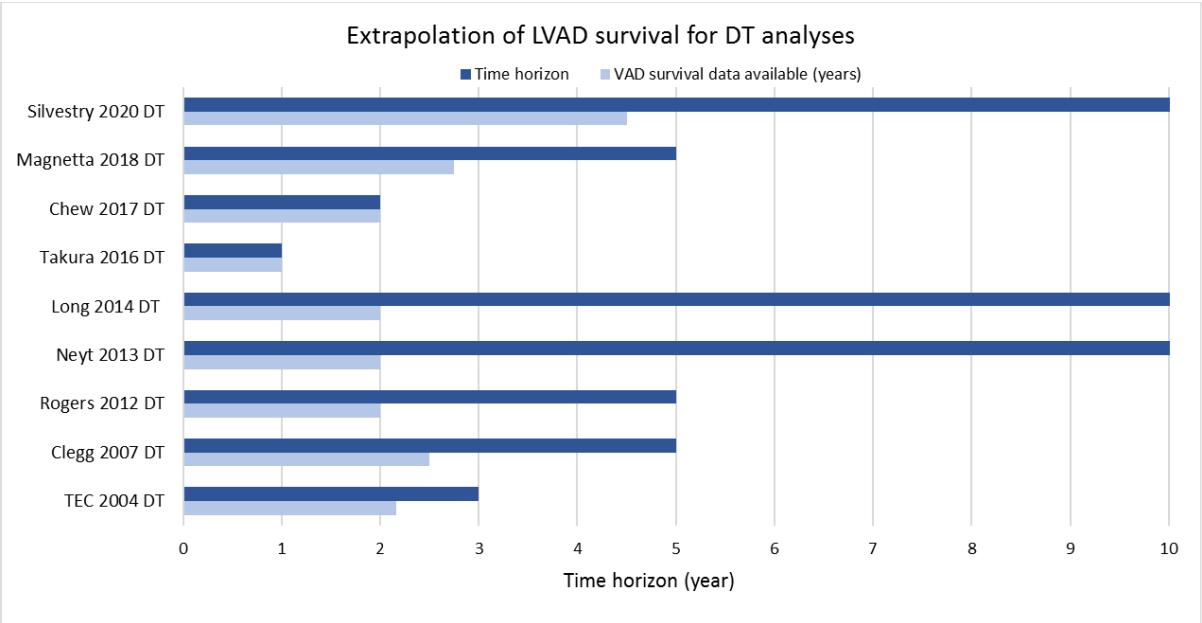
The follow-up period of LVAD survival and the period of extrapolation to the time horizon was presented in Figure 3-5 and Figure 3-6. Three studies did not explicitly report the time horizon in years. The extrapolation methods applied were an exponential distribution (93, 94, 96, 100, 104, 109), Weibull distribution (110, 111), constant hazard (92, 95, 98, 103) or linear interpolation (105, 106). The longer time horizons were associated with the BTT indications, as patients could potentially receive a HTx and hence expected survival was longer.

Figure 3-5: Extrapolation of LVAD and post-HTx survival for BTT analyses



Abbreviations: BTT, Bridge To Transplant; DT, Destination Therapy; VAD, Ventricular Assist Device.
Note: Silvestry et al. (2020), Long et al. (2014) Baras Shreibati et al. (2016) and Mahr et al. (2020) reported lifetime horizons.

Figure 3-6: Extrapolation of LVAD survival for DT analyses

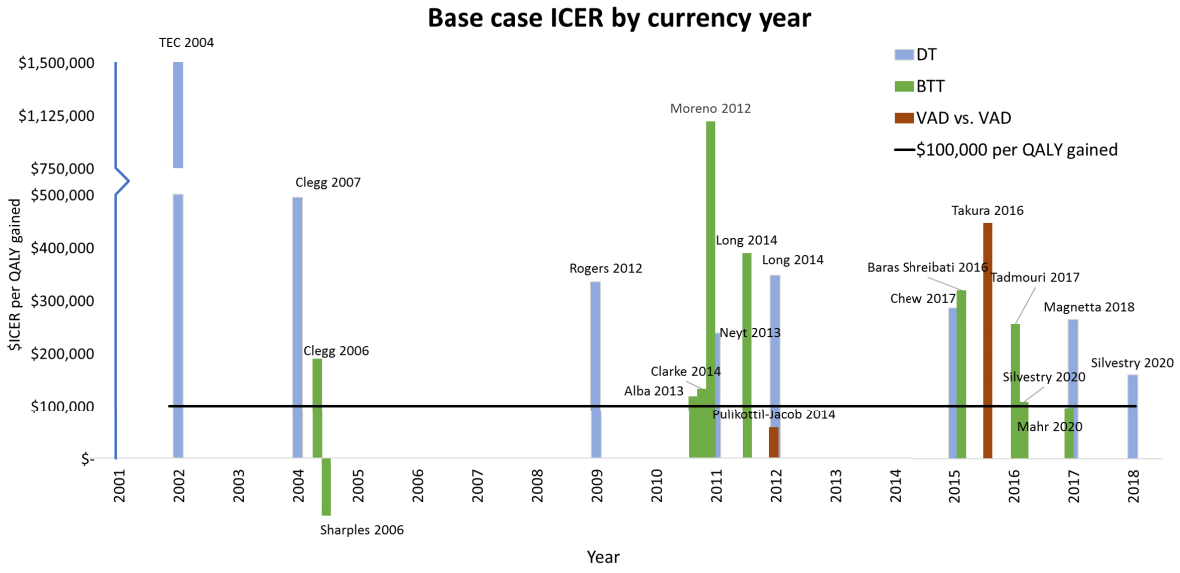


Abbreviations: BTT, Bridge To Transplant; DT, Destination Therapy; VAD, Ventricular Assist Device.
Note: Silvestry et al. (2020), Long et al. (2014) and Neyt et al. (2013) reported lifetime horizons.

3.3.4 Cost-effectiveness results

The ICERs of the included studies demonstrated that VADs were not cost-effective at $50,000 per QALY gained[16] (Figure 3-7). The reported base case ICERs from included studies were inflated and converted (if applicable) to Australian dollars ($2018) and were plotted against the reported year of currency. The general trend of the included studies were high ICERs (98, 107-109), but two recent studies (110, 111) reported BTT ICERs below US$100,000 per QALY gained. In one instance, Sharples et al. (2006) reported a base case ICER that was dominated (VAD vs inotrope medical management) – that is, the use of VADs was more costly and less effective than the alternative. There were two VAD vs VAD comparisons, second and third generation VADs in BTT with ICER of AUD$58,162 (£23,530 per QALY gained in 2012)(100) and implantable CF vs extracorporeal in DT with an ICER of AUD$461,203 (US $303,104 per QALY gained in 2016). Tadmouri et al. (2017) presented an ICER of LVAD (BTT+DT) vs. OMM of €123,109 [$AUD 255,062] per QALY gained (108) and conclude that '[t]he ICER exceeds the minimal WTP threshold adopted in France (€50 000/QALY), but is significantly lower than that adopted for some rare conditions or oncology drugs (€300 000/QALY)'.(108)

Figure 3-7: Plot of ICER by currency year reported for all included studies – LVAD



Note: Reported base case ICERs from included studies inflated and converted (if applicable) to Australian Dollars ($2018). Sharples et al. (2006) reported a base case ICER that was dominated (VADs vs. inotrope dependent patients). Long et al. (2014) and Silvestry et al. (2020) reported two indications of VADs (BTT and DT) separately. Alba et al. (2013) presented cost per life year gained ($111,600 per LY gained).

[16] No explicit threshold exists in Australia, but $50,000 per QALY gained may be considered an unofficial threshold for the purpose of this thesis.

For the HTx ICERs, van Hout et al. (1993) reported costs (in Dutch guilders which have been converted to Euros) of €26,160 (AU$ 55,176) and €32,627 (AU$ 68,816) per LY gained and per QALY gained respectively.(118) This was based on an average waiting time of 141 days (0.4 years) and mean survival after 1 year post-transplant was 10.98 years. In Long et al. (2014), HTx vs OMM was $96,900 (AU$166,705) per QALY gained for 5.6 months on the waiting list. Therefore, the HTx non bridged vs OMM scenarios generally produced lower ICERs than the LVAD comparisons.

3.3.4.1 Wait time for HTx and impact on ICER

For the BTT models, some studies attempted to address the issue of the HTx wait list with a health state. Long et al. 2014 estimated the median wait list time of 5.6 months from the US Scientific Registry of Transplant Recipients (SRTR) as the base case.(96) Alternative scenarios were 'immediate' HTx and 'wait-list 12 months'. The model included a waitlist health state in the HTx strategy; patients remained in the waitlist health state for the required time and then moved to a *'perioperative survival'* or *'perioperative death'* health state. An assumption of a constant hazard rate was applied so that 77% of these patients received a heart within one year. The base case ICER was $96,900 per QALY gained ($USD 2012) with a wait time for HTx of 5.6 months and the ICER reduced when wait time for HTx increased to 12 months.

Alba et al. (2013) also explicitly incorporated a health state for the wait list: *'VAD'*, *'HF waiting'*, *'HTx'* or *'Death'*.(94) Their model applied a lower probability of transitioning to the health state 'HTx' from 'HF waiting' as time passed, i.e. between 0 to 3 months the transition probability from *'HF waiting'* to *'HTx'* was 0.56 and from 1 year onwards a reduced annual probability of 0.06 was applied.(94) This assumption takes into account a reduced probability of HTx the longer a patient waits. One of the reasons why the waiting time for a HTx may differ is blood type. In blood groups A or O, primarily in high-risk patients, BTT-VAD represents a more cost-effective therapy. However, in blood group AB or B patients (with waiting time median 2.5 months) BTT-VAD was less cost-effective.(94)

Moreno et al. (2012) utilised scenario analyses and incorporated different wait times referred to as 'bridging intervals' with 6 months (base case), 12 months and 18 months.(93) The longer the wait time for a HTx (18 months vs. 6 months), the more cost-effective the BTT strategy. Another method to reflect changes in capacity was reducing the monthly transplant rates, to reflect increase in referrals to the HTx wait list.(88) Sharples et al. (2006) reduced transplant probabilities in inotrope-dependent (OMM) patients from 58% to 30% in month 1 and from 15% to 10% in month 2.(92) The resulting median ICER was at £145,900 (Currency Year 2004) per QALY gained for VAD compared to inotrope-dependent patients. This contrasts with the base case of VAD compared to inotrope-dependent where VAD was dominated. In fact, of the six different sensitivity analyses reported, the

reduction in transplant rate was the only assumption that returned a positive ICER, i.e. in all other analyses VAD was dominated by the inotrope-dependent comparator.

The health states in Long et al. (2014) for the HTx only to OMM comparison included a *'waitlist'* health state, and the longer the wait time for a HTx the worse the survival, with ICERs increasing compared to patients on OMM. In the comparison of HTx vsOMM, when the wait time for a HTx increased from 5.6 months to 12 months, QALYs reduced from 4.70 to 3.41 (8.48 to 6.18 LY). If a patient received a HTx immediately, i.e. no wait time, then that patient had 7.67 QALYs (13.76 LY) over the lifetime horizon. This is similar to the median survival of 14 years in HTx recipients aged 50-59 years in Australia.(149) Conversely, van Hout et al. (1993) calculated that 55% of all referred patients were placed on the waiting list, and that of these patients 52% (29% of the referred population) were transplanted. The average waiting time was estimated at 151 days and average survival on the waiting list was 141 days. The model takes into account the annual number of patients referred to the transplant centres; pre-transplant duration distributions; and the annual number of donor hearts, which influences the wait time.

3.4 Discussion

The updated review of the literature reporting CEA of LVAD or unbridged HTx focussed on the modelling approaches employed in the CEAs which concluded that cohort-state transition models were most commonly used and in one DES model of heart organ transplantation.(118) Recently, another systematic literature review included 12 LVAD papers published between 2006 and 2017; it identified the same papers with the exception of four papers published prior to (102, 103, 105, 109) or since (89) the search.The systematic literature review by Schmier et al. (2019) identified that the ICERs in the included studies for the seven BTT and five DT VADs were similar and not cost-effective.(89) It should be noted that the purpose of the current review was to examine the differences in modelling approaches.

In terms of the use of LVADs as BTT, there were nine studies identified in the current review (92-96, 98, 100, 102, 108, 110, 111) and these highlighted that LVADs continue to be a costly treatment for patients awaiting a donor heart or ineligible for a HTx. The publications reviewed by Seco et al. (2017) reported ICER values (in USD, currency year as reported in papers) between $84,963 to $414,275 per QALY gained.(82) The authors had determined that an ICER value below $100,000 per QALY gained was considered 'cost-effective' and considered that two studies presented ICERs below this threshold.(95, 150) Similarly, two recent BTT analyses reported ICERs below US$100,000 per QALY gained.(110, 111)

Due to the high ICERS produced, a common theme discussed in the studies was the threshold for cost-effectiveness. The concept of a WTP threshold has been, and continues to be, an area of much debate.

It has been suggested that thresholds for ICERs are in the range of $25,000 to $100,000 per QALY gained (USD) depending on the country.(151) In Australia, recent estimates suggest an ICER threshold of $28,033 (range $20,758-$37,667 per QALY gained).(18) A limitation of the review relates to the analysis of the cost-effectiveness results in light of the thresholds used in different jurisdictions. In addition, comparisons of cost-effectiveness in economic evaluations across jurisdictions is challenging due to differences in health systems and type of care provided. Similarly, there are differences in the costs of medical services, medical devices and pharmaceuticals across jurisdictions.

Another area of interest was the available data to inform the survival of patients. The broader challenges in the assessment of cost-effectiveness of implantable medical devices such as LVADs have been noted in the literature.(152, 153) There are no RCTs of BTT compared to non-bridged HTx due to ethical considerations.(154) In clinical practice, the patients who receive non-bridged HTx compared to those who receive a LVAD, may not have comparable disease severity. This has implications for the availability of comparative effectiveness estimates between patients bridged with a LVAD and unbridged HTx. Consequently, there is the potential for bias in registry data due to patient selection. As there are no RCTs in HTx vs OMM, registry data for survival estimates are relied on, specifically ISHLT for HTx and UNOS for OMM.(96) However, given the regimented nature of ESHF care in hospitals, registry data can provide a rich source of information regarding costs and outcomes.

Donated hearts are from deceased persons who have previously provided consent (confirmed by next of kin) and are therefore limited in supply. Availability of donor hearts is also constrained by the matching process between the donor and the recipient. In practice, this shortage of donor hearts translates into waiting time for a HTx once a patient is added to the waiting list. In the current review of the 11 BTT analyses, eight did not include a *'waiting list'* health state or address waiting time in a scenario analysis. It is apparent that many existing BTT economic evaluations do not account for this in their structure, representing a limitation of the literature.

Adjustment of the waiting list period was demonstrated to be an important factor in three studies (96, 93, 94). Two studies (96, 94) explicitly included a *'waiting list'* health state, and increasing the waiting time for HTx once a VAD was implanted (BTT) improved the cost-effectiveness ratio compared to HTx alone. This was illustrated by Long et al. (2014), where in the comparison of BTT vs HTx, a longer wait time from 5.6 months to 12 months for HTx improved the ICER for the BTT strategy by 15%.(96) Therefore, economic evaluations should take into account the wait time for a HTx and the quality of life impact and mortality risks incurred.

When a patient is considered for a HTx, the process may require multiple assessments for eligibility for the waiting list. This is known as screening. Waiting list processes were modelled by van Hout et al. (1993)(118); patients were referred to the centre and this was either an initial screening with a

decision to add onto the *'waiting list'*, *'temporarily not indicated for HTx'*, *'definitely not indicated for HTx'* and *'death'*. The study was able to address these interactions by utilising discrete event simulation, which used real data on the time a patient was screened for implant and noted if this was the first or subsequent screening. The number or patients and their time on the waiting list, the number of donor organs, the matching-criteria between donor and recipients and survival after implant were incorporated into the model.

End-of-life treatments are usually associated with higher cost-effectiveness thresholds. This is because newer treatments are generally expensive and for patients who are in need of life-saving treatment, the relative improvement can be quite small. Decision-makers tend to accept higher ICERs and implicitly use a higher threshold for life-saving therapies. It can be argued that LVADs are an 'end-of-life treatment' and that ICERs should be evaluated in this light.(75) This is similar to renal replacement therapy with dialysis, where kidney transplant is the only alternative.(155)

A strength of the current review is that it included VADs as both BTT and DT as well as unbridged HTx. The focus of the review and analysis was on the model structure and data sources used. No economic evaluations have been conducted from the Australian perspective. This is significant as the usefulness of a HTA is often dependent on its applicability to the local jurisdiction. An Australian decision-maker would be interested in an HTA set in Australia as the population, clinical practice and costs vary between Australia and other countries.

3.5 Conclusion

It is apparent that the use of VADs in ESHF patients will continue despite high ICERs. Therefore, it may be more appropriate to focus on how to better utilise VADs in clinical practice. There is a need to compare a range of treatment strategies (96) given these treatment modalities are not provided in silos. Given that organ transplants are considered the gold standard, it is unlikely that new economic evaluations will be conducted comparing transplantation to a 'do nothing' strategy. The current review illustrated the importance of taking into account wait times for HTx in a BTT comparison. This was only addressed in a handful of studies and is a major limitation of the current literature, as the longer the wait time for a HTx, the more cost-effective the BTT strategy.

Economic evaluations of HTx could consider the use of discrete event simulation as conducted in van Hout et al. (1993)(118) and consider patients dying while waiting for a HTx, potential wastage of a donor heart if no match is found, and average wait time for a HTx. This can be used to inform policy planning; for instance, van Hout et al. (1993) concluded that 2 transplant centres were required in The Netherlands and that the number of transplants would stabilise at 80 hearts.(118) There have been no studies that considered the HTx waiting list in the current Australian context. Consequently, an

evaluation of the potential impact of changes with respect to the availability of ESHF treatment modalities and when to provide these treatments in Australia is needed.

4 CHAPTER 4: ASSESSMENT OF PATIENT DATA OF END-STAGE HEART FAILURE TREATMENTS

4.1 Introduction

This chapter summarises the available data from the literature including published RCT and registry data and Australian individual patient registry data for heart transplants (HTx) or left ventricular assist devices (LVADs) to inform the economic evaluations in Chapters 5 and 6. Information was collated on the costs, quality-of-life impacts and time-to-event such as death and transplant. A key component of this chapter is the review and analysis of individual-level patient data from St Vincent's Hospital Sydney (SVHS), the largest transplant centre in Australia.

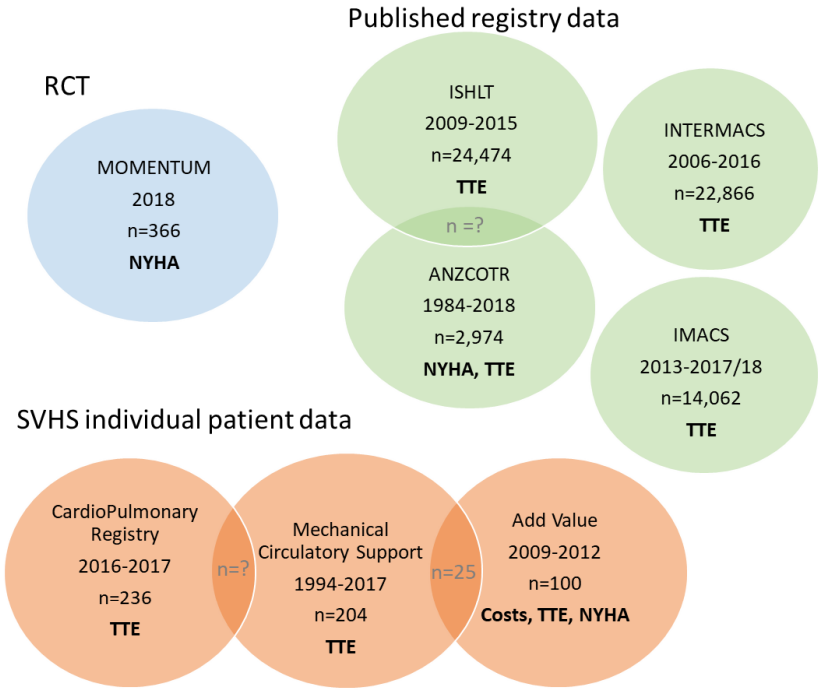
RCTs underpin the strongest level of evidence of the efficacy of interventions because the design is intended to eliminate bias.(156) The National Health and Medical Research Council (NHMRC) in Australia determined the highest level of evidence was RCTs, followed by evidence obtained from comparative studies with concurrent controls (cohort studies), e.g. case-control studies; then evidence obtained from comparative studies with historical control (e.g. two or more single-arm studies); and, finally, evidence obtained from case series.(156) The study design will influence the internal and external validity[17] of the data.(156, 157)

4.2 Methods

The following section described the methods of two types of data analysis 1) the extraction of published RCT and registry data; and 2) analysis of SVHS individual patient data, see Figure 4-1.

[17] Internal validity refers to the extent to which the results of a study are likely to approximate to the 'truth'. It is a prerequisite for external validity. External validity also known as applicability or generalisability refers to the degree to which the effects observed in a study are applicable outside of the study in routine clinical practice.

Figure 4-1: Summary of data source for data extraction and analysis



Abbreviations: NYHA, New York Heart Association; RCT, randomised controlled trial; SVHS, St Vincents Hospital Sydney; TTE, time-to-event.

4.2.1 Part A: Data extraction of published sources: RCTs and registry data

4.2.1.1 Review of published clinical evidence

A review of the literature conducted as part of this thesis identified a number of RCTs and observational registry datasets that can be used to evaluate the effectiveness of LVADs and HTx in patients. Details of the search strategy are presented in the Appendices (section 8.5.1). The search identified no RCTs comparing outcomes of patients receiving a LVAD as a bridge to HTx versus HTx only. If a patient is implanted with a LVAD while on the HTx waiting list, this is known as a bridge to transplant (BTT). If a patient receives a LVAD before being added to the HTx waiting list, this is known as bridge to candidacy (BTC). If there is no intention to transplant, this is known as destination therapy (DT).

There were four RCTs (REMATCH (121), HeartMate II DT (130), ENDURANCE DT (131) and MOMENTUM 3 (54)) of LVADs compared to OMM or an alternative LVAD (Table 4-1). Three RCTs (130, 121, 131) were in HTx ineligible populations and were not included. The MOMENTUM 3 trial enrolled HTx eligible patients (40%, 149/366) and was included for data extraction.[18](54)

[18] The MOMENTUM 3 trial compared two HeartMate LVADs, these LVADs are not used at St Vincent's Hospital Sydney; rather, HeartWare devices are used. Therefore, an indirect comparison between ENDURANCE and MOMENTUM 3 trial used HeartMate II as the common comparator was relied on to compare HeartWare and

Table 4-1: Description of randomised controlled trials in LVADs

Trial	REMATCH[130]	HeartMate II DT[121]	ENDURANCE[131]	MOMENTUM 3[54, 158, 159]
Trial ID	NCT00000607	NCT00121485	NCT01166347	NCT02224755
Year	2001	2009	2017	2018
Int	PF	HeartMate II CF	HeartWare CF	HeartMate 3 CF
Comp	OMM	HeartMate XVE PF	HeartMate II CF	HeartMate II CF
N (Total; Int: Comp)	129; 68 : 61	200; 134 : 66	445; 297 : 148	366; 190 : 176
Age, year, (Int: Comp)	66 : 68	62 : 63	64 : 66	61 : 59
Males (%) (Int: Comp)	78 : 82	81 : 92	76 : 82	79 : 81
NYHA	IV	IIIB or IV	IIIB or IV	IIIB or IV
Indication	DT	DT	DT	BTT (n=91), BTC (n=58), DT (n=217)
Trial type	Superiority	Superiority	Non-inferiority	Non-inferiority
Primary outcome (ITT)	Death	Survival at 2 years free from disabling stroke or reoperation to repair or replace the device		

Abbreviations: BTC, Bridge To Candidacy; BTT, Bridge To Transplant; CF, continuous flow; Comp, comparator; DT, Destination Therapy; Int, intervention; ITT, intention-to-treat; NYHA, New York Heart Association; OMM, Optimal Medical Management; PF, pulsatile-flow.

The included observational studies for the outcomes of LVADs and HTx are presented in Table 4-2 (study descriptions are provided in the Appendices, sections 8.5.2, 8.5.3, 8.5.4 and 8.5.5). Briefly, the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) enrolled patients with MCS from the USA since 2006. The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry includes hospitals outside the USA that have a mechanical circulatory support device program since 2013. The Australia and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) is a registry of Australian and New Zealand patients with heart and/or lung transplant data collected since February 1984. The International Society for Heart and Lung Transplantation (ISHLT) reports heart and lung transplants from around the world since 2009.

Table 4-2: Included studies in purposive literature review

Country	N	Period	Age, mean (years)	Gender (male)	VAD support	Ref.
Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)						
U.S	22,866	2006-2016	NR	NR	100%	(51, 56)
The International Society for Heart and Lung Transplantation Mechanically Assisted Circulatory Support (IMACS)						
35 countries	14,062	2013-2017/8	45% 60-79; 42% 40-59	78%	100%	(160, 161)
Australia and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR)						
AU, NZ	2,974†	1984-2018	48	67%	39%	(70, 162)
The International Society for Heart and Lung Transplantation (ISHLT)						
Wordwide	24,474	2009-2015	54 to 55	75%	43%	(80)·(163)

† All Hearts (heart kidney, domino, retransplants, heterotopic, DCD) from 1984 to 2018(70)

4.2.1.2 Data extraction of published registry data

Extracted data included time to death, time to transplant and New York Heart Association (NYHA) level (Table 4-3). Quality-of-life (QoL) measures were not useable for the economic evaluation due to the

HeartMate III. Given that the non-inferiority primary outcome was met in both MOMENTUM 3 and ENDURANCE, it was assumed that the results from MOMENTUM 3 were applicable to the use of HeartWare devices at SVHS.

reporting of separate domains only or a visual analogue scale score, which is not preference based (see Appendix 8.6.1 for a description of available data). For the time-to-event curves the methodology of digitising the curves and calculation of the transition probabilities assuming constant hazard are presented in Chapter 5.

Table 4-3: Extracted data for the economic evaluation

	Demographics	Survival	NYHA
VAD			
MOMENTUM	Age, gender	Competing outcomes of HTx or Death.	NYHA
INTERMACS	NR	KM of death.	-
IMACS	NR	KM of death.	-
HTx			
ANZCOTR†	Age, pre-transplant support.	C-E (actuarial) curves, by age group.	NYHA
ISHLT	Age, gender; pre-transplant support.	KM by pre-transplant MCS use.	-

†. Data on waiting list activity and days on waiting list was extracted.
Abbreviations: C-E, Cutler-Ederer; KM, Kaplan Meier; NR, not reported, NYHA, New York Heart Association, OS, overall survival.

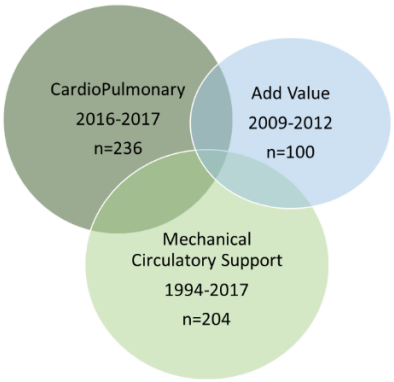
4.2.2 Part B: Data analysis of SVHS individual patient data

4.2.2.1 St Vincents Hospital Individual Patient Data

Three individual patient datasets from St Vincent's Hospital Sydney (SVHS) were analysed (Figure 4-2). The 'Advanced Heart Failure management and mechanical circulatory assist therapy study' ('Add Value study') is a retrospective, activity-based costing study established to collect patient level costs associated with LVAD therapy. The study was approved by the New South Wales Populations Services Human Research and Ethics committee (HREC LNR/13/SVH/169). Patients were consecutively added to the orthotopic HTx waiting list at SVHS between July 2009 and June 2012 and data were linked to Admitted Patient Data Collection (APDC) and Emergency Department Data Collection (EDDC).

The Mechanical Circulatory Support ('MCS') Registry is a prospective registry that collected data from consecutively implanted patients between 1994 to March 2017. The purpose was to report to the global registry, IMACS. The CardioPulmonary Registry ('CPR') data is a prospective registry of patients on the heart and lung transplant wait list from 1991 to June 2017. The registry reports to the Australia and New Zealand Organ Donation (ANZOD) Registry. There was an overlap of the VAD patients in the Add Value and MCS datasest. The patients from the Add Value dataset would have been captured in an earlier data-cut of the CPR registry. However, these datasets were not linked.

Figure 4-2: Datasets in the individual patient data analysis



4.2.2.1.1 Analysis plan of SVHS individual patient data

All statistical analyses were conducted using STATA® Version 15 (Statcorp, College Station, TX, USA).

4.2.2.1.1.1 Descriptive statistics

Tests of significance on baseline data between those who received an LVAD and those who did not were undertaken (164, 165). Continuous data were assessed for normality via plotting a histogram and Q-Q plots to observe major departures from a normal distribution(166). Normally distributed data were tested using the parametric test student t-tests and reported as mean ± standard deviation, while non-normally distributed data were tested using non-parametric tests using Wilcoxon rank sum tests and presented as median.(166) Categorical data were compared using chi-square tests for equal proportions or Fisher's exact tests where numbers were small, and were reported as percentages. A two-sided p-value of 0.05 was considered to be statistically significant.

4.2.2.1.1.2 Time-to-event analysis

The descriptive statistics, median survival time and 10% remaining at risk, log rank test for statistical significance (166) were reported. KM survival analyses were conducted to estimate the transition probabilities for patients to adjust for non-informative censoring. Non-informative censoring occurs when the observation is incomplete due to random loss of follow-up by the study end. There were three main outcomes of interest for LVAD recipients: alive on LVAD, heart transplanted or died on LVAD. The study end dates for the three datasets were: 1) Add Value of 30 June 2014; 2) MCS of 31 March 2017 and 3) CPR of 9 July 2018.

To address selection bias in observational studies there were adjustments for potential confounding; interaction variables were included in the Cox Proportional Hazard (CPH) model (see 8.7.1 for discussion of CPH) and the survival curves were stratified based on applicable groups (e.g. HTx). If the

CPH regression had ties for time to death these were adjusted for using the Breslow method.[19] The CPH assumes the groups are balanced, as in a RCT; this is not the case in a retrospective cohort, where group differences are due to prognostic factors (such as NYHA) rather than treatment. Competing risks is a type of informative censoring and occurs when one or more events alters the probability of occurence of the first.(167) Time to death after VAD has a competing risk for HTx. The KM curve treats competing events as censored and removal of censored observations results in upwards bias (overestimation).[20] The cumulative incidence of events is the complement of the KM function. The naïve KM curves and the cumulative incidence function (corrected for competing risks) were reported using the method described by Putter et al. (2006).(168) For competing risk analysis, the Fine and Gray's subhazard model was used in lieu of the CPH.(169)

4.2.2.1.1.3 Patient cost analysis

Costs are reported in 2016 Australian dollars unless specified otherwise and costs were inflated using the Health Inflator (74) (Chapter 5 and 6 inflated costs to $2019). The reference cost weight (AR-DRG Version 8) for admissions in 2015/2016 was $5,198.70 (170) and the average cost of an ED presentation was $404.52 (171)(inflated from $396 in 2009-2010). Cost data tend to have highly skewed distribution with long, heavy right tails with a mean higher than the median(172). The statistics reported include mean, standard deviation, median, 95% CI and standard error.

Censored cost data occurs when death is not observed in every patient so that lifetime medical cost is subject to censoring. Naïve methods for handling censoring include complete case analysis and full sample analysis.(172) There are two classes of statistical methods to address censored cost data: 1) time-restricted medical cost, and 2) joint distribution with survival time.(173, 174) Imposing a time-restriction, e.g. cost of one year post intervention, was not used as the survival (death or cross-over) at one year was statistically different between the groups. Instead, the Zhao and Tian (ZT) estimator using the KM estimator and the inverse probability weighting methods with cost history was conducted via hcost in STATA.(175) A regression analysis accounting for $0 months indicated most patients had same-day admissions (check-ups) so that there were few months without admissions.

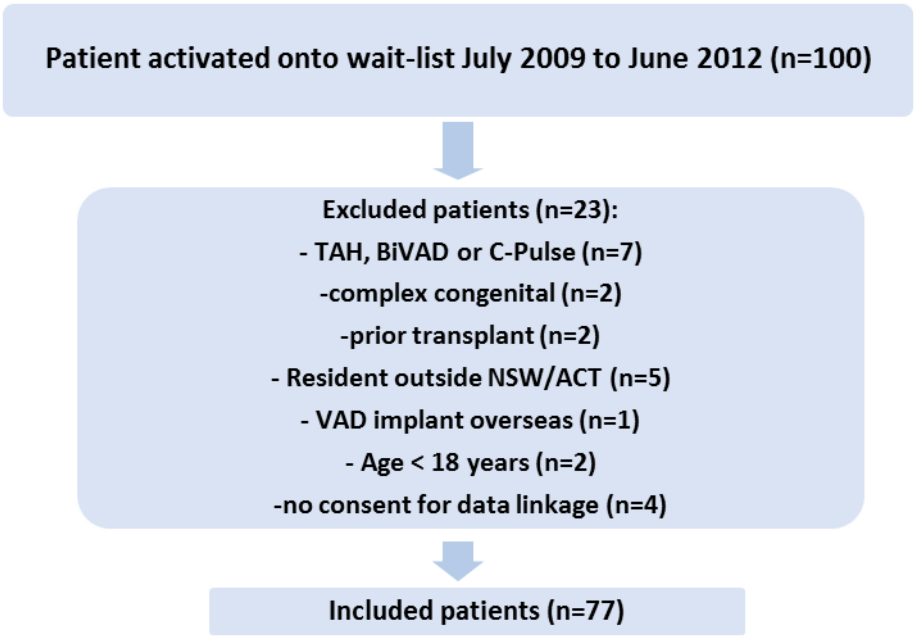
4.2.2.1.2 'Add Value' dataset description

Overall, 100 patients were on the HTx waiting list between July 2009 and June 2012 at SVHS.(165) There were 23 exclusions, resulting in 77 patients (Figure 4-3). The data were collected one year prior

[19] The proportional hazards model assumes the hazard function is continuous and there are no tied survival times. Tied events do occur due to how time is recorded. Therefore, the partial likelihood must be modified. The Breslow method uses the largest risk pool for each tied failure event as the order of events is unknown.
[20] https://www.stata-journal.com/sjpdf.html?articlenum=st0059

to LVAD implantation or, if no LVAD, then one month prior to activation on the wait list until 20 June 2012.(165, 176) APDC and EDDC were obtained at least a year prior to a patient receiving a VAD or being waitlisted. Admissions were reported by the diagnosis (ARDRG[21] code). Presentations to an ED were coded by urgency related and urgency disposition groups.[22]

Figure 4-3: Add Value study cohort and exclusion criteria



Abbreviations: BiVAD, bi-ventricular assist device; TAH, total artificial heart

4.2.2.1.3 Analyses for APDC/EDDC dataset

4.2.2.1.3.1 Demographic and prognostic variables

The descriptive statistics of demographic, prognostic and pre-operative support variables at baseline were reported. The variables were reported for the total sample, by LVAD receipt and the four subgroups BTT, VAD with no HTx, HTx only and OMM only. Three events (two deaths and one HTx) after the censored date were removed.

[21] Australian Refined Diagnosis Related Groups (ARDRGs) is an Australian admitted patient classification system which provides a clinically meaningful way of relating the number and type of patients treated in a hospital (hospital casemix) to the resources required by the hospital. Each ARDRG represents a class of patients with similar clinical conditions requiring similar hospital services.

[22] Classification of presentation to emergency services are known as urgency disposition group (UDG) and presentations to emergency departments are known as urgency related groups (URG). Both classifications group presentations on the basis of type of visit, episode end status and triage. The difference is that URGs include diagnosis by major diagnostic block.

4.2.2.1.3.2 Functional status NYHA and INTERMACS

NYHA and INTERMACS[23] status was measured at baseline of HTx wait list activation or pre-VAD. Due to small sample size, the INTERMACS score was not used to determine the change in functional status. The follow-up data was collected a year post VAD implant, where possible, or just prior to censorship at HTx or death.(165) The usefulness of this data is limited due to the varied timing. The change in NYHA status at baseline and at follow-up were assessed using cross-tabulations.

4.2.2.1.3.3 Time-to-event analyses

The time-to-event analyses are reported in Table 4-4. The analyses of LVAD recipients were divided into BTT and BTC indications with different start dates, waiting list addition versus LVAD implant, respectively. This was to ensure that waiting time for BTT patients were not underestimated as BTC patients were added to the waiting list upon date of LVAD implant. The LVAD to HTx analysis was adjusted for competing risk of death. The KM curves of study entry to death ignored *'Alive post-HTx'* and *'Alive post-VAD'* and so were not included. Similary, the KM curves of study entry to HTx ignored the *'Alive post-VAD'* and were not included.

Table 4-4: Survival analyses for Add Value dataset

Analysis	Failure (event)	Censored	Study-start	Study-end
Study entry to VAD	VAD	Alive at study-end, death	WL or VAD	VAD, HTx, death, study-end
VAD receipt to HTx	HTx, Death	Alive at study-end	VAD	HTx, death, study-end

Note: STATA excluded events that happen before or on the same date that the person entered the waitlist. Therefore, BTC were excluded. Therefore, 0.1 days was added to the date of the event to prevent exclusion [pg. 74 in Juul Svend STATA book](166).
Abbreviations: HTx, heart transplant, N/A, not applicable; WL, waiting list; VAD, ventricular assist device.

4.2.2.1.3.4 Cost of ESHF from APDC and EDDC

Admitted Patient Data Collection

All variables are presented in Table 8-19 of the Appendix. Of the 77 patients, there were 1,983 hospital admissions. AR-DRG information included episode start and end date, cost weight (a)[24] and major diagnostic code.(178) Clinical expert review was used to determine if admissions needed to be excluded. A summary of admissions by major diagnostic code was presented for the subgroups. The date of VAD or HTx was used to categorise admissions within each subgroup (Table 8-20). The method to estimate the cost per admission is presented in the Appendices (section 8.9.3); briefly, the cost

[23] The INTERMACS score subdivides NYHA Class III and IV into 7 levels with a score of 1 being the most severe.(177)
[24] Cost weights are available from a to f. Cost weight a includes the most items such as emergency department, intensive care unit and overheads etc.

weight for each observation of the ARDRG codes were multiplied by a reference cost weight (value = 1) of $5,189.70 (2016 AUD).

Emergency Department Data Collection

Excluding patients who had not provided consent for linking resulted in 705 (94%) observations. ED costs were calculated using the cost weights by urgency and disposition group (171)(see Table 8-23). The urgency and disposition group were estimated using triage category, visit type and mode of separation (admitted or not)(179) (Figure 8-6).

Combined APDC and EDDC

Overall, 77 patients had 2,688 observations including admissions (n=1,983) and presentations (n=705). To avoid double-counting the ED presentations, those that were admitted were excluded as these would be captured in APDC ED cost component. There were 25 deaths with death admission captured for some patients; see Figure 8-7 for cost of last month observed. The timing of observations for each patient were grouped and linked to a health state (Table 4-5). The health states were *'waiting list'*, *'alive with VAD'* and *'alive with HTx'*. The index admission length of stay (LOS) spanned several days for HTx admission (Group 6) and VAD admission (Group 2). In post-HTx (Group 7), the days since index hospitalisation end date were calculated and categorised into monthly intervals for one year, then 12 months inclusive. This procedure was repeated for observations subsequent to LVAD admission (Groups 3 and 4). The date of activation onto waitlist was the starting point for Groups 1, 5 and 8 for pre-VAD (no HTx), pre-HTx and no VAD or HTx (OMM) respectively.

Table 4-5: Groups of episodes of care

Group	Group	Health State	Use in model
1	pre-VAD	Wait list	Per cycle
2	intervention-VAD	Alive with VAD	Once off as enter health state
3	post-VAD and no HTx	Alive with VAD	Per cycle
4	post-VAD and pre-HTx	Alive with VAD	Per cycle
5	pre-HTx no VAD	Wait list	Per cycle
6	intervention HTx	Alive with HTx	Once off as enter health state
7	post-HTx	Alive with HTx	Per cycle
8	OMM	Wait list/ Not eligible	Per cycle

Abbreviations: HTx, heart transplant; OMM, optimal medical management; VAD, ventricular assist device

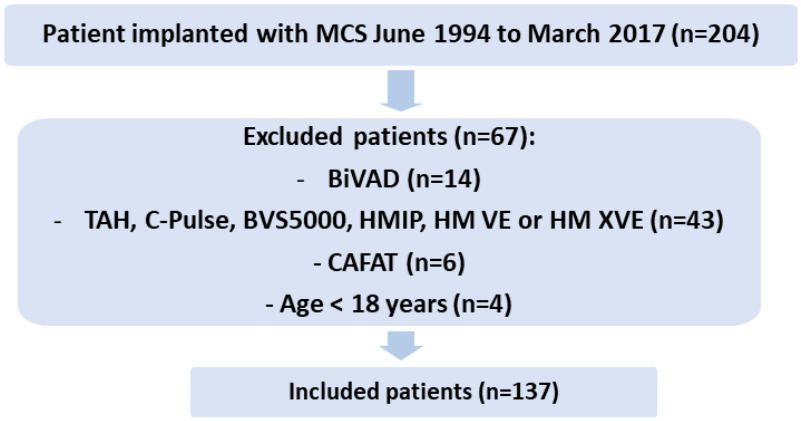
Costs in each health state

The average total cost per patient per health state was calculated (see section 4.2.2.1.1.3 for the methods). The costs were averaged across the patients in each month to explore the spread of costs.

4.2.2.2 'Mechanical Circulatory Support' dataset description

Overall, 204 patients were implanted with MCS between June 1994 and 31 March 2017 at SVHS. This analysis consisted of 137 patients with CF devices[25] with 67 exclusions (Figure 4-4). Demographic, prognostic and implant details are presented in Table 8-26. There are three mutually exclusive outcomes of interest; 1) Alive with LVAD in place; 2) Transplant and 3) Death before transplantation.

Figure 4-4: Mechanical Circulatory Support Registry and exclusion criteria



Abbreviations: Caisse de Protection Sociale de Nouvelle-Calédonie Medivac program transporting critically-ill heart patients from Noumea.

4.2.2.2.1 Analyses for Mechanical Circulatory Support data

4.2.2.2.1.1 Demographic and prognostic variables

The demographic variables were age and gender at baseline (Table 8-26). The prognostic/pre-operative variables were INTERMACs class and whether any of the patients had the following therapies: IABP, ECMO or ventilation. Details of the type of MCS included type of flow, device, configuration and indication, surgical details and interoperative outcomes.

4.2.2.2.1.2 Time-to-event analyses

The time-to-event analyses of LVAD implant to death were adjusted for competing risks of HTx (Table 4-6). The dataset did not continue follow-up after a patient was transplanted and so death was treated as a censored observation and was not appropriate for the economic model.

Table 4-6: Summary of time-to-event analyses

Analysis	Failure	Censored	Study-start	Study-end
VAD receipt to death	Death	Alive at study-end, HTx	Implant date	HTx, death or study-end

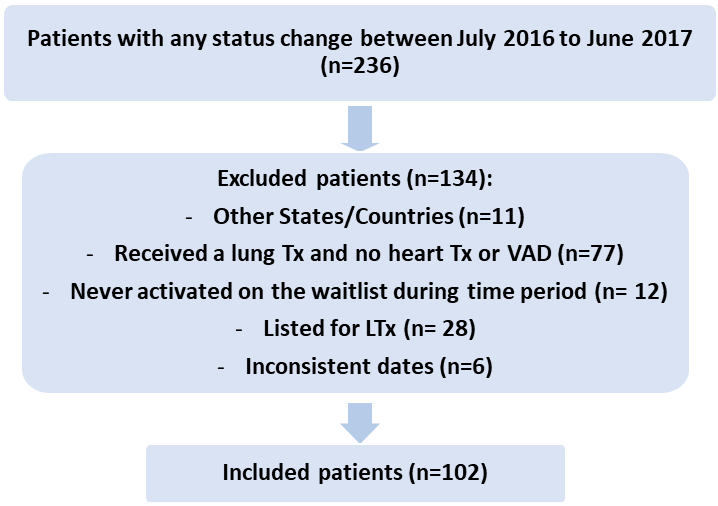
4.2.2.3 'CardioPulmonary Registry' dataset description

The CPR included patients referred to SVHS for assessment onto the heart and lung transplant waiting list from 1 July 2016 to 30 June 2017. The date of a status change or operation was recorded. Of the

[25] VentrAssist by Ventracor and HVAD™ and Miniaturized Ventricular Assist Device (MVAD®) by HeartWare.

236 patients, 134 were excluded (Figure 4-5). Age and gender were not recorded. In a 12 month period, patients could be activated on the waitlist multiple times due to retransplant, re-activation or new activation.[26] Dates of initial activation,[27] VAD or HTx were extracted and could be prior to 1 July 2016. The last 'On Hold' date was extracted for total time waiting. Patients were coded as alive on waitlist if 'On-Hold' or 'Active' by 9th of July 2018.

Figure 4-5: Excluded patients from CPR dataset analysis



4.2.2.3.1 Analysis for CardioPulmonary Registry data

4.2.2.3.1.1 Time-to-event analyses

The time-to-event analyses from date on waiting list or VAD receipt are presented in Table 4-7. Most VADs were received before waitlist activation or during a previous activation on the waitlist.

Table 4-7: Summary of time-to-event analyses

Analysis	Failure	Censored	Study-start	Study-end
Waitlist to HTx, competing risk	HTx	Alive, death	Waitlist	HTx,death or study-end
Waitlist to Not eligible	Removal from waitlist		Wait-list	
VAD to HTx	HTx or death		VAD	
VAD to not eligible	Removal from waitlist	Alive, HTx, Death	VAD	

Note: Removal from waitlist due to reasons 'Too sick', 'Too well', 'Patient reason' and 'Patient declined'.

[26] Re-transplant refers to a subsequent heart transplantion after successful initial transplant. Re-activation on the waiting list refers to candidates who were previously placed 'On hold' and activated again. New activation can be the first activation on the waiting list or subsequent activation for another organ, e.g. heart and kidney.
[27] First during the study period or the date of activation preceding the study start date.

4.3 Results

4.3.1 Pre-modelling studies for the economic evaluation

The pre-modelling studies from the published and individual datasets are summarised in Table 4-8. The Add Value dataset informed the cost. The term time-to-event analysis is used for describe time to both death and non-death outcomes (e.g. HTx or VAD). The economic model (Chapter 5) includes the following health states: '*waiting list*', '*removed*', '*death*', '*Alive post-VAD*', '*Alive post-HTx*' and *'ineligible'*.

Table 4-8: Pre-modelling substudies for the economic evaluation

Study	Data/Variables	Purpose in the economic evaluation
MOMENTUM 3		
NYHA	NYHA	Distribution of NYHA Class at baseline and post-intervention to estimate QALY.
TTE: VAD to HTx	Competing outcomes of HTx or Death.	Transition probabilities *'VAD'* to *'HTx'*.
ANZCOTR		
NYHA	Pre-transplant status.	Distribution of NYHA Class pre-transplant.
TTE: HTx to death	Cutler-Ederer survival curves	Transition probabilities *'HTx'* to *'Death'*.
Waiting list activity	Annual snapshot of waitlist removals from ineligibility, transplant and death.	Transition probabilities *'waiting list'* to *'HTx'*. Transition probabilities *'waiting list'* to *'removed'*. Transition probabilities *'waiting list'* to *'Death'*.
ISHLT		
TTE: HTx to death	KM survival curves	Transition probabilities *'HTx'* to *'Death'*.
INTERMACS		
TTE: VAD to HTx	Competing outcomes of HTx or Death.	Transition probabilities *'VAD'* to *'HTx'*.
TTE: VAD to death	KM survival curves of BTT Listed	Transition probabilities *'VAD'* to *'Death'*.
IMACS		
TTE: VAD to HTx	Competing outcomes of HTx or Death.	Transition probabilities *'VAD'* to *'HTx'*.
TTE: VAD to death	KM survival curves of BTT Listed	Transition probabilities *'VAD'* to *'Death'*.
Add Value		
Demographics	Age, Gender, prognostic data	Description of patient demographics.
NYHA	NYHA	Proportion in NYHA Class at baseline and post-intervention to estimate QALY.
APDC Costs	Cost of admissions by AR-DRG.	Hospital cost, pre- and post- intervention
EDDC Costs	Cost of presentations by UDG.	
TTE: wait list to VAD	Study Entry. Event is VAD.	Transition probabilities *'waiting list'* to *'VAD'*.
TTE: VAD to HTx	Date of VAD. Event is HTx or Death.	Transition probabilities *'VAD'* to *'HTx'*.
Mechanical Circulatory Support		
Demographics	Age; Gender	Description of patient demographics.
TTE: VAD to death	Date of VAD. Event is Death or HTx	Transition probabilities *'VAD'* to *'Death'*.
CardioPulmonary Registry		
TTE: wait list to HTx	Date of activation. Event is HTx	Transition probabilities *'waiting list'* to *'HTx'*.
TTE: wait list to Removed	Date of activation. Event is Removal – 'Hospital reason', 'too well', 'too sick', 'Patient reason' and 'Patient declined'	Transition probabilities *'waiting list'* to *'Removed'*.
TTE: VAD to HTx	Date of VAD. Event is HTx.	Transition probabilities *'VAD'* to *'HTx'*.
TTE: VAD to Removed	Date of VAD. Event is removal.	Transition probabilities *'VAD'* to *'Removed'*.

Abbreviations: APDC, Admitted Patient Data Collection; AR-DRG, Australian Refined-Diagnosis Related Group; EDDC, Emergency Department Data Collection; HTx, Heart Transplant; NYHA, New York Heart Association; TTE, time-to-event; QALY, quality-adjusted life year; UDG, Urgency and Disposition Group; VAD, Ventricular Assist Device.

4.3.2 Part A: Data extraction of published data sources

4.3.2.1 MOMENTUM 3

Based on the competing risks analysis, just over 20% of the patients were transplanted at 2 years. NYHA status were measured from baseline to 24 months. There were no significant differences between the groups; with most in NYHA class IV at baseline(180), the baseline results represent *'waiting list'* NYHA status in the model (Table 4-9).

Table 4-9: NYHA Class over time in MOMENTUM 3 trial

	Centrifugal flow pump					Axial-Flow pump				
	N	NYHA I/II	NYHA III/IV	III	IV	N	NYHA I/II	NYHA III/IV	III	IV
Baseline	189	0%	100%	5%	95%	172	0%	100%	3%	97%
3 month	170	68%	32%	-	-	148	75%	25%	-	-
6 month	161	78%	22%	-	-	136	80%	20%	-	-
12 month	139	81%	19%	-	-	115	89%	11%	-	-
18 month	119	85%	15%	-	-	92	77%	23%	-	-
24 month	113	79%	21%	-	-	83	81%	19%	-	-

Note: Each treatment arm over time had p<0.0001. No statistically significant difference between treatment arms over time (p=0.30).
Source: adapted from Mehra et al. (2018)(54) and Cowger et al. (2018)(180).

4.3.2.2 INTERMACS

In the first year post-VAD for those on the waiting list, 53% remain alive on LVAD, 34% are transplanted, 12% died and 1% recovered[47]. The KM curves indicate that survival for DT patients was lower than for BTT patients in 2013-2016 (p<0.001).[47]

4.3.2.3 IMACS

In the IMACS report, of the devices implanted 93% were LVADs and for all devices, 40% were implanted as DT, followed by 30% BTC and 29% BTT (153) (Table 8-6). The competing outcomes analysis for CF-LVAD devices (censoring at transplant or recovery) of 3,642 BTT patients demonstrated that at the end of 12 months, 58% were alive with device, 28% transplanted, 13% died and <1% were recovered.(153) The 2013-2014 KM survival curve from CF-VAD by indication (BTT vs BTC vs DT) to death (censored at transplant or recovery) indicated a survival rate at 12 month for BTT 85%, BTC 82% and DT 77% with median survival not reached.(153) This highlights the lower survival between BTT and BTC.

4.3.2.4 ANZCOTR

In 2018, the mean age of 141 paediatric and adult HTx recipients (all types, not just OHT) was 48 years (min 1 year and max 70 years)(181)(see Appendix 8.5.4). The Cutler-Ederer survival curves from 1964-2018 by HTx type and recipient age were obtained.(149) The majority of patients had a NYHA status IV or III pre-transplant, with 61% in 2015 increasing to 93% in 2018 (Table 8-8). In recent years, around 40% of HTx recipients had been supported by a VAD before receiving HTx. In a given year, patients

start as 'active' and some 'on hold' from the previous year may be re-activated in the current year (Table 4-10). Caveats to the wait list dynamics reporting include that those removed from the waiting list are subsequently relisted and are not unique patients. For urgent transplant, patients may be placed on the waiting list and removed quickly, and annual census numbers do not represent this type of activity.(182)

Table 4-10: Waiting list activity, n

	2015	2016	2017	2018
'Active' at start of year (1st January)	68	59	53	72
New Additions during year	117	140	109	173
'On hold' to 'Active' from previous year	17	11	10	9
Removals from Waiting List (Permanent)				
W1 - Transplant Performed	106	129	117	141
W2 - Patients condition Improved	1	4	3	2
W3 - Too ill, e.g. new development of contraindications	8	13	9	11
W4 - Patient declined	2	0	2	4
W5 - Transferred to an interstate list	0	0	0	1
W6 - Died waiting	5	6	8	9
W7 - Removed - unspecified	2	0	2	2
Total at Year end - (Active)	59	55	55	80
Total at month end inactive (On Hold)	NR	NR	9	4

Abbreviations: NR, not reported
Source:(149, 181)·(70)

4.3.2.5 ISHLT

In 2002-2008, the KM survival curve after adult transplant indicated a median survival of 11.9 years.(80) In recent years there is no difference in survival between patients bridged with CF VADs and not bridged (no inotropes/no LVADs).(80) However, those who received ECMO prior to transplant were more likely to die post-transplant.(80)

4.3.2.6 Published data extraction for the economic evaluation

Data sources that provided an estimate for the same transition probabilities were collated and used as the base case or sensitivity analysis and were determined in Chapter 5 (Table 4-11). Chapter 5 includes a discussion of applicability of these estimates to the population of interest.

Table 4-11: Data extraction for the economic evaluation

Substudy	Results	Use in the economic evaluation
HTx		
ANZCOTR		
NYHA	Pre-transplant status for all ages. Average from 2012 to 2016 was 40% in NYHA I and II, 51% in NYHA III and 9% in NYHA IV.	The 5-year average of NYHA class on *'Wait-list'*. Utility values were attached to NYHA class. It includes paediatrics and may not be representative.
Waiting List activity per calendar year	Annual Probability from 2015-2016: Waiting list to waiting list = 32% (67/207); Waiting list to removed = 8% (16/207); Waiting list to transplanted = 57% (118/207); Waiting list to death = 3% (6/207). VAD transitions not reported.	Converted the proportions per group per year into rates per year and then annual transition probabilities. Constant probabilities were assumed. See caveats in the reporting of waitlist dynamics.
Survival with HTx	Cutler-Ederer curves by age group for all HTx types. Recipients aged 50-59 years had median % alive of 14 years.	Transition probability of 'HTx' to 'Death'. Does not take into account censoring. See Chapter 5.
ISHLT		
Survival with HTx	KM with median survival (2002-2008) 11.9 years for adult HTx. Median survival for 2009-2014 not reached. KM curve from 2005-2015 by pre-transplant status.	Transition probability of *'HTx'* to *'Death'*. Survival on HTx is the same between bridged and non-bridged individuals.
VAD		
MOMENTUM 3 (CF vs. CF)		
TTE: VAD to HTx	Around 20% of the patients were transplanted at 2 years	Transition probability from '*Alive post-VAD'* to *'HTx'* using the competing outcomes analysis (death) up to 24 months. See Chapter 5.
NYHA	At baseline 0% in NYHA class I or II for both groups and at 12 months, 81% and 89% at 12 months for the study device and control device, respectively.	The proportion of NYHA at baseline and 1 year. Distribution linked to utility value in *'waiting list'* and '*alive post-VAD'* health state. Assumed split between NYHA I and II/ NYHA III and IV is 50%.
INTERMACS		
Survival	Competing outcomes (HTx, death and recovery) for BTT CF-LVAD 2015-2016 at 12 months: 53% alive, 34% transplanted, 12% died and 1% recovered.	Transition probabilities from *'alive post-VAD'* to *'HTx'* up to 24 months. See Chapter 5.
Time to event	KM for CF-VAD (BTT vs. DT) to death 2013-2016 with survival rate at 24 month at 77% for BTT and median survival not reached. KM for BTT in 2008-2012, survival rate at 24 months 76% with follow-up to 72 months with median survival reached.	Transition probability from 'Alive post-VAD' to 'Death'. For BTT, the 2008-2012 curve was used with data on 1,922 (484 deaths) patients until 72 months. See Chapter 5.
IMACS		
Survival	Competing outcomes (HTx, death and recovery) for BTT CF-LVAD implants 2013-2014 at 12 months: 58% alive, 28% transplanted, 13% dead and <1% recovery.	Transition probability from 'Alive post-VAD' to 'HTx' using competing outcomes analysis up to 48 months. See Chapter 5.
Time to event	KM for CF-VAD (BTT vs. BTC vs. DT) to death from 2013-2014 with survival at 12 months: 85% for BTT, 82% for BTC, and 77% for DT. Median survival not reached.	Transition probability from '*Alive post-VAD'* to '*Death*' health states. See above for method.

Abbreviations: ANZCOTR, Australia and New Zealand Organ Transplant Registry; BTC, Bridge To Candidacy; BTT, Bridge To Transplant; CF, continuous-flow; DT, Destination Therapy; HTx, Heart Transplant; KM, Kaplan-Meier; LVAD, left ventricular assist device; NYHA, New York Heart Association; OMM, Optimal Medical Management; PF, pulsatile-flow; SD, Standard deviation; VAD, Ventricular Assist Device;

4.3.3 Part B: Data analysis of SVHS individual patient data

4.3.3.1 Add Value cohort

The 77 patients waitlisted from July 2009 to June 2012 were classified into two groups: LVAD (n=25) and no LVAD (n=52) (Figure 8-2). By the end of the study period, there were 25 deaths: LVAD (n=11) and no LVAD (n=14). The patients received a LVAD and later a HTx (n=20), received a LVAD only (n=5), received a HTx only (n=42) or received neither LVAD or HTx (n=10).

4.3.3.2 Demographics and baseline clinical characteristics

The baseline demographics of all patients, with or without LVAD, are presented in Table 4-12. Compared to non-LVAD patients, LVAD patients had worse NYHA Class IV at baseline (p<0.001) and albumin (p<0.01) and were more likely to receive IABP (p<0.001) and IV inotropes (p<0.001). A summary by subgroup is presented in Table 8-10. Tests of significance were conducted for the subgroups and results are consistent with the LVAD vs no LVAD comparison, although albumin levels were higher in the no LVAD group (p<0.05). The subgroups have small sample size, so caution should be used when drawing comparisons.

Table 4-12: Demographics and clinical indicators at baseline in Add Value cohort

Characteristics	Sub-category	Total (n=77)	LVAD (n=25)	No LVAD (n=52)	p-value†
Sex	**Male n (%)**	53 (69)	18 (72)	35 (67)	ns
	Female n (%)	24 (3)	7 (28)	17 (33)	
Age (year)	**Mean (SD)**	49.35 (11.33)	47.37 (13.70)	50.30 (10.02)	ns
	Median	50.17	48.67	51.75	
	Min-Max	20.74 – 71.83	20.74 - 68.61	27.52 - 71.83	
NYHA class at baseline	**I n (%)**	0 (0)	0 (0)	0 (0)	p<0.001
	II n (%)	11 (24)	0 (0)	11 (24)	
	III n (%)	26 (57)	0 (0)	26 (57)	
	IV n (%)	34 (48)	25 (100)	9 (20)	
	Missing	6	0	6	
IMACs at baseline	**1 n (%)**	8 (19)	8 (32)	0 (0)	p<0.001
	2 n (%)	16 (38)	16 (64)	0 (0)	
	3 n (%)	2 (5)	1 (4)	1 (6)	
	4 n (%)	2 (5)	0 (0)	2 (12)	
	5 n (%)	0 (0)	0 (0)	0 (0)	
	6 n (%)	4 (10)	0 (0)	4 (24)	
	7 n (%)	8 (19)	0 (0)	8 (47)	
	NA n (%)	2 (5)	0 (0)	2 (12)	
	Missing	35	0	35	
LVEF (%)	**Mean (SD)**	25.71 (13.03)	21.04 (7.66)	27.87 (14.43)	ns
	Median	22.00	20.00	25.00	
	Min – Max	10.00-70.00	10.00-35.00	10.00-70.00	
	Missing	1	1	0	
Albumin (g/L)	**Mean (SD)**	41.00 (7.21)	37.38 (6.08)	42.67 (7.12)	p<0.01
	Median	42.00	37.00	44.00	
	Min -Max	23.00-55.00	25.00-47.00	23.00-55.00	
	Missing	1	1	0	
Ischaemic Heart Disease	**No n (%)**	63 (83)	18 (72)	45 (88)	ns
	Yes n (%)	13 (17)	7 (28)	6 (12)	
	Missing	1	0	1	
Biventricular pacing at baseline	**No n (%)**	47 (64)	18 (72)	29 (59)	ns
	Yes n (%)	27 (36)	7 (28)	20 (41)	
	Missing	3	0	3	
ICD at baseline	**No n (%)**	13 (17)	7 (28)	6 (12)	ns
	Yes n (%)	62 (83)	18 (72)	44 (88)	
	Missing	2	0	2	
IABP at baseline	**No n (%)**	61 (81)	12 (48)	49 (98)	p<0.001
	Yes n (%)	14 (19)	13 (52)	1 (2)	
	Missing	2	0	2	
IV inotropic medicine at baseline	**No n (%)**	31 (55)	0 (0)	31 (79)	p<0.001
	Yes n (%)	25 (45)	17 (100)	8 (21)	
	Missing	21	8	13	

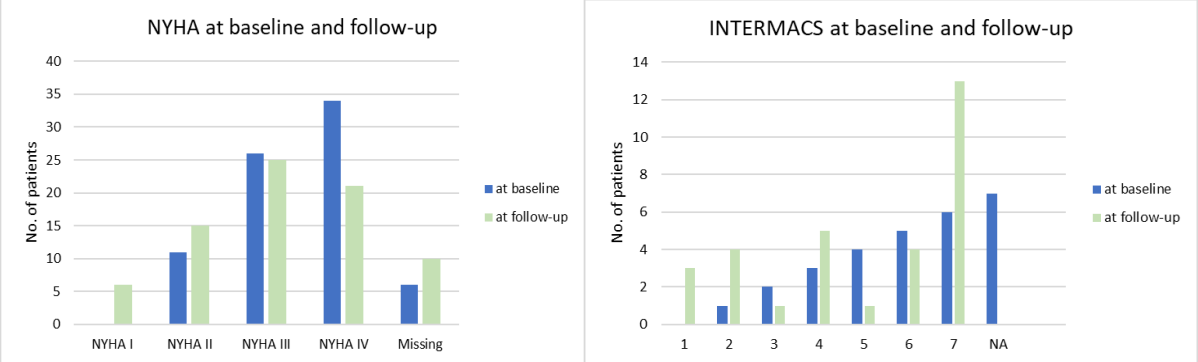
Note: percentages may not add up to 100% due to rounding errors. †Comparison between LVAD and non-LVAD patients.
Abbreviations: IABP, intra-aortic balloon pump; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction (%); min, minimum; max, maximum; n, number of observations; N, Number of sample; SD, standard deviation.

4.3.3.3 Change in functional NYHA status

4.3.3.3.1 Change between baseline and follow-up

There were 66 patients with observations at baseline and follow-up with missing data (n=5) (Table 8-11). At baseline there were no NYHA Class I patients; however, at follow-up there were 6. Cross-tabulations of NYHA status in the subgroups are presented in Appendix 8.8.3. NYHA and INTERMACS status measured at baseline and follow-up is presented in Figure 4-6.

Figure 4-6: NYHA and INTERMACS at baseline and follow-up



4.3.3.3.2 VAD or HTx at follow-up

The follow-up NYHA for the LVAD and HTx subgroups is presented in Table 4-13. Only 6 patients received a LVAD without a HTx; therefore, no comparisons can be made between the groups.

Table 4-13: NYHA at follow-up, all interventions

	All intervention	All VAD no transplant	All HTx regardless of LVAD
NYHA I (%)	6 (10)	0 (0)	6 (12)
NYHA II (%)	13 (22)	1 (17)	12 (23)
NYHA III (%)	23 (40)	1 (17)	22 (42)
NYHA IV(%)	16 (28)	4 (67)	12 (23)
Total observations (%)	58 (100)	6 (100)	52 (100)
Missing	9	0	9

Note: tab nyha_2 if lvad==1 | htx_excl==1; tab nyha_2 if lvad==1 & htx_excl==2; tab nyha_2 if htx_excl==1

4.3.3.4 Time-to-event analysis

4.3.3.4.1 Time to event – study entry to LVAD

Of the 25 LVAD recipients, 18 patients were implanted before the date of activation on the waiting list; hence, this analysis underestimates the waiting time for an LVAD (Table 4-14). The median time to LVAD was not reached. No log-rank test was conducted as there were no subgroups of interest.

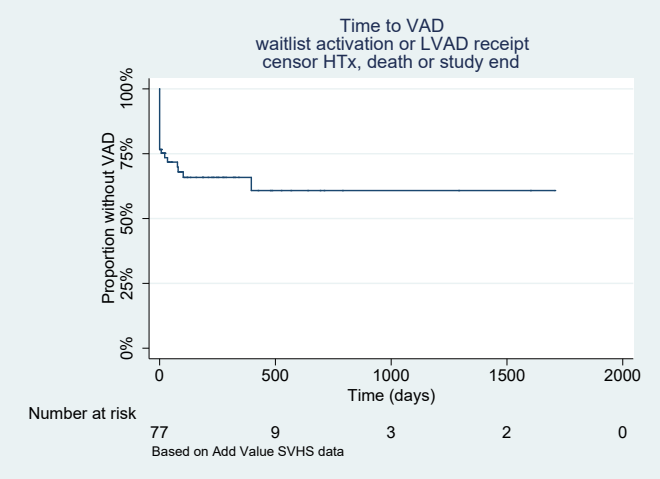
Table 4-14: Summary statistics for days on wait list to LVAD

waitdayVADfromWL	Total
Subjects, n	77
Failures, n	25
Survival time: 25%; 50%; 75%	22.01; NE; NE
10% remaining at risk; SE (95% CI)	0.0097; - (0.0097, 0.0097)†

Note: † Recorded as 0 and recoded as 0.01 days so the observations were not excluded.
Abbreviations: NE=not evaluable

The KM plot of time to LVAD from waitlist activation, which was 0 for BTC patients, is presented in Figure 4-7. Neither age at activation nor gender were statistically significant variables associated with time to LVAD once listed on the waiting list (Table 8-16).

Figure 4-7: Kaplan-Meier plots for time-to-LVAD receipt from wait list activation, all patients



4.3.3.4.1.1 Time to event – VAD to WL (BTC)

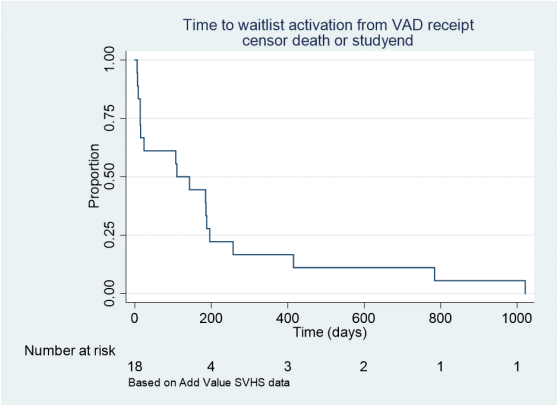
For the 18 patients who received a VAD and were then activated on the waitlist, the median time from VAD receipt to eligibility onto the waitlist was 110 days (Table 4-15).

Table 4-15: Summary statistics for VAD to wait list for BTC patients

Days from VAD to WL (BTC)	Total
Subjects, n	77
Failures, n	18
Survival time: 25%; 50%; 75%	14; 110; 196
10% remaining at risk; SE (95% CI)	7; NE (6, 14)

The KM plots for time from VAD to waitlist activation in all 18 patients are presented in Figure 4-8. The KM plots by gender and HTx receipt are presented in Figure 8-4. Based on the log-rank test, neither variable was statistically significant. Based on the CPH model, age at activation, gender and HTx receipt were all statistically insignificant variables associated with time from VAD to waitlist (Table *8-17*).

Figure 4-8: KM plots for time from VAD to waitlist activation in BTC patients



4.3.3.4.1.2 Time to event –WL to VAD (BTT)

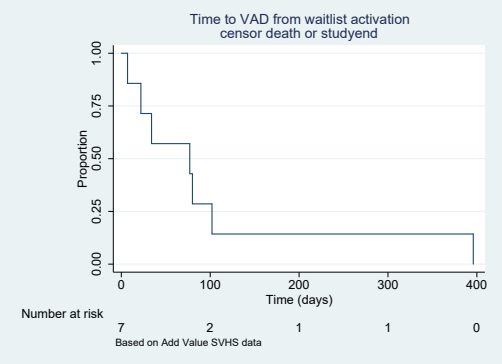
The summary statistics for time from waitlist to VAD for the 7 BTT patients are presented in Table 4-16. The median time to VAD was 77 days (2.6 months).

Table 4-16: Summary statistics – Time from waitlist to VAD -BTT patients

Days from WL to VAD (BTT)	Total
Subjects, n	77
Failures, n	7
Survival time: 25%; 50%; 75%	22; 77; 102
10% remaining at risk; SE (95% CI)	7; NE (7, 34)

The KM plot for time from waitlist to VAD is presented in Figure 4-9. There was no statistically significant difference in wait time for gender or HTx (see Figure 8-5 for the KM plots). Based on the CPH model, age at activation, gender and HTx receipt were statistically insignificant variables associated with time from waitlist to VAD (Table 8-18).

Figure 4-9: KM plots for time from waitlist activation to VAD for BTT



4.3.3.4.2 Time to event – LVAD to death

Of the 25 LVAD recipients, 76% (19/25) were transplanted with the last transplant at 1,329 days (45 months) (Table 4-17). Median survival time was reached at 482 days. The competing event of interest was death equating to 16% (4/25) of the LVAD recipients so that 2 LVAD recipients remained alive at

study end date. Whether a patient received their LVAD as a BTC or BTT had no impact on their time to HTx or time to death, although these are small sample sizes.

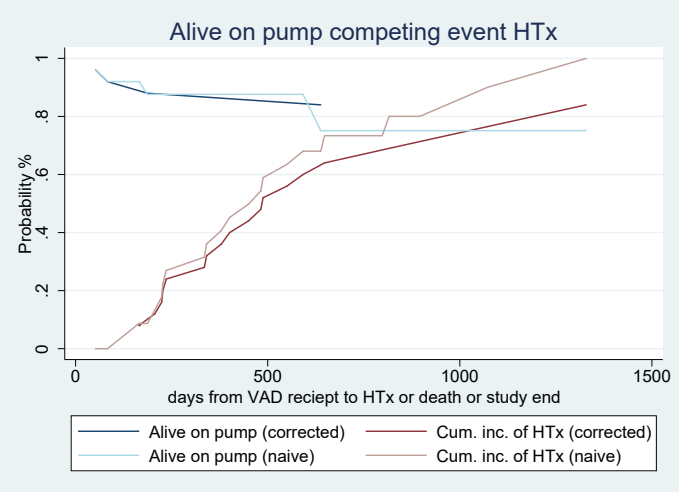
Table 4-17: Summary statistics for variable days until HTx from VAD receipt

Vadhtxday	Total VAD	HTx	Death	Censor
Subjects, n	25	19	4	2
Failures, n	19	19	4	2
Survival time: 25%; 50%; 75%	236, 482, 816	227, 401, 592		
10% at risk; SE (95% CI)	206, 56.5 (165,236)	165, - (165, 227)	-	-
Log rank test (BTC vs. BTT)	BTC: 18; BTT: 7	BTC: 15; BTT: 4; p=0.64	BTC: 3; BTT:1; p=0.91	-
One-year survival % (95% CI)	63.91 (40.59, 80.07)	57.89 (33.21, 76.26)		

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; HTx, heart transplant; SE, standard error; VAD, ventricular assist device.

The cumulative incidence for competing risks is plotted in Figure 4-10. In the competing event regression, the event of interest is death and the competing event was HTx. Neither age at activation nor gender were statistically significant.

Figure 4-10: Competing risks cumulative incidence of time to HTx, competing event death



4.3.3.5 Admitted Patient Data Collection (APDC)

The 77 patients had 1,983 admissions with range of 2 to 82 observations per patient. All variables are presented in section 8.9.1 of the Appendix. The APDC included 19 deaths captured in the admissions out of the 25 deaths.[28] The most common Major Diagnostic Category[29] (MDC) for each subgroup was 'Circulatory System' (39%), followed by 'Factors Influencing Health Status'[30] (24%) (Table 4-18). Two MDCs ('Burns' and 'Newborns') had no admissions. Two admissions within the MDC 'Pregnancy' were due to peripartum cardiomyopathy. Therefore, no admissions were excluded from the analysis.

[28] Of the 25 deaths, 19 were captured in APDC, 3 occurred in ED and 3 occurred outside of NSW.
[29] Major diagnostic categories (MDCs) are 23 mutually exclusive categories for all principal diagnoses (AR-DRGs). The diagnoses correspond to a single body system or aetiology, reflecting the speciality providing care. This preliminary partitioning into categories occurs before a diagnosis related group is assigned.
[30] Major Diagnostic Code includes the AR-DRG Z64B 'Other Factors Influencing Health Status, Sameday'.

Table 4-18: Number of admissions in each Major Diagnostic Category by treatment subgroups

Major Diagnostic Category	pre-VAD	int VAD	post-VAD, no HTx	post-VAD, pre-HTx	pre-HTx	int HTx	post-HTx	not eligible	Total	%
Pre-MDC	3	25	0	0	2	61	3	3	97	5%
MDC 01 Diseases and disorders of the nervous system	5	0	2	8	5	0	29	1	50	3%
MDC 02 Diseases and disorders of the eye	2	0	1	1	0	0	11	3	18	1%
MDC 03 Diseases and disorders of the ear, nose, mouth and throat	2	0	0	0	4	0	8	2	16	1%
MDC 04 Diseases and disorders of the respiratory system	10	0	5	3	48	0	39	9	114	6%
MDC 05 Diseases and disorders of the circulatory system	128	1	13	35	256	0	259	82	774	39%
MDC 06 Diseases and disorders of the digestive system	11	0	2	4	19	0	53	5	94	5%
MDC 07 Diseases and disorders of the hepatobiliary system and pancreas	0	0	0	0	4	0	4	4	12	1%
MDC 08 Diseases and disorders of the musculoskeletal system and connective tissue	2	0	0	0	2	0	8	2	14	1%
MDC 09 Diseases and disorders of the skin, subcutaneous tissue and breast	2	0	6	0	3	0	12	3	26	1%
MDC 10 Endocrine, nutritional and metabolic diseases and disorders	0	0	1	1	7	0	6	3	18	1%
MDC 11 Diseases and disorders of the kidney and urinary tract	1	0	2	0	14	0	144	5	166	8%
MDC 12 Diseases and disorders of the male reproductive system	0	0	0	0	1	0	0	1	2	0%
MDC 13 Diseases and disorders of the female reproductive system	0	0	1	0	1	0	1	1	4	0%
MDC 14 Pregnancy, childbirth and the puerperium	2	0	0	0	0	0	0	0	2	0%
MDC 15 Newborns and other neonates	0	0	0	0	0	0	0	0	0	0%
MDC 16 Diseases and disorders of the blood, blood forming organs, immunological disorders	2	0	1	3	6	0	1	4	17	1%
MDC 17 Neoplastic disorders (haematological and solid neoplasms)	6	0	0	0	0	0	7	0	13	1%
MDC 18 Infectious and parasitic diseases	0	0	0	0	0	0	0	0	0	0%
MDC 18 Infectious and parasitic diseases	4	0	7	7	2	0	22	4	46	2%
MDC 19 Mental diseases and disorders	0	0	2	0	1	0	0	3	6	0%
MDC 20 Alcohol/drug use and alcohol/drug induced organic mental disorders	0	0	0	1	0	0	0	0	1	0%
MDC 21 Injuries, poisoning and toxic effects of drugs	0	0	0	0	0	0	0	1	1	0%
MDC 21 Injuries, poisoning and toxic effects of drugs	1	0	0	3	6	0	6	2	18	1%
MDC 22 Burns	0	0	0	0	0	0	0	0	0	0%
MDC 23 Factors influencing health status and other contacts with health services	3	0	7	42	11	0	406	3	472	24%
Unrelated OR DRGs	0	0	1	0	1	0	0	0	2	0%
Error DRGs	0	0	0	0	0	0	0	0	0	0%
Sum of different types of AR-DRG in each group	68	2	31	43	102	1	128	64	493	
No. of APDC episodes of care	184	26	51	108	393	61	1019	141	1,983	100
No. of patients†	24	25	4	18	42	61	56	10	77	

Abbreviations: APDC, Admitted Patient Data Collection; DRG, Diagnosis Related Group; HTx, Heart Transplant; int, intervention; MDC, major diagnostic category; OR, operating room; VAD, ventricular assist device.
Note: The interventions VAD and HTx interventions are coded as pre-MDC category for resource intensive admission and hence not included in MDC 5.

4.3.3.5.1 Cost of admitted patient episodes of care

The average costs for all admissions, VAD or HTx are presented in Table 4-19. VAD admissions were on average $260,654 (SD $39,552), and twice as expensive as HTx admissions. As expected, the mean cost of both interventions is higher than the median, indicating the distribution is left-skewed.

Table 4-19: Total costs of all admitted patient episodes of care

	Obs.	Mean	SD	Median	Min	Max
Total	1983	$15,465	$40,551	$3,160	$416	$377,020
VAD admission	25	$260,654	$39,552	$245,119	$229,185	$377,020
HTx admission	61	$126,333	$54,928	$103,080	$96,379	$355,440

Note: cost weight for VAD is 50.14 and HTx is 24.30.

4.3.3.6 Emergency Department Data Collection (EDDC)

There were 705 included observations and a summary of the EDDC variables is presented in Table 8-22. Three out of the 25 deaths occurred in ED: Died in ED (n=2) and dead on arrival (n=1). The average cost of an ED visit is presented in Table 8-25. Patients who presented to the ED and were subsequently admitted were more costly than those who only presented to the ED. ED presentations that were subsequently admitted (n=395) would be captured in the APDC dataset.

4.3.3.7 Combined APDC and EDDC

Of the 2,688 observations some occurred on the same date, leading to 2,163 unique observations. There were 245 ED presentations that did not result in an admission (705 for all ED presentations) (Table 8-22*Table 8-22*). If mode of separation was 4, 5, 6, 7, 8 or 9, these were included in the analysis. Therefore, the included sample of 2,228 consisted of 1,983 admissions and 245 ED presentations. Of the 77 patients and the 2,228 observations, the least costly and most costly patient over the follow-up period available were $19,054 and $1,098,542 respectively.

4.3.3.7.1 Grouping observations – admissions and ED presentations

The number of observations (N=2,228) in each subgroup are presented in Table 8-25. Each subgroup was linked to a health state. Most observations occurred in the post-HTx period, which corresponded with the longest follow-up. The average length of stay for VAD insertion and HTx was 54 days (range 18-116 days) and 34 days (range 3-137 days) respectively (Table 4-20). One patient received a VAD and had no subsequent hospitalisation until a HTx admission. Therefore, the post-VAD group consisted of 18 patients (Group 4) who subsequently crossed over to HTx and four Group 3 patients who did not receive a HTx. Observations occurring before activation on the wait list or VAD were not included. In the post-HTx group, the last observation began at 1,568 days (4.3 years), although 50% of observations occurred within the first 168 days post-HTx.

Table 4-20: Days since starting event in each group

Group	Start point	Patient, N	Obs.	mean	SD	Median	Min	Max
pre-VAD	Date activated on wait list	4	21	191	112	206	13	336
intervention-VAD	Admission start date	25	25	54	25	47	18	116
post-VAD and no HTx	Index VAD end date	4	56	384	239	336	44	718
post-VAD and pre-HTx	Index VAD end date	18	128	280	192	294	32	1285
Group 3 or 4 combined	Index VAD end date	22	205	256	214	234	0	1211
pre-HTx no VAD	Date activated on wait list		83	237	209	173	3	785
intervention HTx	Admission start date	61	61	34	28	25	3	137
post-HTx	Index HTx end date	56	1,097	289	301	168	9	1568
omm	Date activated on wait list	10	86	538	389	492	9	1462

Abbreviations: HTx, heart transplant; Max, maximum; Min, minimum; Obs, observation; omm, optimal medical management; VAD, ventricular assist device; SD, standard deviation.

4.3.3.7.2 Costs of episodes of care for each subgroup

The cost of the 2,228 observations ranged from $73 to $377,020 with an average of $13,805 (Table 4-21). The most costly admission was the LVAD with an average of $250,683, followed by HTx ($124,302). Some patients died during the index admission (operation): 8% (2/25) of VAD patients and 8% (5/61) of HTx patients. Therefore, the sample size is smaller for the post-intervention groups.

Table 4-21: Cost of the episodes of care in each group

Group	Patient, N	Obs, N	Mean	SD	Median	Min	Max
1: pre-VAD	24	217	$12,011.42	$2,196.42	$7,647.29	$202.26	$143,094.20
pre-VAD BTC	17	153	$10,739.62	$21,869.55	$4,647.64	$202.26	$143,094.20
pre-VAD BTT	7	64	$15,051.83	$22,053.46	$8,632.44	$327.66	$130,986.40
2: intervention-VAD	25	26*	$250,683.30	$63,887.02	$245,118.70	$1,668.78	$377,020.20
3: post-VAD and no HTx	4	56	$11,232.35	$8,961.77	$10,218.05	$202.26	$42,343.41
4: post-VAD and pre-HTx	18†	128	$7,346.92	$10,904.80	$3,062.03	$202.26	$64,760.21
5: pre-HTx no VAD	42	489	$11,320.46	$25,413.80	$4,242.14	$72.81	$234,753.50
6: intervention HTx	61	62*	$124,302.30	$56,773.43	$103,079.80	$436.88	$355,440.30
7: post-HTx	56	1,097	$4,564.94	$12,430.24	$1,299.68	$72.81	$255,791.60
8: omm	10	153	$11,856.27	$23,273.74	$7,226.19	$72.81	$147,707.50
Total	77	2,228	$13,805.26	$38,546.18	$1,871.53	$72.81	$377,020.20

†. 1 patient received a VAD and soon received a HTx so that there were no admissions. *1 observation included the ED visit
Abbreviations: HTx, heart transplant; Max, maximum; Min, minimum; Obs, observation; omm, optimal medical management; VAD, ventricular assist device; SD, standard deviation.

4.3.3.8 Total cost per patient per group

The total hospital costs in each patient over the entire follow-up period ranged from $19,054 to $1,098,542. uses the total cost per month with appropriate zero cost months per patient. The OMM group consisted of 10 patients whose costs were included in the waitlist/OMM group (n=35).

Table 4-22: Total cost per patient in first year, no adjustment for censoring or explantatory variables

	n	N	Costs	SE	CI lower	CI upper
post HTx	56	648	$51,021	$6,588	$37,819	$64,224
post VAD	23	268	$56,301	$10,662	$34,188	$78,413
wait list/OMM	35	280	$40,923	$12,784	$14,943	$66,903
OMM	10	105	$47,368	$24,848	-$8,841	$103,578
pre VAD (BTC)	17	204	$71,007	$12,728	$44,024	$97,989
pre VAD (BTT)	7	84	$116,220	$28,551	$46,359	$186,082

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; CI = confidence interval; HTx, Heart Transplant; NYHA, New York Heart Association; OMM, optimal medical management; SE, standard error; VAD, ventricular assist device.

4.3.3.8.1 Regression analysis

The linear regression model for the group costs is presented in Table 4-23. None of the explanatory variables were statistically significant. The mean cost per patient in the post-HTx group was $52,198 after adjusting for age, gender and NYHA status at baseline. This was similar to the mean post-VAD costs of $56,060. All patients had NYHA status IV at baseline so NYHA status was omitted from the regression due to collinearity. When accounting for age, gender and baseline NYHA status, the not eligible group (n=8 due to missing data) had higher costs of $58,780 compared to the *'waitlist'* group at $46,488. For the first year pre-VAD BTC costs (representing the *'Ineligible'* health state), at least a full year of hospitalisation costs were collected so that no censoring was assumed.

Table 4-23: Linear regression for mean cost per patient

	Alive post-HTx	**Alive post-VAD**	**Wait-list/not eligible**	**OMM**	**Pre-VAD BTC**	**Pre-VAD BTT**
	n=56	n=22	n=33	n=10	n=17	n=7
Age (mean years)	49.52	48.79	50.32	54.37	45.95	50.81
Sex (Female %)	29%	27%	24%	30%	29%	14%
NYHA (Class 2 %)	15%	0%	17%	25%	0%	0%
NYHA (Class 3 %)	35%	0%	57%	63%	0%	0
NYHA (Class 4 %)	50%	100%	27%	13%	100%	100%
	Coefficients (robust SE)	Coefficients (robust SE)	Coefficients (robust SE)	Coefficients (robust SE)	Coefficients (robust SE)	Coefficients (robust SE)
_cons	$92,126.88	$66,282.77	-$81,553.45	-$94,891.35	$32,195.79	-$76,611.11
	($49,324.)	($50,285.36)	($80,884.08)	($89,482.68)	($31,767.96)	($246,210.5)
age	-$731.08	-$317.90	$1,579.95	$1,962.36	$1,112.00	$3,859.39
	($942.86)	($983.73)	($1,579.95)	($5,137.45)	($5,137.45)	($4,535.61)
_Isexrecode_1	$18,542.15	$19,388.65	-$35,283.26	-$70,005.22	-$41,771.98*	-$22,888.08
	($16,698.28)	($19,699.6)	($18,889.16)	($89,482.68)	($18,858.55)	($59,752.17)
_Inyha_1_3	-$21,338.13	0	$6,369.77	$86,685.83	0	0
	($21,428.17)	(omitted)	($26,403.3)	($51,493.79)	(omitted)	(omitted)
_Inyha_1_4	-$3,274.86	0	$39,497.39	$110,407.60	0	0
	($22,631.)	(omitted)	($41,543.98)	($97,273.56)	(omitted)	(omitted)
Observations	600	268	245	81	204	84
F	0.92	0.48	1.5	.	4.85	.
Prob > F	0.4601	0.6224	0.2265	.	0.0225	.
d.f	4	2	4	4	2	1
clusters	52	23	31	8	17	7
R^2	0.0852	0.0465	0.2248	0.4312	0.297	0.2021
Mean cost per patient per year	$52,197.94	$56,060.03	$46,488.42	$58,780.08	$71,006.50	$116,214.87

Note: Adjusted for cluster by patient id. Six patients had missing NYHA status at baseline. *p=<0.05

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; d.f, degree of freedom; HTx, Heart Transplant; NYHA, New York Heart Association; OMM, optimal medical management; SE, standard error; VAD, ventricular assist device

4.3.3.8.2 Adjustment for censoring

Adjustment for censoring using the ZT estimator (cost history) method (175) per patient in Year 1 is presented in Table 4-24. The waiting list group was most subject to censoring with a mean waiting time of 241 days. For the health states *'Post-HTx'*, *'Post-VAD'* and *'Waiting list'*, the values adjusted for censoring were used; however, none were adjusted for covariates because the hcost method in STATA did not allow for it. However, since none of the explanatory variables (age, sex, NYHA) were statistically significant based on the regression results for those three health states in Table 4-23, it is unlikely to significantly bias the results. Similarly, for the pre-VAD BTc costs, although sex is statistically significant at $p<0.05$, the linear regression and adjustment for censoring results were similar and hence the adjustment for censoring results was used in the model. Another benefit of the hcost method is that the SE are reported for use in sensitivity analyses in Chapter 5.

Table 4-24: Total costs per year adjustment for censoring

	n	N	Costs	SE	CI lower	CI upper	Days	SE	CI lower	CI upper
Corrected for censoring, cost history method (ZT estimator)										
post HTx	56	648	$55,063	$7,516	$40,333	$69,793	351	8	336	366
post VAD	23	268	$54,484	$10,369	$34,162	$74,807	290	22	247	333
waiting list/OMM	35	280	$33,751	$9,193	$15,734	$51,769	241	19	203	279
OMM	10	105	$40,721	$19,652	$2,204	$79,237	312	29	256	369
pre VAD BTC	17	204	$71,007	$12,348	$46,804	$95,209	365	.	.	.
pre VAD BTT	7	84	$116,220	$26,433	$64,413	$168,028	365	.	.	.

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; CI, confidence interval; HTx, heart transplant; SE, standard error; VAD, ventricular assist device; ZT, Zhao and Tian.

4.3.3.9 MCS cohort

The first MCS implant occurred on 3 June 1994 and most recent on 21 December 2016, with the first CF implant on 26 October 2004. A comparison of the demographic and prognostic variables of the full sample and those that received a CF device and non-CF devices is presented in Table 8-27. The youngest recipient was 12 years old. In the comparison of CF patients to non-CF patients, CF patients were older ($p<0.01$) and more likely to have received an IABP at baseline ($p<0.01$). Tests of significance were conducted for baseline variables between the included and excluded cohort (Table 4-25). The mean age of the excluded cohort was lower than the included cohort ($p<0.001$).

Table 4-25: Demographic and prognostic variables in MCS – included patients

Characteristics	Sub-category	All (n=204)	Incl. (n=137)	Not Incl. (n=67)	p-value†
Sex	Male n (%)	162 (79)	109 (80)	53 (79)	ns
	Female n (%)	42 (21)	28 (20)	14 (21)	
Age (year)	Mean (SD)	50.40 (14.58)	53.69 (12.93)	43.69 (15.49)	p<0.001
	Median	53.67	57.21	49.59	
	Min-Max	12.34 – 75.70	18.53 – 75.70	12.34-64.80	
IMACs at baseline	1 n (%)	68 (33)	38 (28)	30 (45)	p<0.05
	2 n (%)	113 (56)	79 (58)	34 (51)	
	3 n (%)	23 (11)	20 (15)	3 (5)	
IABP at baseline	No n (%)	150 (74)	74 (66)	60 (90)	p<0.001
	Yes n (%)	54 (26)	47 (34)	7 (10)	
ECMO at baseline	No n (%)	180 (88)	120 (88)	60 (90)	ns
	Yes n (%)	24 (12)	17 (12)	7 (10)	
Ventilation at baseline	No n (%)	174 (85)	122 (89)	52 (78)	P<0.05
	Yes n (%)	30 (15)	15 (11)	11 (23)	

Abbreviations: ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; IMACS, International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support; SD, Standard deviation.
†Comparison between included and not included patients.

4.3.3.10 Implant details and surgery

Details of the CF implants in the 137 patients are presented in Table 8-28. There were three types of CF devices implanted, with the most common type being the HVAD (76%). Of the indications, most were BTT (93%), with 6% for DT and 1% for BTC. At study end around 50% of patients had been transplanted.

4.3.3.11 Time-to-event analyses

4.3.3.11.1 Time to event – VAD to death

The summary statistics for days alive on pump are presented in Table 4-26. The start date was date of implant and event of interest was death, and patients were censored if they were alive at study end or transplanted. Of the 137 patients, 41 patients died while supported by a VAD. The median survival time was 1,069 days for all 137 patients. There were no statistically significant differences in the number of deaths between males and females.

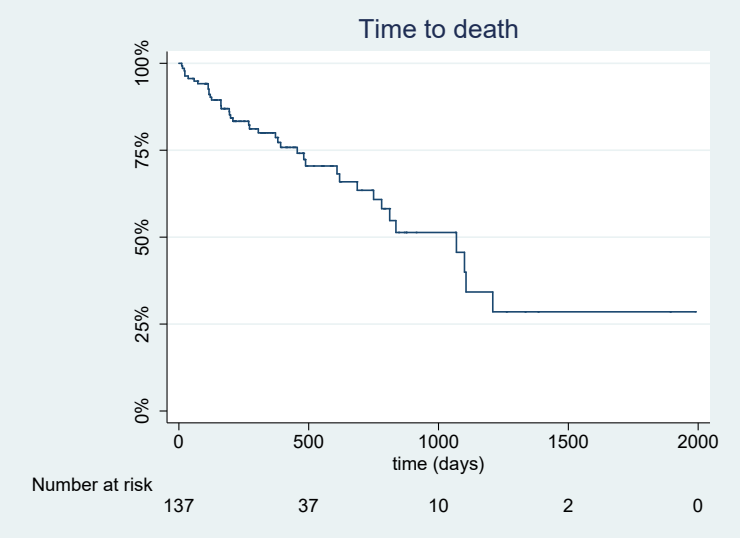
Table 4-26: Summary statistics for alive on pump

Died on pump	Total	Male	Female
Subjects, n	137	109	28
Failures (death), n	41	33	8
Survival time: 25%, 50%; 75%	456; 1,069; NE	481; 1069; NE	306; 836; NE
10% remaining at risk; SE (95% CI)	126; 34.34 (59, 199)	126; 52.93 (23, 269)	116; 39.45 (59, 163)
Log-rank test		p=0.39	

Abbreviations: NE=not evaluable; SE=standard error

The KM plots for time to VAD are presented in Figure 4-11. There were no statistically significant differences in prognostic variables such as gender, pre-ECMO or INTERMACS (Figure 8-10). The CPH regression model results indicated that, gender, age of implant and INTERMACS at baseline were statistically insignificant predictors of death (Table 8-29).

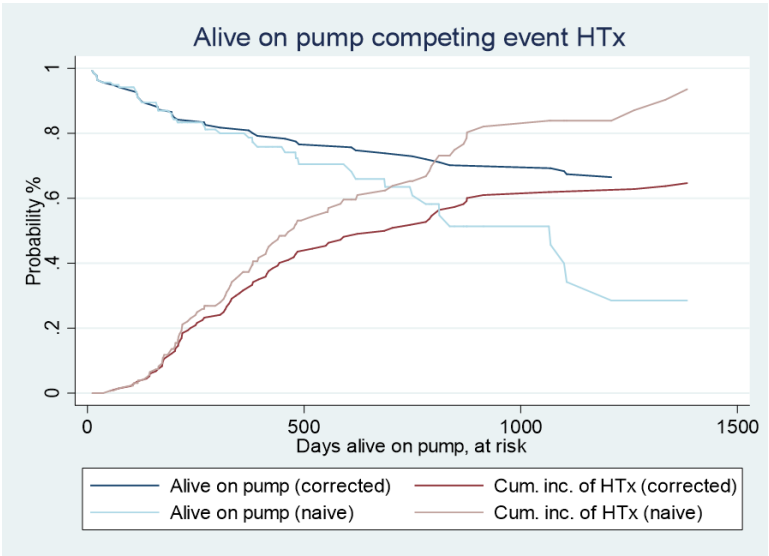
Figure 4-11: Kaplan-Meier plots of survival for days alive on pump, event death



4.3.3.11.1.1 Time to death from VAD with competing event HTx

HTx is a competing risk to death for those alive with a VAD. Figure 4-12 illustrates the probability of death or transplant adjusted for competing events. Of the 137 included patients, 77 received a HTx and 41 had died, with the remaining 19 alive on pump at the end of the study period.

Figure 4-12: Alive on pump with competing risk of HTx



Based on the Fine and Gray model for competing risks, when taking into account competing risks the older patients were statistically significantly more likely to die (p=0.022) (Table 4-27). After adjusting for gender, ECMO and INTERMACS ast baseline, age was still statistically significant, with older patients more likely to die.

Table 4-27: Fine and Gray model for subhazards time to death, competing event HTx

Variable	Univariate		Multivariate		
Age	SHR: 1.03; p=0.022	SHR: 1.03; p=0.021	SHR: 1.04; p=0.018	SHR: 1.03; p=0.016	SHR: 1.04; p=0.017
gender	SHR: 1.04; p=0.093	SHR: 1.49; p=0.374			SHR: 1.51; p=0.33
ECMO	SHR: 0.49; p=0.084		SHR: 0.41; p=0.046		SHR: 0.42; p=0.075
INTERMACS	SHR: 0.87; p=0.56			SHR: 0.74; p=0.23	SHR: 0.96; p=0.89

4.3.3.12 CPR cohort

Of the 102 included patients, 57 heart transplants were conducted and 4 patients were bridged with a VAD. Of the patients who were active on the waitlist during the study period, 28 had received a VAD during the study period or beforehand. Of the VADs, 18 (64%) were BTT and 10 (36%) were BTC.

4.3.3.13 Time-to-event analyses

4.3.3.13.1 Time to event- waitlist to HTx

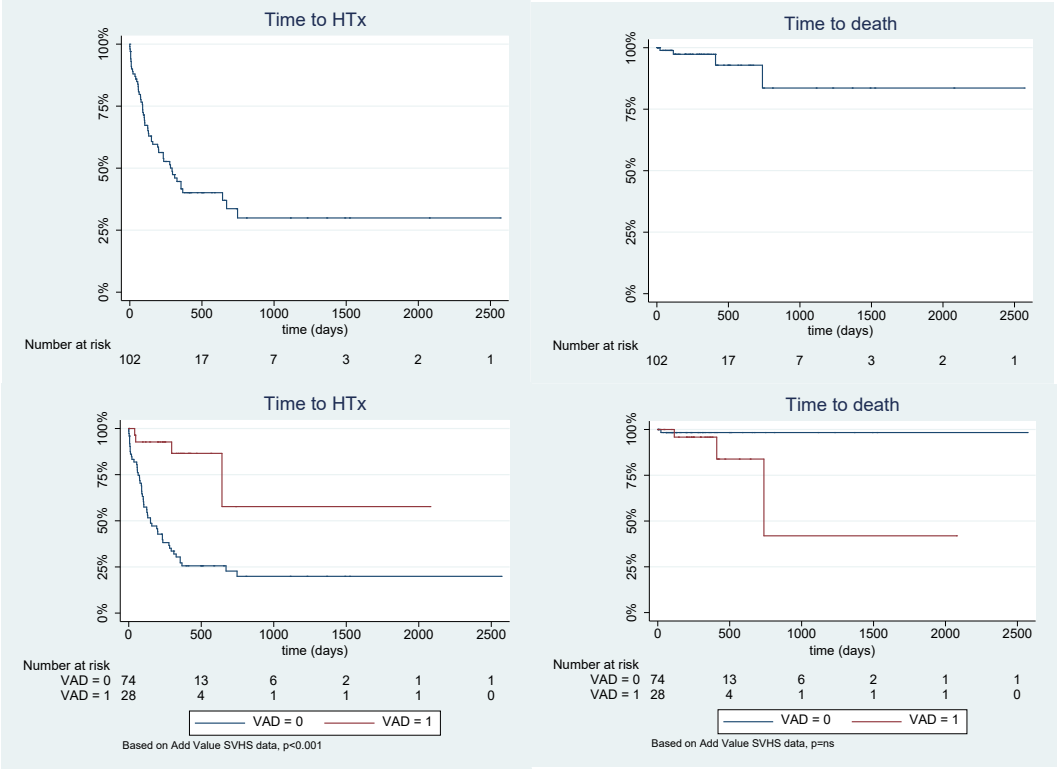
The summary statistics for the survival dataset days waiting for the event HTx or Death are presented in Table 4-28. The median time to HTx once listed was 293 days (9.6 months). Of the 57 HTx recipients, 4 were supported with a VAD, with bridged patients waiting longer for a VAD (p<0.001). However, once they were transplanted the risk of death was not different.

Table 4-28: Summary statistics for time on waitlist

Time waiting	**HTx**	**Death**
Subjects, n	102	102
Failures, n	57	4
Survival time: 25%, 50%; 75%	89; 293; NE	NE; NE; NE
10% remaining at risk; SE (95% CI)	6; 2.98 (0.001, 19)	22; NE (22,115)
Log rank test (no VAD vs. VAD)	No VAD: 53, VAD: 4, p=0.000	No VAD: 1, VAD: 3, p=0.058

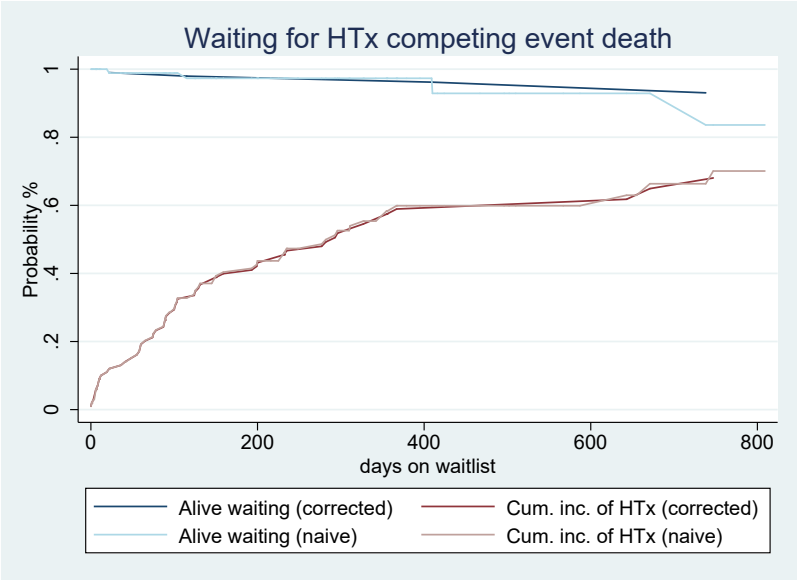
The KM plots for waitlist days with events HTx or death by VAD receipt are presented in Figure 4-13. The CPH model indicated that receiving a VAD led to a longer time to HTx (HR: 0.14, p<0.001), but receipt of VAD did not impact on time to death (Table 8-30).

Figure 4-13: Kaplan-Meier plots of survival for days on waitlist, event HTx (left) or death (right)



Due to the small number of deaths, the rate of HTx corrected for deaths was very similar to the uncorrected curve (Figure 4-14). The Fine and Gray model indicated that the subhazard ratio of time to HTx with competing event of death for those who received a VAD was statistically significantly longer than those who did not [SHR: 0.14, 95% CI: 0.05-0.39, p=0.000].

Figure 4-14: Waiting for HTx with competing risk of death



4.3.3.13.2 Time to event – Waitlist to Removal

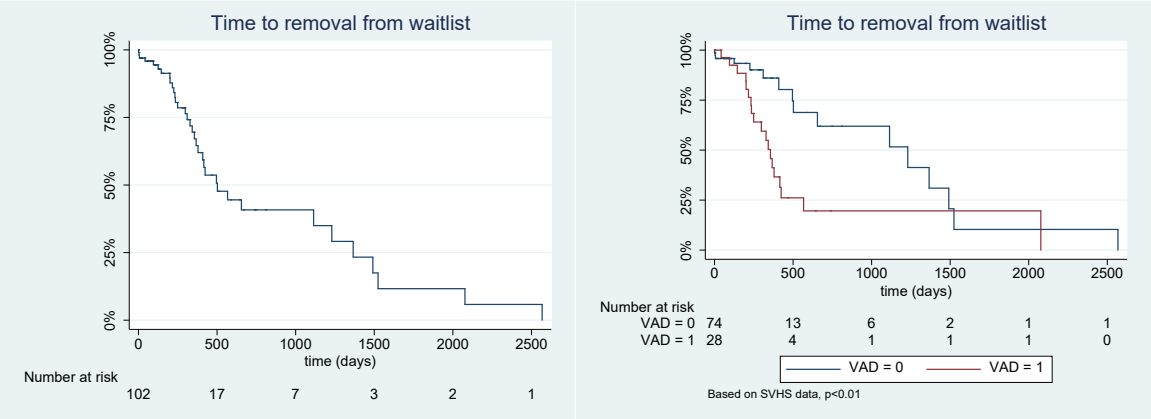
Of the 102 waiting patients, 35 were removed due to condition improvement or deterioration or 'other' (Table 4-29). The median time to '*Removed*' health state was 502 days (1.4 years).

Table 4-29: Summary statistics for days on wait list until removal

Time to Removal	Total
Subjects, n	102
Failures, n	35
Survival time: 25%, 50%; 75%	310; 502; 1366
10% remaining at risk; SE (95% CI)	42; 46.68 (1, 145)
Log rank test (no VAD vs. VAD)	no VAD:16 vs. VAD:19, p=0.0043

The Kaplan-Meier plot of time on waitlist until removal is presented in Figure 4-15. The CPH model indicated that receiving a LVAD meant a shorter time until removal (HR: 2.64; p=0.0058).

Figure 4-15: KM plots of survival for days waiting until removal, all (left) and by VAD (right)



4.3.3.13.3 Time to event – VAD to HTx

Of the 28 VAD recipients, 4 were transplanted and 3 died, with median time to event not reached for either outcome (Table 8-31). The Kaplan-Meier plot of time to HTx or death from VAD is presented in Figure 8-10. Due to the small number of events for both HTx and death, the competing risk analysis was based on small event numbers (Figure 8-11).

4.3.3.13.4 Time to event – VAD to Removal

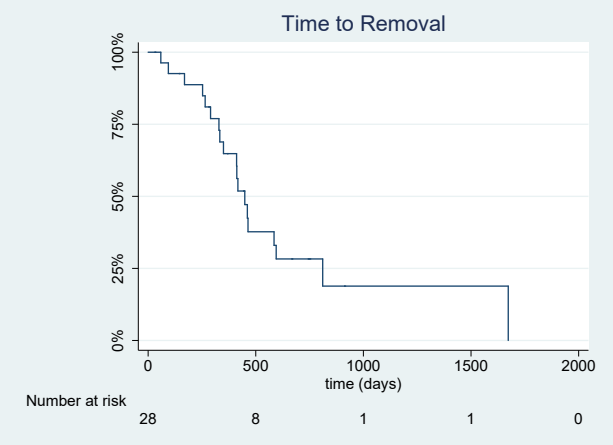
Of the 28 VAD recipients, 19 were removed from the waitlist, with a median time of 449 days (1.2 years) (Table 4-30).

Table 4-30:Summary statistics of alive on pump to removal

Time to Not eligible	Not eligible
Subjects, n	28
Failures, n	19
Survival time: 25%, 50%; 75%	329; 449; 811
10% remaining at risk; SE (95% CI)	94; NE (59, 265)

The Kaplan-Meier plot of time on waitlist until removal is presented in Figure 4-16.

Figure 4-16: Kaplan-Meier plots of survival for alive on pump until removal from waitlist



4.3.4 Pre-modelling studies and use in the economic evaluation

The pre-modelling studies in the economic model are summarised in Table 4-31.

Table 4-31: Pre-modelling substudies for the economic evaluation

Substudy	Results	Use in the economic evaluation
Add Value		
Demographics	Mean age 49.4 years with 67% male.	Age and gender distribution used for model population.
NYHA status	At baseline on the waiting list and Post-intervention after LVAD or HTx.	Cross-sectional proportion in each Class at follow-up for those who received VAD and/or HTx.
APDC	Resource use split into 8 mutually exclusive groups by LVAD or HTx receipt. Calculated cost per month over time.	Intervention index admissions for VAD and HTx. For health states post-VAD, post-HTx, waitlist and not eligible, admissions combined with ED only visits.
EDDC	As above. Excluded ED visits that had a mode of separation as an admission.	Estimated average per person in first 12 months accounting for censoring.
TTE: wait list to VAD	Of the 25 VADs,18 received prior to being waitlisted (BTC). When BTC set to 0.01 wait days so not excluded from survival analysis, median survival NE. When BTC (n=18) median survival to 'waitlist' was 110 days, when BTT (n=7) median survival to 'VAD' was 77 days.	Transition probability from *'Waitlist'* to *'Alive post-VAD'*. Combined BTC and BTT so that wait time might be underestimated. The BTC analysis used for transition probability '*Alive-post-VAD*' to *'Waitlist'* for those ineligible for HTx.
TTE: VAD to death with competing event HTx	Median survival was 482 days to receive HTx if patient received a VAD. Cumulative incidence plotted.	Transition probability from *'Alive post-VAD'* to *'HTx'* after adjusting for competing risk of death.
Mechanical Circulatory Support		
Demographics	The included patients had a mean age of 54 years with 80% males.	Assess applicability to Add Value study.
TTE: VAD to death with competing event HTx	Median survival was 1,069 days to death (not accounting for competing risks). The one year probability of survival was 80% (naïve) and 81.7% (corrected for competing event HTx).	Used for the transition probability of '*Alive post-VAD'* to *'Death'* after competing risk adjustment. The probabilities were converted into transition probabilities assuming constant hazards.
CardioPulmonary Registry		
TTE: waitlist to HTx	Median survival to receive HTx was 293 days in the 57 patients. Adjusted for deaths (n=4), death median survival NE. Of the 57 HTx, 4 were bridged.	Transition probability *'Waitlist'* to *'HTx' (non-bridged,* n=53). Despite a small number of transplanted patients were supported with VAD (7%, 4/57), there is bias from cross-over. The time to HTx was statistically significantly longer for those supported with VAD. VAD is a health state in the model.

Substudy	Results	Use in the economic evaluation
TTE: waitlist to removed	Median survival to removal due to ineligibility or VAD was 502 days in 35 patients.	Transition probability of *'Waitlist'* to *'Removed'*
TTE: VAD to HTx	Median survival NE, there were 4 bridged and 3 deaths.	Not used due to small event numbers.
TTE: VAD to removed	Median survival to removal was 449 days in the 28 patients.	Transition probability of *'Alive post-VAD'* to *'Removed'*.

Abbreviations: HTx, heart transplant; NE, not evaluable; NYHA, New York Heart Association; TTE, time-to-event; VAD, ventricular assist device.

4.4 Discussion

4.4.1 Bias in clinical evidence due to study design

Due to the lack of data from RCTs comparing LVAD bridged to non-bridged HTx, observational studies were analysed to inform the economic evaluations in Chapter 5 and 6. Registry data can be useful in assessing the effectiveness of devices.(183). The main findings from the Add Value and the linked hospital admissions dataset were the differences between health status and costs across bridged and non-bridged patients. It was confirmed that the NYHA health status of LVAD recipients was worse than those unbridged. Further, the cost of LVAD implant was twice the cost of HTx transplant; however, in the year following the intervention the costs between the two groups were similar, even after accounting for censoring.

A key finding from the CPR dataset was the status changes on the HTx waiting list including reason for removal from waiting list and the time from listing to *'Removed'* or *'HTx'*. The datasets from SVHS illustrated events surrounding the HTx waiting list, and indicated it was appropriate to have a '*waiting list*' health state. The Add Value data indicated that the use of LVAD can extend the time that a patient waits for a HTx, thus allowing more time for a suitable donor to be found. In the time-to-event analysis of study entry to HTx, those who received an LVAD remained on the waiting list longer than those that did not, even after controlling for age and gender (p=0.02) [Data on file].

The published registry datasets were non-comparative retrospective cohort studies.(156, 157) A retrospective cohort is subject to a number of biases. One such bias is selection bias, leading to the differences in baseline charateristics between those patients who received an LVAD and those who did not. Since there is no randomisation, the baseline characteristics of patients are not balanced across the arms. This may cause confounding, which is defined as a bias that distorts the exposure-disease or exposure-outcome relationship.(184) These issues are relevant to the SVHS individual patient datasets.

There are methods to assess the comparative effectiveness in retrospective observational databases to adjust for bias, including propensity scoring, instrumental variable and inverse probability weighting

methods.(184-187) In a published review of cost-effectiveness analysis studies (n=81) that used observational data, 51% used regressions, 25% matched on individual covariates and 22% matched on propensity score (187). This chapter adjusted costs for censoring and the regression results indicated no statistically significant differences in age, gender or NYHA. However, the time-to-event analyses assumed that the groups are balanced as in an RCT. This may not be the case in a retrospective cohort. Therefore, caution should be used when interpreting these results. When available, KM curves were adjusted for age, gender and NYHA.

The SVHS dataset demonstrated the use of LVADs in clinical practice as BTT (7/25) and BTC (18/25) and highlighted that LVADs increase the pool of patients who would become eligible for a heart transplant. There is likely to be confounding by indication in the BTC and BTT patients. BTC patients may have worse baseline characteristics than BTT patients and have worse survival (censoring at transplant or recovery).(161) Consequently, the effect of LVAD may be underestimated in BTC patients when compared to BTT patients, if no appropriate matching or correction for baseline characteristics is undertaken. Consequently, a true comparative effectiveness of bridged HTx and non-bridged HTx cannot be conducted.

4.4.2 Applicability of clinical evidence to Australian ESHF

This chapter included an analysis of international and Australian data. The current analysis included CF devices, which is consistent with the INTERMACS and IMACS analysis in Chapter 2. It also reflects the focus of the more recent cost-effectiveness literature described in Chapter 3. The analysis excluded BiVADs, which formed 9% (14/151) of the MCS sample; however, results were consistent despite BiVAD patients being more likely to be on ECMO at baseline. BiVADs are more costly than a single LVAD and associated with worse outcomes than LVADs.(160) Excluding BiVADs from the analysis may lead to underestimating the cost of VADs and overestimating the outcomes. Right ventricle failure is commonly seen in patients during implant of LVAD, resulting in the need for a BiVAD.(188)

The linked administrative hospitalisations were used to estimate the cost of each health state. However, there are some challenges in conducting costing studies comparing VAD to HTx. An Australian study identified that 'in supporting a group of patients to a transplant outcome who would surely have died prior to that end point without the mechanical support… it seems evident that the VAD group were sicker than the transplant group overall, thus contributing more to costs of care'.(164) This highlights the challenge in directly comparing the two interventions in a single dataset due to bias. The subsequent hospitalisation cost post-LVAD depends on whether the patient is discharged to go home or to another facility (e.g. rehabilition or acute care), and this depends on pre-implant status such as INTERMACS level and use of ECMO.(189)

4.4.3 Strengths and limitations of costing analysis

In the Add Value analysis, diseases of the circulatory system were the most common diagnostic category at 30% and 25% for post-VAD and post-HTx respectively. In the post-HTx group, there were 40% same-day visits and 14% kidney dialysis. In the post-VAD (pre-HTx or no HTx) group, there were 31% same-day visists and 9% infectious diseases diagnostic category. This is consistent with a French study indicating prominence of monitoring heart transplant DRGs and kidney dialysis in those post-HTx (bridged with a VAD).(108) In our sample, no admissions were excluded because all were deemed to be at least partially related to ESHF. An Australian costing analysis excluded 5% (20/405) of admissions, including elective orthopaedic procedures, trauma and one minor burn.(164)

The costing analysis was subject to administrative censoring, i.e. rolling admission with a fixed stopping date. Other published VAD vs HTx cost analyses limited costs to the first year, with some studies only including patients who were alive for at least one year (164, 190, 191). This method can potentially introduce bias, as limiting data to those who lived for at least 12 months ignores patients who had died or were lost to follow-up pre 12 months. Other analyses included patients who may have died within the first year(192), or to 1, 3, 5 and 7 years, with available cost data depending on whether patients were alive.(193) One paper considered the cost of the index admission and not subsequent admissions (194), which would bias against VADs. A strength of this analysis is the adjustment for censoring using the ZT method, accounting for cost history.(175) This is one of numerous reweighted estimators to use for censored data. A recent review of options to deal with censored data concluded that there was no definitive option, however, a weighted estimator approach was preferred{Wijeysundera, 2012 #616}. However, the hcost program [ZT method] used in STATA does not allow for adjustment by covariates. In this analysis, not adjusting by covariates is unlikely to be problematic as the explanatory variables (age, gender and NYHA status) were not statistically significant in the regression analysis. It is acknowledged that based on a small sample size in the subgroups, the likelihood of obtaining a statistically significant result would be small.

4.4.4 Strengths and limitations of time-to-event analysis

The ANZCOTR Annual Report presented actuarial survival curves using the Cutler-Ederer method and statistical significance was calculated using Log Rank testing.(149) Cutler-Ederer analysis assumes that withdrawals occur randomly, and for large samples on average halfway between each interval, and the probability of survival at one interval, although conditional on surviving previous intervals, is independent of the probability of survival at the prior interval(s).(195) Consequently, Cutler-Ederer curves do not take into account censoring, unlike KM curves. This is unlikely to be an issue if follow-up is relatively complete and, given that it is a national database, it should not be strongly biased.

The time-to-event analysis of time to HTx was subject to competing event of death. In the MCS dataset, once patients were transplanted they were no longer followed up, meaning survival post-HTx is unknown. Only the time-to-event analysis activation onto waitlist to VAD implant was used in the economic evaluation, and that was not subject to competing risks. Despite conducting competing risks adjustments for VAD to death, the time-to-event analyses were based on small sample sizes compared to INTERMACS and IMACS, which may have implications for the robustness of the estimates.

4.4.5 Limitations of missing data

A limitation of the Add Value dataset related to the missing data on clinical covariates at baseline and at follow up (timing was close to time of death, transplant or 1-year post VAD implant). The date of follow-up differed between patients after the intervention. This was particularly important for NYHA at follow-up and it is unclear how this may translate to the longer-term benefit of VAD or HTx. There were only 6 patients with an LVAD that did not 'cross-over' to a HTx with follow-up data. None of the datasets included patient-reported outcomes such as quality of life. Therefore it was not possible to link quality-of-life outcomes to survival in this data. The NYHA classification was used to estimate the symptoms. Therefore, simplifying assumptions may need to be made to incorporate NYHA and utility change in the economic evaluation. A limitation of the CPR dataset was the lack of age or gender reported. However, given paediactric transplants are not conducted at SVHS it is likely these patients would be similar to the Add Value patient dataset.

4.5 Conclusion

There is a lack of RCTs comparing the effectiveness and costs of bridged vs non-bridged HTx. Despite this, there is a rich literature of observational studies of the outcomes of VADs as a bridge and DT, and of the outcomes for HTx. Although registries may lack internal validity, they tend to have high external validity, making them valuable sources of data. Observational datasets can be relied on to estimate the cost-effectiveness of health technologies. However, statistical adjustments may be required to adjust for the selection bias in these study designs.

In this thesis, the observational data from SVHS with linked administrative data informed the time-to-event analyses, quality-of-life impact and costs in the models for Chapter 5 and Chapter 6. The time-to-event analyses relied on in the models inform the waitlist transition health states and provided a more fulsome picture of the activities on the HTx waitlist and how LVADs are used in Australian clinical practice, namely as a BTT and sometimes BTC. The models also rely on the published national and international registries of HTx and VAD time-to-event analyses due to the larger sample sizes. This way, the best available data was selected for use in the economic evaluations.

5 CHAPTER 5: MARKOV MODEL FOR REAL-WORLD RESTRICTIONS IN TREATMENT POLICIES IN ESHF

5.1 Introduction

The aim of this chapter is to assess the cost-effectiveness of current policy and hypothetical policies for the treatment of end-stage heart failure (ESHF). The gold standard treatment for ESHF is heart transplantation (HTx); however, the shortage of suitable donors means that demand outstrips supply. Once added to the transplant waiting list (i.e. deemed eligible for a transplant), some patients are well enough to return home, while others may require mechanical ventilation in hospital. If a patient's condition worsens significantly, they may be removed from the waiting list or die from heart failure. Occasionally, durable mechanical circulatory support (MCS) in the form of a left ventricular assist device (LVAD) can be used as a bridge to transplant (BTT) or bridge to candidacy (BTC), the main difference being that BTT patients are eligible for the transplant waitlist while BTC patients are potential candidates for the waitlist.

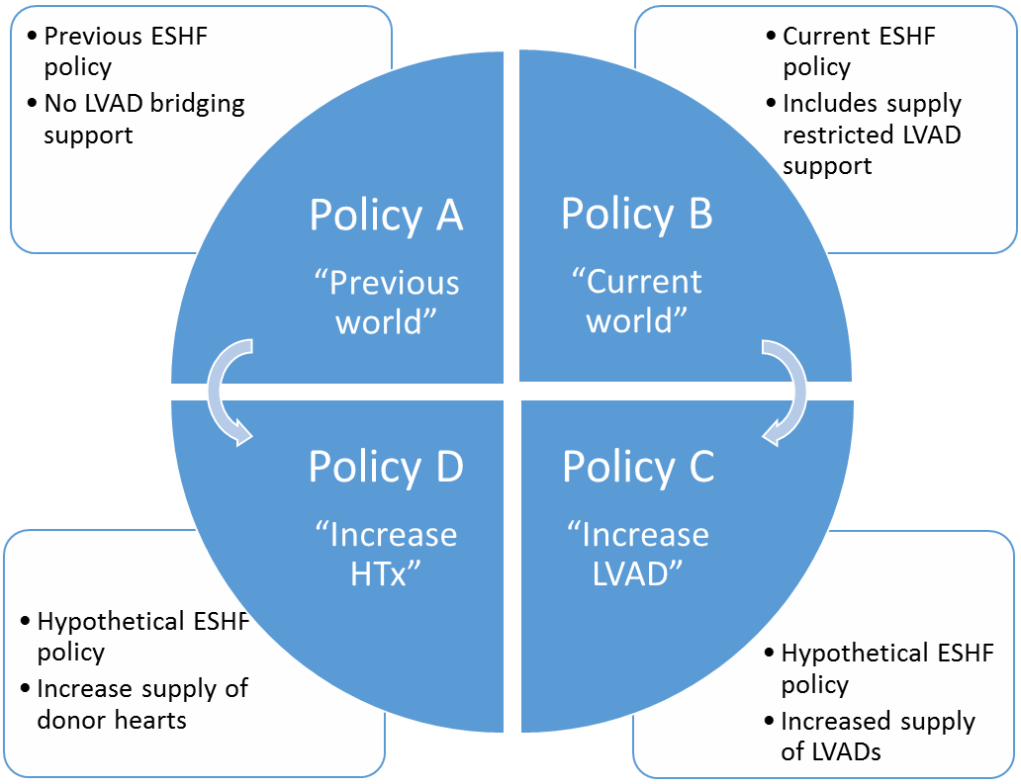
The intrinsic value of a LVAD is that it buys the patient time while a suitable donor heart is found (BTT) or the patient becomes eligble for the transplant waitlist (BTC). Hence, LVADs are regarded as a life-saving therapy. This assertion is supported by the findings of Chapter 4, which demonstrated that the use of MCS can extend the time that a patient waits for a HTx, hence allowing more time for a suitable donor to be found. Chapter 2 demonstrated that the waiting list dynamics in St Vincents Hospital Sydney (SVHS) differ to other transplant Units in Australia, which in part is due to LVADs increasing the pool of patients who later become eligible for a HTx via BTC, as shown in Chapter 4. Therefore, when considering the cost-effectiveness of policies for ESHF it is important to consider the impact of LVADs on the transplant waiting list and the supply of donor hearts. Given the potential impact of LVADs on the waiting list, it was surprising that only a handful of published economic evaluations (94, 96) considered the waiting list as a health state in ESHF models (Chapter 3).

In general, patients who are eligible for a HTx are healthier or younger than those who are ineligible. Consequently, patients who are supported by LVAD prior to receiving a HTx are generally sicker than those without. This was reinforced in the analysis of the SVHS Add Value registry data when comparing the prior treatments at baseline (e.g. intra-aortic balloon pump)(165) in Chapter 4.

Four policy alternatives are compared: the previous ESHF policy, with no LVAD bridging support (Policy A); the current ESHF policy, which includes supply restricted LVAD support (Policy B); a hypothetical ESHF policy with an increased supply of LVADs (Policy C); and a hypothetical ESHF policy with an increased supply of donor hearts, holding the current level of LVAD support constant (Policy D) (see Figure 5-1). Policy A and Policy B were chosen as these policies represent the current restrictions

compared to the world without the use of LVAD support. The two hypothetical supply alternatives of Policy C and Policy D represent expanded availability scenarios from Policy A and Policy D. Policy C is consistent with increasing the supply cap of LVADs by 20% (n ~ 30, rather than 25; see Table 2-5). Policy D is based on increasing the supply of donor hearts, which could be possible through a media campaign to boost the donation rate and the use of ex vivo preservation of donor hearts using the Organ Care System® 'Heart in a box' (196) for half of total HTx.

Figure 5-1: Schematic of ESHF Policies for economic evaluation



The aim of this chapter is twofold. The first aim is to estimate the real-world cost-effectiveness of the current policy (restricted supply of LVADs and HTx) to treat patients with ESHF in Australia. This represents an ex-post estimation of the cost-effectiveness. The second aim is to examine alternative policies, such as increasing the supply of donor hearts (without LVADs) or increasing the supply of LVADs (without increasing the supply of donor hearts). These hypothetical policies seek to determine how restricted supply impacts the overall cost-effectiveness of therapies to treat ESHF. The total budget impact of each policy is also considered.

5.2 Methods

5.2.1 Model overview

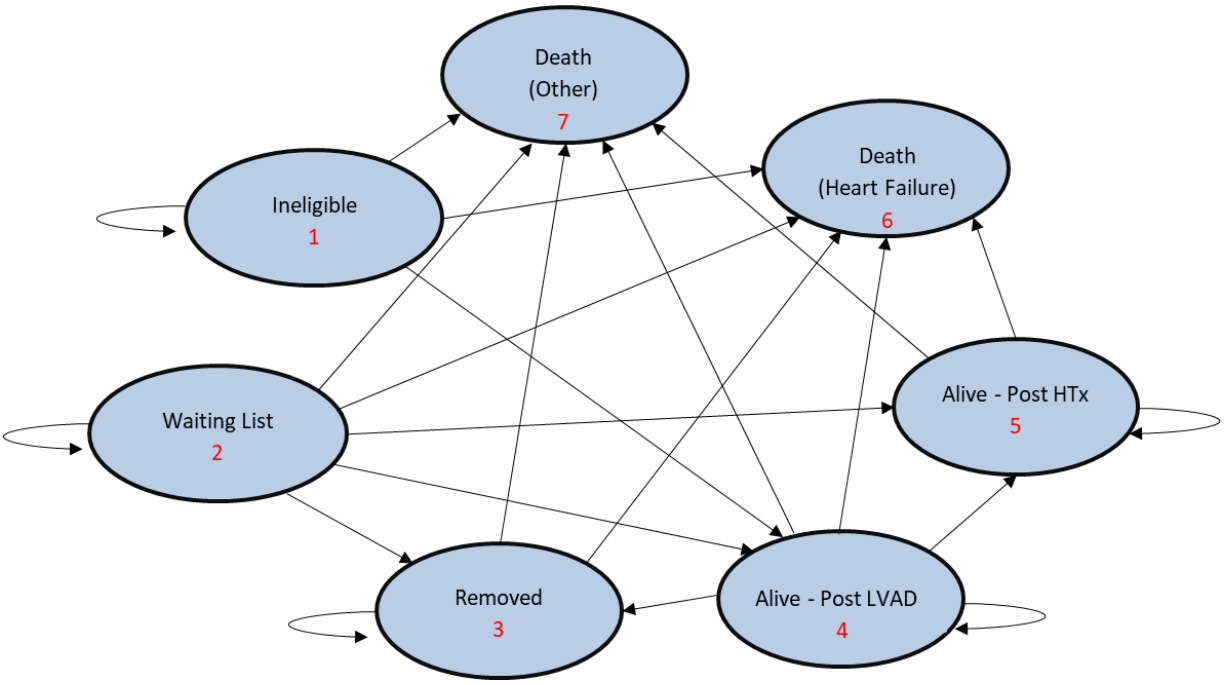
A cost utility analysis (CUA) was developed, based on a state transition cohort Markov model using TreeAge® Pro 2018 software (TreeAge Software, Inc, Williamstown, Massachusetts, USA). The model time horizon was 20 years based on data available from ANZCOTR and patients entered the model aged 50 years. Costs and benefits were discounted by 5% per annum.(197) The model utilised a healthcare system perspective. All costs are presented in 2019 Australian dollars unless specified otherwise. Costs were inflated using the Health Inflation Index (198) to 2017 using the average 2003-2017 index to estimate 2019. Costs from overseas were converted to Australian dollars using purchasing power parity (PPP).(97) Annual cycles were used. A half-cycle correction[31] was applied which assumed that half of the initial and final costs and quality-adjusted life years (QALYs) are accrued.

5.2.2 Health states and model structure

A Markov model was chosen as this is in line with the cost-effectiveness literature for ESHF (199) (see Chapter 3). As demonstrated in Chapter 4, a significant proportion of LVAD recipients are implanted prior to addition onto the HTx waiting list. A Markov model was constructed with seven health states: 1) *'Ineligible'* for HTx; 2) *'Waiting list'*; 3) *'Removed'* from the waiting list; 4) *'Alive post-VAD'* implant; 5) *'Alive post-HTx'*; 6) '*Death'* due to heart failure; and 7) *'Death (other causes)'* based on age-related non-cardiac mortality (Figure 5-2). The current model included more health states than the typical three-health-state BTT CEAs identified in Chapter 3; this was possible due to the data available in Chapter 4. The '*Ineligible'* health state accounts for patients who are not eligible for HTx due to renal failure but who may be supported by a BTC VAD (and hence could transition to *'Alive post-VAD'* and would be eligible for HTx). A patient on the *'Waiting list'* could receive a VAD or HTx, die, or be removed from the waitlist due to health reasons. Patients who enter the *'Alive post-VAD'* stage are able to transition to *'Alive post-HTx'* or die.

[31] In traditional Markov models, a patient accumulates the full cycle's state reward at the beginning of each cycle with transitions occurring at the end of each cycle. This assumption is not reasonable, as a portion of the cohort will leave the state during the cycle.

Figure 5-2: Markov model structure



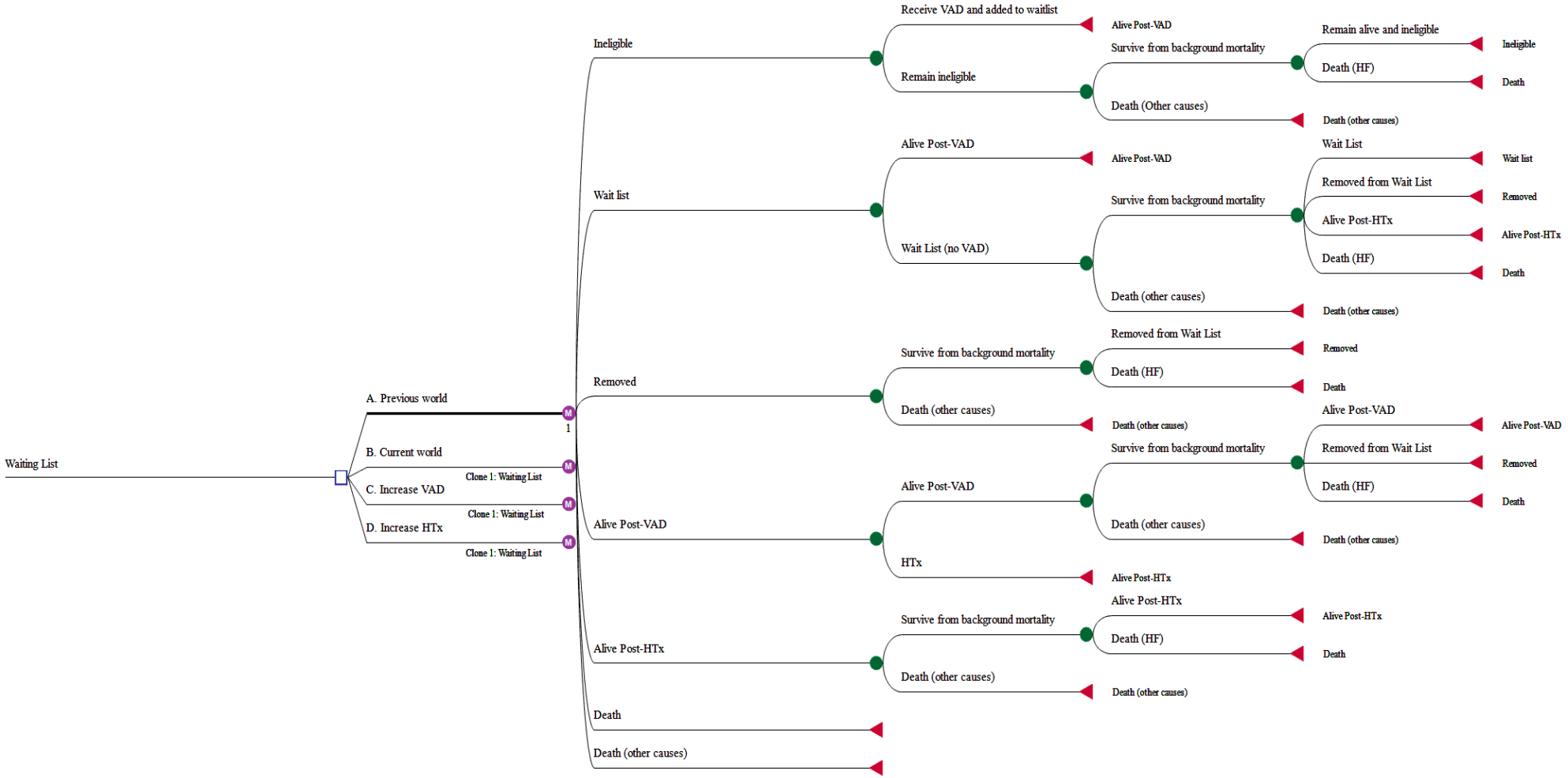
5.2.2.1 Model Assumptions

The model was underpinned by the following assumptions.

- No health state for perioperative survival or complications after LVAD or HTx.
- The same transition probabilities from *'Waiting list'*, '*Removed'* and *'Ineligible'* health states to either of the death health states. Multiplication factors of 1.5 and 1.6 were applied for the higher chance of death from the *'Removed'* patients and *'Ineligible'* patients respectively. It was assumed a higher factor would apply for those who were never eligible compared to those who were removed from waiting list.
- The proportion in each NYHA Class in the health states *'Ineligible'*, *'Waiting List'*, *'Removed'*, *'Alive Post-VAD'* and *'Alive Post-HTx'* remained constant over time.
- Patients in the *'Removed'* health state would have the same average NYHA Class as those on the *'Waiting list'*, hence quality of life in those health states is the same. This is justified as medical reasons for removal may be deterioriation of kidney function, which would not affect heart failure symptoms.

The tree diagram with the policies is presented in Figure 5-3. The comparison of Policy A (the previous ESHF policy) and Policy B (the current ESHF policy) would capture the differences with and without VADs. Policy C and Policy D would capture the differences in the proportions of patients beginning in the *'Alive post-VAD'* or *'Alive post-HTx'* health states rather than *'Waiting list'*.

Figure 5-3: Tree Diagram showing treatment options of expanded supply of VAD or donor hearts



5.2.3 Model data

5.2.3.1 Patient population and setting

The model population is based on Add Value (n=77, median 50 years old and 69% males) (see Table 4-12 in Chapter 4). Of the 77 patients, 25 received a LVAD (18 as BTC and 7 as BTT) and were New York Heart Association (NYHA) Class IV. In total, 61 patients received a HTx. Of these, 19 were bridged with a LVAD, meaning 6 patients died or remained alive on LVAD by study end. Patients in the LVAD group were more likely to have an intra-aortic balloon pump (IABP) ($p<0.001$) and be on inotropic IV medication at baseline than the non-LVAD group ($p<0.001$).

5.2.3.2 Initial probabilities

The initial probability for each health state for all policies are presented in Table 5-1. Under all policies, 10% of the population are ineligible for a HTx and begin in the *'Ineligible'* health state. Under Policy A and Policy B, the remaining 90% of patients begin in the *'Waiting list'* health state. Under Policy B, some patients transition to the VAD health state from the '*Ineligible'* health state as BTC or *'Waiting list'* health state as BTT. Under Policy C, a proportion (20%) immediately receive a VAD, avoiding the *'Waiting list'* health state. Finally, under Policy D a proportion (20%) immediately receive a HTx, avoiding the '*Waiting list'* health state. In a sensitivity analysis, the 'waiting list' health state was removed so that patients either began in the *'Ineligible'*, *'Alive post-VAD'* and *'Alive post-HTx'* health state.

Table 5-1: Initial probability of starting in each health state in each strategy

	Ineligible	Wait List	VAD	HTx
Base case				
Policy A	10%	90%	0%	0%
Policy B	10%	90%	0%	0%
Policy C	10%	70%	20%	0%
Policy D	10%	70%	0%	20%
No 'Ineligible' health state				
Policy A	0%	100%	0%	0%
Policy B	0%	100%	0%	0%
Policy C	0%	80%	20%	0%
Policy D	0%	80%	0%	20%
No 'Waiting list' health state†				
Policy A	10%	0%	0%	90%
Policy B	10%	0%	36%	54%
Policy C	10%	0%	56%	34%
Policy D	10%	0%	0%	90%

Note: †The remaining cohort (90%) is split as 40% bridged (90% * 40% = 36%). Policy C was assumed to have additional 20% beginning in VAD health state. Policy A = Previous policy no LVAD, Policy B = Current policy with LVAD, Policy C = Policy B with increase LVAD, Policy D = Policy A with increase HTx.
Assumptions based on personal communication with Professor Christopher Hayward, St Vincent's Hospital Sydney.

5.2.4 Pre-modelling studies

Pre-modelling studies were conducted to assess the applicability and translation of evidence into the economic model. A summary of the included pre-modelling studies is presented in *Table 5-2*. The methods to estimate the transition probabilities from time-to-event analyses of the published data and SVHS datasets are presented in Chapter 4. Extrapolation was conducted on the transition probability from *'Alive Post-VAD'* to *'Death'*. The international registry and RCT data were compared to Australian data to assess applicability of the patient population and outcomes.

Table 5-2: Summary of pre-modelling studies and their data sources

Pre-modelling study	Source of data
Transition probabilities (time-to-event analysis)	
Age-related mortality	Australian Bureau of Statistics Life Tables, section 5.2.4.1.13
'Waiting list' to 'Death'	ANZCOTR, section 5.2.4.1.2
'Waiting list' to 'Removed'	SVHS CPR, section 5.2.4.1.3
'Waiting list' to 'Alive Post-HTx'	SVHS CPR, section 5.2.4.1.4
'Waiting list' to 'Alive Post-VAD'	SVHS Add Value, section 5.2.4.1.5
'Alive Post-VAD' to 'Removed'	SVHS CPR, section 5.2.4.1.9
'Alive Post-VAD' to 'Alive Post-HTx'	INTERMACS; MOMENTUM 3 trial; IMACS; SVHS Add Value; SVHS MCS, section 5.2.4.1.10
'Alive Post-VAD' to 'Death'	INTERMACS; SVHS MCS, section 5.2.4.1.11
'Alive Post-HTx' to 'Death'	ANZCOTR; ISHLT, section 5.2.4.1.12
'Removed' to 'Death'	Assumption, section 5.2.4.1.8
Extrapolation	
Extrapolation of 'Alive Post-VAD' to 'Death'	INTERMACS, section 5.2.4.1.11
Applicability	
Applicability of international data to Australia	MOMENTUM 3, INTERMACS, IMACS, ISHLT, ANZCOTR, SVHS Add Value and MCS, section 5.2.4.3

Abbreviations: ANZCOTR, Australia and New Zealand Organ Transplant Registry; CPR, cardiopulmonary registry; HTx, heart transplant; IMACS, International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; ISHLT, International Society for Heart & Lung Transplantation; MCS, mechanical circulatory support; SVHS, St. Vincent's Hospital Sydney; VAD, ventricular assist device;

5.2.4.1 Transition probabilities

Time-dependent transition probabilities were used to build a clinically realistic model. Survival analysis methods have been described in Chapter 4. The transition probability was calculated as 1 minus the ratio of the survivor function at the end of the interval to the survivor function at the beginning of the interval: $tp(tu) = 1 - S(t)/S(t-u)$, where S is the survivor function and u is the length of the Markov cycle.(200) Patients remain in the state with the probability of 1 minus sum of the other transition probabilities.

5.2.4.1.1 Published survival curves, methods to derive data

Pseudo-individual patient data were generated from published Kaplan-Meier curves (see section 8.12 for detailed methods). The published curve was pasted into Enguage Digitizer[32] with survival curves estimated per month using linear interpolation ('Vlookup' function in Excel®). In this chapter, the Hoyle and Henley (2011) method was used, which estimated underlying individual patient data using the survival probabilities at each time point *t* from the KM curve as *S(t)*, and the number of patients at risk as *R(t)*(201). Tierney et al. (2007) provide a spreadsheet using extracted KM data to estimate hazard ratios (HR) and patient numbers at risk if these were not reported.(202) The numbers of events and censorships were estimated assuming censoring is constant within each time interval and the events are interval censored, and it was assumed that at maximum follow-up time no patients were at risk, as all patients are censored.(201)

5.2.4.1.2 Time-to-Event - Waiting list to Death

Transition probabilities were estimated from the *'Waiting list'* health state to *'Death' and 'Death (Other)'*. The possible options from waiting list were 1) remain without intervention; 2) removed from waiting list due to 'patient condition improving', 'too ill', 'patient declined', 'transferred to interstate list' or 'removed unspecified'; 3) heart transplant; and 4) death due to 'died waiting'. The transition probabilities are presented in Table 5-3. Over 2015-2016 there were an average of 207 patients.(149) The probability of death was converted to rates using the formula P=1-exp(-r*t) and converted back to annual probabilities after adjustments for age-related mortality. Based on clinical expert opinion, the transition probability of 2.9% annually for death on the waiting list was underestimated due to some patients being removed and dying soon after, as follow-up stops after removal. Hence, the transition probability of *'waiting list'* to *'Death'* was adjusted as 0.02637*2 (clinical expert opinion). The transition probability from 'waiting list' to 'Death (Other)' was based on age-related mortality and remained unadjusted.

Table 5-3: Transition probabilities for HTx waiting list health states, N=207

Transition probability	Wait list activity	n	% over a year	Rate for a year
	Total remain on wait list end of period	67	32.4%	-
'wait list' to *'removed'*	Total removed from wait list (no HTx)	16	7.7%	-
'wait list' to *'HTx'*	Total transplanted	118	57.0%	-
''	Total death	6	2.9%	-
wait list' to *'Death (heart failure)*	Death from heart failure		2.6%	0.0262
'wait list' to *'Death (other causes)'*	Death from 'other causes' – age related	-	0.26%	0.0027

Source:(149)

[32] http://markummitchell.github.io/engauge-digitizer/

5.2.4.1.3 Time-to-Event – Waiting list to Removed

In the CPR dataset, there were 102 patients on the waiting list with 35 removal events due to deterioration or improvement (Figure 4-15). See Table 8-38 for the transition probabilities.

5.2.4.1.4 Time-to-Event – Waiting list to HTx

The transition probabilities for receiving a HTx were corrected for the competing risk of death for those not supported by VAD. The Add Value and CPR analysis indicated that if a patient received a VAD, this led to a longer time to HTx. The time to HTx for those who were not supported with VAD and corrected for competing death (n=1) was based on 53 patients. See Table 8-39 for the transition probabilities.

5.2.4.1.5 Time-to-Event - Waiting list to VAD

In Add Value, for patients on the waiting list, patients were censored if they received a HTx, died or at study end. The Kaplan-Meier plot of time to VAD assuming BTC patients wait 0.01 days is presented in Figure 4-7. However, using the BTC patients underestimates the time to VAD so only BTT patients (n=7) are used for the transition probabilities for time to VAD implant once listed on HTx wait list (see section 8.13.5).

5.2.4.1.6 Time-to-Event – Ineligible to VAD

In Add Value, of the 25 patients who received a VAD during the study period 18 received a VAD before being listed on the waiting list. The Kaplan-Meier plot of time to receive a VAD and added onto the waiting list (n=18) is presented in Figure 4-8. See Table 8-37 for the transition probabilities.

5.2.4.1.7 Time-to-Event – Ineligible to Death

It was assumed that the patients who were initially ineligible for a HTx had a higher risk of death than those currently on the waiting list. Therefore, the transition probability for *'Ineligible'* to *'Death'* is the same as *'Waiting List'* to *'Death'* with a multiplier of 1.6 applied. The multiplier was tested in the sensitivity analysis.

5.2.4.1.8 Time-to-Event - Removed to death

It was assumed that the persons removed from the waiting list had a higher risk of death than those who were on the waiting list. Therefore, the transition probability for *'Removed'* to *'Death'* is the same as *'Waiting List'* to *'Death'* with a multiplier of 1.5 applied. The multiplier was tested in the sensitivity analysis.

5.2.4.1.9 Time-to-Event – VAD to Removed

In the CPR dataset of the 28 patients who received a VAD, 19 were removed from the wait list during the follow-up period. The Kaplan Meier curve is presented in Figure 4-16. See Table 8-41 for the transition probabilities.

5.2.4.1.10 Time-to-Event –VAD to HTx

There were three published data sources (see Chapter 4) that conducted competing outcomes analysis of VAD to HTx with competing events death and alive on pump (*Table 5-4*). The MOMENTUM 3 trial had 59% indicated for DT, so the time to HTx would be underestimated. Of the SVHS datasets, the CPR dataset did not have enough events to estimate transition probabilities. The IMACs included recent data with the largest sample size and indication of BTT listed with data up to 48 months (4 years). At 12 months, IMACS BTT Listed patients had 28.1% transplanted, which was consistent with the MCS estimate of 31.6%. However, at 24 months, IMACS BTT Listed patients had 42% transplanted, which was lower than the MCS estimate of 50.9%.

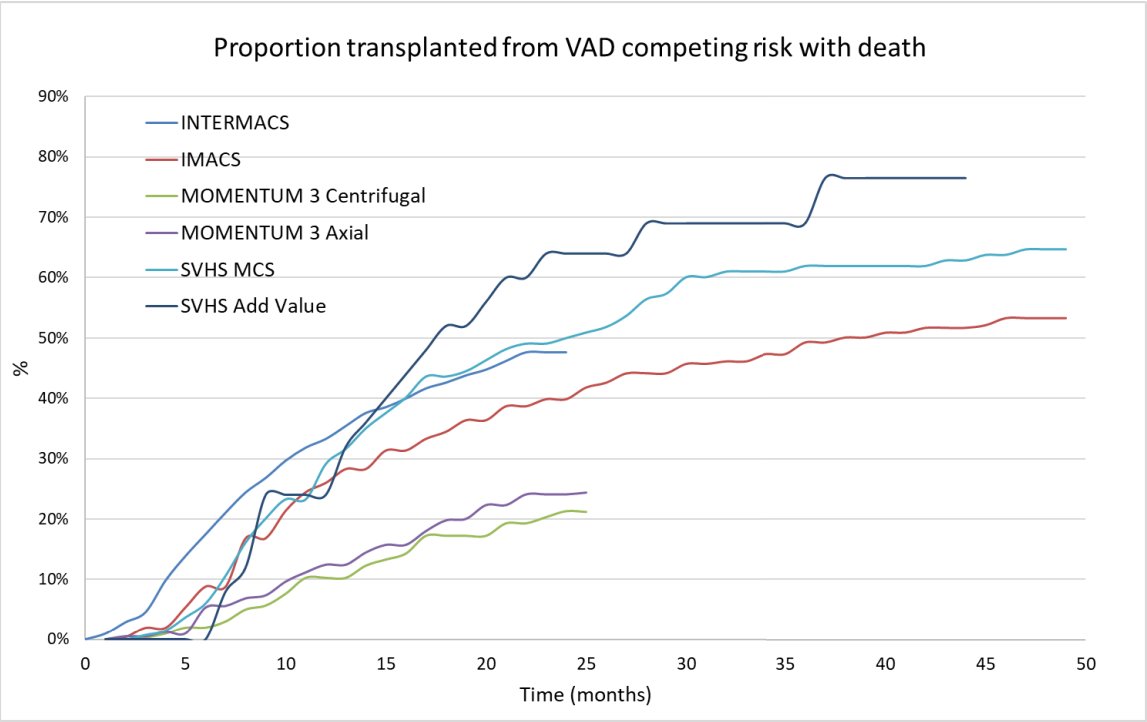
Table 5-4: Sources of transition probability from VAD to HTx

	INTERMACs(51)	**IMACS**	**MOMENTUM 3 trial**	**Add Value**	**MCS**
N	1,375	3,642	366	25	137
Time period	2015-2016	Jan 2013- Dec 2016	2014-2015	2009-2012	2004-2016
Type of VAD	CF-LVADs	CF-LVADs	CF-LVADs, centr and axial		CF-LVADs
Indication	BTT Listed (100%)	BTT Listed (100%)	BTT (25%), BTC (16%), DT (59%)	BTT (72%); BTC (28%)	BTT (93%), BTC (1%), DT (6%)
Follow-up	24 months	48 months	24 months	44 months	45 months
Transplanted at 12 months (%)	34%	28.1%	~ 10% centr and ~12% axial	32.0%	31.6%
Transplanted at 24 months (%)	~47%	~42%	21.2% centr and 24.4% axial	64.0%	50.9%

Abbreviations: CF, continuous flow; BTC, bridge to candidacy; BTT, bridge to transplant.

The different estimates of proportion transplanted over time are presented in Figure 5-4 and associated transition probabilities in Table 8-42. The base case relied on the SVHS MCS data for the estimated transition probabilities between post-VAD to post-HTx (*Table 8-43*). It was assumed that the after 48 months (4 years) there would be 0% transitioning to HTx.

Figure 5-4: Proportion transplanted from VAD from various sources

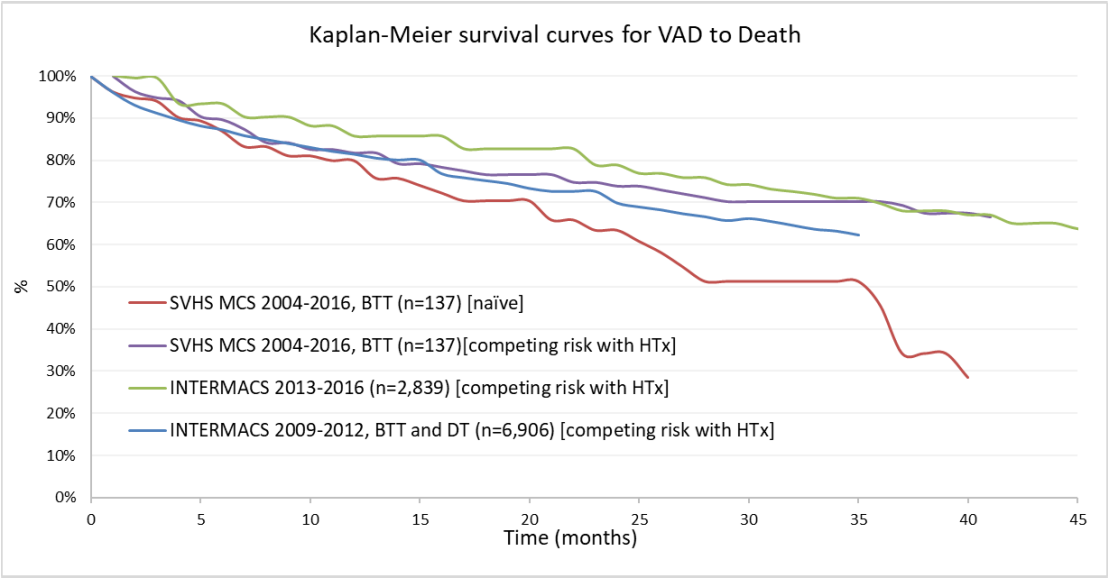


5.2.4.1.11 Time-to-Event – VAD to Death

The survival curves from VAD to death were extracted from INTERMACS and SVHS MCS (Figure 5-5). The two INTERMACS curves indicate that including the DT patients increases the chance of death.(51) The MCS data had fewer patients (n=137) in the analysis and hence the INTERMACS data were preferred. The published INTERMACs KM curve for CF LVAD/BiVAD BTT recipients between 2013 and 2016 (n=2,839) was used for the transition probability *'Alive post-VAD'* to *'Death'*. The base case relied on the KM curve up to 48 months and assumed that afterwards the monthly transition probability of death was 0.009.[33](96) See Table 8-44 for the transition probabilities. The BTT (2013-2016) KM curve was extrapolated to 72 months (6 years) and applied in the sensitivity analysis. The transition probabilities using the SVHS MCS data was applied in the sensitivity analysis. See Section 8.12 for methods.

[33] Long et al. (2014) assumed for HTx eligible patients after 4 years, the monthly transition to HTx was 0.009.

Figure 5-5: Survival curves in SVHS MCS compared to INTERMACS data

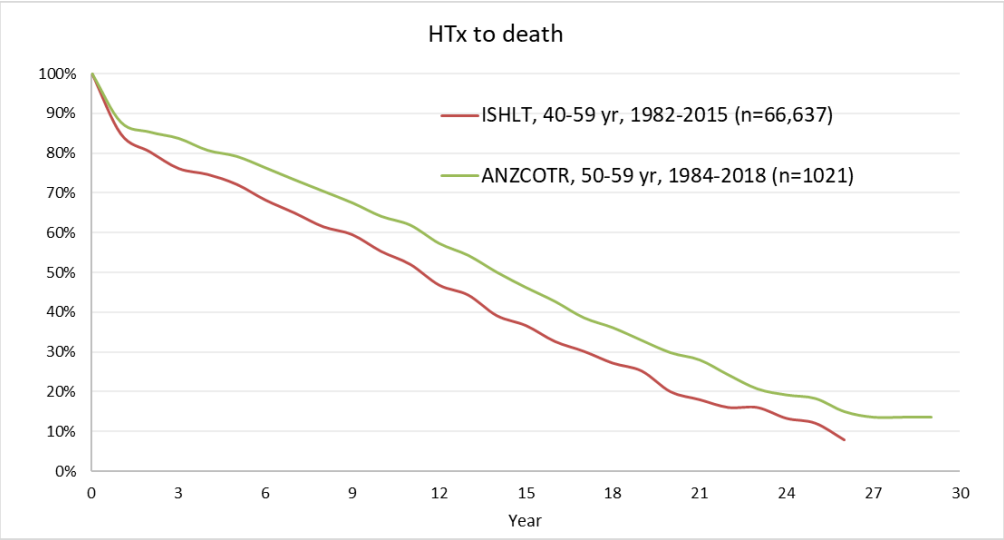


Source: Figure 9 in Kirklin 2017 (51)

5.2.4.1.12 Time-to-Event - HTx to death

The model assumed that survival of HTx recipients was the same regardless of whether they were bridged by VAD, as done in Sutcliffe et al. (2013)(52). This assumption is supported by ISHLT indicating the survival of adult HTx recipients bridged with CF-LVADs vs no LVADs (with or without inotropes) was not statistically significantly different (163)(see Figure 8-16). The ANZCOTR 2016 Annual Report presented the Cutler-Ederer Survival curves (life table) for all HTx recipients by age groups (0-16 years, 17-39 years, 40-49 years, 50-59 years and >59 years) from 1984 to 2018.(70, 149) Those aged 50-59 years (N=1,021) were used in the model as this was the mean age in the Add Value population, and had a median survival of 14 years (*Figure 5-6*). The ISHLT survival curves for adult HTx by age group were split by 40-59 years (median survival was 10.9 years) and were tested in the sensitivity analysis. See Table 8-46 for transition probabilities for ANZCOTR.

Figure 5-6: Survival Curves for heart transplant recipients from ANZCOTR and ISHLT



Source (70, 149, 163)

5.2.4.1.13 Time-to-Event – Age related mortality

Background age-related mortality rates from the ABS were used to determine the transition probability to death from non-heart failure causes.(203) These mortality rates were not corrected to explicitly exclude heart failure causes as the impact would be negligible. The weighted average rate (qx^{34}) of males and females was calculated using the sex distribution from the AddValue dataset of 69% males (53/77). A 50-year-old in Australia can expect to live for another 33.6 years (weighted ex^{35}); therefore, the life expectancy would be almost 84 years. The rates were converted to probabiliies using the formula: p=1-exp(-r*t); see Table 8-46.

5.2.4.2 Extrapolation of survival

5.2.4.2.1 Extrapolation methods

The parameterisation of a range of distributions is presented in the Technical Appendix. The fitted distributions included Weibull, exponential, log-normal, log-logistic and Gompertz. PBAC guidelines note it is preferable to use observed time-to-event data rather than modelled data up to the time point at which the observed data becomes unreliable as a result of small numbers of patients remaining event-free.(197) The PBAC Guidelines specify that the following steps be followed when conducting extrapolations:

[34] Qx is the proportion of persons dying between exact age x and exact age x+1.

[35] Ex is the expectation of life at exact age x.

- Assess whether an assumption of proportional hazards is appropriate beyond the observed data.
- Fit a range of alternative survival models to the observed data (e.g. Weibull) including flexible approaches (e.g. piecewise spline models[36]).
- Assess goodness of fit using visual inspection, Akaike's information criterion (AIC) and Bayesian information criterion (BIC). Justify the base case and test a number of the best-fitting models in the sensitivity analysis.
- Determine the plausibility of the predictions in the unobserved period (e.g. the ongoing hazard ratio, the point of convergence and residual survival in each arm).(197)

5.2.4.2.2 Extrapolation of survival with VAD

The model relied on the published Kaplan-Meier curves for BTT (2013-2016) CF-LVAD in the INTERMACS Registry.(51) The fit statistics for the distributions are presented in *Table 5-5*. The Generalised Gamma had the lowest AIC and BIC, followed by the Weibull. The Weibull distribution was used as the Generalised Gamma model could not converge using the flexsurv and flexsurvreg function in R.

Table 5-5: INTERMACS VAD survival for 36 months, fit statistics for distributions

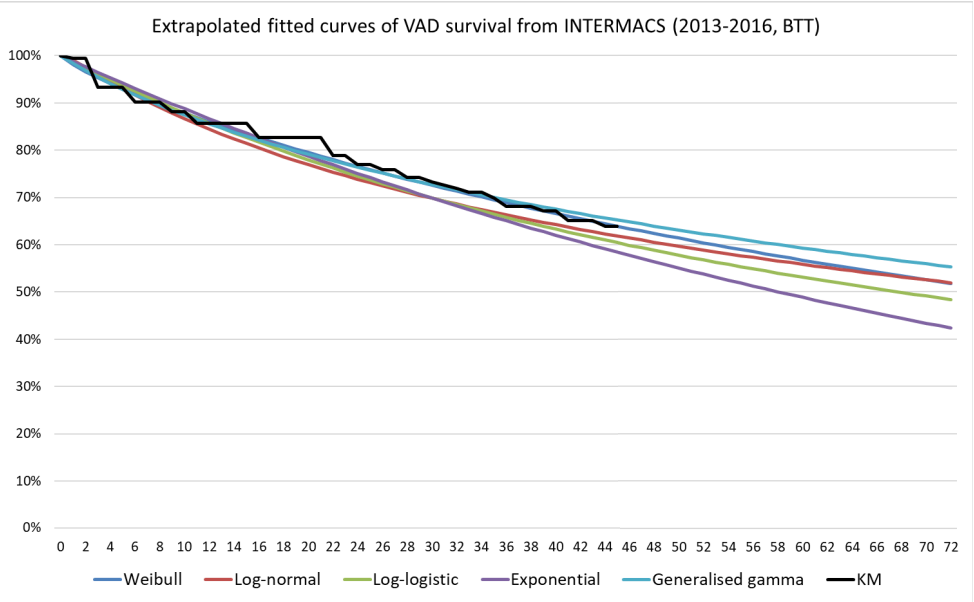
	Log-likelihood	AIC	BIC	Intercept	Intercept SE	log_scale	log_scale SE
Weibull	-2487.45	4978.90	4990.66	4.78	0.11	0.20	0.04
Log-normal	-2499.93	5003.87	5015.62	4.37	0.06	0.62	0.02
Log-logistic	-2509.40	5022.80	5034.55	4.21	0.06	-0.04	0.03
Exponential	-2497.78	4999.55	5011.30	4.43	0.05	4.24	N/A
Logistic	-2736.50	5477.00	5488.75	32.84	0.85	2.30	0.04
Generalised gamma	-2481.61	4967.23	4978.98	-	-	-	-
Gompertz	-3776.60	7557.19	7568.94	-	-	-	-

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion; SE, standard error.

The sensitivity analyses relied on the fitted curves extrapolated to 72 months (6 years) using the Weibull distribution (*Figure 5-7*). See *Table 8-45* for the transition probabilies.

[36] Spline functions have multiple points of inflexion and are a method of modelling a continuous covariate without meeting stringent assumptions of a linear scale.(167)

Figure 5-7: Extrapolation of VAD survival from INTERMACS (2013-2016, BTT)



Source: Figure 9, Kirklin 2017(51)

5.2.4.3 Applicability

The assessment of applicability of data from the published US data to Australian ESHF patients is presented in

Table *5-6*. The variables compared were country, age, gender, NYHA and indication. The INTERMACS 2012 report (134) noted the mean age of VAD recipients was higher than for the VAD recipients in Australia. This may be related to the higher proportion of DT recipients (ineligible for HTx) in the INTERMACS registry compared to Australia. Overall, the patients in the INTERMACS may have worse prognosis than the SVHS patients, meaning that using INTERMACS data for LVAD survival may underestimate survival. The use of SVHS MCS data for LVAD survival was tested in a scenario analysis. The IMACS registry was used for the transition from *'Alive post-VAD'* to *'Alive post-HTx'* using the BTT listed curves.

Table 5-6: Applicability of published US data to Australian ESHF patients

Attribute	MOMENTUM 3	INTERMACS	IMACs	ISHLT	ANZCOTR	SVHS Add Value	SVHS MCS (CF devices)
Data type	RCT	Published registry	Published registry	Published registry	Published registry	Retrospective cohort, IPD	Registry, IPD
Country	U.S.	U.S	Worldwide, 35 countries	Worldwide, 75% of HTx activity	Australia and New Zealand	Australia	Australia
Time period	2014-2015	2006-2016	2013-2017/18	2009 to June 2016	1984-2016	2009-2013	2004-2016
n	366	17634, Kirklin et al. 2017.	14,062	30,503	2,974 (1984-2018)	77	137
Age, years, mean	61 study device and 59 control device	NS 56 years Kirklin et al. 2012	23% 30-49 60% 50-60 years	55	48	49.5	53.7
Gender, male n (%)	79% study device and 81% control device	NR	NR (79%)	NR (75%)	2,003 (67%)	53 (69%)	109 (80%)
NYHA, n(%)	N=366 NYHA III/IV = 366 (100%)	NA	NA	-	N=124 NYHA I/II = 38 (31%) NYHA III = 72 (58%) NYHA IV = 14 (11%)	N=71 NYHA I = 0 (0%) NYHA II = 11 (15%) NYHA III = 26 (37%) NYHA IV = 34 (48%)	NA
INTERMACS, n (%)	NR	N= 6,701, Kirklin et al. 2015. 1 = 961 (14%) 2 = 2416 (36%) 3 = 198 (30%) 4 = 968 (15%) 5 = 198 (3%) 6 = 81 (1%) 7 = 44 (1%) Not specified = 46 (1%)	1 = 2,405 (17%) 2 = 4,714 (34%) 3 = 4,558 (32%) 4 = 1,817 (13%) 5 = 298 (2%) 6 = 87 (1%) 7 = 66 (1%) Not specified = 117 (1%)	NR	NR	N=42[a] 1= 8 (19%) 2 = 16 (38%) 3 = 2 (5%) 4 = 2 (5%) 5 = 0 (0%) 6 = 4 (10%) 7 = 8 (19%) Not specified = 2 (5%)	N=151 1 = 38 (28%) 2 = 79 (58%) 3 = 20 (15%) 4 = 0 5 = 0 6 = 0 7 = 0
Indication, n (%)	BTT = 91 (25%) BTC = 58 (16%) DT = 217 (59%)	BTT = NR (26%) BTC = NR (23%) DT = NR (50%)	BTT = 3,984 (28%) BTC = 4,072 (29%) DT = 5,724 (41%) Other = 282 (2%)	Pre-HTx VAD 43.7% (LVAD + RVAD)	Pre-HTx VAD	BTT = 7 (28%) BTC = 18 (72%) DT = 0 (0%)	BTT = 127 (93%) BTC = 2 (1%) DT = 8 (6%)

Abbreviations: ANZCOTR, Australia and New Zealand Organ Transplant Registry; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; N/A, Not Applicable; NS, not specified; NYHA, New York Heart Association;SVHS, St. Vincent's Hospital Sydney.
Note: a – Data only collected 42/77 patients, therefore 35 patients missing.

5.2.5 Health outcomes

The main outcome was the Quality-Adjusted Life Year, which includes both mortality and morbidity. Life Years (LY) were measured, the cause of death could be attributed to heart failure or background age-related mortality. Quality of life was associated with the NYHA class, which is impacted by the type of intervention received. Numbers of deaths, HTx and VADs were reported. Trackers were applied in the model to estimate the proportion of patients experiencing a bridged HTx or unbridged HTx and for BTC VAD or BTT VAD. A microsimulation was run for 1,000,000 simulations to obtain the proportions of the abovementioned trackers.

5.2.5.1 NYHA Functional Status and Quality of Life

The NYHA classification of heart failure is extensively used as a functional classification of disease state.(204) There are four classes of NYHA: I, II, III and IV, with NYHA IV being the most severe. Mapped EQ-5D scores to each NYHA class were applied to the distribution of NYHA from the SVHS Add Value dataset. This approach was similar to that used in published economic evaluation (95, 100), discussed in Chapter 3.(107)

5.2.5.1.1 Utility values for NYHA Class

Quality of Life was not measured directly in the SVHS Add Value patients so the model relied on published values. The PBAC guidelines require that the source and method from externally derived health state utilities be described(197). The published utility values for NYHA classes are presented in *Table 5-7*. The mapped EQ-5D scores to NYHA class were reported by Göhler et al.(2009)(120) and these were relied on in the base case. The range of values from Lewis et al. (2001)(205) were not used in the model but indicate consistency with the Göhler et al. values.

Table 5-7: Utility values for NYHA Classses

Health State	Value	Upper	Lower	Min-Max	Tool	N, Country	Source
NYHA Class I	0.855	0.845	0.864		EQ-5D	1,395 subjects, Eplerenone Post-acute	(120)
NYHA Class II	0.771	0.761	0.781			Myocardial Infarction Heart Failure	
NYHA Class III	0.673	0.665	0.69			Efficacy and Survival Study	
NYHA Class IV	0.532	0.48	0.584			(EPHESUS) trial. U.S.	
NYHA Class I and II	-	-	-	0.8-1	Average	99 subjects, mean NYHA score of 2.9,	(205)
NYHA Class III and IV	-	-	-	0.3-0.65	TTO and SG	mean age 52 years. U.S.	

Abbreviations: EQ-5D, European Quality of Life-5 Dimensions; NYHA, New York Heart Association; SG, standard gamble; TTO, time trade-off.

5.2.5.1.2 Proportion in NYHA Classes

The NYHA status for each health state is presented in *Table 5-8*. Patients in the *'Ineligible'* health state would have NYHA scores from the seven BTC patients in Add Value. The *'Waiting list'* health state NYHA scores were based on the 366 MOMENTUM 3 patients and it was assumed to be the same for the *'Removed'* health state. The Add Value reported the NYHA class at follow-up admission at 1-year post VAD (n=6), pre-HTx (n=52) or pre-death. In a scenario analysis, post-VAD distribution was based on the adjusted ROADMAP figures. Relative change in average NYHA score post-LVAD from baseline is 42% (3.46-2)/2. Assume that 42% of baseline NYHA III and NYHA IV will be distributed across the lower level NYHA equally to get NYHA average of 3.16.

Table 5-8: Proportion in each NYHA Class status in each health state

	Proportion in each NYHA class			
Health State	**NYHA I**	**NYHA II**	**NYHA III**	**NYHA IV**
Base case				
Baseline, waiting list n=366(180)	0.00%	0.00%	4.04%	95.96%
Removed, assumption	0.00%	0.00%	4.04%	95.96%
Ineligible, n=18 (bridge to candidacy) Add Value	0.00%	0.00%	0.00%	100.00%
Alive Post-HTx, n=52 Add Value	11.54%	23.08%	42.31%	23.08%
Alive Post-VAD, n=6 Add Value	0.00%	16.67%	16.67%	66.67%
Death (HF), assumption	0	0	0	0
Death (other causes), assumption	0	0	0	0
Additional sources				
Pre-transplant status, all ages, 2016(149)	38%		58%	11%
Wait List, n=71 Add Value	0.00%	15.49%	36.62%	47.89%
Scenario Analysis - ROADMAP, n=71(206)				
Baseline, average = 2	0	0	54%	46%
Post-LVAD, average = 3.46	25%	52%	21%	2%
Adjusted Add Value using ROADMAP, average = 3.16	14.07%	14.07%	14.07%	57.8%

Source: estimated from AddValue, ANZCOTR 2016 and ROADMAP

5.2.6 Resource use and Costs

There are two types of costs: the one-time cost as a patient enters a health state (if applicable) and the ongoing hospitalisations for the health states. The initial hospitalisation cost for LVAD and HTx was provided in Table 4-19; see Chapter 4.

5.2.6.1 Initial costs

Donor heart procurement

The procurement costs for donor hearts are built into the infrastructure of hospitals and are therefore challenging to identify. The Australian Hospital Pricing guidelines specify three episodes in posthumous organ donation: 1) donor episode prior to death (not relevant in this analysis); 2) posthumous care episode; and 3) recipient episode (APDC dataset).(207) The posthumous care

episode is allocated as 'care type 9 – organ procurement –posthumous'[37] and the National Hospital Cost Data Collection (NHCDC) reported the cost of organ procurement from 48 hospitals and 295 separations in Australia for 2015-2016, the average cost per separation being $27,651 (170) ($29,647 (170) in $2019).

Under Policy D, the hypothetical increase in available donor hearts was due to donation by circulatory death (DCD) and a promotional campaign. DCD via the Organ Care System for 50% of HTx at $40,000 each was applied.(196) In 2018, 14% of HTx performed were DCDs (8/54) at SVHS. The cost of an advertising campaign in Australia would be ~$17.8M(208, 209) based on 2010-2012 data. To inform the model, these costs were divided by the number of organ recipients (deceased and live, n=10,714) in 2016-2017 (210), amounting to $1,665 dollar per organ recipient.

Ventricular Assist Device Procurement

The cost of the VAD prosthesis ($95,000 (76)) which is reimbursed by the Federal Government to private health insurers is included in the APDC admission of $279,478. In a scenario analysis, the cost of the LVAD prosthesis was reduced by 50% and 75% (see *Table 5-9*).

Table 5-9: Price reductions in VAD prosthesis, $2019

Previous Value	New Value Calculation	Interpretation	Cost of device
$279,478.25	-	Base case	$95,000
$279,478.25	$231,978.25	50% reduction in the cost of the device	$47,500
$279,478.25	$208,228.25	75% reduction in the cost of the device	$23,750

Heart-failure related death

The cost of death from organ failure in a public hospital was $18,151 in 2010 ($21,615) (211) and was applied to the *'Death'* state. A scenario analysis was conducted adding the cost of death from organ failure as a transition rather than a terminal pay-off.

5.2.6.2 Hospitalisations in each health state

Chapter 4 presented the analysis of linked administrative Admitted Patient Data Collection (APDC) and Emergency Department Data Collection (EDDC) from the Add Value retrospective cohort. Hospital data was collected up to a year prior to VAD implant or activation on HTx wait list of 77 patients in NSW. A discussion of the potential confounding issues in the retrospective analysis is presented in Chapter 4. The patients and their observations were classified into the four alive health states, *'Waiting list'*, *'Removed'*, *'Alive with VAD'* and *'Alive with HTx'*.

[37] The Guidelines specify that the Costing Practitioner should consider the following resources for the posthumous care episode: Setting (generally intensive care); Medical/clinician; Nursing; Drugs; Other resources (such as pathology).

Subsequent hospitalisations post-intervention

The average number of hospitalisations per patient for the first 12 months post-VAD and post-HTx was calculated; see Chapter 4 for more details of the costing methodology. This analysis was adjusted for censoring using the Zhang and Tian estimator(175). The Add Value dataset included 25 VADs and 61 HTx recipients with observations for 23 and 56 recipients respectively (as presented inTable 4-24). The cost of subsequent admissions post-VAD and post-HTx were similar in the first 12 months post intervention. The cost of hospitalisation in the *'Waiting list'* health state, observations pre-VAD, pre-HTx (no VAD) and no VAD or HTx were included. The costs of hospitalisations for the *'Removed'* health state were those who did not receive a VAD or HTx since the date of activation onto the wait list. The costs of hospitalisation for the *'Ineligible'* health state were the 12 months prior to VAD for those who were BTC (not yet listed on waitlist).

5.2.7 Model parameters

The transition probability sources are described in *Table 5-10*. The model relied on time-dependent transition probabilities from SVHS. For the transition from *'Alive post-VAD'* to *'Alive post-HTx*' and *'Alive post-VAD'* to *'Death'*, IMACS and INTERMACS were relied on due to longer follow-up allowing for more mature data. The ANZCOTR database informed the transition from *'Alive post-HTx'* to *'Death'* as well as constant transition probability from *'Waiting List'* to *'Death'*, rather than a time-dependent one.

Table 5-10: Transition probability model parameters

Transition probability	Formula in TreeAge	Source
tp_ineligible_death	tp_WL_death*m_ineligible	Assumption
tp_ineligible_deathOther	tbl_age_rel_mort[startAge +_stage;val_col_age_rel_mort]	ABS(203)
tp_ineligible_postvad	tbl_inelig_VAD[startAge+_stage/12;val_col_ineligible_VAD]	SVHS Add Value
tp_postHTx_death	tbl_HTx_death[startAge+_stage;val_col_HTx_death]	ANZCOTR
tp_postHTx_deathOther	tbl_age_rel_mort[startAge +_stage;val_col_age_rel_mort]	ABS
tp_postVAD_death	tbl_VAD_death[startAge +_stage/12;val_col_VAD_death]	INTERMACS
tp_postVAD_deathOther	tbl_age_rel_mort[startAge +_stage;val_col_age_rel_mort]	ABS
tp_postVAD_remove	tbl_VAD_HTx[startAge+_stage/12;val_col_VAD_HTx]	SVHS CPR
tp_postVAD_postHTx	tbl_VAD_removed [startAge+_stage/12;val_col_VAD_remove]	IMACS
tp_remove_death	tp_WL_death*m_notelig	Assumption
tp_remove_deathOther	tbl_age_rel_mort[startAge +_stage;val_col_age_rel_mort]	ABS
tp_WL_death	0.026376708*2	ANZCOTR
tp_WL_deathOther	tbl_age_rel_mort[startAge +_stage;val_col_age_rel_mort]	ABS
tp_WL_posthtx	tbl_WL_HTx[startAge+_stage/12;val_col_WL_HTx]	SVHS CPR
tp_WL_postvad	tbl_WL_VAD[startAge+ _stage/12;val_col_WL_VAD]	SVHS Add Value
tp_WL_remove	tbl_WL_removed[startAge+_stage/12;val_col_WL_remove]	SVHS CPR

The model parameters are presented in Table 5-11.

Table 5-11: Model parameters

Description	Value	Lower	Upper	SE/SD	Distribution	alpha	beta/lambda	Source
Costs ($AUD 2019)								
Cost of campaign in policy D	$1,664.6	$832.3	$3,329.3	$1,664.6	Gamma	1.00	0.001	(208-210)
Death due to organ failure	$21,615.1	$10,807.5	$43,230.1	$21,615.1	Gamma	1.00	0.000	(211)
Ineligible for waiting list pre-VAD	$76,135.5	$50,184.3	$102,084.6	$13,240.1	Gamma	33.07	0.000	Add Value, APDC and EDDC
HTx subsequent admissions	$59,039.8	$29,519.9	$118,079.7	$8,058.3	Gamma	53.68	0.001	Add Value, APDC and EDDC
HTx index admission	$135,456.4	$103,339.0	$381,109.5	$58,894.4	Gamma	5.29	0.000	Add Value, APDC and EDDC
VAD subsequent admissions	$58,419.2	$29,209.6	$116,838.5	$11,117.6	Gamma	27.61	0.000	Add Value, APDC and EDDC
VAD admission initial + prosthesis	$279,478.3	$245,736.0	$404,247.9	$42,408.6	Gamma	43.43	0.000	Add Value, APDC and EDDC
HTx organ procurement	$29,647.9	$14,823.95	$59,295.80	$29,647.90	Gamma	1.00	0.000	(170)
HTx DCD via OCS in policy D	$49,647.9	$24,824.0	$99,295.8	$49,647.9	Gamma	1.00	0.000	{St Vincent's Health Network Sydney, 2015 #602}, assume 50%
Removed admissions	$43,661.5	$21,830.7	$43,661.5	$21,070.9	Gamma	4.29	0.000	Add Value, APDC and EDDC
Waiting list admissions	$36,188.7	$18,094.3	$36,188.7	$9,856.7	Gamma	13.48	0.000	Add Value, APDC and EDDC
Global Variables								
discount rate	0.05	0.03	0.07	-	Beta	-	-	(197)
multiplication factor 'ineligible'	1.6	1.50	1.70					Assumption
multiplication factor 'removed'	1.5	1.40	1.60					Assumption
Cohort start age (years)	50							Add Value
Time horizon	20							Assumption
Probabilities [a]								
% with HTx in D	0.20	0.10	0.30	0.40	-	-	-	Assumption
% with VAD in C	0.20	0.10	0.30	0.40	-	-	-	Assumption
% on WL in A	0.90	0.80	1.00	0.30	-	-	-	Assumption
% on WL in B	0.90	0.80	1.00	0.30	-	-	-	Assumption
% on WL in C	0.70	0.60	0.80	0.46	-	-	-	Assumption
% on WL in D	0.70	0.60	0.80	0.46	-	-	-	Assumption
% in ineligible health state	0.10	0.05	0.20	0.30	-	-	-	Assumption
NYHA Class I post HTx	0.12	0.04	0.22	0.04	Beta	5.88	45.12	Add Value, follow-up with HTx
NYHA Class I ineligible	0.00	-	-	0.00	Beta	-	-	Add Value, VAD as BTC
NYHA Class I VAD	0.00	-	-	0.00	Beta	-	-	Add Value, follow-up with VAD
NYHA Class I on waiting list[a]	0.00	-	-	0.00	Beta	-	-	Baseline value(180)
NYHA Class II post HTx	0.23	0.13	0.35	0.06	Beta	11.77	39.23	Add Value, follow-up with HTx
NYHA Class II ineligible	0.00	-	-	0.00	Beta	-	-	Add Value, VAD as BTC
NYHA Class II VAD	0.17	0.00	0.56	0.15	Beta	0.83	4.17	Add Value, follow-up with VAD

Description	Value	Lower	Upper	SE/SD	Distribution	alpha	beta/lambda	Source
NYHA Class II on waiting list[a]	0.00	-	-	0.00	Beta	-	-	Baseline value(180)
NYHA Class III post HTx	0.42	0.29	0.56	0.07	Beta	21.58	29.42	Add Value, follow-up with HTx
NYHA Class III ineligible	0.00	-	-	0.00	Beta	-	-	Add Value, VAD as BTC
NYHA Class III VAD	0.17	0.00	0.56	0.15	Beta	0.83	4.17	Add Value, follow-up with VAD
NYHA Class III on waiting list[a]	0.04	0.02	0.06	0.01	Beta	14.74	350.26	Baseline value(180)
NYHA Class IV post HTx	0.23	0.13	0.35	0.06	Beta	11.77	39.23	Add Value, follow-up with HTx
NYHA Class IV ineligible	1.00	-	-	0.00	Beta	-	-	Add Value, VAD as BTC
NYHA Class IV VAD	0.67	0.25	0.96	0.19	Beta	3.33	1.67	Add Value, follow-up with VAD
NYHA Class IV on waiting list[a]	0.96	0.94	0.98	0.01	Beta	350.26	14.74	Baseline value(180)
Transition Probabilities								
Waiting list to death	0.0264*2	0.027	0.09	0.02	Beta	10.862	195.138	(149) with assumption
Ineligible to death	Waitlist_death * m_ineligible	0.05	0.13	0.02	Beta	17.38	188.621	(149) with assumption
Removed to death	Waitlist_death * m_removed	0.05	0.12	0.02	Beta	16.29	189.707	(149) with assumption
ineligible to Death Other	Various	-	-	-	Beta	-	-	(212)
ineligible to VAD	Various	-	-	-	Beta	-	-	Add Value, SVHS
HTx to death	Various	-	-	-	Beta	-	-	(149)
HTx to Death Other	Various	-	-	-	Beta	-	-	(212)
VAD to death	various if cycle < 3 years then 3% annual probability	-	-	-	Beta	-	-	(51),(96)
VAD to Death Other	Various	-	-	-	Beta	-	-	(212)
VAD to HTx	various if cycle < 4 years then 0% annual probability	-	-	-	Beta	-	-	MCS Registry, SVHS
VAD to removed	Various	-	-	-	Beta	-	-	CPR Registry, SVHS
Remove to Death Other	Various	-	-	-	Beta	-	-	(212)
waiting list to Death Other	Various	-	-	-	Beta	-	-	(212)
waiting list to HTx	Various	-	-	-	Beta	-	-	CPR Registry, SVHS
waiting list to VAD	Various	-	-	-	Beta	-	-	Add Value, SVHS
waiting list to removed	Various	-	-	-	Beta	-	-	CPR Registry, SVHS
Utility Values								
NYHA Class I	0.855	0.85	0.86	0.01	Beta	1191.87	202.13	(120)
NYHA Class II	0.771	0.76	0.78	0.01	Beta	1074.77	319.23	(120)
NYHA Class III	0.673	0.67	0.69	0.01	Beta	938.16	455.84	(120)
NYHA Class IV	0.532	0.48	0.58	0.01	Beta	741.61	652.39	(120)

Abbreviations: APDC, Admitted Patient Data Collection; CPR, CardioPulmonary Registry; DCD, donation after circulatory death; EDDC, Emergency Department Data Collection; HF, heart failure; HTx, heart transplant; NHCDC, National Hospital Cost Data Collection, NYHA, New York Heart Association; OCS, Organ Care System; WL, waiting list; VAD, ventricular assist device. Policy A = Previous policy with no LVAD, Policy B = Current policy with LVAD, Policy C = Policy B with increase VAD, Policy D = Policy A with increase HTx.

Note: a. The NYHA Class status for the Ineligible health state was assumed to be the same as for the Waiting list and Removed.

b. Add Value was a retrospective cohort study of patients at SVHS. CPR and MCS are registries of HTx waiting list patients and MCS recipients at SVHS, respectively.

c. Uncertainty around parameters was based on sampling error where available. The alpha and beta parameters for the beta distributions (probabilities and utilities) and alpha and lambda parameters for gamma distributions (costs) were calculated. Beta distribution alpha and beta; alpha = ((%^2*(1-%)/(SE^2))-%); beta = alpha*(1-%)/%. Gamma distribution alpha = (mean^2)/(SD^2), if SD unknown assume same as mean, lambda = 1/(SD^2/mean). For cost, if the SD, maximum and minimum were not available it was assumed that costs were halved (lower) and doubled (upper) and that SD was equal to the mean. Where dispersion data were not available, confidence intervals were calculated using the sample mean and N. Standard errors were calculated from sample proportions using [sqrt (pop % (1 – pop %)/N)]. The 95% lower and upper confidence intervals are estimated as follows; =betainv (0.025 for lower or 0.975 for upper, alpha, beta).

A probabilistic sensititivity analysis was conducted. Probabilistic distributions were fitted by method of moments, where the mean and standard errors reported are equated to the estimates of mean and SE of the given distribution. These equations are then solved to give the appropriate distribution parameters. The alpha and beta parameters for the beta distribution (probabilities and utilities) and alpha and lambda parameters for gamma distribution (costs) were calculated.[38] For cost, if the SD, maximum and minimum were not available it was assumed that costs were halved (lower) and doubled (upper) and that SD was equal to the mean. Where dispersion data were not available, confidence intervals were calculated using the sample mean and N.[39]

5.2.8 Markov model validation

Model validation was based on the guidelines by Assessment of the Validation Status of Health-Economic decision models (AdViSHE) Validation.(213) Face validity was assessed by clinical expert Dr Christopher Hayward, a cardiologist from SVHS. Face validity was also assessed via the model structure published economic models in ESHF. Operational validation refers to validation against empirical data. These model traces were compared with empirical data using data sources used in the model (dependent validation) to the ANZCOTR. The median survival reported in the age-matched cohort (50-60 years) in the ANZCOTR Annual Report was 14 years compared to the modelled output in Policy D.

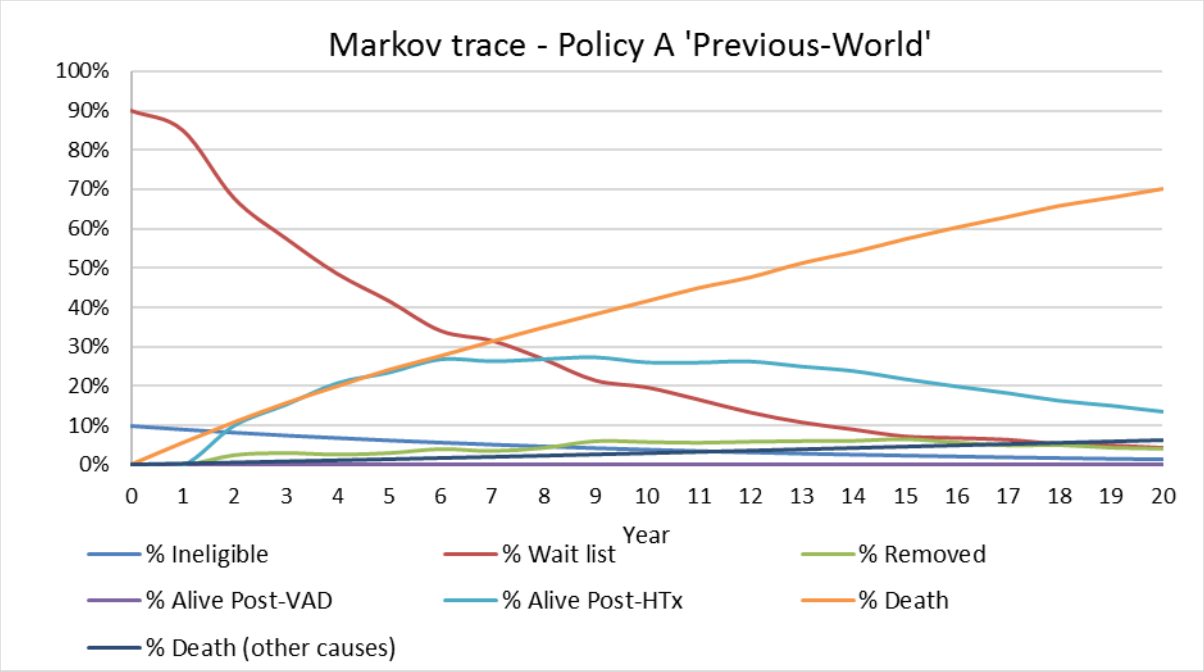
Model traces provide a depiction of the model and inform the face validity of the model logic, computerisation and external validity.(197) The Markov traces test the logic of the patient flow through the model, the proportion of patients are listed in each health state at each time point. The Markov traces for the policy options are presented in *Figure 5-8* to *Figure 5-11* over the 20-year time horizon.

Under Policy A, patients remain on the waiting list much longer than under Policy B ('Current world') because there is no opportunity to be supported with a VAD in the interim. Another key difference is that under Policy A, 10% of patients who begin in the *'Ineligible'* health state either remain or transition to the death health states. However, under Policy B some patients are able to transition to VAD and are then added to the waitlist. Some patients are able to transition to an LVAD after 1 year because the cycle length is 1 year.

[38] Beta distribution alpha and beta; alpha = ((%^2*(1-%)/(SE^2))-%); beta = alpha*(1-%)/%. gamma distribution alpha = (mean^2)/(SD^2), if SD unknown assume same as mean, lambda = 1/(SD^2/mean)

[39] Standard errors were calculated from sample proportions using [sqrt (pop % (1 – pop %)/N)]. The 95% lower and upper confidence intervals are estimated using =betainv (0.025 for lower or 0.975 for upper, alpha, beta)

Figure 5-8: Markov traces of Policy A



The difference between Policy C and Policy B is that a proportion of patients (20%) begin in the *'Alive post-VAD'* health state. More patients remain in the *'Alive post-VAD'* health state in Policy C compared to Policy B (Figure 5-9). Under Policy C, slightly less time is spent than under Policy B in the *'Alive post-HTx'* health state.

Figure 5-9: Markov traces of Policy B

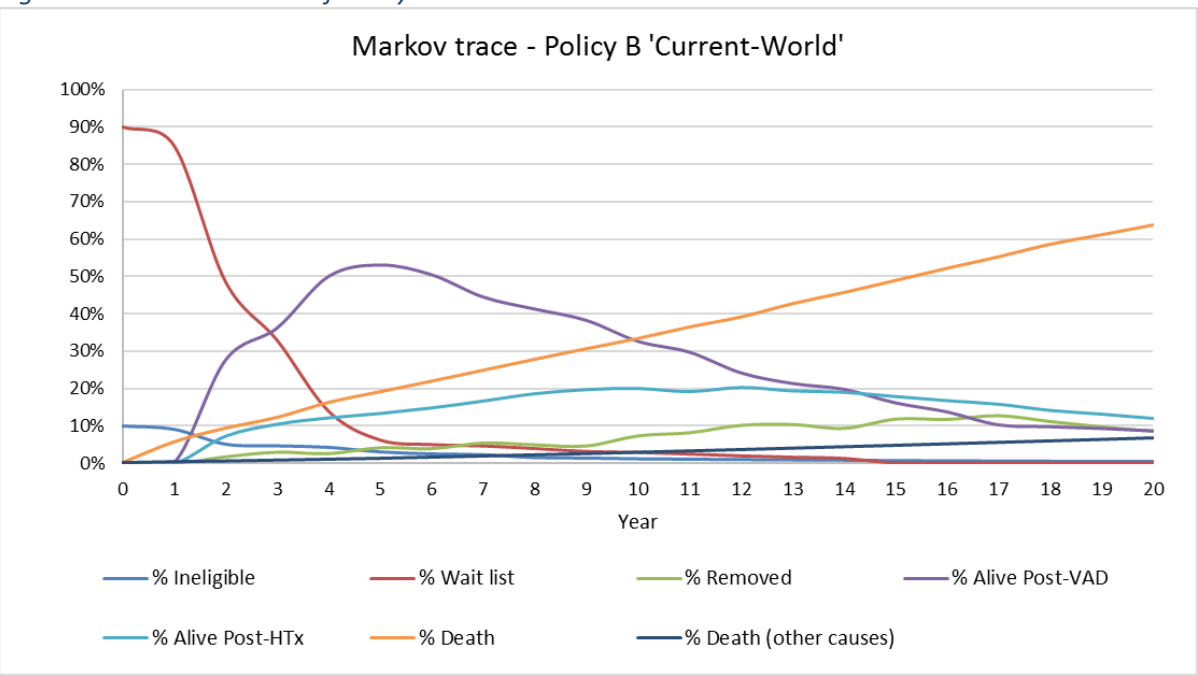
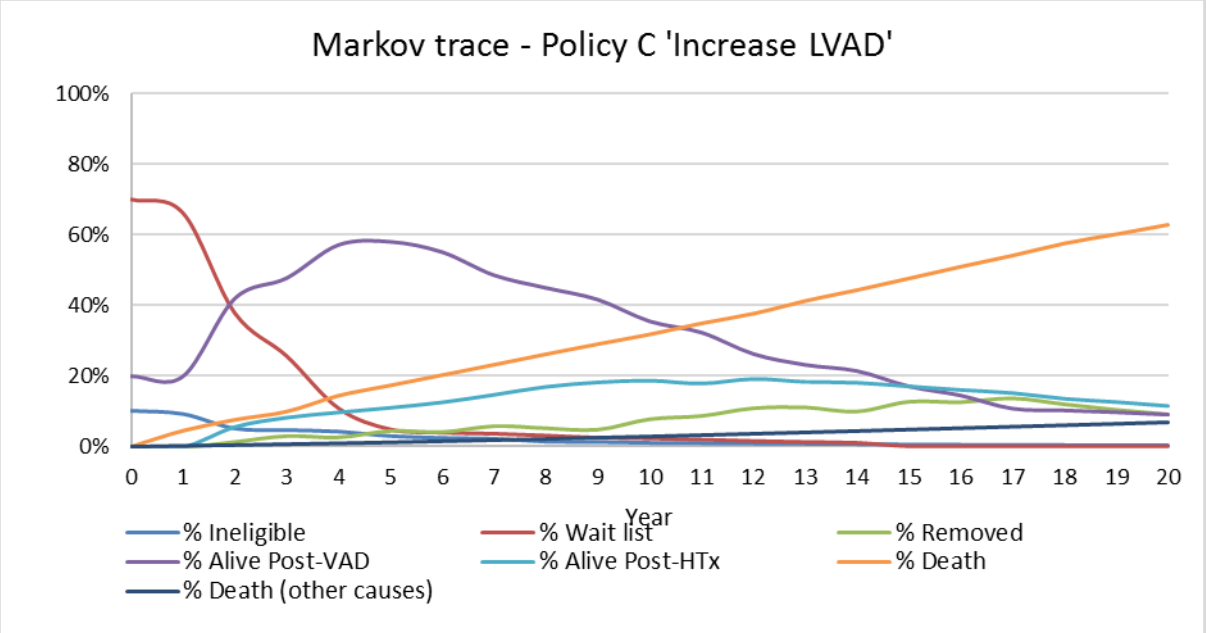
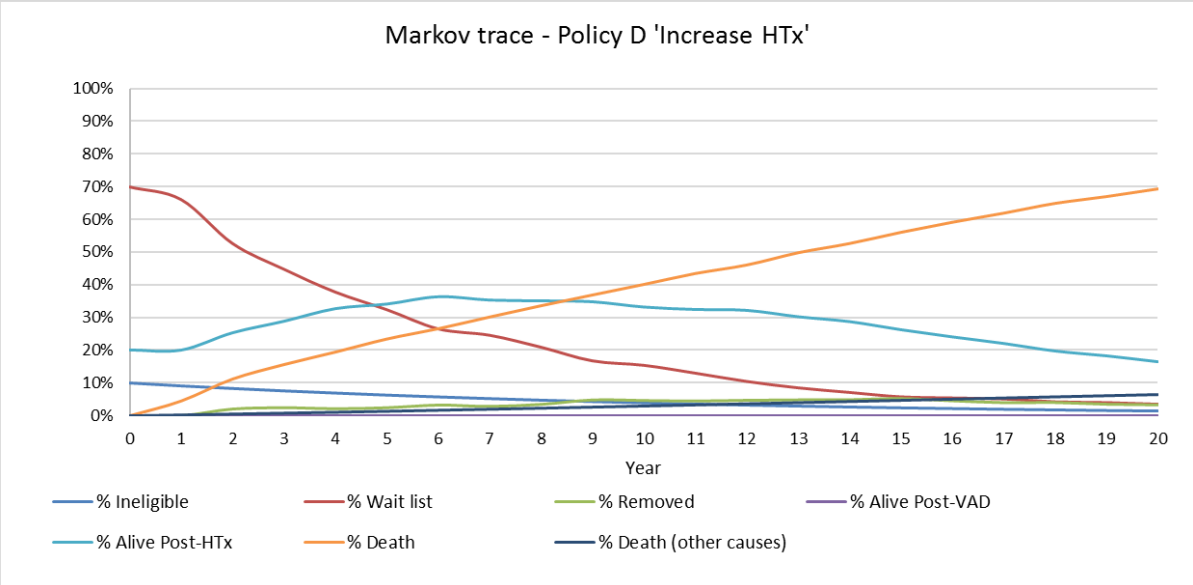


Figure 5-10: Markov traces of Policy C



In Policy D, more patients begin and remain in the '*Alive post-HTx*' health state (Figure 5-11). Consistent with Policy A, no time is spent in the *'Alive post-VAD'* health state.

Figure 5-11: Markov traces of Policy D



5.2.9 Sensitivity analysis

Sensitivity analyses were conducted to identify the main drivers of uncertainty in the model and in accordance with the published guidelines.(214) There are three common types of sensitivity analyses in economic modelling: 1) first-order uncertainty; 2) second-order uncertainty; and 3) probabilistic

sensitivity analysis.(200) First-order uncertainty refers to uncertainty around model assumptions and is addressed via scenario analysis – for instance, assuming that the starting age of the modelled cohort is older and updating the associated survival curves. Second-order uncertainty refers to uncertainty around parameters used within the model. For example, individual parameters such as utility values may be higher or lower than used in the base model. This is addressed by conducting one-way sensitivity analyses by using the 95% CI of the utility estimate. Similarly, a two-way or multiway sensitivity analyses can be conducted on parameter estimates to determine the joint parameter uncertainty. Both first-order and second-order uncertainty are deterministic methods. Probabilistic sensitivity analysis involves the simultaneous consideration of uncertainty around the variables in the model (as stochastic distributions)(8, 200).

5.2.9.1 Probabilistic sensitivity analysis

The cost-effectiveness acceptability curve (CEAC) is used to summarise the joint uncertainty of incremental mean costs and effects (as plotted on the cost-effectiveness plane). The question is summarised as follows: CEAC (λ) = probability[(λ$Effect_A$-$Effect_B$)-($Cost_A$-$Cost_B$)] > 0). The CEAC indicates the probability that an intervention is cost-effective at various ICER thresholds. Time-dependent monthly transition probabilities were applied to appropriate transitions. For months with transition probabilities set to 0 (mean is 0%), a normal distribution of mean = 0, standard deviation =0 was applied rather than a beta distribution.

5.2.9.2 Scenario analyses

Scenario analyses included the following:

1) Removing the *'Ineligible'* health state to exclude BTC patients (see Table 5-1);

2) Transition probabilities from *'Alive post-VAD'* to *'Alive post-HTx'* based on IMACS(161) not MCS;

3) A utility decrement for those removed from the waiting list (0.01);

4) No cost of HF-related death (set to $0);

5) Price reduction of VAD prosthesis (50% = $47,500, and 75% = 23,750, *Table 5-9*);

6) Alternative time horizons (15 years, 10 years, 5 years);

7) Transition probability from *'Waiting list'* to *'Alive post-VAD'* from Year 3 onwards, 50% rather than 0%;

8) Transition probability from *'Alive post-VAD'* to *'Death'* extrapolated to 6 years using Weibull distribution, or using SVHS MCS data to 48 months (n=137) rather than INTERMACs KM curve to 48 months followed by monthly transition probability of 0.009;

9) NYHA class post-VAD adjusted from ROADMAP(206) with NYHA I 14.07%, NYHA II 14.07%, NYHA III 14.07% and NYHA IV 57.8% (*Table 5-8*).; and

10) Removing the *'Waiting list'* health state (see Table 5-1).

5.3 Results

5.3.1 Base-case results

Health outcomes of Policies

Over the 20-year time horizon, patients spent most of their time in death health states under Policy A, followed by Policy D, Policy B and Policy C at 45%, 44%, 38%, and 37% respectively (see Markov traces, Figure 5-8 to Figure 5-11). Most heart failure-related deaths were in Policy A (70%), followed by Policy D (69%), Policy B (64%) and Policy C (63%). There were more VADs implanted in Policy C than B (71% vs. 64%) (*Table 5-12*). The most HTx were conducted in Policy D (49%), followed by Policy A (37%), Policy B (29%) and Policy C (28%). This is reflected in the amount of time spent in the *'Alive Post-HTx'* health state, with the most in Policy D (28%), followed by Policy A (20%), Policy B (15%) and Policy C (14%).

Table 5-12: Average number of deaths, HTx and VAD conducted for the average patient (n=1)

Policy	Death, n	HTx, n	VAD, n	HF-related death
20 years				
Policy A	0.76	0.37	0.00	0.70
Policy B	0.70	0.29	0.64	0.64
Policy C	0.70	0.28	0.71	0.63
Policy D	0.76	0.49	0.00	0.69

Note: Policy A = Previous policy no LVAD, Policy B = Current policy with LVAD, Policy C = Policy B with increase LVAD, Policy D = Policy A with increase HTx.

The proportion of patients experiencing HTx and VAD was further analysed (Table 5-13). Heart transplanted patients under Policy B had around half (15%/28%) bridged and under Policy C more than half (17%/28%) were bridged. Under Policy D, 49% of the cohort experience a HTx; this is because 20% begin in this health state compared to Policy A. For patients who experienced a VAD, under Policy B and Policy C 6% of the patients were bridge to candidacy patients.

Table 5-13: Average proportion of HTx and VAD breakdown

Policy	HTx	Bridged HTx	Unbridged HTx	HTx at start	VAD	VAD BTC	VAD BTT	VAD at start
20 years								
Policy A	**37%**	0%	37%	0%	**0%**	0%	0%	0%
Policy B	**29%**	15%	14%	0%	**64%**	6%	58%	0%
Policy C	**28%**	17%	11%	0%	**71%**	6%	45%	20%
Policy D	**49%**	0%	29%	20%	**0%**	0%	0%	0%

Note: Policy A = Previous policy no LVAD, Policy B = Current policy with LVAD, Policy C = Policy B with increase LVAD, Policy D = Policy A with increase HTx.

Comparison to common baseline (Policy A)

The cost-effectiveness of the current ESHF policy was compared against the previous ESHF policy (Policy A), i.e. prior to the introduction of LVADs. The average benefit associated with Policy A was 10.35 life years saved (LYS) and 4.70 QALYs at a cost of $854,569 per patient over the 20-year time horizon. Compared to policy A, the incremental benefit of policy B is 0.37 LYS (10.72 LYS) and 0.49 QALYs (5.19 QALYs) at an additional cost of $866,506 ($1,709,347). This means that the incremental cost effectiveness ratio (ICER) of the current ESHF policy is $1,721,075 per QALY gained.

The incremental benefit of Policy C is 0.46 LYS (10.81 LYS) and 0.61 QALYs (5.31 QALYs) at an additional cost of 1,056,910 ($1,914,479) per patient over the 20-year horizon. This would yield an ICER of $1,780,350 per QALY gained when compared to Policy A. The incremental benefit of Policy D is 0.06 LYS (10.41 LYS) and 0.24 QALYs (4.94 QALYs) at an additional cost of $312,168 ($1,166,737) per patient over the 20-year horizon. This would yield an ICER of $1,274,605 per QALY gained when compared to Policy A.

Table 5-14: ICER per death avoided between Policies (time horizon 20 years, discounted)

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention Death	Comparator Death	Incremental Death	ICER per death avoided
Time horizon, 20 years (base case)							
Policy B vs. A	$1,709,347	$854,569	$854,778	0.70	0.76	-0.06	$14,208,902
Policy C vs. A	$1,941,479	$854,569	$1,086,910	0.70	0.76	-0.07	$16,120,886
Policy D vs. A	$1,166,737	$854,569	$312,168	0.76	0.76	-0.01	$34,994,796

Note: Policy A is 'Previous world', Policy B is 'Current world', Policy C is 'Increase VAD' and Policy D is 'Increase HTx'

Table 5-15: ICER per LY gained between policies (time horizon 20 years, discounted)

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention LY	Comparator LY	Incremental LY	ICER per LY gained
Time horizon, 20 years (base case)							
Policy B vs. A	$1,709,347	$854,569	$854,778	10.72	10.35	0.37	$2,305,167
Policy C vs. A	$1,941,479	$854,569	$1,086,910	10.81	10.35	0.46	$2,379,831
Policy D vs. A	$1,166,737	$854,569	$312,168	10.41	10.35	0.06	$4,998,196

Note: Policy A is 'Previous world', Policy B is 'Current world', Policy C is 'Increase VAD' and Policy D is 'Increase HTx'

Table 5-16: ICER per QALY gained between policies (time horizon 20 years, discounted)

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention QALY	Comparator QALY	Incremental QALY	ICER
Time horizon, 20 years (base case)							
Policy B vs. A	$1,709,347	$854,569	$854,778	5.19	4.70	0.50	$1,721,075
Policy C vs. A	$1,941,479	$854,569	$1,086,910	5.31	4.70	0.61	$1,780,350
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605

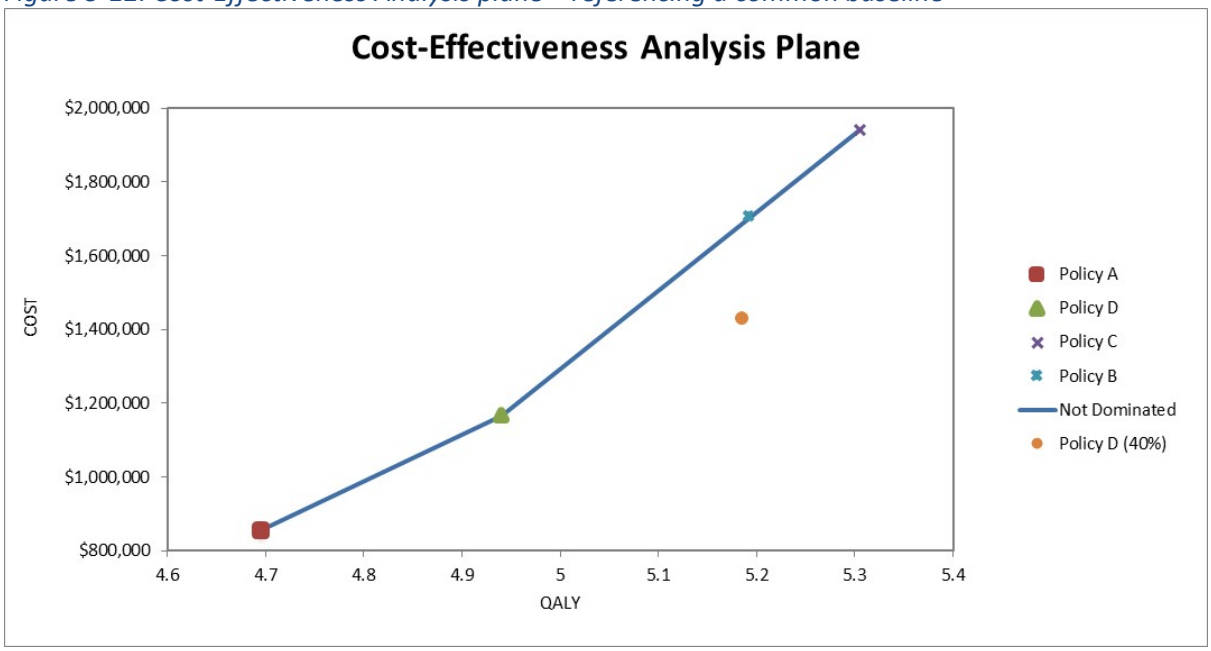
Compared to Policy A, none of the policies would be considered cost-effective using standard WTP thresholds. The largest health gains (and costs) are associated with the implantation of LVADs. Increasing the number of HTx had modest health gains compared to Policy A, which demonstrates

that one of the main benefits of implanting VADs is the ability to treat those patients previously considered ineligible for HTx (i.e. BTC).

Comparison based on least costly alternative

An incremental analysis was conducted and the interventions were ranked from least to most costly (Policy A < Policy D < Policy B < Policy C). There were no dominated options, although Policy B was extendedly dominated[40] by a combination of Policy D and Policy C.(8) Using this ranking, the ICER for Policy D compared to Policy A was $1,274,605 per QALY gained and the ICER for Policy C compared to Policy D was $2,119,155 per QALY gained. In the comparison against current practice, the ICER for Policy C vs. Policy B of $2,155,438 per QALY gained and Policy D vs. Policy B of $2,038,927 per QALY gained. The cost-effectiveness analysis plane is presented in *Figure 5-12* and Figure 5-13. A scenario analysis illustrated that 40% of patients would need to receive a HTx and avoid the *'Waiting list'* health state to receive the same 5.19 QALY gain as Policy B.

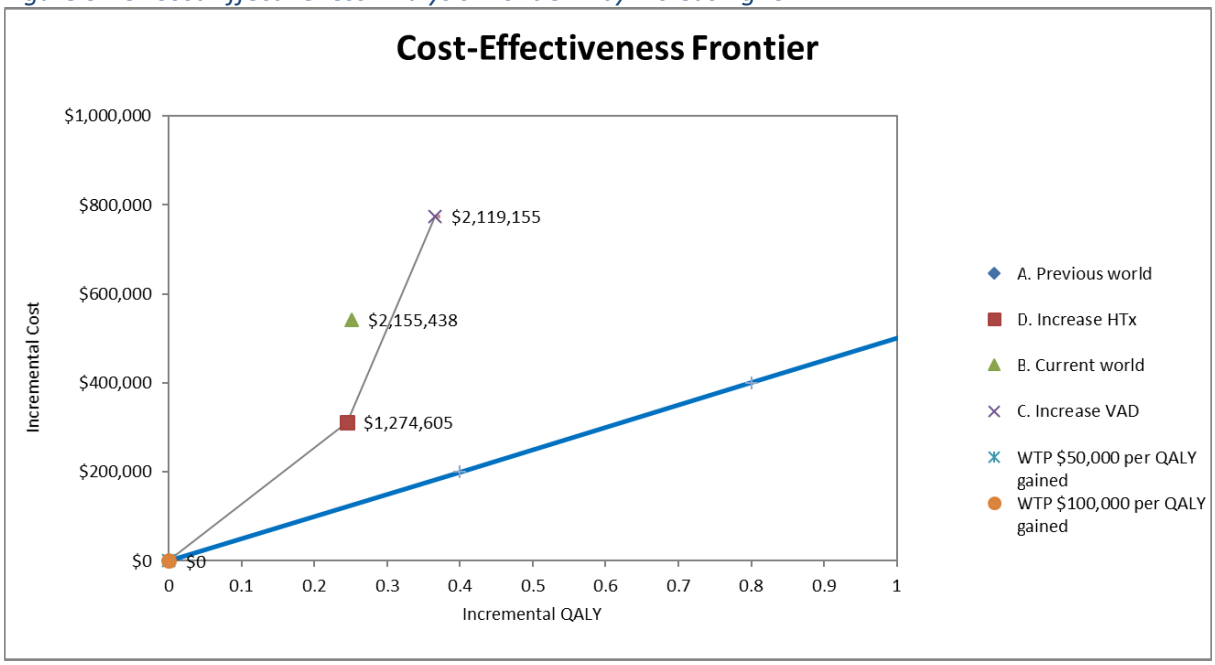
Figure 5-12: Cost-Effectiveness Analysis plane – referencing a common baseline



Abbreviations: HTx, heart transplant; QALY, quality-adjusted life year; VAD, ventricular assist device
Note: Policy B is an extendedly dominated option.

[40] Policy B has a higher incremental cost-effectiveness ratio (relative to Policy C) and fewer benefits than Policy C.

Figure 5-13: Cost-Effectiveness Analysis Frontier – by increasing ICER



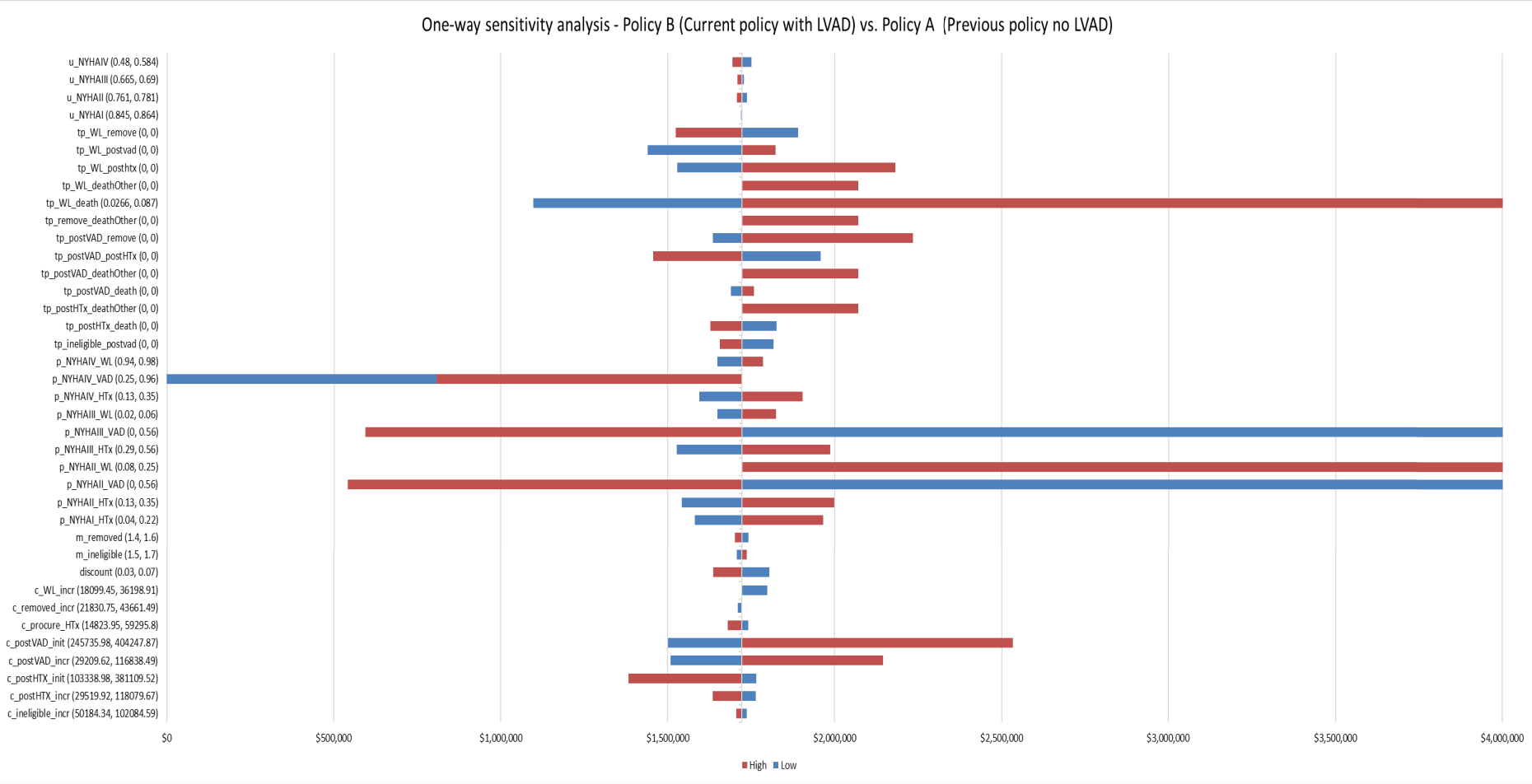
Abbreviations: HTx, heart transplant; QALY, quality-adjusted life year; VAD, ventricular assist device
Note: Policy B is an extendedly dominated option.

5.3.2 Sensitivity analyses

5.3.2.1 One-way sensitivity analyses

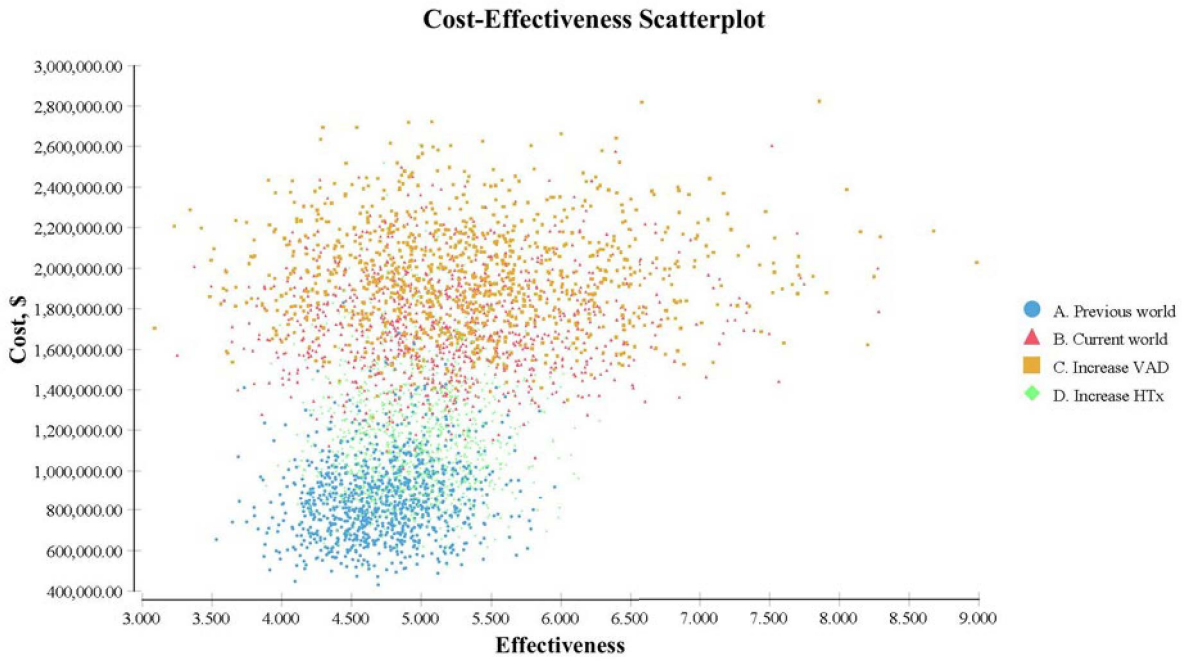
The tornado diagram for the one-way sensitivity analyses is presented in *Figure 5-14*. The rate at which patients die while on the waitlist is a main driver of the model because the tp_WL_death is a constant annual transition probability that affects two transitions: *'Wait list'* to *'Death'* and *'Removed'* to '*Death*'.

Figure 5-14: Tornado plot for one-way sensitivity analyses (Policy B vs. Policy A)



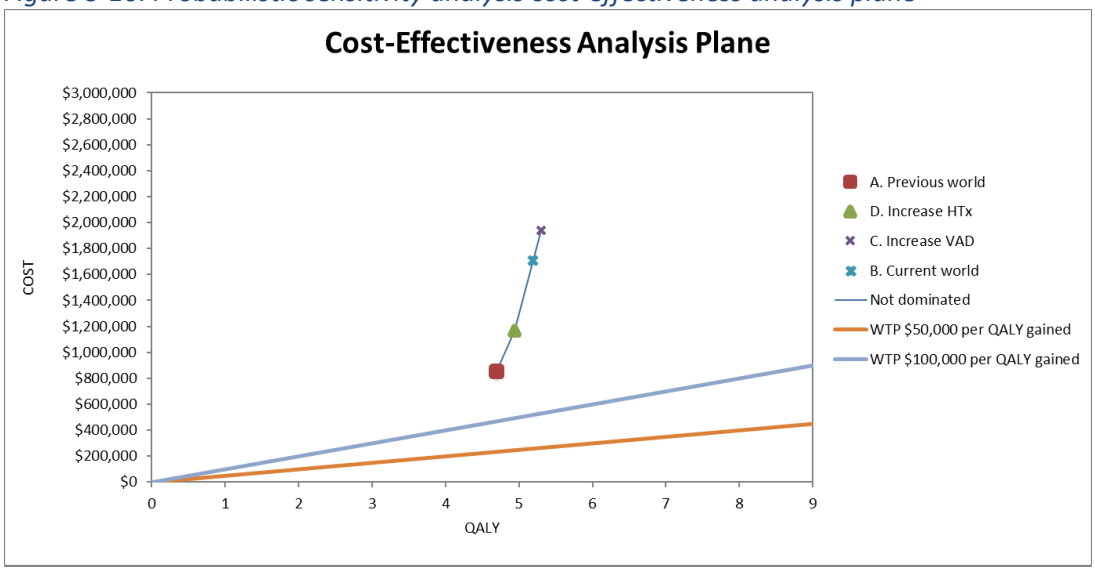
5.3.2.2 Probabilistic sensitivity analyses

Figure 5-15: Cost-effectiveness scatter plot



Abbreviations: HTx, heart transplant; VAD, ventricular assist device

Figure 5-16: Probabilistic sensitivity analysis cost-effectiveness analysis plane



Abbreviations: HTx, heart transplant; QALY, quality-adjusted life year; VAD, ventricular assist device
Note: Policy B is an extendedly dominated option by a combination of Policy C and Policy D.

5.3.2.3 Scenario analyses

The results were robust to most model assumptions with the largest impact from reducing the time horizon, which made all alternatives less cost-effective than Policy A (Table 5-17). For Policy B and C, reducing the price of VADs improved the ICER. Removing the '*Ineligible'* health state increased the ICER, making it less cost-effective, indicating the benefit of including BTC patients in the model. Removing the *'Waiting list'* health state so that 40% of the cohort begin with a VAD (36%) and remaining cohort with HTx (54%) or Ineligible (10%) increased the ICER, making Policy B significantly less cost-effective, indicating that ignoring the waiting list health state underestimated the value of VADs. Extrapolating the VAD to Death survival curve to 6 years (rather than 4 years) using the Weibull distribution reduced the ICER from $1.72 to $1.28 million per QALY gained. Using the NYHA data from Add Value and the ROADMAP study (non-randomised observational study post-LVAD, n=97) so that the post-VAD status was improved reduced the ICER from $1.72 million to $1.37 million per QALY gained.

Table 5-17: ICER per QALY gained between Policies (time horizon 20 years, discounted) and scenario analyses

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention QALY	Comparator QALY	Incremental QALY	ICER
Time horizon, 20 years (base case)							
Policy B vs. A	**$1,709,347**	**$854,569**	**$854,778**	**5.19**	**4.70**	**0.50**	**$1,721,075**
Policy C vs. A	**$1,941,479**	**$854,569**	**$1,086,910**	**5.31**	**4.70**	**0.61**	**$1,780,350**
Policy D vs. A	**$1,166,737**	**$854,569**	**$312,168**	**4.94**	**4.70**	**0.24**	**$1,274,605**
Remove ineligible health state							
Policy B vs. A	$1,734,882	$878,992	$855,889	5.27	4.82	0.45	$1,911,644
Policy C vs. A	$1,967,014	$878,992	$1,088,021	5.38	4.82	0.56	$1,937,448
Policy D vs. A	$1,196,713	$878,992	$317,721	5.07	4.82	0.24	$1,297,278
Time horizon, 15 year							
Policy B vs. A	$1,524,843	$729,585	$795,258	4.70	4.29	0.41	$1,954,686
Policy C vs. A	$1,754,463	$729,585	$1,024,879	4.80	4.29	0.51	$2,005,527
Policy D vs. A	$1,017,966	$729,585	$288,382	4.51	4.29	0.22	$1,307,449
Time horizon, 10 year							
Policy B vs. A	$1,159,119	$523,971	$635,148	3.77	3.50	0.27	$2,384,836
Policy C vs. A	$1,376,839	$523,971	$852,868	3.85	3.50	0.35	$2,417,626
Policy D vs. A	$764,788	$523,971	$240,816	3.67	3.50	0.18	$1,374,481
Time horizon, 5 year							
Policy B vs. A	$491,043	$240,902	$250,141	2.24	2.15	0.10	$2,606,325
Policy C vs. A	$679,266	$240,902	$438,364	2.30	2.15	0.16	$2,816,480
Policy D vs. A	$396,957	$240,902	$156,055	2.25	2.15	0.11	$1,451,168
VAD to HTx transition probability, IMACS							
Policy B vs. A	$1,715,036	$854,569	$860,467	5.19	4.70	0.49	$1,752,551
Policy C vs. A	$1,946,753	$854,569	$1,092,184	5.30	4.70	0.61	$1,803,687
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
Utility decrement for removed health state (0.01)							
Policy B vs. A	$1,709,347	$854,569	$854,778	5.18	4.69	0.49	$1,729,991
Policy C vs. A	$1,941,479	$854,569	$1,086,910	5.30	4.69	0.61	$1,789,120
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.69	0.25	$1,268,671
Cost of death set to $0							

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention QALY	Comparator QALY	Incremental QALY	ICER
Policy B vs. A	$1,630,293	$759,680	$870,613	5.19	4.70	0.50	$1,752,959
Policy C vs. A	$1,866,326	$759,680	$1,106,646	5.31	4.70	0.61	$1,812,677
Policy D vs. A	$1,074,610	$759,680	$314,930	4.94	4.70	0.24	$1,285,881
50% reduction in VAD cost							
Policy B vs. A	$1,555,815	$854,569	$701,246	5.19	4.70	0.50	$1,411,943
Policy C vs. A	$1,746,863	$854,569	$892,294	5.31	4.70	0.61	$1,461,571
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
75% reduction in VAD cost							
Policy B vs. A	$1,479,050	$854,569	$624,481	5.19	4.70	0.50	$1,257,378
Policy C vs. A	$1,649,555	$854,569	$794,986	5.31	4.70	0.61	$1,302,182
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
50% annual probability from waitlist to VAD Year 3 onwards							
Policy B vs. A	$1,759,229	$854,569	$904,660	5.22	4.70	0.53	$1,713,824
Policy C vs. A	$1,980,276	$854,569	$1,125,707	5.33	4.70	0.63	$1,773,393
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
VAD to Death extrapolated using Weibull distribution to 6 years							
Policy B vs. A	$1,826,883	$854,569	$972,314	5.45	4.70	0.76	$1,280,629
Policy C vs. A	$2,071,101	$854,569	$1,216,532	5.60	4.70	0.90	$1,351,478
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
VAD to Death using SVHS MCS data							
Policy B vs. A	$1,721,469	$854,569	$866,900	5.22	4.70	0.52	$1,654,848
Policy C vs. A	$1,933,389	$854,569	$1,078,820	5.29	4.70	0.59	$1,813,576
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
NYHA Class post-VAD adjusted from ROADMAP Study							
Policy B vs. A	$1,709,347	$854,569	$854,778	5.32	4.70	0.63	$1,367,260
Policy C vs. A	$1,941,479	$854,569	$1,086,910	5.46	4.70	0.77	$1,415,318
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605
No waiting list							
Policy B vs. A	$2,299,804	$1,912,570	$387,235	5.82	5.80	0.02	$20,415,219
Policy C vs. A	$2,468,003	$1,912,570	$555,433	5.77	5.80	-0.02	Dominated
Policy D vs. A	$2,084,408	$1,912,570	$171,838	5.80	5.80	0.00	N/A
Policy D start 40%							
Policy D vs. A	$1,428,929	$854,569	$574,360	5.19	4.70	0.49	$1,172,577
Cost of death as transition not absorbing state							
Policy B vs. A	$1,639,563	$770,294	$869,269	5.19	4.70	0.50	$1,750,254
Policy C vs. A	$1,875,325	$770,294	$1,105,031	5.31	4.70	0.61	$1,810,033
Policy D vs. A	$1,084,999	$770,294	$314,705	4.94	4.70	0.24	$1,284,963

Abbreviations: HTx, heart transplant; ICER, incremental cost-effectiveness ratio; IMACS, International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support; QALY, quality-adjusted life year; VAD, ventricular assist device; Note: Policy A is 'Previous world', Policy B is 'Current world', Policy C is 'increase VAD' and Policy D is 'increase HTx'.

5.3.3 Budget Impact Analysis

The real-world event numbers of patients on the HTx waiting list, number of transplants and use of LVADs in Australia are presented in Table 5-18. The 3-year average adult cohort on the waiting list (n=165) and the 10% ineligible for the waiting list (n=12) were calculated from 2016-2018.(70) There were 93 orthotopic HTx conducted in Australian adults in 2016-2018.(70) The annual maximum LVAD cap from each of the four institutions (St Vincents Hospital, Sydney; The Prince Charles Hospital, Brisbane; The Alfred Hospital, Melbourne; and Fiona Stanley Hospital, Perth) were 90 LVADs and around 55 used in 2018 (personal communication Prof. Chris Hayward). The proportion of HTx and VAD per average patient as presented in Table 5-12 were multiplied by the estimated cohort of 177

(165+12) patients for the real-world estimate and policy alternatives. The estimated policies had underestimated the proportion of HTx conducted, which was around 57%, with Policy D being the closest at 49%. Further, the estimated policies had overestimated the proportion of VAD conducted, which was around 40% while Policy B and Policy C had estimated 64% and 71% respectively.

Table 5-18: Validation of event numbers with real-world

	Waitlist	Ineligible	HTx	VAD	HTx as % of cohort	VAD as % of cohort
Real-world (2016-2018)	165	12	93	55-90	57%	40%
Policy A	-	-	65	0	37%	0%
Policy B	-	-	53	114	29%	64%
Policy C	-	-	50	126	28%	71%
Policy D	-	-	86	0	49%	0%

The annual cohort was multiplied by 20 years to estimate the number of HTx, VADs and deaths (see Table 5-19). The average number of HTx, VADs and HF-related deaths as estimated in the model was converted into a proportion and multiplied by the 20 year cohort. The fewest HF-deaths occurred in Policy C over the 20 years (n=2,235) at a cost of $1.94 million followed by Policy B (n=2,268) at a cost of $1.71 million.

Table 5-19: Budget impact analysis

	% per patient			Cohort, 20 years (N=177 per year)			Cost, 20 years
	HTx	VAD	HF-related death	HTx	VAD	HF-related death	
Policy A	37%	0%	70%	1,299	-	2,489	$854,569
Policy B	29%	64%	64%	1,042	2,265	2,255	$1,709,347
Policy C	28%	71%	63%	985	2,514	2,223	$1,941,479
Policy D	49%	0%	69%	1,718	-	2,452	$1,166,737

Abbreviations: HF, heart failure; HTx, heart transplant; VAD, ventricular assist device.
Policy A = no VAD bridging support, Policy B = current ESHF policy including supply restricted VAD support, Policy C = Increase VAD, Policy D = Increase HTx.

5.4 Discussion

The results suggest that Policy C offers the most benefits as 'Increase VADs' resulted in the largest QALY gains. This indicates that moving away from the current supply cap of VADs (Policy B) would generate more health gain. Next, it was estimated that the current Policy B would produce the most health gains, followed by Policy D 'Increase HTx' and then the previous Policy A. As expected, Policy C was the most costly alternative because of the cost of LVAD implantion. The next most costly alternative was Policy B, then Policy C and Policy A.

The results suggest that the implementation of the current policy of VADs used as BTT or BTC is unlikely to be cost-effective from the Australian public healthcare payer perspective under existing WTP

thresholds. A 75% reduction in the price of the VAD prosthesis would significantly reduce the ICER; however, it would still remain above currently used WTP thresholds.

Importantly, decision-makers might be interested in whether the current use of VADs is cost-effective. Policy B 'Current world' was an extendedly dominated option as it has a higher ICER and fewer benefits than Policy C. Policy B reflects the current use of VADs in Sydney, while Policy C is more reflective of current practice in The Alfred Hospital, Melbourne. The supply caps of VADs are implemented by each transplanting centre based on their respective state government budget constraints. The results indicate that the VAD cap is mainly in place as a measure to control expenditure (rather than improve any notion of cost-effectiveness). Many existing economic evaluations have reported higher WTP threshold for VADs.(183) However, by funding non-cost-effective treatments there is the potential to displace interventions that would have resulted in more health gains.

The policy implications of increasing the supply of HTx were explored. HTx rates have increased steadily in Australia and New Zealand since 1984.(70) Recently, donation after circulatory death (rather than brain death) has been trialled at SVHS with ex vivo preservation using the 'Heart in a Box'. More mainstream uptake of this technology could potentially impact on the donor pool. Policy D returned an ICER of $1.27 million compared to Policy A. However, increasing the donor pool is challenging given the match criteria of blood type, making a scenario of 'no waiting list' unrealistic. A scenario analysis illustrated that 40% of patients would need to begin in the *'Alive -post HTx'* and avoid the *'Waiting list'* health state to receive the same 5.2 QALY gain as under Policy B.

Additionally, increasing the number of HTx may have resource implications for individual transplant units; this was not taken into account in the current evaluation. Anecdotally, HTx procedures result in rescheduling of routine surgeries such as cardiac artery bypass grafts. This can have flow-on implications for the units and the health outcomes of non-HTx patients, which are not usually considered in health technology assessment.

5.4.1 Strengths and limitations

This is the first economic evaluation of VADs from the Australian perspective and the model was informed by real world registry data from SVHS. SVHS treats a significant proportion of the ESHF patients in Australia, being one of only four transplant units. Hence, model inputs including costs were likely applicable to the Australian healthcare system as a whole.

The value of organ replacement technologies such as LVADs is to buy patients time while they wait for a HTx. Therefore, the difference between the current restriction and the previous use of HTx only is that some patients are able to wait longer for a HTx or remain alive long enough to become eligible to

be on the HTx waiting list. The model structure included health states not identified in the literature (*'Ineligible'* and *'Removed'*) to ensure the model was clinically realistic. In particular, the *'Ineligible'* health state was included to separate BTC from BTT patients and demonstrates the benefit of LVAD in buying time for potential candidates. Exclusion of the *'Ineligible'* health state increased the ICER to $1.9 million per QALY gained, indicating that including BTC patients made Policy B slightly more cost-effective because a proportion of patients were able to avoid a *'death'* health state (or delay entry). Other studies relying on registry data did not disaggregate BTC and BTT patients in their model.(108)

A limitation of this study is the relatively small sample size of patients records from SVHS compared to larger international registries. However, this sample was representative of the Australian population. Furthermore, SVHS did not collect quality-of-life data directly and instead NYHA status was used as a proxy for QoL changes. Despite the lack of QoL data, NYHA status has been shown to be highly predictive of QoL in HF.(120) The cost data were from a retrospective cohort (2009-2012) and clinical practice may have changed since then; however, these costs were inflated to 2019 prices. The multiplication factor applied to *'Waiting list'* to *'Death'* was based on assumptions. The transition probabilities were considered clinically reasonable and the one-way sensitivity analysis of the multiplication factors identified that these were not model drivers.

A cohort model was applied. LVAD patients tend to be sicker than unbridged HTx patients, meaning that there is patient heterogeneity. Patients in the LVAD group were more likely to have an intra-aortic balloon pump ($p<0.001$) and be on inotropic IV medication than the non LVAD group ($p<0.001$). Another challenge of modelling the waiting list using a cohort model is that all patients wait the same amount of time. However, registry data indicates there is variability in waiting time, with mean wait time being 164 days (min 1 day and max 1,043 days).(149) A patient's waiting time is affected by their blood type match with the donor. Therefore, an individual level model may offer a more realistic method of modelling the HTx waiting list.

5.5 Conclusion

This analysis has found that the introduction of LVADs as an organ replacement therapy for HTx produced more QALYs and was more costly than the previous situation (without LVADs). However, under current WTP thresholds, and even an optimistic threshold, the current use of LVADs is not cost-effective, which is consistent with the findings from Chapter 3. The analysis indicated the budget impact of the LVAD cap within the Australian transplant institutions, with existing restrictions designed to manage financial constraints rather than to improve cost-effectiveness.

6 CHAPTER 6: DISCRETE EVENT SIMULATION MODEL FOR REAL-WORLD RESTRICTIONS IN TREATMENT POLICIES IN ESHF

6.1 Introduction

6.1.1 Discrete event simulation and dynamic simulation modelling

Dynamic simulation modelling is an interactive representation of the modelled system that anticipates the upstream and downstream consequences of changes.(215) The three dynamic simulation methods are systems dynamics (SD), agent-based modelling (ABM) and discrete event simulation (DES). In health technology assessment (HTA), ISPOR recommendations (SIMULATE[41] checklist) are available for the appropriate dynamic simulation modelling methods for a research question.(31, 215) Typically, ABM and SD are used to model dynamic transmission models, particularly in infectious diseases, the main difference between the two methods being that ABM is stochastic while SD is deterministic.(34) DES was traditionally used outside health care, in transport supply and logistics and business processes (e.g. call centres) due to its application in operations management.(45, 30). DES is useful in addressing decision problems in relation to resource use, as queues are explicitly embedded.(216)

6.1.2 Applications of discrete event simulation in health technology assessment

Resource constraints are not usually explicitly considered in HTA; for example, if a patient requires a new drug it is assumed that resource is available immediately, without delay to the patient. Cohort models are commonly used, such as decison trees or state-transition Markov models (15,21), which are closed-form equations and as such cannot model interactions. There are two applications of DES in HTA: 1) non-constrained resource models and 2) constrained-resource models.(216) In a non-constrained model, DES may be preferable to a Markov model because time-to-event is best described stochastically rather than through fixed time intervals.(216) Furthermore, DES is able to track individual paths throughout the model as patients enter the model sequentially, meaning that patient heterogeneity can be incorporated.

In a constrained model, queues are used to mimic competition for resources. Public hospital elective surgical waiting lists are examples of a non-physical queue. Constraints in the number of surgeons, nursing staff and operating theatres means that patients are added to a waiting list, thus delaying

[41] ISPOR System, Interactions, Multilevel, Understanding, Loops, Agents, Time, Emergence (SIMULATE) guidelines.

treatment.(38) Patients will remain in the queue until their appointment arrives, their condition deteriorates (e.g. require emergency surgery) or they leave the queue and join a shorter waiting list in a private hospital.

Queues and waiting lists are common in health care, so constrained resources should be modelled when the time to access treatment has significant effects on patient costs or outcomes (e.g. delay in receiving a heart transplant (HTx)). The concept of resource constraints is easily applied to donated organs, which are significantly supply constrained and are allocated based on a combination of expected survival (of the recipient), blood type, and donor and recipient weight compatibility. Obtaining an organ is a stochastic process that arises from the interaction of the characteristics of the waiting list and the specific donor-recipient allocation rules. A patient's eligibility for a HTx can change over time, mainly due to their health status. Mechanical circulatory support, such as left ventricular assist device (LVAD), can buy patients more time on the waiting list or allow patients to become eligible for a HTx when used as a bridge to candidacy (BTC).

A queuing system consists of: the population; the nature of patient arrival; the service time and mechanism; queuing behaviour; and the queuing discipline.(44) Queuing behaviour refers to 'drop-out', such as a patient voluntarily leaving the queue, deterioration in health leading to waiting list removal, or death. The queuing discipline is based on match and priority, i.e. if a patient is listed as urgent, they may receive a HTx before someone who has waited longer, controlling for the same blood type.

6.1.2.1 Decision problem

The aim of this chapter was to model the treatments for end-stage health failure (ESHF), as described in Chapter 5, using DES to explicitly capture the associated resource constraints and waiting lists in the economic evaluation. In the DES model base case, queuing was enabled to represent the natural history of the waiting list and incorporate allocation of LVADs and HTx. A DES model without queuing was created to cross-validate with the Markov model in Chapter 5. The results between the two DES models (with and without queuing) are compared and contrasted to the Markov model.

As with Chapter 5, the objective of this economic evaluation is twofold: 1) to assess the cost-effectiveness of the current ESHF policy and the previous ESHF without LVADs, and 2) to assess the cost-effectiveness of expanded availability policies for patients with ESHF to the previous ESHF policy. Four policy alternatives were compared in this analysis:

- Policy A - the previous ESHF policy, with no LVAD bridging support;
- Policy B - the current ESHF policy, which includes supply restricted LVAD support;
- Policy C - a hypothetical ESHF policy with an increased supply of LVADs; and,

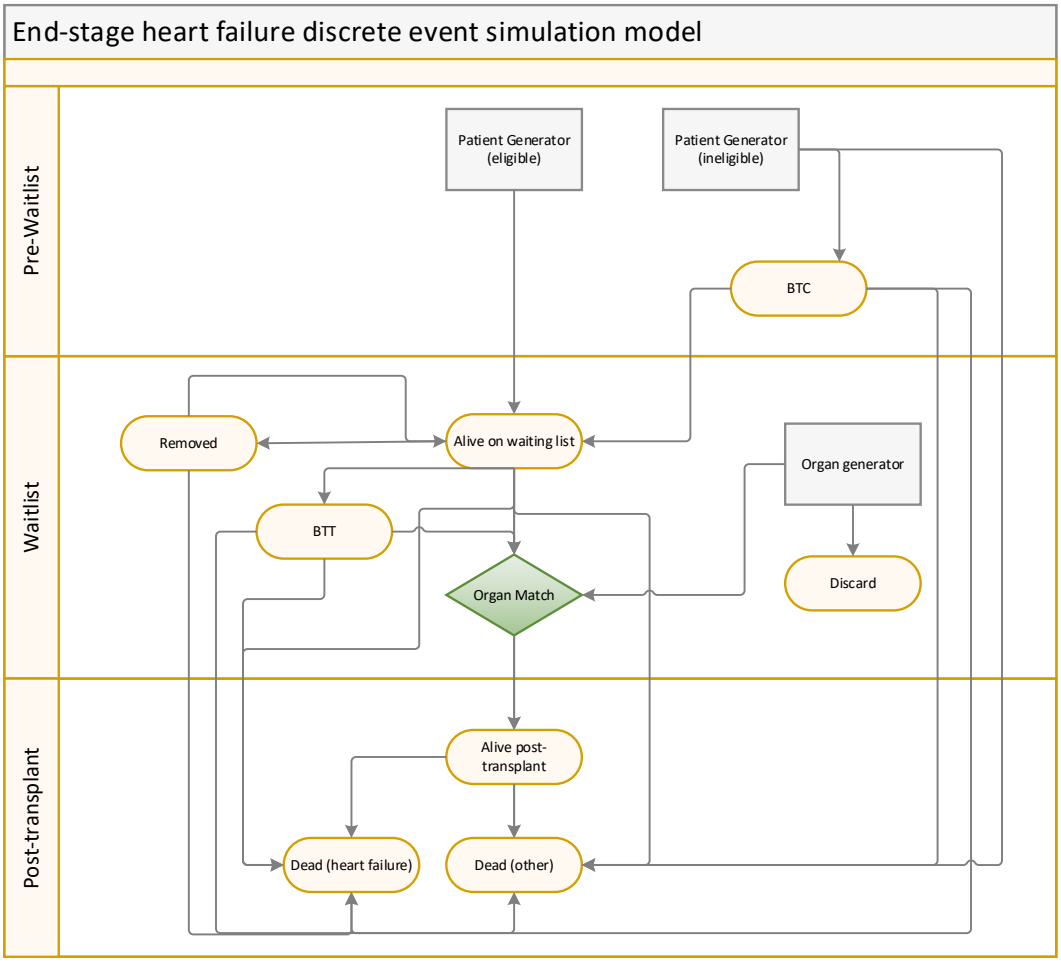
- Policy D - a hypothetical ESHF policy with an increased supply of donor hearts, holding the current level of LVAD support constant.

6.2 Methods

6.2.1 Model structure

The schematic flowchart of Policy B is structured as pre-waiting list events, waiting list events and post-waiting list events (*Figure 6-1*). The events considered were: LVAD implant for ineligible patient, patient death from the waiting list, removal from waiting list, LVAD implant for eligible patient, heart transplant (HTx), and patient death after HTx. Each event modifies the current flow of patients in the waiting list and the number of patients that are eligible for LVAD implant or HTx.

Figure 6-1: Flowchart of discrete event simulation model



Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant.

6.2.2 AnyLogic Software

TreeAge Pro was used to build the Markov model in Chapter 5, but although TreeAge software contains DES functions, it does not support agent interaction and queues.(217) Thus, this model was

developed using specialised simulation software AnyLogic (AnyLogic 8, St Petersburg, Russia). This is an ABM simulation software that allows for user-written code in Java. The ISPOR-SMDM Guidelines for modelling using DES were followed during the development of the model.(218) Using specialised software with visualisation functionality assists in increasing the transparency of the model to reviewers.(218) A summary of the process modelling blocks in AnyLogic is presented in Table 6-1.(215, 31) Agents or entities can represent people, places or items, they have attributes and consume resources while experiencing events.[42](31) Attributes are variables specific to the agent (e.g. age) and can be used to incorporate memory. Crucial to the current DES model is the Match block, which allows patients on the waiting list and donor organs to be matched.

Table 6-1: Components of a discrete event simulation in AnyLogic

	Component	Description
	Source	Agents consume resources or experience events arrive in the model
	Parameter	Attributes of entities
	Delay	Stochastically delays patients for a given amount of time.
	Match	Synchronises two streams of agents by matching pairs according to a given criteria. The agents that have not been matched are stored in two queues (one for each stream). Once the new agent arrives at either of the input ports, it is checked for match against all agents in the queue for the other stream. If the match is found both agents exit the Match object at the same time.
	Combine	Waits for two agents to arrive and outputs a new agent
	Select Output	Routes incoming agents to one of up to 5 output ports depending on probabilistic or deterministic conditions.
	Sink	Disposes agents
	Wait	A buffer or queue of agents allowing for manual retrieval.

Source:(219)

The model components in Queue and No Queue DES model are presented in Table 6-2. The structures for the queuing model and No Queue model in AnyLogic are presented in *Figure 6-2* and Figure 6-3 respectively. The queuing simulation was driven by the following agent arrivals: patient (eligible or ineligible) arrival, organ arrival, and LVAD device arrival in Policy B and Policy C. There were two match processes between patients and a LVAD device for BTC (waiting list ineligible) or BTT (waiting list

[42] Technically speaking, entities are a feature of DES models whilst agents are a feature of ABMs, AnyLogic® builds hybrid models that include both in the same model.

eligible). Once a patient enters the HTx matching process (or LVAD as a bridge to HTx), they await a compatible donor organ based on the previously described matching criteria (Chapter 2; see Table 2-3). Once a donor match is found, patient flow is driven by post-HTx survival. In addition, patients could be removed from the waiting list and experience a death event.

In order to remove queuing for the No Queue model, the following steps were implemented:

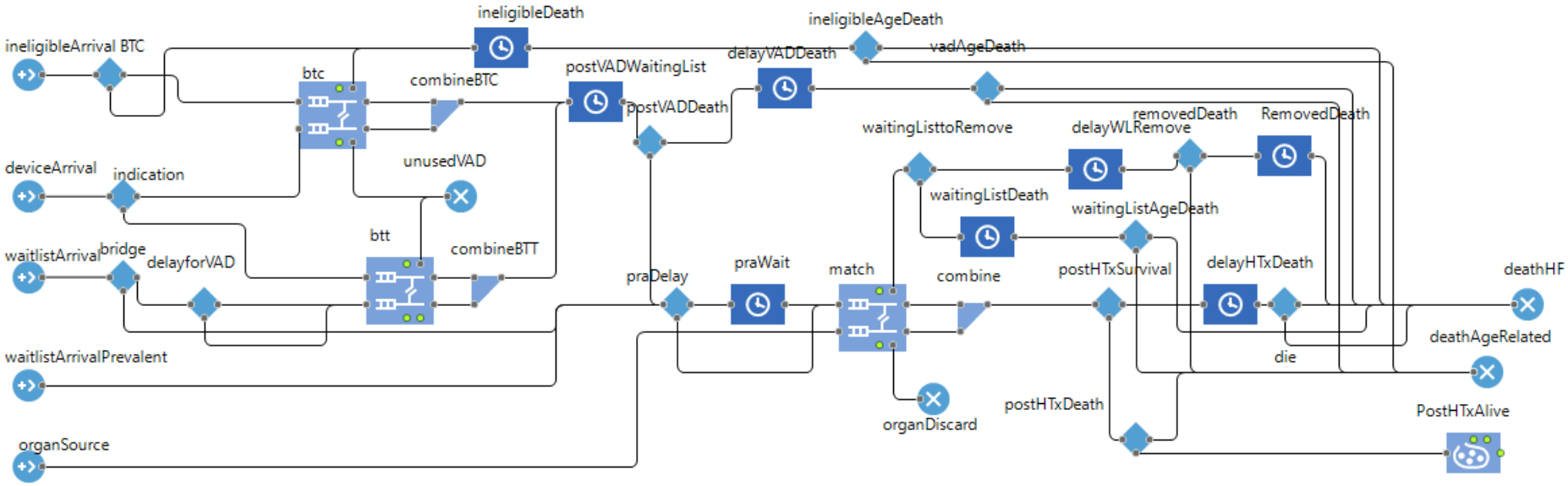
- Removed *'deviceArrival'* and *'organSource'* source blocks as patient intervention is not affected by resource availability.
- Removed *'waitlistArrivalPrevalent'* patients source block and all waitlisted patients arrive at t=0.
- Removed the LVAD matching blocks (*'btc'* and *'btt'*), and the corresponding combine blocks (*'combineBTC'* and *'combine BTT'*) and the *'unusedVAD'* sink. Replaced with delay blocks (*'delayBTC'* and *'delayBTT'*) with custom distribution of time-to-event, *'ineligible'* to *'Alive post-VAD'* and *'waiting list'* to *'Alive post-VAD'*, respectively.
- Removed the waiting list and HTx matching blocks including *'praDelay'*, *'praWait'*, *'match'*, *'combine'* and *'organDiscard'*. Replaced with delay block '*delayVADtoHTx'* with custom distribution of time-to-event, '*Alive post-VAD'* to *'Alive post-HTx'*.
- Replaced *'match'* block timeout for patients leaving the queue with a delay block *'delayVADRemove'* and *'delayWLRemove'*.
- All patients arrive at t=0, rather than as a Poisson distribution rate.
- Addition of *'PolicyC'* selectOutput to direct flow of patients to *'postVADWaitingList'* delay block to represent Policy C.
- Addition of *'PolicyD'* selectOutput to direct flow of patients to *'postHTxSurvival'* SelectOutput to represent Policy D.

Table 6-2: Description of model components in Queue and No Queue DES model

Item	Description	Queue	No Queue
Source			
ineligibleArrival	Patients ineligible for the HTx waiting list enter	✓	✓
deviceArrival	LVADs enter	✓	×
waitlistArrival	Patients added to the HTx waiting list enter	✓	✓
waitlistArrivalPrevalent	Patients on the HTx waiting list already enter	✓	×
organSource	Donor organs enter	✓	×
Sink			
deathHF	Patients die from HF	✓	✓
deathAgeRelated	Patients die from age-related mortality	✓	✓
unusedVAD	LVADs that are not implanted are discarded	✓	×
organDiscard	Donor organs that are unmatched are discarded	✓	×
Match			
Btc	Patients ineligible for a HTx receive an LVAD	✓	×
Btt	Patients eligible for a HTx receive an LVAD	✓	×
match	Patients on the waiting list are matched with a donor organ	✓	×
Combine			
combineBTC	Patients are implanted as BTC	✓	×
combineBTT	Patients are implanted as BTT	✓	×
combine	Patients are transplanted	✓	×
Delay			
ineligibleDeath	Time to death for patients not implanted with LVAD	✓	✓
postVADWaitingList	Delay post-LVAD implant surgery until added to HTx waiting list	✓	✓
delayVADDeath	Time to death for patients implanted with LVAD	✓	✓
delayWLRemove	Time to removal from waiting list	✓	✓
RemovedDeath	Time to death from removal from waiting list	✓	✓
praWait	Delay for panel reactive antibody score in obtaining a match	✓	×
waitingListDeath	Time to death from waiting list	✓	✓
delayHTxDeath	Time to death from HTx	✓	✓
delayBTC	Time to LVAD implant for patients ineligible for HTx	×	✓
delayBTT	Time to LVAD implant for patients on HTx waiting list	×	✓
delayVADRemove	Time to removal from waiting list since LVAD implant	×	✓
delayVADtoHTx	Time to HTx since LVAD implant	×	✓
delayWLHTx	Time to HTx since added to the waiting list	×	✓
SelectOutput			
BTC	Patient ineligible for HTx will receive an LVAD or die	✓	✓
Indication	Device is for BTC or BTT	✓	×
Bridge	Patient on HTx waiting list receive an LVAD or unbridged HTx	✓	×
delayforVAD	Patient waiting time for an LVAD	✓	✓
postVADDeath	Patient to die with LVAD or receive a HTx	✓	×
ineligibleAgeDeath	Patient ineligible for HTx to die from HF or age-related mortality	✓	✓
vadAgeDeath	Patient with LVAD to die from HT or age-related mortality	✓	✓
praDelay	Pateint waiting time for HTx due to panel reactive antibody score	✓	×
waitingListtoRemove	Patient to be Removed from waiting list or die on waiting list	✓	✓
removedDeath	Patient removed from waiting list to die from HF or age-related mortality	✓	✓
waitingListAgeDeath	Patient on waiting list to die from HF or age-related mortality	✓	✓
postHTxSurvival	Patient with HTx to die from HF or alive/die from age-related mortality	✓	✓
die	Patient with HTx to die from HF or age-related mortality	✓	×
postHTxDeath	Patient with HTx to die from age-related mortality or remain alive	✓	✓
postVAD	Patient with LVAD implant to receive a HTx or be removed from HTx waiting list or die with LVAD implant	×	✓
waitlingListtoHTx	Patient on HTx waiting list to receive HTx or die	×	✓
PolicyC	Patients immediately receive an LVAD or wait for an LVAD	×	✓
PolicyD	Patients immediately receive a HTx or remain on the HTx waiting list	×	✓

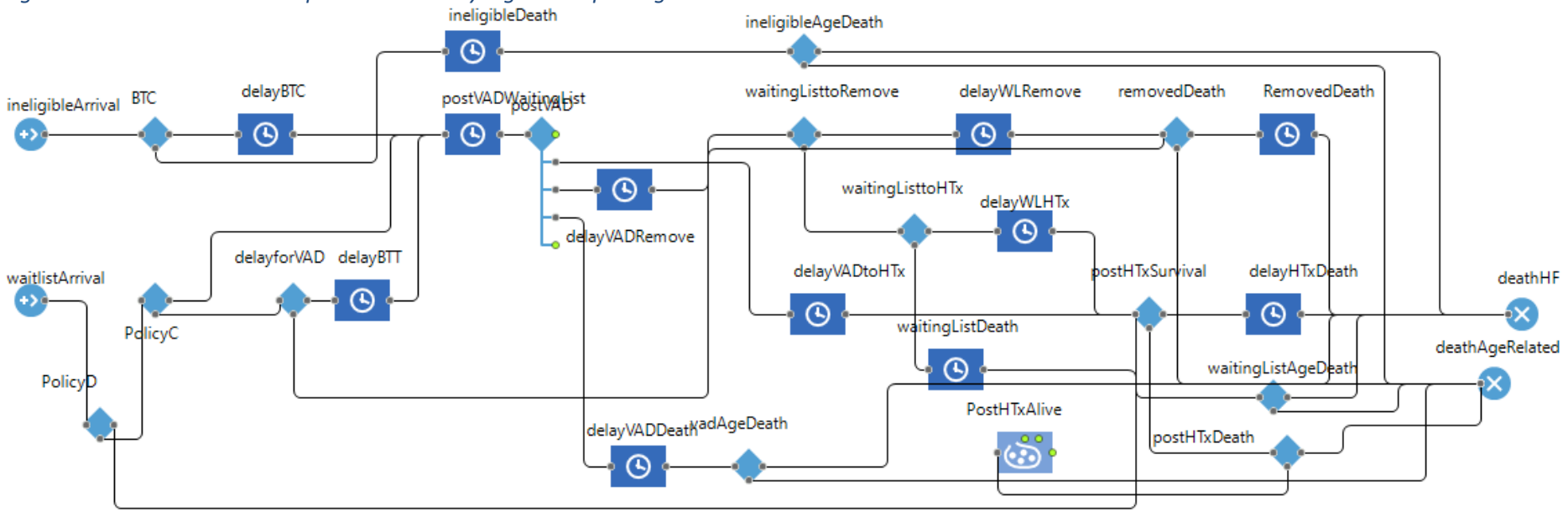
Abbreviations: BTC = bridge to candidacy, BTT = bridge to transplant, HF= heart failure, HTx = heart transplant, LVAD = left ventricular assist device, VAD = ventricular assist device,WL = waiting list

Figure 6-2: Model structure implemented in AnyLogic –with queuing



Abbreviations: BTC = bridge to candidacy, BTT = bridge to transplant, HF= heart failure, HTx = heart transplant, VAD = ventricular assist device, WL = waiting list

Figure 6-3: Model structure implemented in AnyLogic – no queuing



Abbreviations: BTC = bridge to candidacy, BTT = bridge to transplant, HF= heart failure, HTx = heart transplant, VAD = ventricular assist device, WL = waiting list

6.2.2.1 Existing DES models

A review of the literature identified one published DES model of heart transplantation (discussed in detail in Chapter 4).(118) The purpose of the study was to estimate the cost-effectiveness of the baseline scenario of a Dutch heart transplant programme compared to a non-transplant scenario in the Netherlands. To conduct the study, the authors included the annual number of patients referred to the transplant centres; pre-transplant duration distributions; the annual number of donor hearts; post-transplant survival and costs.(118) They estimated that after 1994, 'on average two donor hearts are not used because of not achieving a match between the donor and recipient' (118), representing discarded organs.

A number of studies in liver and kidney organ transplantation (17, 128, 220) have used a DES approach to model the cost-effectiveness of various programme options. Shechter et al. (2005) included five modules; 'patient generator', 'liver organ generator', 'pre-transplant natural history', 'organ match' and 'post-transplant survival'.(220) Unique to DES models in organ transplantation are the use of agent generators to model the arrival of a patient and donor organ, a queue for waiting lists and an organ match. Both Davis (1987) and Stahl (2007) included separate queues for organ replacement technologies (i.e. dialysis and hypothetical tissue-engineered organs respectively) and explored the impact of these technologies on the waiting lists.(17, 128) Requirements for this model included national waitlist list details and and allocation algorithm based on priority and first-in first-out (FIFO) and donor pool details.(17)

The current model differs from Shechter et al. (2005) in that there are two 'patient generators', for 1) those eligible to be activated onto the waiting list and 2) those ineligible for the waiting list. The current model's pre-transplant module incorporates two additional matching events relating to LVADs implanted as either a BTC or BTT. However, similar to Schecter et al. (2005), the model includes a donor organ and LVAD device generator. In the post-transplant survival module there are two 'death' events, 1) due to heart failure and 2) age-related background mortality.

6.2.2.2 Policies

The probability of entering the Markov model via specific health states in Chapter 5 was used to incorporate Policies A-D into the model. The base case DES model reflects the current transplant policy (Policy B), under which 90% of the patients are '*waitlistArrival*' and the remaining 10% are *'ineligibleArrival',* which means that 90% begin on the waiting list as they are already worked up and deemed eligible while the remainder are ineligible but may become eligible over time. To estimate the expanded availability policies – namely, Policy C for LVADs and Policy D for HTx – the previous model applied a 20% probability of starting in the *'Alive post-VAD'* or *'Alive post-HTx'* health state. The current AnyLogic model tested those policies using two methods. The first most closely reflects the

Markov model method (1 and 2) and is used in the DES No queue model, and the second method (3 and 4) explicity adjusts the availability of resources in the DES with queuing model.

1) Policy C = redirect 20% of *'waitlistArrival'* into *'postVADWaitingList'* so that 20% are immediately bridged with an LVAD.
2) Policy D = redirect 20% of *'waitlistArrival'* into *'postHTxSurvival'* so that 20% are immediately matched with a donor heart.
3) Policy C = increase the probability by 20% in the 'bridge' from 40% to 60% and increasing the supply of LVAD resource pool *'deviceArrival'* by 20% from 55 to 90.
4) Policy D = increase the supply of the donor organs by increasing the arrival rate of organSource by 20% from 325 to 390.

The difference between the previous ESHF policy with no VAD bridging support (Policy A and D) and VAD bridging support (Policy B and C) is depicted by the setting *'deviceArrival'* rate to 0, '*Arrival BTC'* select output to 0 and *'bridge'* select output to 0. The difference between Policy A and D is that under Policy D the intervention cost of receiving a donor organ accounts for the promotion campaign and donation after circulatory death (DCD) procurement cost.

6.2.2.3 Assumptions

The model was underpinned by the same assumptions in Chapter 5 unless otherwise specified.

6.2.2.3.1 Organ allocation

The current DES model included assumptions about the organ allocation process (described in detail in Section 2.3). The waiting list is reordered every time a new organ is donated, because donor and candidate characteristics are compared based on blood type and weight compatibility. The organ is transplanted to the first candidate to accept the offer, following a first-in first-out (FIFO) queuing discipline. A timeout rate for organs of 6 hours was applied to represent the maximum cold ischaemic time for organs (221). When the timeout limit is met, the unused donor organ is discarded. Similarly, patients are removed from the waiting list after a 6-month timeout limit and flow to either a Removal or Death event from the waiting list. The first match criterion was blood type (see *Table 6-3*) with AB blood type the universal recipient and O blood type the universal donor. The second match criterion is based on the recipient weight being within 20% ± donor weight.

Table 6-3: Blood type matching algorithm

	Donor			
Recipient	**O**	**B**	**A**	**AB**
AB	1	1	1	1
A	1	0	1	0
B	1	1	0	0
O	1	0	0	0

Source: adapted from https://www.donateblood.com.au/learn/about-blood

Depending on a patient's panel reactive antibody (PRA), the score may affect the time to receiving a matched donor organ. In this model, it was assumed that PRA remains constant over a patient's lifetime and does not change. There are a number of reasons why a patient may become more sensitised over time; these include childbirth and blood transfusions, especially from LVADs. Therefore, these events would increase PRA score and consequently reduce the chance of finding a match.

6.2.3 Parameter estimation

The model inputs were the same as described in Chapter 5 unless specified otherwise. New parameters estimated for the DES model were the number of agents. Attributes were assigned to agents to enable the matching process. Transitions between events were estimated as distributions of time to an event as the model was a continuous-time model.(222) Half-cycle corrections are not needed unlike in Markov models because time is modelled continuously.(223)

6.2.3.1 Distributions

Probability distributions were sampled during a model run to assign attributes (e.g. gender or age) to agents. Discrete distributions were used for categorical data and continuous distributions (e.g. normal distribution) for continuous data. The rate of donation of organs and arrival of patients and VAD devices are independent of each other. These arrivals are random and estimated using the Poisson distribution.(44)

Time-to-event curves are sampled to estimate the transition between events. The sampled value between 0 and 100% represents the proportion of the population who remain event-free at the time at which the agent experiences the event of interest (e.g. death). There are two types of time-to-event distributions applied: custom empirical distributions and standard parametric distributions. For custom empirical distributions the tables of Kaplan-Meier, Cutler-Ederer or life tables were converted into distributions to be sampled rather than the transition probabilities used in the Markov model. These custom empirical distributions were relied on as while the AnyLogic software supports 39 types of distributions, commonly used health economic modelling distributions, such as Gompertz, generalised gamma and log-logistic, are not supported. Analyses for the standard parametric distributions (Weibull, Log-normal, Log-logistic, Generalised Gamma, Exponential and Gompertz) were conducted in STATA using *streg* and R using *survreg* and *flexsurvreg* (see section 8.14.4 for more information) but were not applied in the DES model.

6.2.3.2 Agents

The agents in the DES model were ESHF patients, donor organs and LVADs. In the DES without queuing model, all agents arrived at t=0, rather than as a rate throughout the year. The number of ESHF patients in the modelled system was based on the Australian adult population (Table 6-4). The 3-year average from 2016-2018 on the waiting list was obtained from Australia and New Zealand Organ Transplant Registry (ANZCOTR).(162) Two types of waiting list arrivals were modelled. The first were the 48 prevalent patients who are active on the waitlist from the previous year, and the second were 117 incident patients who are added throughout the year. Based on expert advice, 10% of the cohort (n=12) began as 'Ineligible' and were waiting for a VAD as BTC prior to being added to the waiting list. The difference between the eligible and ineligible patients was the different NYHA status in the two groups, with ineligible patients tending to have a worse NYHA score.

The number of donors per year was taken from Australia and New Zealand Organ Donation (ANZOD) Registry Annual Report (224), which provided data on all Australian donors. Of the 510 suitable deceased donor organs, a request for the organ was made on 387 occassions; of these, 358 provided consent and 109 were retrieved with a total of 98 transplanted.(224) A Poisson arrival rate of 325 was used, which is the proportion of donor organs with next of kin consent adjusted for the adult population (358 * 91%). The organ supply drives the search algorithm, since the patients have a life expectancy of days to years while the donor organs only have a viability of hours.

The LVAD supply was defined using a Poisson distribution and was assumed to be equally distributed throughout the year, rather than all occurring at the beginning of the year. For devices not used at the end of 1 year, these were unused and represent the budget restarting each year. The maximum capacity was the annual LVAD cap from each of the four units in Australia (St Vincents Hospital, Sydney (n=25); The Prince Charles Hospital, Brisbane (n=35); The Alfred Hospital, Melbourne (n=20); and Fiona Stanley Hospital, Perth (n=10)). This equated to maximum capacity of 90 LVADs per year with the supply replenished every year (personal communication Dr Chris Hayward). The transplant units provided the annual LVAD cap as a range and the actual useage in 2018 (Table 2-5). From the 2018 data, a low cap was estimated as 75 devices and a high cap was estimated as 90 devices with an average of 55 devices. For Policy B, the DES model with queuing assumed that 55 devices are available each year, and in the expanded availability policy (Policy C), 90 devices were available.

Table 6-4: Agent arrival parameters in the model

Parameter	Value	Lower, Upper	Description	Source
Initial patients	48	39,58	Initial number waiting at time t=0, 3-year average (2016-2018)	(70)
Additional patients	Rate (117)	Rate (94,141)	3-year average yearly arrivals of new patients on waiting list (2016-2018)	(70)
Additional ineligible patients	Rate (12)	Rate (10,15)	Assume 10% of additional candidates	Assumption
Organ	Rate (325)	Rate (260,390)	Donor organs offered, next of kin consent provided adjusted for 9% paediactric population in 2017	(224)
Organ Policy D	Rate (390)	Rate (312,468)	As above for Policy D (20% increase)	
Device Policy B	Rate (55)	Rate (44,66)	Utilisation across four transplant units in AU.	Table 2-5
Device Policy C	Rate (90)	-	Capacity across four transplant units in AU.	Table 2-5
Device Policy A/D	0	-	No LVADs available	-

Note: Rates are applied as Poisson distributions. Lower and upper estimates are 20% of the base case.

6.2.3.3 Agent attributes

The agents 'Eligible patient', 'Ineligible patient' and 'Donor Organ' have attributes determined at baseline (*Table 6-5*). Variables were based on individual patient data or distributions estimated from the literature. The characteristics age, gender and weight were from the 77 patients in the SVHS Add Value dataset. The DES model differs from the Markov model in that patients' ages are randomly assigned and range between 21 and 72 years old, rather than all being assigned an age of 50 years. Patient heterogeneity was incorporated via age-related mortality for Death (Other) and applying different post-HTx survival based on age bracket of HTx receipt. The blood type for patients and donor organs was based on the Australian population distribution reported by Donate Blood, the Australian blood and blood products donation service.(225) The Device arrivals have no attributes, with match to a patient is contingent on its availability.

Table 6-5: Summary of attributes of agents

Attribute	Type	Summary statistics, mean (SD); n (%)	Code	Source
All agents				
Blood Type	Distribution	O: 49%; A:38%; B:10%; AB: 3%	Option and Dist.	Donate blood
Eligible and Ineligible patient				
Age (years)	Individual	49.35 (11.33) [min 20.77 – 71.83]	Table	Add Value
Sex	Distribution	Male: 53 (69%), Female: 24 (31%)	Option and Dist.	Add Value
Weight (kg)	Individual	76.36 (17.24)	normal(17.24,76.36)	Add Value
PRA	Distribution	Various	Table	SVHS
Eligible patient				
NYHA at baseline	Distribution	N= 366; II: 4% IV: 96%	1:0; 2:0; 3:0.04; 4: 0.96	MOMENTUM 3
Ineligible patient				
NYHA at baseline	Distribution	N= 18; IV:100%	1:0; 2:0; 3:0; 4: 1	Add Value
Donor organ				
Weight (kg)	Distribution	80.26 (19.87)	normal(19.87, 80.26)	HILDA Wave 18

Abbreviations: cm = centimetres; kg = kilogram; NYHA = New York Heart Association; PRA = panel reactive antibody;
Note: normal distribution (standard deviation, mean). Custom distribution column 1 = value and column 2 = weight.

6.2.3.3.1 Age and Gender

The SVHS Add Value dataset reported baseline age in all 77 patients. The mean and median ages were 49.4 and 50.1 years respectively (range 20.7-71.8 years). Over two-thirds of the sample were male (53/77).

6.2.3.3.2 Blood type

The distribution of blood type in the Australian population is presented in *Table 6-6*. The total (positive and negative) distribution of blood type was used in the model. The distribution of blood type was assumed to be the same between donor organs and eligible or ineligible patients.

Table 6-6: Blood type distribution in Australia

	Positive	Negative	Total
O	40%	9%	49%
A	31%	7%	38%
B	8%	2%	10%
AB	2%	1%	3%

Source: (225)

6.2.3.3.3 Weight

Recipients

The SVHS Add Value dataset reported baseline weight in 76 patients (with 1 missing value). The average patient weight was 76.4kg (SD: 17.2kg, min 45 kg, max 124 kg) and the normal distribution was applied as an attribute to both eligible and ineligible patients.

Donors

The Household, Income and Labour Dynamics in Australia (HILDA) survey, (Wave 18, 2019) is a nationally representative broad social and economic longitudinal survey. This dataset was used to estimate the weight distribution of donors in Australia. The Deed of Confidentiality (143408) for NCLD datasets was approved by the Australian Data Archive on 29 December 2019. The Wave 18 sample consisted of the Main (Wave 1) 7,616 households and 2,023 top-up (Wave 11) households to total 9.639 households and 17,434 persons interviewed.(226) The relevant age range for donors was 15 to 50 years old, the sample was restricted to persons with weight > 0 (weight -10kg for missing data). The resulting sample equated to 7,936 adults with mean weight 80.3 kg (SD: 19.9kg, min 35 kg, max 219 kg). The distribution of weight in the Australian population is presented in Figure 8-17.

6.2.3.3.4 Panel Reactive Antibody

The PRA is an immunologic test for the presence of circulating antibodies to a random panel of donor lymphocytes. These are antibodies to human leukocyte antigen A, B, and DR in the serum. In a sample of patients at SVHS (n=26), 50% had a PRA of 0% indicating no antibodies to the panel, with max 94% and an average 21%. In a published kidney transplant model, the distribution was estimated for those below <80% and greater than 80% to indicate highly sensitised and the associated relative risk of getting a match was applied(227). The current model assumed that patients with a PRA >= 80% would have to wait an additional 3 months using a Delay block to find a match compared to those who did not.

6.2.3.4 Time-to-event probabilities

A summary of the time-to-event distributions used in the Markov model and converted for the DES model is presented in *Table 6-7*. Custom empirical distributions based on the survival curves used to inform the transition probabilities in Chapter 5 were used in the base-case of this analysis. This was to ensure consistency between the two models. Waiting times to various events were sampled from a series of custom empirical time-to-event distributions using fixed probabilities at time points (e.g. 12 months). The model was run in days and the custom empirical distributions are reported in months or years so adjustments were made as appropriate.

Table 6-7: Summary of time-to-event distributions for the discrete event simulation model

Transition	Distribution	Applied	Source
Model base case			
Annual age related mortality	Custom empirical distribution.	Probability in IneligibleAgeDeath SelectOutput; Probability in vadAgeDeath SelectOutput; Probability in waitingListAgeDeath SelectOutput; Probability in removedDeath SelectOutput; Probability in postHTxDeath SelectOutput	ABS
Waiting List to Death	Discrete probability distribution. 0.02637*2	Delay time in waitingListDeath	ANZCOTR
Ineligible to Death	Discrete probability distribution. 0.02637*2 * 1.6	Delay time in ineligibleDeath Delay	Assumption
Removed to Death	Discrete probability distribution. 0.02637*2* 1.5	Delay time in RemovedDeath Delay	Assumption
Ineligible to Alive postVAD	Custom empirical distribution. Use btc Match. Policy A and D set to 0%.	Probability in BTC SelectOutput	SVHS Add Value
Alive post-HTx to Death	Custom empirical distribution. 17-39 years, 40-49 years, 50-69 years and 60+ years	Delay time in delayHTxDeath Delay	ANZCOTR
Alive post- VAD to Death	Custom empirical distribution. Sensitivity analysis: Weibull distribution shape = 4.784, scale = 0.195	Probablity in postVAD SelectOutput5 Delay time in delayVADDeath Delay	INTERMACS

Transition	Distribution	Applied	Source
Waiting List to Alive post-VAD	Custom empirical distribution. Use btt Match.	Probability in delayforVAD SelectOutput	SVHS Add Value
Waiting List to Removed	Custom empirical distribution.	Probability in waitingListtoRemove SelectOutput Delay time in delayWLRemove Delay	SVHS CPR
DES transitions			
Bridge to transplant probability	40%. Policy C is 60% and Policy A and Policy D is 0%	Probability in bridge SelectOutput	SVHS Add Value
Organ discard	6 hours	Timeout in *'match'* Match	SVHS guidelines
Patient removal from matching process	6 months	Timeout in *'match'* Match	
PostVAD-WL	3 month	Delay time in postVADWaitingList	Assumption
PRA delay	3 months	Delay time in *'praWait'* Delay	
VAD discard	1 year	Timeout btc Match Timeout btt Match	
Cross-validation to Markov model in DES No Queue model			
Ineligible to VAD	Custom empirical distribution	Delay time in delayBTC Delay	SVHS Add Value
Waiting list to VAD	Custom empirical distribution	Delay time in delayBTT Delay	SVHS Add Value
postVAD to postHTx	Custom empirical distribution. Weibull distribution shape = 3.499, scale -0.286	Delay time in delayVADtoHTx Delay	IMACS
Alive post-VAD to Removed	Custom empirical distribution.	Probablity in postVAD SelectOutput5 Delay time in delayVADRemove Delay	SVHS CPR
Waiting List to posthtx	Custom empirical distribution.	Delay time in delayWLHTx Delay	SVHS CPR

During the analysis, age-related mortality using ABS Life Tables and post-HTx survival using Cutler-Ederer curves were estimated using a Gompertz function (sections 8.14.2 and 8.14.3). For *'Alive post-VAD'* to *'Death'* the Weibull distribution was chosen because although the AIC and BIC were lower for generalised gamma, AnyLogic did not support this distribution (*Table 8-53*). The Weibull distribution for post-VAD survival was tested as a sensitivity analysis in Chapter 5. For *'Alive post-HTx'* to '*Death'* a custom distribution was applied using the published Cutler-Ederer survival curves. The probability of death after HTx was adjusted according the age band at which a patient had received their HTx. Therefore, at the end of the 20-year time horizon, a 30-year-old HTx recipient has a 52% probability of death while a 50-year-old HTx recipient has a 70% probability of death (*Table 6-8*). This differs from the Markov model in which it was assumed that the cohort of 50 years old all had the same probability of death post-HTx based on the 50-59-year age band.

Table 6-8: Cutler-Ederer Survival Curves probability of death post-HTx ANZCOTR (1984-2018)

	17-39 years			40-49 years			50-59 years			60+ years		
Month	**Mean**	**Lower**	**Upper**	**Mean**	**Lower**	**Upper**	**Mean**	**Lower**	**Upper**	**Mean**	**Lower**	**Upper**
0	0	0	0	0	0	0	0	0	0	0	0	0.
1	0.121	0.096	0.148	0.111	0.088	0.137	0.123	0.104	0.144	0.171	0.138	0.206
2	0.145	0.118	0.174	0.127	0.102	0.154	0.148	0.127	0.170	0.199	0.164	0.236
3	0.185	0.155	0.217	0.134	0.108	0.162	0.164	0.142	0.187	0.223	0.186	0.262
4	0.203	0.172	0.236	0.151	0.124	0.180	0.194	0.170	0.219	0.237	0.199	0.277
5	0.222	0.190	0.256	0.175	0.146	0.206	0.209	0.185	0.234	0.267	0.228	0.308
6	0.242	0.209	0.277	0.214	0.183	0.247	0.238	0.212	0.265	0.297	0.256	0.339
7	0.260	0.226	0.295	0.24	0.207	0.274	0.268	0.241	0.296	0.334	0.292	0.377
8	0.281	0.246	0.317	0.273	0.239	0.309	0.297	0.269	0.325	0.359	0.316	0.403
9	0.310	0.274	0.347	0.299	0.264	0.336	0.326	0.298	0.355	0.397	0.353	0.442
10	0.332	0.295	0.370	0.331	0.295	0.368	0.36	0.331	0.390	0.417	0.373	0.462
11	0.354	0.317	0.392	0.367	0.330	0.405	0.382	0.352	0.412	0.467	0.422	0.512
12	0.376	0.338	0.415	0.384	0.346	0.423	0.428	0.398	0.458	0.524	0.479	0.569
13	0.387	0.349	0.426	0.394	0.356	0.433	0.458	0.428	0.489	0.555	0.510	0.600
14	0.398	0.360	0.437	0.426	0.387	0.465	0.501	0.470	0.532	0.573	0.528	0.618
15	0.416	0.377	0.455	0.468	0.429	0.507	0.539	0.508	0.569	0.603	0.558	0.647
16	0.442	0.403	0.481	0.524	0.485	0.563	0.574	0.544	0.604	0.643	0.599	0.686
17	0.460	0.421	0.499	0.537	0.498	0.576	0.615	0.585	0.645	0.666	0.623	0.708
18	0.494	0.455	0.533	0.55	0.511	0.589	0.64	0.610	0.669	0.72	0.678	0.760
19	0.506	0.467	0.545	0.565	0.526	0.604	0.672	0.643	0.700	0.774	0.735	0.811
20	0.515	0.476	0.554	0.588	0.549	0.626	0.703	0.675	0.731	0.786	0.748	0.822
21	0.538	0.499	0.577	0.645	0.607	0.682	0.721	0.693	0.748	0.786	0.748	0.822
22	0.558	0.519	0.597	0.684	0.647	0.720	0.759	0.732	0.785	0.85	0.816	0.881
23	0.570	0.531	0.609	0.721	0.685	0.756	0.794	0.769	0.818	0.85	0.816	0.881
24	0.570	0.531	0.609	0.73	0.694	0.764	0.809	0.784	0.833	0.893	0.863	0.919
25	0.604	0.565	0.642	0.741	0.706	0.775	0.818	0.794	0.841	-	-	-
26	0.620	0.581	0.658	0.748	0.713	0.781	0.851	0.829	0.872	-	-	-
27	0.649	0.611	0.686	0.786	0.753	0.817	0.865	0.843	0.885	-	-	-
28	0.672	0.634	0.708	0.82	0.789	0.849	0.865	0.843	0.885	-	-	-
29	0.713	0.677	0.748	0.85	0.821	0.877	0.865	0.843	0.885	-	-	-
30	0.732	0.696	0.766	0.85	0.821	0.877	0.865	0.843	0.885	-	-	-
31	0.760	0.726	0.793	0.85	0.821	0.877	-	-	-	-	-	-
32	0.760	0.726	0.793	0.9	0.875	0.922	-	-	-	-	-	-
33	0.760	0.726	0.793	0.9	0.875	0.922	-	-	-	-	-	-
34	0.760	0.726	0.793	0.9	0.875	0.922	-	-	-	-	-	-

Source: ANZCOTR 2018(70)

6.2.3.5 Global variables

Random numbers

The stochastic nature of the model comes from the random numbers used to implement the selection from distributions, meaning that the results will differ slightly for each model run. The base case model agent arrivals were modelled using a rate based on the Poisson distribution; therefore, each model run had a different number of patients and resources. In order to ensure reproducible results during model development, a fixed seed was applied.[43]

[43] To improve stability of the model one can increase the number of replications of simulations or increase the number of individuals being modelled (30, p184). Stability of model runs differences to be less than 5% or 1% difference in the mean ICER.(218)

Discounting

Discounting of costs and benefits occurred at a rate of 5% p.a.(197)

Simulation time

The model was run for 20 years,with analyses conducted at 6 months and every year from 1 to 20 years to calculate the impact of discounting on costs and benefits.

6.2.3.6 Quality of Life

As with the Markov model, quality of life was applied to the DES model using utility values (120) (Table 5-7) based on the proportion in each NYHA class (Table 5-8). Unlike the Markov model, the current model applied the average QoL values for each transition to event by multiplying the average weighted QoL by the NYHA distribution directly, rather than applying these separately. These average weighted QoL values for each event-based health state were multiplied by the average number of days spent between each event weighted by the proportion of patients who experience that event.

Table 6-9: Average Quality of Life

Health State	Ineligible	Waiting list/Removed	Post-HTx	Post-LVAD	Adjusted Post-LVAD
n	18	366	52	6	71
Source	Add Value	MOMENTUM 3	Add Value	Add Value	Add Value, ROADMAP
Utility value					
NYHA I = 0.855	0	0	0.0987	0	0.1203
NYHA II = 0.771	0	0	0.1779	0.1285	0.1084
NYHA III = 0.673	0	0.0272	0.2847	0.1122	0.0947
NYHA IV = 0.532	0.5320	0.5105	0.1228	0.3547	0.3075
QoL per year	0.5320	0.5377	0.6841	0.5953	0.6309

Abbreviations: HTx, heart transplant; LVAD, left ventricular assist device; NYHA, New York Heart Association; QoL, quality of life

For the one-way sensitivity analysis the NYHA proportions and utility values were not implemented in the model as two separate sets of parameters, but, rather, were multiplied to provide the average QoL for a particular event-based health state (Table 6-10). Therefore, the upper and lower estimates of average QoL were calculated based on the upper and lower estimates of the utility values NYHA proportions. The same scenario analysis for QoL post-VAD of 0.6309 was applied based on the analysis of ROADMAP data.

Table 6-10: Quality of life values in sensitivity analyses

		Change in utility value		Change in NYHA proportion		
	Base case	Lower	Upper	Lower	Upper	Scenario analysis
QoLPostHTx	0.684077	0.665231	0.706615	0.399751	1	-
QoLPostVAD	0.595333	0.557667	0.6345	0.137794	1	0.630881
QoLIneligible	0.532	0.48	0.584	-	-	-
QoLRemoved	0.537694	0.487471	0.588281	0.513866	0.562192	-
QoLWaitlist	0.537694	0.487471	0.588281	0.513866	0.562192	-

6.2.3.7 Costs

The model included the same costs as in the Markov model; however, the health state annual costs *'Ineligible'*, *'Waiting List'*, '*Removed'*, *'Alive post-VAD'* and *'Alive post-HTx'* were calculated as a per diem cost (*Table 6-11*). The calculated per diem cost is multiplied by the average number of days spent between each event weighted by the proportion of patients who experience that event. The event specific costs that occur once – LVAD implant hospital admission, the HTx hospital admission and procurement cost for the donor heart – and the cost of death assigned to heart-failure related deaths are multiplied by the number of events experienced in each model run. The total accumulated one-off costs are then divided by the patient cohort (sum of ineligible and eligible patients).

Table 6-11: Costs applied in the model - ($AUD 2019)

Description	Per event		Source
VAD index admission initial + prosthesis	$279,478.3	-	Add Value, APDC and EDDC
HTx index admission	$135,456.4	-	Add Value, APDC and EDDC
HTx organ procurement - posthumous	$29,647.9	-	(170)
Cost of campaign in policy D	$1,664.6	-	(208-210)
HTx DCD via OCS in policy D	$49,647.9	-	{St Vincent's Health Network Sydney, 2015 #602}, assume 50%
Death due to organ failure	$21,615.1	-	(211)
	Per Year	**Per diem**	
Ineligible for waitlist pre-VAD	$76,135.5	$208.59	Add Value, APDC and EDDC
HTx subsequent admissions	$59,039.8	$161.75	Add Value, APDC and EDDC
VAD subsequent admissions	$58,419.2	$160.05	Add Value, APDC and EDDC
Removed admissions	$43,661.5	$119.62	Add Value, APDC and EDDC
Waiting list admissions	$36,188.7	$99.15	Add Value, APDC and EDDC

6.2.3.8 Outcomes

Standard HTA outcomes include mean QALYs and costs (both undiscounted and discounted). In addition, operational outcome measures were reported.(23, 216) Therefore, event counts include the number of HTx, number of VADs and average waiting time for a HTx.

6.2.4 Validation

A recently published DES checklist was followed regarding validation.(228) The model was assessed for face validity, internal validity and external validity.(23) Face validity refers to the model reflecting the problem accurately. Internal validity was conducted throughout model development to ensure that the model logic, programming and calculations were accurate.(30) External validity was conducted to assess whether the model results reflect what happens in the real world. External validity consists broadly of dependent validation, independent validation and predictive validation.(30) Predictive validation was not conducted as there were no ongoing trials or unpublished registry data collection available.

6.2.4.1 Face validity

Face validity was assessed using clinical expert opinion (Prof. Christopher Hayward, SVHS) of the model structure. The approach taken was similar to the development of the Markov model in Chapter 5. Similarly, the DES model was developed with the Markov model structure in mind.

6.2.4.2 Internal validity

The model logic was checked during model development with the model simulated after incremental changes to the model structure (addition of blocks). Other checks included turning blocks on/off as part of modelling the various policies to ensure patient flow was as expected. Unused blocks are grey shaded post-simulation while used blocks are blue with agent numbers reported at the appropriate in and out ports.

6.2.4.3 External validity

This model relied on 2016-2018 data from ANZCOTR , specifically the 3-year average of adult HTx in Australia for external validation (Table 6-12). The method applied was similar to that in Stahl et al. (2007), where four main calibration parameters were identified in the liver transplant model and compared to published UNOS data.(17) The four parameters and acceptable ranges were the model waiting list length (±2 percent), number of transplants (±2 percent), deaths while waiting for a transplant (±5 percent), and time to transplant (±11 percent). The same parameters – excluding deaths while waiting – were used to validate this DES model. The deaths after removal from the waiting list could not be retrieved from the ANZCOTR because only those who died while on the waiting list were captured. The current model includes deaths from those who were removed from the waiting list (and were no longer followed up), those who received a VAD and those who were *'Ineligible'*.

Table 6-12: Validation parameters

Parameter	Value	Description and motivation	Source
Transplants	93	3-year average yearly orthotopic adult transplants *N (2016-2018)*	(70)
Waiting Time	153 (200)	3-year average yearly mean and SD *(2016-2018)*	(70)
Waiting list queue end of year	44	3-year average total on waiting list at end of year orthotopic adult transplants N (2016-2018)	ANZCOTR 2016, 2017, 2018

6.2.4.4 Comparison to Markov model

The methodology for cross-validation was similar to that presented in Standfield et al. (2017)(38), and hence, two models were developed: 1) DES model with queuing, and 2) DES model without queuing to calibrate the Markov model from Chapter 5. The model was cross-validated to the Markov model developed in Chapter 5 to ensure that the same decision problem was being addressed.

6.2.5 Sensitivity Analysis

6.2.5.1 One-way sensitivity analysis

A one-way sensitivity analysis analogous to the sensitivitiy analysis counducted in Chapter 5 was undertaken to assess the parameter uncertainty and determine whether the same parameters as identified in Chapter 5 influence the DES model's robustness. In order to conduct the sensitivity analyses, a number of changes in parameters were adjusted:

- The NYHA proportions and utility values were not implemented in the model as two separate sets of parameters, but rather were multiplied to provide the average QoL for a particular event. Therefore, the upper and lower estimates of average weighted QoL were calculated (Table 6-10).
- Post-HTx survival from the Cutler-Ederer survival curves from ANZCOTR by age groups (17-39 years, 40-49 years, 50-59 years and 60+ years) compared to 50-59 years only in Chapter 5 (Table 6-8).
- In Chapter 5, patients entered the model at age 50 and the age-related mortality life table was referenced from age 50 onwards. The current model included the age distribution from Add Value (aged 20-72 years) and hence an extended life table was referenced (Table 8-56).
- All transition probabilities used in Chapter 5 are now cumulative survival probabilities and so the lower and upper 95% confidence intervals were estimated (Table 8-57 toTable 8-62).

In addition to the parameters that formed the sensitivity analysis in Chapter 5, the new DES model specific parameters analysed include:

- Patient, device and organ arrival based on lower and upper estimates of 20% (Table 6-4).
- Patient and organ weight (Table 6-5).
- Panel reactive antibody delay for those with score of ≥ 80% (*'praWait'*)
- Timeout from match block for patients and organs (Table 6-7).

6.2.5.2 Scenario analyses

A number of scenario analyses were replicated from Chapter 5 that had an impact on the ICER. Specifically, Scenarios 5, 6, 8, 9 were replicated and two structural analyses were the removal of *'Ineligible'* (Scenario 1) and *'Waiting list'* (Scenario 10) health state; however, given the changes in the model structure further adjustments were made. Additional scenario analyses based on the new model parameters included:

- Turning off the delay provided by a high panel reactive antibody score (set praDelay to 0).

- Donor organ and patient weight matching algorithm expanded to ±30% or reduced to ±10% not ±20%.
- Donor organ and patient matching algorithm based on blood type only or weight only.

The risk of rejection of donor organs was not incorporated into the model from changes made to the matching criteria.

6.3 Results

6.3.1 Validation

The average proportion of patients experiencing the events between the two DES models is presented in Table 6-13. The main difference between the two DES models was the proportion of patients experiencing a VAD event in Policy B, with 39% DES with queuing model compared to 85% DES No Queue model. Between the two DES models, the proportion experiencing a HTx was similar between Policy B and Policy C, but lower between Policy A and Policy D in the No Queue model. Correspondingly, there are fewer patients in the DES with queuing model who experience a *'Removed'* event. In the Markov model, the proportion experiencing a HTx event was the lowest amongst the three models and the proportion experiencing a VAD event was in between the DES with and without queuing model.

Table 6-13: ***Average proportion of patients experiencing event***

	HTx	VAD	Ineligible	Removed	Waiting List	Death
Policy A						
DES with Queuing	70%	0%	9%	8%	91%	38%
DES No Queuing	33%	0%	7%	33%	93%	76%
Markov model	37%	0%	0%	0%	90%[a]	76%
Policy B						
DES with Queuing	63%	39%	8%	7%	96%	41%
DES No Queuing	51%	85%	7%	33%	99%	62%
Markov model	29%	64%	0%	0%	90%[a]	76%
Policy C						
DES with Queuing	61%	60%	9%	5%	98%	42%
DES No Queuing	51%	89%	7%	33%	99%	65%
Markov model	28%	71%	0%	0%	70%[a]	70%
Policy D						
DES with Queuing	75%	0%	10%	5%	90%	33%
DES No Queuing	46%	0%	7%	23%	93%	66%
Markov model	49%	0%	0%	0%	70%[a]	70%

[a] Based on initial probabilities starting in each health state.

For the DES models, to estimate the average proportion of time spent between events, the average sum of days to the events was divided by the number of each event. The average proportion of time spent by the patients in each health state over the 20 years between the three models is presented in Table 6-14. The differences between the average proportion of time spent in the 'health states' between the models is reflective of the differences in the proportion experiencing such events. For

instance, patients spend more time in the HTx health states in the DES with queuing model than any of the other models. Another notable difference between the Markov model and the DES models is that there is significantly more patient time spent in the waiting list health state in the Markov model.

Table 6-14: ***Average proportion of time spent in each health state over time horizon***

	HTx	VAD	Ineligible	Removed	Waiting List	Death
Policy A						
DES with Queuing	65%	0%	0%	0%	4%	31%
DES No Queuing	28%	0%	0%	0%	5%	67%
Markov model	20%	0%	4%	4%	26%	45%
Policy B						
DES with Queuing	49%	20%	1%	0%	4%	26%
DES No Queuing	39%	12%	1%	0%	4%	44%
Markov model	15%	27%	2%	7%	11%	38%
Policy C						
DES with Queuing	48%	22%	0%	0%	2%	27%
DES No Queuing	38%	12%	1%	0%	4%	45%
Markov model	14%	31%	2%	8%	8%	37%
Policy D						
DES with Queuing	70%	0%	0%	0%	3%	27%
DES No Queuing	41%	0%	0%	0%	4%	55%
Markov model	28%	0%	4%	3%	20%	44%

6.3.1.1 Throughput and event number results

The event numbers and throughput statistics for the three models compared to the ANZCOTR data are presented in Table 6-15. The external validation data represents the current ESHF Policy with use of LVADs (Policy B). In the DES with queuing model the event numbers for VAD, HTx and Death were divided by 20 years to estimate the average number of events per year. The base case DES model with queuing VAD numbers was most consistent with VAD use in Australia. For example, in the DES model with queuing, 54 VADs were in one year (distinct to Year 1), which is similar to the 55 to 90 per year predicted by the ANZCOTR data. The equivalent number of VADs used over the model time horizon (not just Year 1) in the DES No Queue model and Markov model was 150 and 113 respectively. In the DES No queue model the 150 VADs were implanted by Year 3, meaning of the 177 patients that entered the model at t=0, 150 were implanted with an LVAD by Year 3 (83 by Year 1 and 144 by Year 2).

For the number of HTx conducted between the models, there were more similarities. In the DES No Queue model, the average yearly HTx was 87 and in Year 1 was 94, and was similar between the DES models with and without queuing (87 and 91 respectively). These numbers are comparable to the 93 reported in the ANZCOTR data.(70) Across the four policies (Policies A to D), the number of HTx in Year 1 differed. Policy D was associated with the highest number of HTx in Year 1 and Policy A the least (full ranking: Policy D > Policy A > Policy C > Policy B). This ranking is as expected and reflects the supply of donor hearts and the supply of alternative treatments (VADs). The ranking was also consistent across all models, DES with queuing and the Markov model.

The number of HF related deaths were higher in the DES No Queue model and the Markov model compared to the DES with queuing. However, there was a difference in the ordering of policies. The time to transplant was estimated to be on average 153 days from 2016-2018 based on ANZCOTR data, which is less than the 217 days estimated in the DES with queuing model, and the 318 days estimated in the DES No Queue model. In the DES No Queue model, all patients arrived at t=0 (Day 0) and the transition to events was modelled at t=365 (Day 365) to reflect the same yearly cycles as in the Markov model. Therefore, it is possible that the DES No Queue model overestimates the time to transplant days because patients must remain in that health state for at least one year. In the DES with queuing model, patients were added to the waiting list as soon as they received an LVAD and the 'postVADWaitingList' delay block was used to add 3 months to the waiting time to reflect the 'On hold' period, which may explain the higher time to transplant compared to the 153 days reported in ANZCOTR.

Table 6-15: Throughput and event number results – 20 year experience

	VADs	HTx	HF Deaths	Patients	Time to transplant (days)
DES with queuing					
Policy A	0	1,898	841	2713	183.28
Policy B	1,077	1,742	1,033	2746	217.34
Policy C	1,556	1,591	1,009	2605	108.09
Policy D	0	1,963	799	2607	132.95
DES No queuing [a]					
Policy A	0	58	133	177	383.42
Policy B	150	91	108	177	317.72
Policy C	158	91	112	177	280.55
Policy D	0	82	111	177	340.32
Markov model [a]					
Policy A	0	65	124	177	-
Policy B	113	52	113	177	-
Policy C	126	49	111	177	-
Policy D	0	86	123	177	-
External Validation (2016-2018) in ANZCOTR					
Real-world, per year	55-90‡	93	-	177	153 (SD 200)

Note:
‡Personal communication with Professor Christopher Hayward, St Vincent's Hospital Sydney.
a. In the DES No Queue and Markov model, in Policy B and Policy C most VADs were received at the beginning of Cycle 2 (Year 2) due to the yearly transitions as all patients began in the 'Ineligible' or 'Waiting list' health state but not the 'Alive post-VAD', therefore, 113 VADs were provided over the first few years.

A comparison of patient flow throughout the models are presented in Table 6-16. The interpretation of the DES No Queue model Policy A is that of the 177 patients entering the model at t=0 days, 59 will die in the first year (Table 6-16) and a total of 133 will die over the 20-year time horizon (Table 6-15). This differs from the interpretation of the DES with queue model, in Policy A, under which of 175 patients that enter the model throughout Year 1, 31 die in Year 1 but the remaining patients will die over the 20-year time horizon. The average number of deaths per year over the 20-year time horizon is 47, indicating more patients will die on average in the later years.

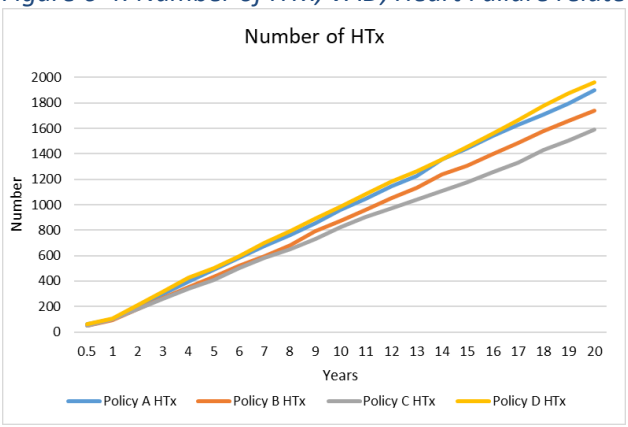
Table 6-16: Throughput and event number results – Year 1 experience

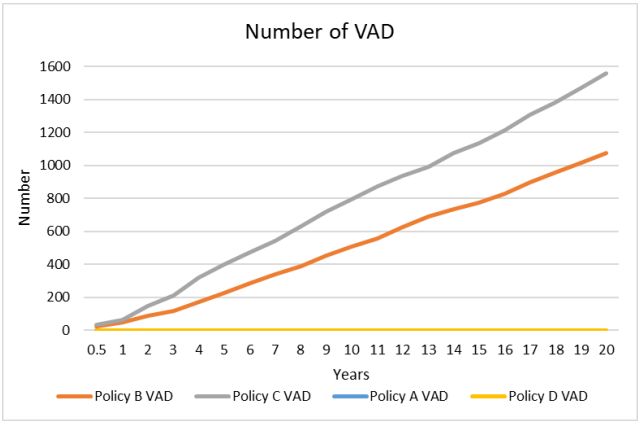
	VADs	HTx	HF Deaths	Patients
DES with queuing				
Policy A	0	101	31	175
Policy B	46	94	18	171
Policy C	64	99	16	169
Policy D	0	108	36	187
DES with queuing, yearly average†				
Policy A	0	95	47	136
Policy B	54	87	52	137
Policy C	78	80	50	130
Policy D	0	98	40	130
DES No queuing				
Policy A	0	18	59	177
Policy B	83	2	10	177
Policy C	101	5	5	177
Policy D	0	48	52	177
External Validation (2016-2018) in ANZCOTR				
Real-world	55-90‡	93	-	177

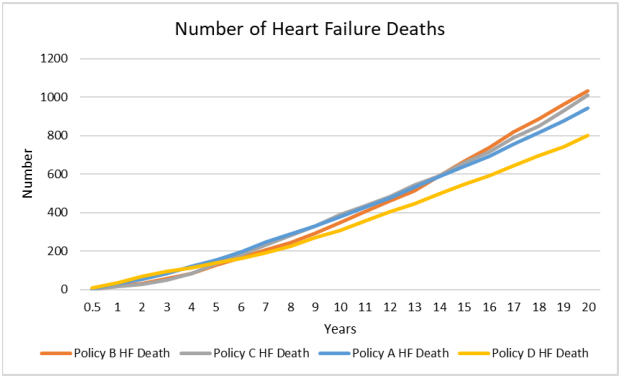
†The DES with queuing model numbers for VADs, HTx, HF Deaths and patient numbers divided by 20 to obtain average per year. These are crude counts not adjusted for different sample sizes due to applying a random Poisson rate for patient arrival for each simulation.
‡Personal communication with Professor Christopher Hayward, St Vincent's Hospital Sydney.

The numbers of HTx, VAD and HF-related deaths across the policy alternatives over the 20 years in the DES with queuing model are presented in Figure 6-4. In the early years, Policy D had the most heart failure-related deaths but by the end of the model time horizon had significantly fewer heart failure-related deaths.

Figure 6-4: Number of HTx, VAD, Heart Failure related deaths over the 20 years – DES with queuing

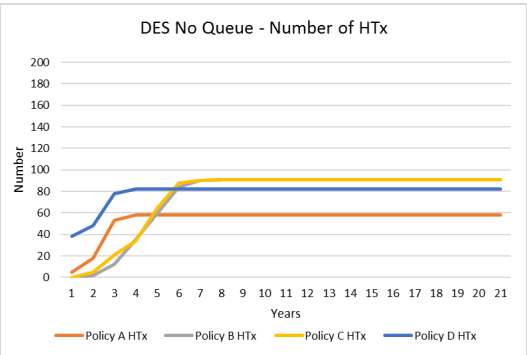


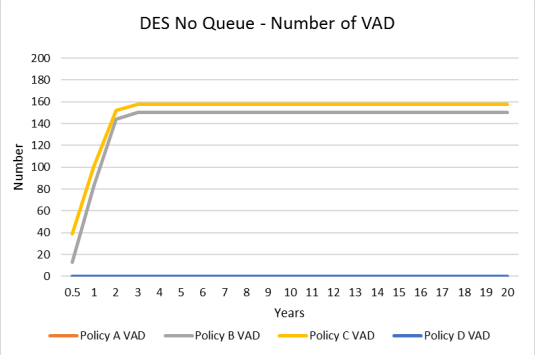


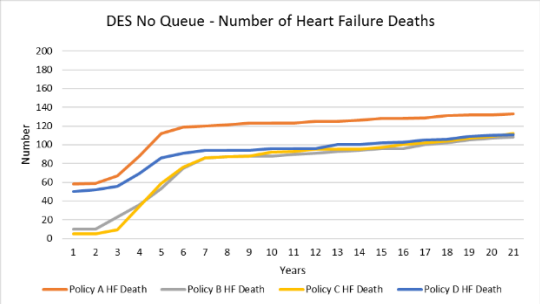


In the DES No Queue model, the flow of patients between the policies indicates that both Policy B and Policy C delay the receipt of heart tranplants compared to Policy A and Policy D; under these policies, there are fewer heart failure related deaths in the early years (Figure 6-5).

Figure 6-5: Number of HTx, VAD, Heart Failure related deaths over the 20 years – DES No queuing







6.3.1.2 Disaggregated Costs

The disaggregated costs are provided in Table 6-17. The numbers of HTX, VAD and HF-related death events were adjusted for the patient number. The total undiscounted costs between the two DES models were slightly higher in the DES No Queue model than the DES with queuing model for all the alternatives except for Policy A.

Table 6-17: Disaggregated costs

	Policy A	Policy B	Policy C	Policy D
DES with Queuing				
HTx	$313,367,430	$287,611,203	$262,680,496	$366,626,919
VAD	$0	$300,998,075	$434,868,157	$0
Deaths	$20,339,771	$22,328,357	$21,809,596	$17,270,433
Undiscounted Intervention	$333,707,201	$610,937,635	$719,358,248	$383,897,352
Patient number	2,713	2,746	2,605	2,607
Undiscounted Intervention adjusted	$123,003	$222,483	$276,145	$147,256
Undiscounted Hospital	$429,267	$548,943	$539,396	$456,897
Undiscounted Total Costs	$552,270	$771,426	$815,541	$604,153
DES No Queuing				
HTx	$9,576,033	$15,024,466	$15,024,466	$15,315,032
VAD	$0	$41,921,738	$44,157,564	$0
Deaths	$2,874,803	$2,334,426	$2,420,887	$2,399,272
Undiscounted Intervention	$12,450,836	$59,280,630	$61,602,916	$17,714,303
Patient number	177	177	177	177
Undiscounted Intervention adjusted	$70,344	$334,919	$348,039	$100,081
Undiscounted Hospital	$362,883	$647,320	$643,291	$516,934
Undiscounted Total Costs	$433,227	$982,239	$991,330	$617,015

6.3.2 Cost-effectiveness results

6.3.2.1 Base-case results

Comparison to common baseline (Policy A)

The results presented here are the cost-effectiveness estimates of the current ESHF policy (Policy B) and expanded supply policies (Policy C and Policy D) compared with the previous ESHF policy (Policy A), i.e. prior to the introduction of LVADs. The ICER per LY gained between the policies was presented in Table 6-18. The DES model ICERs per LY gained are significantly lower compared to the Markov model due to the smaller incremental cost to Policy A and larger incremental benefit to Policy A. Another notable difference is the fewer LY gained between Policy C and Policy B in the DES models compared to the Markov model, which estimated that Policy C had the most LY gained. In the DES with queuing model, the Policy C option provides LVADs to patients at a faster rate; however, there is no corresponding increase in the available supply of donor hearts.

Table 6-18: ICER per LY gained between Policies (time horizon 20 years, discounted)

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention LY	Comparator LY	Incremental LY	ICER
DES with queuing							
Policy B vs. A	$508,235	$363,850	$144,385	6.38	4.95	1.43	$100,964
Policy C vs. A	$542,446	$363,850	$178,595	6.25	4.95	1.30	$137,148
Policy D vs. A	$399,108	$363,850	$35,258	5.24	4.95	0.29	$121,288
DES No queuing							
Policy B vs. A	$763,895	$309,174	$454,720	7.91	4.45	3.47	$131,123
Policy C vs. A	$979,894	$309,174	$670,719	7.90	4.45	3.46	$194,116
Policy D vs. A	$441,676	$309,174	$132,502	6.15	4.45	1.70	$77,921
Markov model							
Policy B vs. A	$1,709,347	$854,569	$854,778	10.72	10.35	0.37	$2,305,168
Policy C vs. A	$1,941,479	$854,569	$1,086,910	10.81	10.35	0.46	$2,379,832
Policy D vs. A	$1,166,737	$854,569	$312,168	10.41	10.35	0.06	$4,998,194

The ICER per discounted QALY gained are presented in Table 6-19. When the LYs were adjusted for QoL, the incremental benefit in the DES models more closely resembled the Markov model.

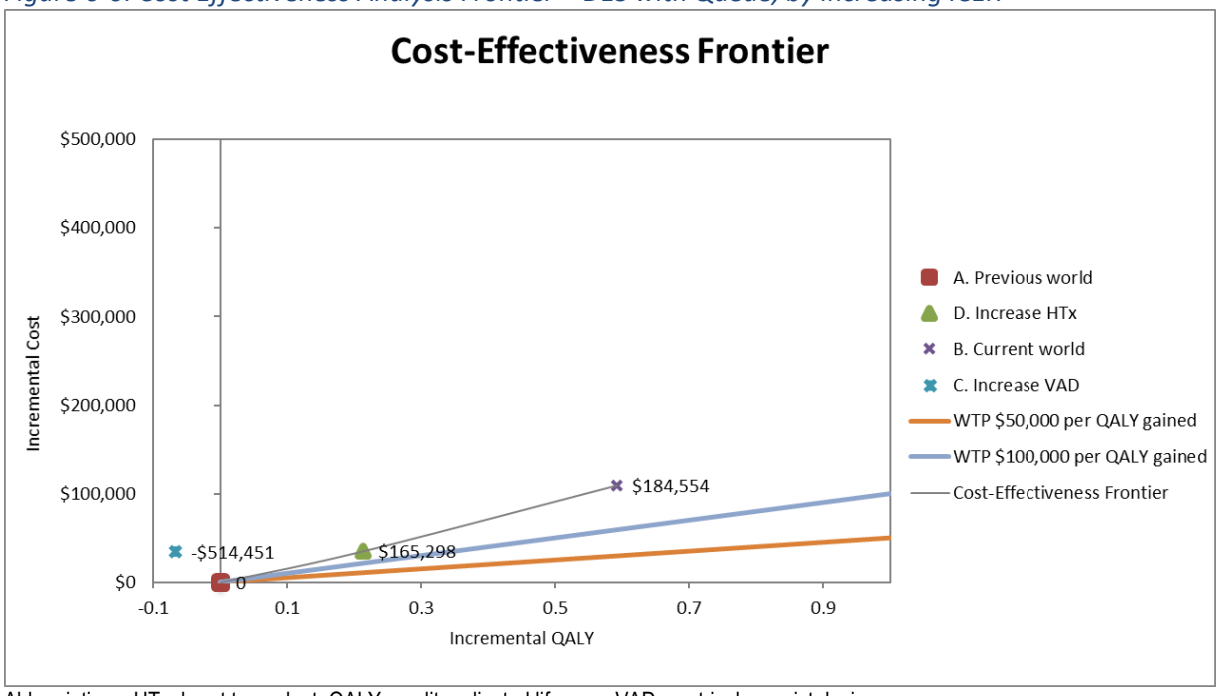
Table 6-19: ICER per QALY gained between Policies (time horizon 20 years, discounted)

	Intervention Cost	Comparator Cost	Incremental Cost	Intervention QALY	Comparator QALY	Incremental QALY	ICER
DES with queuing							
Policy B vs. A	$508,235	$363,850	$144,385	4.13	3.33	0.80	$179,450
Policy C vs. A	$542,446	$363,850	$178,595	4.06	3.33	0.74	$241,985
Policy D vs. A	$399,108	$363,850	$35,258	3.54	3.33	0.21	$165,336
DES with no queuing							
Policy B vs. A	$763,895	$309,174	$454,720	5.08	2.91	2.17	$209,171
Policy C vs. A	$979,894	$309,174	$670,719	5.08	2.91	2.17	$309,474
Policy D vs. A	$441,676	$309,174	$132,502	4.09	2.91	1.18	$112,407
Markov model							
Policy B vs. A	$1,709,347	$854,569	$854,778	5.19	4.70	0.50	$1,721,075
Policy C vs. A	$1,941,479	$854,569	$1,086,910	5.31	4.70	0.61	$1,780,350
Policy D vs. A	$1,166,737	$854,569	$312,168	4.94	4.70	0.24	$1,274,605

Comparison based on least costly alternative

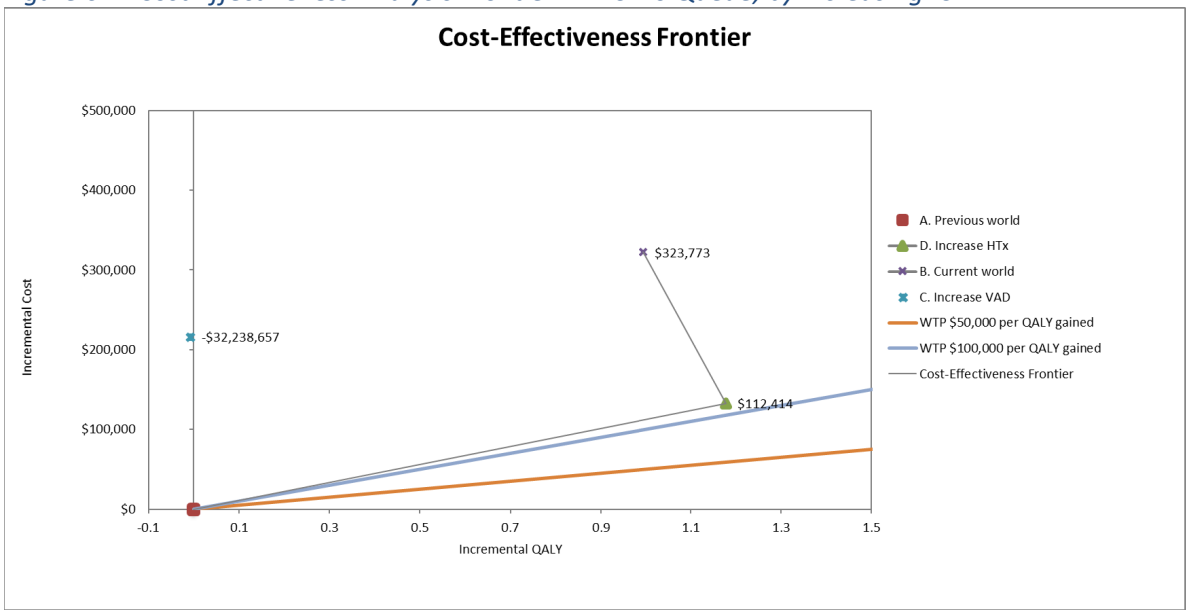
An incremental analysis was conducted for the DES with queuing model and the interventions were ranked from least costly to most costly (Policy A < Policy D < Policy B < Policy C). In the comparison against current practice, in the DES with Queue and DES No Queue model, the ICER for Policy C vs. Policy B was more costly, but provided fewer QALYs, further, the ICER for Policy D vs. Policy B was less costly and provided fewer QALYs. In the DES with queuing model and DES No Queue model, Policy C is a dominated option (Figure 6-6 and Figure 6-7). This means that Policy B is cheaper and produces more QALYs than Policy C in the DES models.

Figure 6-6: Cost Effectiveness Analysis Frontier – DES with Queue, by increasing ICER



Abbreviations: HTx, heart transplant; QALY, quality-adjusted life year; VAD, ventricular assist device
Note: Policy B is a dominated option.

Figure 6-7: Cost Effectiveness Analysis Frontier – DES No Queue, by increasing ICER



Abbreviations: HTx, heart transplant; QALY, quality-adjusted life year; VAD, ventricular assist device
Note: Policy B is a dominated option.

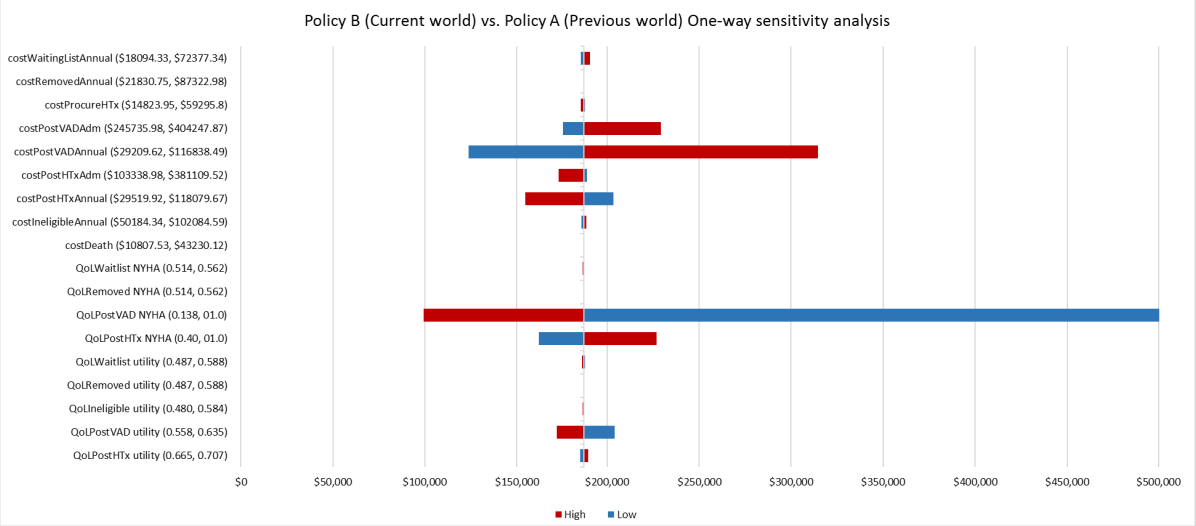
6.3.2.2 Sensitivity Analyses

The sensitivity analyses of ICER results are presented using undiscounted costs and benefits. Given the probabilistic nature of the DES analysis, changes to time-related variables such as delays (*ineligibleDeath)* and timeto-event probabilities caused changes in patient numbers entering the model. Consequently, the cost-effectiveness results of Policy B vs Policy A in the sensitivity analyses cannot be compared to the base case results. Therefore, for analyses where the patient numbers have changed, the impact of the variable change on proportion of patients transplanted will be reported compared to the base case. For variables that do not affect the patient numbers entering the model, such as costs and utility values, the change in ICER is reported.

6.3.2.2.1 One way sensitivity analyses

The tornado diagram for the one-way sensitivity analyses s presented in Figure 6-8. The proportion of patients in NYHA classes post-VAD implant had a significant impact on the ICER. The cost variable that had the largest impact on the ICER were the ongoing hospitalisations for LVAD patients.

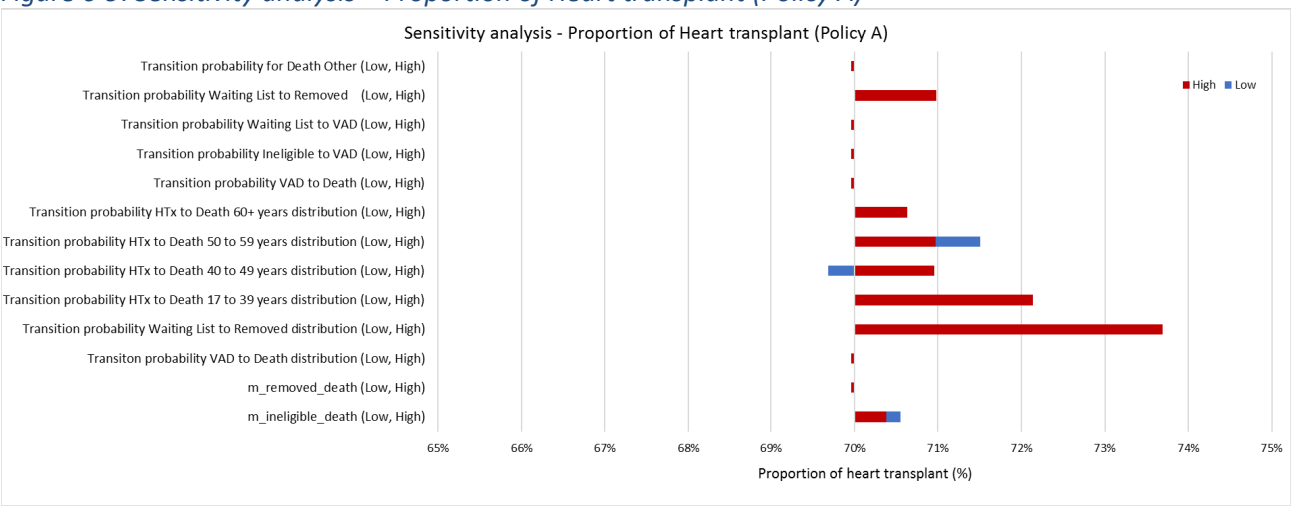
Figure 6-8: Tornado plot for one-way sensitivity analyses of costs and utility (Policy B vs. Policy A)



Note: Results for undiscounted ICERs.

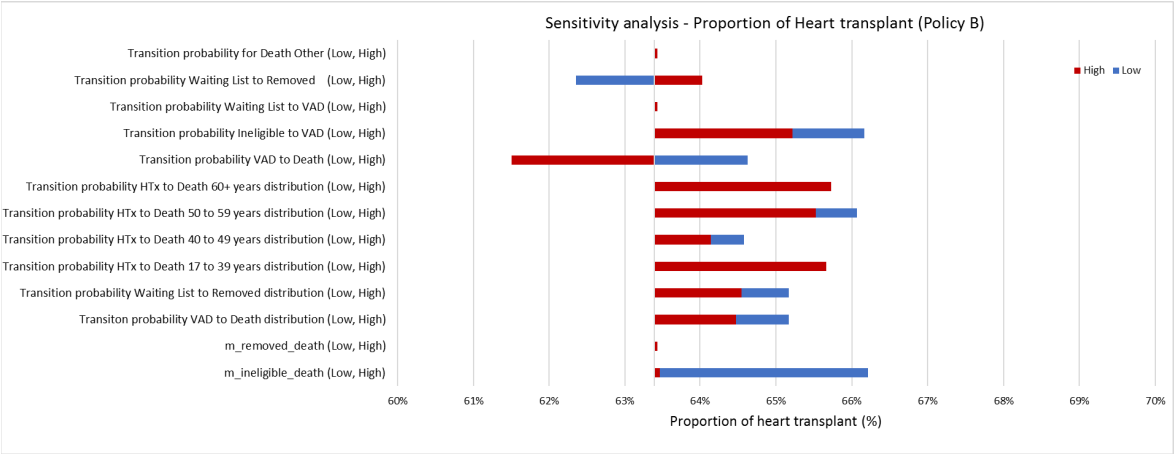
The sensitivity analyses for the lower and upper transition probabilities for Policy A are presented in Figure 6-9. The time-to-event probability that had the greatest impact on the proportion of heart transplants performed was the time from waiting list to removal, with higher rates of removal leading to a higher proportion of transplants.

Figure 6-9: Sensitivity analysis – Proportion of Heart transplant (Policy A)



The sensitivity analyses for the lower and upper transition probabilities for Policy B are presented in Figure 6-10.

Figure 6-10: Sensitivity analysis – Proportion of heart transplant (Policy B)



6.3.2.2.2 Scenario analyses

In the DES model, the same scenario analyses had a smaller impact on the ICER than when run in the Markov model in the previous chapter; however, the direction of the analyses on the ICER were the same for both models (

Table 6-20). The time horizon remained a significant driver of the model results, with shorter time horizons resulting in lower cost-effectiveness.

Table 6-20: Proportional impact of scenario analysis on base case ICER for DES and MM

	DES (undiscounted)	Markov model
Policy B vs. A		
Time horizon, 20 years (base case)	100%	100%
Time horizon, 15 year	108%	114%
Time horizon, 10 year	126%	139%
Time horizon, 5 year	159%	151%
Utility decrement for removed health state (0.01)	100%	101%
Cost of death set to $0	100%	102%
50% reduction in VAD cost	91%	82%
75% reduction in VAD cost	87%	73%
NYHA Class post-VAD adjusted from ROADMAP Study	93%	79%

The impact of the scenario analyses on the proportion receiving a heart transplant are presented in Table 6-21. Removing the ineligible health state so that these patients no longer arrived in the model meant that more patients were transplanted under both Policy A and Policy B. Of the two matching conditions of blood type and patient weight (70% HTx in Policy A), more patients were transplanted if only blood type criteria was applied (91% in Policy A) compared to weight only (77% in Policy A).

Table 6-21: Scenario analyses – Proportion of Heart transplant

	Policy A	Policy B
Base case (undiscounted)	70%	63%
Removing the 'Ineligible' health state to exclude BTC patients	78%	69%
Transition probability from 'Alive post-VAD' to 'Death' extrapolated to 6 years using Weibull;	70%	66%
Turning off the delay in months from high panel reactive antibody score (set praWait to 0).	71%	65%
Donor organ and patient weight matching algorithm expanded to ±30% not ±20%	52%	48%
Donor organ and patient weight matching algorithm reduced to ±10% not ±20%	81%	74%
Removal of patient weight matching algorithm, blood type match only	91%	78%
Removal of blood type matching condition, weight match only	77%	71%
Post-HTx survival based on 50-59 year cohort	70%	64%
Changing the delay in months of post-VAD to Waiting List delay (0)	70%	66%
Double delay in months of post-VAD to Waiting List delay (6)	70%	65%
Patients all aged 50 years old, rather than age distribution from Add Value	70%	63%

A structural sensitivity analysis was conducted using the DES No Queue model to test the impact of removing the *'waiting list'*. The removal of the *'waiting list'* in the DES model required patients to be able to immediately receive a donor organ and not be 'removed' from the list. As such, the DES No Queue model was adjusted so that in Policy A all patients immediately received a donor organ (set Policy D to 100%) and for Policy B all patients immediately receive an LVAD without waiting (set Policy C to 100%) and no patients could be *'Removed'*. Consequently, this analysis resulted in an increase of proportion transplanted in Policy A from 33% to 93% and for Policy B from 51% to 80%.

6.4 Discussion

This chapter sought to compare the impact of incorporating queuing theory into a HTA of ESHF. The heart allocation waiting list is a nonterminating system, meaning it has no formal beginning or end.(17) In a Markov model, the starting cohort of prevalent patients are modelled; in a DES model, however, new patients enter over time, and incident patients as well as the prevalent cohort are modelled. The DES with queuing model reflects the patients competing with each other for resources (LVADs and HTx) as well as the interaction between the patient and the donor organ via the matching algorithm.

The two DES models produced much lower ICERs (Policy B vs Policy A) compared to the Markov model. The DES with queuing model for Policy B vs Policy A produced an ICER of $179,450 per QALY gained while the corresponding analysis in the Markov model produced an ICER of $1.72 million per QALY gained. This difference was driven by both a lower incremental cost and a greater incremental benefit. There were a number of differences in the flow of patients throughout the three models, the main difference being the proportion expected to receive a HTx and VAD, which had flow-on effects on the associated time spent in those health states, benefits gained and costs accrued.

In the Markov model it appeared that Policy C was the most cost-effective option, as Policy B was extendedly dominated by a combination of Policy D and Policy C. However, in the DES model Policy C

was the dominated option, as Policy B produced more benefit and less cost than Policy D. Therefore, based on the DES results the decision-making conclusion would differ in that Policy C may not be preferred to Policy B. Although the Markov model indicated that a combination of the two hypothetical policies involving increased supply of both LVADs and HTx would be the preferred option, this is not particularly useful for decision-makers.

Two DES models were built to explore the impact of queuing. For the DES model without the queue, there was no interaction between patients and patients received VAD and HTx based on the KM curves used in Chapter 5. Naturally, the results from the DES No Queue models were more similar to the Markov model. The corresponding count of the number of LVADs was higher than expected in the real world, but the number of HTx was similar. The estimated time to transplant when the queue was taken into account was more similar to the real world compared to DES No Queue.

The model validation of the average time to transplant between the DES No Queuing model to the average time on waiting list from the ANZCOTR between 2016-2018 of 153 days was lower but comparable to the 217 days estimated under the Policy B 'Current world'. The longer time to transplant estimated under Policy B accounts for the total time to transplant from receipt of LVAD for BTC candidates and those from the waiting list compared to the ANZCOTR, which reports the 'active' time on the waiting list. Further, the DES No Queue model estimated longer time to transplants across all 4 policies compared to the DES with Queuing model and the ANZCOTR results, reflecting the yearly 'cycles' applied in the model to match the Markov model. The time to transplant could not be estimated in the Markov model.

6.4.1 Comparison to published literature

A number of review articles have discussed the merits and drawbacks of DES modelling in HTA, with proponents of DES focussing on the shortcomings of Markov models to support these arguments.(23, 37, 223, 229, 230) The major benefit of DES for HTA is the incorporation of patient heterogeneity. However, it has been suggested that the ability of DES to track individual patient histories is not enough to warrant its use over a Markov model if patient heterogeneity does not influence the cost-effectiveness results.(37) Other benefits include a structural sensitivity analysis when alternative structures can be implemented within a single DES (229) and improved flexibility.(222)

Disadvantages of DES modelling relate to the need for individual patient data (or at least a distribution). Similarly, the lack of modeller and reviewer experience with this methodology and use of specialist licensed software can also be a drawback.

6.4.1.1 Applications of DES models in constrained organ transplant waitlists

Many studies have been identified using DES to model an organ transplantation waitlist (typically liver or kidney) and address transplant policy.(13, 135, 214). No studies have been identified for use as HTA in organ transplantation. Three core features of the organ transplantation waiting list are matching, abandonment and queueing discipline.(231) The current model includes the match in terms of patient and donor attributes being compatible and abandonment of the waitlist by including a 'Removed' event. The model applied a FIFO discipline rather than a priority basis as typically seen in US and European models. In Australia, HTx candidates do not receive a priority score, unlike in the USA which utilises a United Network of Organ Sharing (UNOS) score.(232) In liver transplants, candidates include Model for End-Stage Liver Disease (MELD) scoring system or PELD for paediactric patients.(50) Similarly, kidney transplant candidates receive a score to be placed on a 7-level allocation formula.(50) No such scoring system exists for heart transplants in Australia so it was appropriate to apply a FIFO queuing discipline once a match was found.

Stahl et al. (2007) constructed a DES model of the liver allocation system in the USA to determine the thresholds for production volume, durability, and cost of care for alternative liver organ replacement technologies (e.g partial-liver living-donor transplants).(17) The purpose was to assess the potential impact of new technologies on the liver transplant wait list. The authors validated their model against the UNOS data for liver transplants from 1994 to 2000. The model determined that given the high demand for donor livers, investment in the development any liver organ replacement technologies is cost-effective.(17)

The 'Blood type O problem' is also recognised in liver transplants. Many type-O organs are cross-transplanted to compatible A and B blood groups, causing significant delays in type-O recipients.(231) However, a Canadian queuing model study modelled an ABO-identical transplant policy and found that it would lead to long waiting times for all blood groups.(233) Because DES models can easily incorporate patient and donor characteristics, this match between the two agents can be modelled.

6.4.1.2 Application of DES models in HTA

Jahn et al. (2010) published a DES in a capacity-constrained setting comparing drug-eluting stents (des) and bare-metal stents (bms) with differences in the number of repeated interventions (bms have higher revascularisation rates) and different impacts on waiting times.(234) There were four treatment scenarios with either des or bms in first- or second-line by patient cohort of subgroup S1, S2, S3 and S4[44] (DBDD, DBDB, BBDB, BBBB). There was a queue to receive the first stent in hospital

[44] Subgroups: S1 = nondiabetes with long lesion or narrow vessel; S2 = nondiabetes with short lesion and wide vessel; S3 = diabetes with long lesion or narrow vessel; S4 = diabetes with short lesion and wide vessel. E.g.

(FIFO discipline) and depending on whether this is a des or bms, the revascularisation rate is affected; first stent type also affects time to first CABG, which is expensive. All average costs for stenting scenarios were higher in the capacity-limited DES (max 36 daily stents) compared to the no capacity limit model. All average QALY gains were lower in the capacity-limited DES compared to the no capacity limit model.

This example highlights differences in the ordering of cost-effectiveness when multiple alternatives are compared. In Jahn et al. (2020), in the no capacity limit model, BBBB was the cheapest and least effective (fewest QALYs) scenario; DBDD resulted in €1.6 mill/QALY gained, followed by DBDB of €1.1 mill/QALY gained and finally BBDB of $0.3 mill/QALY gained.(234) However, in the limited capacity model (36 stents daily), the cheapest scenario was DBDB; DBDD resulted in €1.4 mill/QALY gained. In this model, both BBDB and BBBB were dominated options. Therefore, the assumed capacity limit changes the relative cost-effectiveness results.

6.4.2 Limitations

One of the major drawbacks in the current DES with queuing model is that waiting list data does not usually include priorisation rules and queue discipline. Complete data were not available for all status changes in the waiting list, such as re-activation, retransplant and long-term follow-up post transplant.

The development of the model structure was an iterative process. After the initial development of the Markov model, when it came to converting the Markov model to the DES model, it was understood that two transitions were missing. These were 1) patients who were removed from the waiting list, who can be added back on to the waiting list; and 2) patients who were alive post-transplant, who could exerience organ rejection and be added back to the waiting list. Although retransplants can occur, they are infrequent. This highlights that given the additional flexibility of DES, a simple DES model directly translates to a complex Markov model.

6.5 Conclusion

These results demonstrate the importance of considering resource allocation decisons in HTA, specifically when policies are supply-restricted. The organ donation policy in Australia is resource-constrained with a HTx matching algorithm driving time spent on the heart transplant waiting list. This is the first study to apply DES modelling in ESHF in Australia. Decision-makers can use DES to understand the heart tranplant waiting list dynamics and how LVADs can allow more patients to become eligible for a HTx.

DBDD would mean that S2 receive B (bare-metal stent)and S1, S3 and S4 receive D (drug-eluting stent). The same type of stent is assumed for the first- and second-line of treatment.

7 CHAPTER 7: MAJOR FINDINGS AND DISCUSSION

7.1 Main findings of case-study in ESHF

The aim of this thesis was to model the cost-effectiveness of constrained resources in end-stage heart failure (ESHF) using discrete event simulation (DES) and to compare these estimates to a conventional Markov model. Many health technology assessments (HTA) do not consider constrained resources and hence assume unlimited supply of medicines or technologies. In Australia, HTA is used by the Pharmaceutical Benefits Advisory Committee (PBAC) and the Medical Services Advisory Committee (MSAC) to inform reimbursement decisions concerning pharmaceuticals and medical services respectively. In some circumstances, by ignoring constrained resources a decision-maker could be potentially biasing the resource allocation decision. This would particularly be the case for MSAC whereby surgery is the intervention, for PBAC, this would be when drugs require specialist administration or equipment. A common feature of supply constraints is the formation of a queue, where the queue can be physical or non-physical. This thesis focussed on a case-study in ESHF addressing the problem of a non-physical queue as seen with the heart transplant (HTx) waiting list.

Chapter 2 highlighted that the HTx waiting list is a unique type of queue that consists of a matching algorithm between candidate and donor organ queuing discipline. Patients and available donor organs are matched by blood type and weight compatibility. The organ replacement technology of left ventricular assist devices (LVADs) is a mechanical circulatory support that has the ability to be used as a bridging tool to buy patients more time while on the waiting list. LVADs can also affect an ESHF patient's eligibility for the waiting list via bridge to candidacy (BTC). However, LVADs are also subject to a supply cap at each of the four Transplant Units in Australia due to their high cost.

Chapter 3 demonstrated that most economic evaluations of LVADs do not consider the HTx waiting list health state in their model. The economic evaluations that did consider the waiting list problem noted that the longer the waiting time for a HTx, the more cost-effective the use of LVADs as a bridging tool. Chapters 3 and 4 both highlighted that there are no randomised controlled trials (RCTs) in solid organ transplants, so prospective or retrospective observational registry data for bridged HTx are relied on in economic evaluation. The analysis of individual patient data from St Vincents Hospital Sydney (SVHS) in Chapter 4 highlighted the common use of LVADs as BTC for patients previously ineligible for a HTx. Similarly, the use of LVADs is reserved for the sickest patients and is a last resort. This is reflected in the higher cost in the year pre-VAD compared to those without VAD; however, once an LVAD or HTx was provided, the costs to the first year post-VAD or post-HTx were similar, after adjusting for censoring. The international literature demonstrated that survival between bridged and non-bridged HTx patients is comparable.

The results from the Markov model in Chapter 5 and DES model in Chapter 6 were compared and contrasted. The Markov model cost-effectiveness analysis of the current LVAD capped policy in Australia (Policy B) compared to the previous policy of no LVADs (Policy A) resulted in a high ICER that would not be considered cost-effective under current thresholds in Australia. A policy of increasing the supply of LVADs (Policy C) rather than adhering to the current supply cap would be the more cost-effective option, although the overall programme would be more costly, indicating that the cap is intended purely for budget purposes. Policy C was still the preferred option to a policy of increasing the HTx rate only without the use of LVADs (Policy D).

The DES cost-effectiveness analysis of the current LVADs policy (Policy B) resulted in counts of HTx and time to transplant that more realistically reflected real-world data. On average, patients in the Markov model spent less time in the HTx health state but more time in the waiting list health state than in the DES models. This is a byproduct of the yearly cycles applied in the Markov model with no HTx performed in the first year. It is possible that a daily cycle length in the Markov model may have approximated the DES models more closely. The ICERs produced in the DES model, for each policy option, were lower than the comparable ICERs produced in the Markov model, but were still relatively high. In the DES model, Policy D appeared to be the preferred option, rather than Policy C as in the Markov model. This may reflect that the DES Policy C increase in availability of LVADs may not translate to greater health benefits if there is not a corresponding increase in the availability of donor organs. An increase in LVADs only (without an increase in donor organs) grows the number of patients waiting for a donor organ, creating an ever greater backlog of patients on the waiting list.

7.2 Contribution to the literature

This thesis consists of two structurally distinct modelled evaluations that incorporates constrained resources. Typical HTA does not take into account constrained resources and the existence of a waiting list. However, DES can explicitly model the waiting list as a dynamic queuing system of waiting patients and available donor organ that are matched. Of the empirical comparisons of cohort Markov model and DES models identified in Chapter 1, only one (38) had incorporated resource constraints in the form of a waiting list for orthopaedic surgery services. The authors had determined that the resource allocation decision would not change under either model with high-cost effectiveness, but noted that if the consequence of waiting (applied as a disutility) were more severe and the ICERs were closer to the willingness to pay (WTP) threshold, then there may be a difference in the results.

This thesis provided an extensive evaluation of available data sources on outcomes and costs associated with HTX and LVADs, including both RCTs and real-world evidence. In contrast to some earlier literature, I have adjusted for censored costs and competing risks in survival analysis in a broad

range of pre-modelling studies. The modelling component of the thesis is unique because different model structures with and without dynamic queuing are compared. The model structures were used to compare current policy (Policy B) with past (Policy A), but also with plausible what-if scenarios (Policy C and Policy D). There is currently a lack of these types of analyses in HTA aiming to show the impact of alternative modelling approaches while answering current and future policy relevant questions.

During the thesis it was identified that high-cost life-extending therapies such as LVADs are usually associated with a higher ICERs (75); see section 8.1.1 for my peer-reviewed journal article. This is usually due to novel therapies resulting in a much higher incremental cost for a modest improvement in incremental benefit. However, these devices could be considered analogous to certain jurisdictions' life-saving drugs programmes (LSDP). National HTA bodies in Canada, Japan and the UK have programs in which it is acknowledged that cost-effectiveness is not the main focus and instead the concept of 'rule of rescue' is considered. This means that the opportunity cost of the treatment is not deemed the main focus as it is in typical HTA. Consequently, these therapies may be subject to a higher WTP threshold.(75)

In Australia, one of the eight LSDP criteria is embedded in the concept of 'rule of rescue'. In a hypothetical comparison of the eight criteria, LVADs could satisfy the LSDP criteria. LVADs for ESHF can be accepted as 1) rare; 2) the disease of ESHF is identifiable; 3) there is evidence that ESHF reduces life expectancy; 4) the use of LVADs would increase life expectancy; 5) LVADs are clinically effective but fail to meet cost-effectiveness criteria; 6) no alternative drug; 7) no non-drug alternative; and 8) cost of LVADs is an unreasonable financial burden on patients. The criteria that may change in the future are the rarity of ESHF and those eligible for an LVAD given the increasing prevalence of ESHF. Further, the potential pool of LVAD candidates could increase if there was widespread use of LVADs as DT. The conditions listed on the LSDP are typically rare genetic conditions such as Gaucher disease. Similarly, the non-drug alternative is currently HTx, for which eligibility criteria are more restrictive than for mechanical circulatory support. The number of HTx performed in Australia each year continues to grow and the potential for DCD to expand the donor pool may increase this further. Despite this, in a hypothetical comparison it is reasonable to accept that LVADs are life-extending therapies with a high ICER and that under LSDP criteria could be funded.

7.3 Policy impact

7.3.1 Findings from the case-study

The purpose of the case-study was to determine the appropriateness of resource allocation decisions by modelling the waiting list problem in ESHF. The models developed demonstrated the value of

LVADs as a bridging tool for patients on the waiting list to survive at home and to increase the pool of eligible candidates for a donor heart. The use of LVADs is not without a significant financial cost and uncertainty in availability and the timing of donor organ receipt.

Another technology change in the ESHF space has been attempts to increase the potential pool of donor organs via donation after circulatory death (DCD). Typically, donor organs are retrieved after brain death; however, accepting circulatory death organs increases the number of available organs. This has been made possible by improvements in the transport of retrieved donor organs – in particular, the Organ Care System® (OCS), also known as 'Heart in a Box'. A policy of increased use of DCD via 'Heart in a Box' is analogous to Policy D modelled in Chapters 5 and 6. The results of Chapter 6 demonstrated that Policy D was the most cost-effective policy option and resulted in the most HTx conducted; however the significant additional cost of 'Heart in a Box' would have budget impacts for the Transplant Unit, on top of the heart transplantation procedure and care.

An important caveat in the ESHF space is that most treatment is provided in public hospitals, which has implications for reimbursement of therapies. Any cost savings to a public hospital would not be realised in another setting, e.g. the Federal Budget, due to separate funding. Hospital funding source impacts on what services are performed in private hospitals. Liver, heart or lung transplants are only performed in public hospitals and transplant services are not conducted by private hospitals.(235) As LVADs are conducted in the same Transplant Unit as HTx, it is unlikely that MSAC (public funding) will reimburse LVADs performed in private hospitals. This means that it is likely that the use of LVADs will remain capped despite the benefits as a bridging tool. It also means that the prominent use of LVADs as destination therapy (DT) as occurs internationally is unlikely to be realised in Australia.

7.3.2 Potential applications in Health Technology Assessment

There are a number of decision problems in HTA that would benefit from the individual-level modelling and increased flexibility of DES. This method can be easily applied in other organ transplants because most organ transplants have the same waiting list problem. Interestingly, few solid organs have viable organ replacement therapies that affect the eligibility for and dynamics of the waiting list. One example is dialysis in kidney tranplant candidates. One DES model of end-stage liver disease has explored the value of a hypothetical tissue-engineered organ as an organ replacement therapy.(17)

DES could be useful in complex HTA including the sequencing of therapies, especially in the cancer space, as DES can be used to simulate the optimal sequence of therapies that would provide the most cost-effective option. For example, in metastatic colorectal cancer the cost-effectiveness of the type of first-line therapy (e.g. oxaliplatin/irinotecan with or without bevacizumab) affects the cost-effectiveness of the second-line therapy (e.g. bevacizumab if not used in first-line or another

biologic).(236) Single-technology HTA tends to ignore the downstream consequences of using a therapy and tends to apply simplifying assumptions, e.g. post-progression use of the different therapies and impact are the same between both arms. This tends to not reflect reality, as the use of a certain therapy may exclude or allow the use of others, e.g. first-line therapy includes a certain class of drugs, while in the second-line, clinicians may opt for an alternative class with inferior outcomes.

Another complex HTA consideration is co-dependent technologies that rely on a diagnostic tool to direct potential treatment pathways. DES has the ability to simulate and compare multiple pathways as a sequence of events. The cost of the diagnostic tool and the number of persons that test positive can have a significant impact of the cost-effectiveness of the co-dependent treatment. Finally, the cost-effectiveness of clinical care guidelines can be assessed using DES due to the ability to model multiple pathways. Clinical care pathways typically include diagnosis, a clinical disease event, disease progression or relapse, disease-free events, treatment options and death. Examples of DES in cost-effectiveness of clinical guidelines include cancer (237) and atrial fibrillation (238).

Given the flexibility of DES, applications other than HTA can include health care delivery systems. An ISPOR taskforce on the use of dynamic simulation modelling methods in health care delivery research highlighted that standard approaches of decision trees and Markov models were not sufficient for analysing complex health care delivery systems.(31, 215) There are implications for a health service planning perspective, thereby merging operational research with allocative efficiency objectives. For instance, at SVHS, what is the cost-effectiveness of improving the surgical capacity within the Transplant Units in Australia? Surgical capacity can be in the form of intensive care units, surgeons and nursing staff. Given the overlap in use in these resources for other specialised cardiac surgery such as CABG (i.e. not HTx or LVADs), an increase in resource-intensive interventions will have an overflow effect on other surgeries. The introduction of DCD as a policy may reduce the waiting time for HTx but it is important to assess the impact this may have on the Transplant Unit.

7.3.2.1 Impact in budget impact analysis

The importance of budget impact analysis has been discussed in the literature.(239) DES enables utilisation statistics to be captured in the economic model and can hence include budgetary information easily.(234) This may reduce the uncertainty between cost-effectiveness estimates and budget impact analysis estimates, as the same patients are used in the two analyses. However, this is currently not recommended in PBAC guidelines, which specify the use of financial estimates templates for budget impact analysis for ease of comparison across various drug submissions.

A potential application of DES, however, could be in the PBS post-market review space. Occasionally, once a therapy has been recommended for listing and used in clinical practice, a review will be

conducted to ensure that the appropriate patients are receiving the therapy and utilisation is as expected.(240) This is usually the case for therapies that have been listed relying on early evidence and have uncertain long-term benefits, meaning data provision arrangements are required. The use of real-world observational data collected by the PBS can determine if the forecasted utilisation estimates reflect clinical practice. Individual-level data collected for PBS post-market review can make DES a more feasible option in the future.

7.3.2.2 Preferred modelling approaches

From a decision-making perspective, the PBAC prefers cohort-level models where possible; individual-level models are accepted, but their use must be justified.(197) Specifically, the PBAC Guidelines state modellers must '[u]se individual-level modelling approaches only when a defined model structure cannot be feasibly implemented as a cohort-based model. Describe the characteristics of the model structure that prevent using a cohort-based model. Potential factors include baseline heterogeneity, continuous disease or condition markers, time-varying event rates and the influence of previous events on subsequent event rates'.(197) These guidelines do not address the requirement to model resource constraints. This is unsurprising as the PBAC typically receives single-technology HTA submissions that are not subject to resource constraints, i.e. no waiting lists for pharmaceuticals. However, downstream consequences of pharmaceutical therapy may affect a patient's eligibility for a medical service – for examle, in multiple myeloma patients, those who receive bortezomib in first-line may be eligible for an autologous stem cell transplant.

HTA guidelines in Australia have noted the importance of transparency in the modelled evaluations; this reflects the preference for simpler model structures. Therefore, the benefits of DES in HTA have to be balanced against decision-makers' unfamiliarity with the methodology and specialist DES software. For instance, in a review of UK NICE clinical guidelines of atrial fibrillation, the cost-effectiveness of whole care pathways was estimated using DES.(241) The authors presented the findings to the Guideline Development Group (GDG) and found 1) access to specialist DES expertise or training for economic modellers would be necessary to implement this approach in routine guideline development; and 2) some members of the GDG were unfamiliar with, or did not have access to, the software (SIMUL8®) and therefore could not fully review the model.(241) It is reasonable to expect that the same issues would apply to the review of DES HTA applications for PBAC or MSAC in Australia.

7.4 Strengths and limitations of this research

7.4.1 Strength

The systematic literature review of economic evaluations in ESHF was broad and included VADs both as a bridging tool and as destination therapy, as well as HTx only. The breadth of the search allowed

for a more fulsome picture of the existing cost-effectiveness literature in ESHF and a review of the model structures previously implemented. Therefore, a gap in the literature was identified concerning how the waiting list is modelled, and this informed the need to do so in Chapters 5 and Chapters 6 of the thesis.

The ESHF case-study is supported by rich clinical datasets including both linked administrative costing data and outcomes data from the largest HTx transplant centre in Australia. The benefits of having access to such data include the applicability of the data to the Australian population and, consequently, a relevance of a HTA based on such data to the local jurisdiction. The use of registry data ensures strong external validity of the outcomes assessed and allows for generalisability of the waiting list problem to other organ transplant centres.

A particular strength of the case scenario chosen for this thesis is that it involves both complex queuing for transplant waitlist, and resource limitation at two levels – donor availability for transplantation and government-determined resource restriction due to cost of LVADs. Despite this level of complexity, DES was shown to provide very realistic model outcomes, consistent with real-world data.

7.4.2 Limitation

The current thesis does not attempt to model constrained resources using all the modelling methods and focusses on the commonly used cohort Markov model method and DES. A natural alternative to a cohort Markov model may be an individual-level microsimulation model. However, the purpose of using DES was to explicitly model the waiting list as a dynamic queue of patients interacting with donor organs and LVADs. An individual-level microsimulation does not support this functionality. Overall, the purpose of the thesis was not to answer the question of which modelling method is the best but, rather, the question of how can we incorporate resource constraint into HTA using existing modelling methods.

A limitation of the thesis was the smaller sample sizes of the SVHS compared to some of the larger international registries. For instance, the transition of VAD to HTx was based on SVHS data, although scenario analyses using IMACS data indicated negligible impact on the ICER. Similarly, the waiting list transitions were only sourced from SVHS and were based on a small sample size but represents the most applicable data to the decision problem. The waiting list is a complex queuing system and complete data on all status changes such as re-activation from 'On hold' was not available, meaning occasionally the same patients cycle through the model.

Another limitation of the thesis was the limited use of AnyLogic® software in HTA. For instance, TreeAge Pro® was used in the Markov model in Chapter 5 and includes many example models in HTA

based on a variety of health economic modelling methods. AnyLogic® was designed as a simulation tool for business, logistics and manufacturing; this is reflected in the fact that the process modelling library relied on was largely based on the operations of a manufacturing process. The DES applications in healthcare were limited to physical resources such as emergency departments and focussed on utilisation and flow-through but not in HTA. The single HTA example provided by AnyLogic® was not DES, but rather a systems dynamics/agent-based model hybrid of a population who may develop diabetes. Furthermore, the software did not have the distributions commonly used in HTA, such as Gompertz, generalised gamma and log-logistic. It may be useful to repeat the model in a different simulation software (e.g. SIMUL8®) to check for consistency and ease of use.

7.5 Recommendations for further research

The thesis focussed on modelling the waiting list processes and the DES model explicitly incorporated the matching algorithm between candidates and donors. The DES model also incorporated the availability of LVADs as a supply cap. The number of LVADs allocated to hospitals is determined by a memorandum of understanding with the individual state's Department of Health. The adoption of LVADs and the increasing number of HTx (normal and DCD) conducted has an impact on the capacity of the Transplant Unit at SVHS. Overall, there is a trade-off between the LVADs, HTx and routine cardiac surgery as there are capacity constraints within a centre.

The thesis does not take into account the fact that heart transplantation is very resource-intensive and that it occurs within the confines of one of four Transplant Units. The purpose of HTA is to inform resource allocation decisions so as to improve efficiency in a system. By only focusing on one aspect of efficiency, e.g. reducing average length of stay for a hospitalisation, another part of the system may be overburdened, e.g. rehabilitative services.(46) This highlights that a whole-of-system approach is necessary when conducting HTA. Similarly, in Policy D, by increasing the number HTx conducted per year due to increased donor pool due to DCD and 'Heart in a Box', the model currently ignores the impact on routine surgeries such as cardiac artery bypass graft (CABG). It is known that at SVHS there were almost 80 CABG surgeries cancelled and later rescheduled due to emergency HTx surgery in 2016-2018 [data on file].

Further research is recommended on modelling the resources of the entire cardiothoracic Transplant Unit consisting of the physical theatres and capacity for surgeries and the staff including surgeons, nurses and clinicians. A whole-of-system approach to the physical resources that are constrained – such as LVADs, donor organs, surgeons and available beds – should be modelled in addition to the non-physical queue of the cardiothoracic surgery waiting list including CABG, mitral valve replacements etc. and the emergency HTx. Thus, DES will be able to model the costs and benefits of

policy options of LVADs and HTx at SVHS compared to postponing routine surgeries within the centre to reflect clinical reality.

Furthermore, modelling to explore the optimal timing of VAD implant (level of severity – NYHA I or II vs III or IV), and the role of DT in Australia would provide useful information on the various VAD policies. The two main intent strategies for VADs are as DT for patients ineligible for HTx and as BTT or BTC for patients eligible for a HTx. Currently in Australia, reimbursement of VADs is contingent on eligibility for a HTx; therefore, DT is not currently funded. There are two scenarios for DT, one in those typically eligible for HTx and one for those who have less severe HF known as 'DT ambulatory'. Research on the most 'efficient' use of LVAD as a long-term solution may assist decision-makers in finding a more cost-effective application of LVADs.

7.6 Concluding remarks

Overall, the aims of this thesis have been achieved. HTA is conducted to determine resource allocation decisions and there are various methods to model the decision problems. For models where resource constraints such as waiting list are core to the decision problem, using a methodology such as DES that explicitly incorporates queuing theory can be beneficial as it can accurately depict clinical reality. This research represents a novel addition of an application of DES with queuing theory in HTA. There is scope for further research including the modelling of other resources in ESHF, to accurately represent queuing processes in the Transplant Unit and the constant trade-offs between therapies such as LVADs, HTx and routine surgeries.

8 Appendices

8.1 Appendix 1: Funding of ventricular assist devices in Australia

8.1.1 Editorial - 'Why is there discordance between the reimbursement of high cost pharmaceuticals and medical devices? The Funding of Ventricular Assist Devices in Australia' published in Applied Health Economics and Health Policy

Why is There Discordance between the Reimbursement of High-Cost 'Life-Extending' Pharmaceuticals and Medical Devices? The Funding of Ventricular Assist Devices in Australia

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CURRENT OPINION

Why is There Discordance between the Reimbursement of High-Cost 'Life-Extending' Pharmaceuticals and Medical Devices? The Funding of Ventricular Assist Devices in Australia

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Abstract
New health technologies often yield health benefits, but often at a high cost. In Australia, the processes for public reimbursement of high-cost pharmaceuticals and medical devices are different, potentially resulting in inequity in support for new therapies. We explore how reimbursement is different for medical devices compared with pharmaceuticals, including whether higher cost-effectiveness thresholds are accepted for pharmaceuticals. A literature review identified the challenges of economic evaluations for medical devices compared with pharmaceuticals. We used the ventricular assist device as a case study to highlight specific features of medical device funding in Australia. We used existing guidelines to evaluate whether ventricular assist devices would fulfil the requirements for the "Life-Saving Drugs Program", which is usually reserved for expensive life–extending pharmaceutical treatments of serious and rare medical conditions. The challenges in conducting economic evaluations of medical devices include limited data to support effectiveness, device-operator interaction (surgical experience) and incremental innovations (miniaturisation). However, whilst high-cost pharmaceuticals may be funded by a single source (federal government), the funding of high-cost devices is complex and may be funded via a combination of federal, state and private health insurance. Based on the Life-Saving Drugs Program criteria, we found that ventricular assist devices could be funded by a similar mechanism to that which funds high-cost life-extending pharmaceuticals. This article highlights the complexities of medical device reimbursement. Whilst differences in available evidence affect the evaluation process, differences in funding methods contribute to inequitable reimbursement decisions between medical devices and pharmaceuticals.

1 Introduction

The reimbursement of high-cost innovative therapies is challenging, and in many countries, the process of reimbursement differs between pharmaceuticals and medical devices. This discordance between health technology assessments and funding hurdles may lead to inconsistent and inequitable funding decisions.

Key Points for Decision Makers

Evaluation of complex medical devices is more challenging owing to a less well-developed evidence base and small incremental improvements in efficacy over time

High-cost devices are funded through different processes than high-cost pharmaceuticals, which may exacerbate differences in reimbursement

Widespread use of ventricular assist devices is limited because of the high costs; however, ventricular assist devices fulfil many of the eligibility criteria that support funding of life-extending high-cost pharmaceuticals.

There are numerous recent examples of the public reimbursement of high-cost pharmaceuticals. For instance, in Australia in 2016, a range of medicines (e.g. sofosbuvir with ledipasavir or daclatasvir) for hepatitis C infection were listed on the Pharmaceutical Benefits Schedule. Without a government subsidy, a patient "… would have to

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pay up to $100,000" for these medicines [1]. Similarly, ivacaftor was reimbursed for patients with cystic fibrosis with a G551 gene mutation, at an estimated cost of "$300,000 a year per patient", or a total government contribution of $174.5 million over 4 years [2]. The recently US Food and Drug Administration-approved chimeric antigen receptor T cell therapies for rare blood cancers are also expensive, for example, tisagenlecleucel costs $AUD598,453 for a single curative treatment [3]. Interestingly, the funding mechanism for tisagenlecleucel has yet to be determined, although some services in the procedure are already funded [3].

The combination of a life–extending treatment and low patient numbers increases the threshold at which a government body will reimburse a high-cost pharmaceutical therapy. However, this is not usually the case for medical devices, specifically, implantable devices. There are few examples of devices for rare diseases. The US Food and Drug Administration Humanitarian Device Exemption is a marketing approval pathway for treatment and diagnostic medical devices. There are now 70 approvals[1] for diseases that "affect[s] or is manifested in not more than 8000 individuals in the United States per year as eligible for Humanitarian Device Exemption". Of the 28 approved Humanitarian Device Exemption devices from 2007 to 2015, two were temporary right ventricular assist devices [VADs] (Impella RP system and Levitronix Centrimag® right VAD) and one was a paediatric VAD (Berlin Heart EXCOR® Pediatric VAD) [4]. There were eight neurological devices including deep brain stimulation for obsessive compulsive disorder and a stimulating device for amyotrophic lateral sclerosis. These devices are expensive, for instance, neurostimulation therapy via a pulse generator for pain management is available on the prosthesis list for around $25,000 [5]. The question is therefore, why does a pharmaceutical product costing over $100,000 per patient per year achieve reimbursement, but a high-cost device does not?

In this article, we examine why there are differences between pharmaceutical and medical device reimbursements by exploring the regulatory process, availability of evidence and reimbursement mechanism. We conclude with a hypothetical program, analogous to the Life-Saving Drug Program in Australia, which could be used to justify funding high-cost life-extending implantable devices.

2 Devices and Pharmaceutical Regulatory and Reimbursement Processes

In most developed countries, before a medical device is reimbursed it is evaluated for its clinical effectiveness and cost effectiveness. The evaluation of medical devices is more challenging than pharmaceuticals. Health technology assessment guidelines and methods are usually established in the context of pharmaceutical reimbursement, with the UK, Canada and Australia having the most experience [6]. Application to the context of medical devices presents some challenges. For instance, while pharmaceutical companies have experience and capacity in health technology assessments, medical device manufacturers are still in the development phase. Differences in reimbursement and occasionally a lack of property rights further contribute to differences in the incentive for industry to perform cost-effectiveness analyses [7].

Pharmaceutical evidence collection is guided by regulatory requirements. Regulatory requirements are less developed for medical devices. One of the key findings from the European MedtecHTA Project, which aimed to explore the challenges in the assessment of medical devices, was the lack of quantity and quality of evidence [8]. A reluctance to randomise severely unwell patients to sham procedures means that some devices are almost universally untested in randomised clinical trials (RCTs) and there is a reliance on observational and cohort data for medical device assessment. Ciani et al. noted that "existing regulatory processes for MDs [medical devices] generate less clinical evidence than the corresponding processes for drugs" [9]. The authors presented a literature review that concluded medical devices were less likely to have robust RCT data compared with pharmaceuticals [9].

Another difference is the level of skill and training required to use the technology. Administration of a pharmaceutical product is usually operator or prescriber independent, whereas the application of many medical devices requires a highly skilled and multidisciplinary team [10]. Improvements in surgical techniques and increased experience in clinicians, surgeons and allied health workers impact on the effectiveness of the device. Furthermore, the nature of the innovation (e.g. miniaturisation, longer battery life) results in small incremental improvements of medical devices, which also influences their effectiveness long term [10]. Drummond et al. highlighted that diagnostic devices such as magnetic resonance imaging derive value from how the results change subsequent treatments and unlike pharmaceuticals the effect on patients is indirect [11]. Finally, the clinical evidence requirements for market authorisation for each device is lower than pharmaceuticals, leading to swift approval of new market entrants because of the assumption of a 'class effect'. Consequently, there is an incentive for manufacturers to be fast followers rather than investors in trials to demonstrate longer term effectiveness and differences between devices [11].

[1] https://www.fda.gov/forindustry/developingproductsforrarediseasesconditions/default.htm.

3 Use and Cost of Ventricular Assist Devices in Australia

Some of the challenges discussed above are reflected in the use of mechanical circulatory support, such as VADs for patients with end-stage heart failure. Heart transplants (HTxs) are the definitive treatment option for these patients; however, restricted supply of donor hearts means that approximately 30–50% of patients with end-stage heart failure are supported with a VAD while waiting for a transplant. In Australia, around 100 people are waiting for an HTx at any one time, often for up to 2 years [12]. Therefore, VADs represent an alternative to an HTx; however, the high cost associated with the implantation and maintenance of VADs has limited their use. Ventricular assist devices are expensive with the listed price of $AUD95,000 (in 2018) for the pump, and the estimated average cost for the implanting admission is $AUD262,484 [5, 13]. We explore the use of VADs in Australia as a case study of the challenges in medical device assessment and reimbursement.

Ventricular assist devices can be considered a complex intervention because of the dependence of efficacy on the user and the context. That is, efficacy is dependent on the surgeon and implanting team as well as care by the patient, e.g. maintenance of device and driveline site. Ventricular assist devices have undergone incremental product development as devices have improved over time. Continuous-flow second-generation (axial pump) and third-generation (centrifugal pump) devices have superseded first-generation pulsatile-flow VADs [14]. Despite marked differences in the generations, VADs are considered interchangeable with respect to price, which may be owing to the lack of clinical evidence to distinguish the efficacy of different generations. The increasing use of VADs and annually reported registry data by INTERMACS has improved patient selection by providing data on risk factors for post-implantation adverse events and complications [15]. Surgical and post-implant care have further resulted in the reduction in adverse events and device failures. These complexities and gradual improvements have hampered the health technology assessment and reimbursement of VADs, as their value has changed over time.

There are two main indications for VADs. Patients who receive a VAD and later undergo an HTx are known as 'bridge to transplant' (BTT) patients. Alternatively, patients who are ineligible for an HTx can instead receive a VAD as 'destination therapy' (DT). As mentioned above, robust RCT data are lacking for VAD as BTT. Generally speaking, there are few (if any) RCTs on solid organ transplants because of ethical reasons [16]. Hence, cost-effectiveness analyses rely on registry data or local institutional data as the source of clinical evidence [17–23]. There have been four RCTs in DT patients: REMATCH trial (now obsolete pulsatile VAD vs. medical therapy [24]); HeartMate II trial (second-generation VAD vs. pulsatile VAD [25]); and ENDURANCE-(third-generation VAD vs. second-generation VAD) [26] and MOMENTUM 3 trial [27] (third-generation VAD vs. second-generation VAD).

These indications produce different cost-effectiveness estimates as the patient groups differ. Many countries were first interested in reimbursing VAD as BTT, then as DT. Recent systematic literature reviews of the cost effectiveness of VADs have demonstrated that regardless of indication, VADs were not considered cost effective under base-case assumptions [28, 29]. On average, DT incremental cost-effectiveness ratios were higher (less cost effective) than BTT [29]. Nunes et al. noted that none of the cost-effectiveness studies included indirect costs, quality-of-life data were only collected for one of the studies and utility gains may have been underestimated [29]. Most studies use surrogate medical endpoints, such as a 6-min walk distance. Overall, the estimated incremental cost-effectiveness ratios of VADs are above the traditionally accepted threshold. However, the incremental cost-effectiveness ratios of many new pharmaceuticals are also above the accepted threshold, so why is there a difference in reimbursement and access?

4 Funding of Devices and Pharmaceuticals in Australia

In Australia, the healthcare system is reimbursed by different sections of the government. Pharmaceuticals are reimbursed through the Pharmaceutical Benefits Schedule funded by the Federal Australian Government and provided to the patient with a small co-payment. Medical device reimbursement is more complex with multiple purchasers allowing for cost shifting. For instance, providers of VAD implants are reimbursed via the Medicare Benefit Schedule, which is advised by the Medical Services Advisory Committee, a federal government agency. Services listed on the Medicare Benefit Schedule are reimbursed when conducted in the outpatient setting, by a general practitioner and in private hospitals but not in public hospitals. The reimbursement for the implant of a left or right (or bi)VAD is contingent on the patient being on the HTx waiting list or expected to be a suitable candidate, BTT and bridge to candidacy, respectively [30]. Therefore, DT patients are not reimbursed in Australia [14] (see Table 1).

Conversely, the actual devices are allocated to public hospitals that are state government funded. The allocation of devices per hospital is determined on a local basis. For instance, St. Vincent's Hospital Sydney is one of four hospitals in Australia that implant VADs (and perform HTxs in adults) and the current funding arrangement with the New

Table 1 Reimbursement of ventricular assist devices in Australia Source: [46] MBS item 38615 and 38618

Reimbursement criteria for insertion of a left and/or right VAD, for use "as listed on the MBS":	Intent strategy	Funding source
(a) a bridge to cardiac transplantation in patients with refractory heart failure who are: (i) currently on a heart transplant waiting list; or	BTT	Procedure funded by the MBS or public hospital
(ii) expected to be suitable candidates for cardiac transplantation following a period of support on the VAD; or	BTC	Devices allocated to hospitals, which are state government funded
(b) acute post-cardiotomy support for failure to wean from cardiopulmonary transplantation; or	Complications post-heart–lung transplant	
(c) cardio-respiratory support for acute cardiac failure that is likely to recover with short-term support of less than 6 wk	BTR	Procedures not currently performed in the private sector; however, VADs listed on the prosthesis list
Not being a service associated with the use of a VAD as DT in the management of patients with heart failure who are not expected to be suitable candidates for cardiac transplantation	DT	VAD implant procedures are not funded for DT by the MBS

BTC bridge to candidacy, *BTR* bridge to recovery, *BTT* bridge to transplant, *DT* destination therapy, *MBS* Medicare Benefits Schedule, *VAD* ventricular assist device

South Wales Ministry of Health is limited to a maximum of up to 25 devices per year. The number chosen is arbitrary and based on the activity from the previous year. It is linked to the budget available for the New South Wales Ministry of Health. Therefore, the amount differs between states in Australia.

To our knowledge, pharmaceutical products are not restricted in this arbitrary manner. Risk share agreements that include usage caps tend to restrict funding to the company not the supply of medicines to the patient, i.e. once the cap is reached, the company must reimburse the payer (government) [31]. For VADs, individual hospitals are responsible for maintaining the usage cap because of the institutional funding nature of the allocation. Pharmaceuticals typically have centralised national funding arrangements and when combined with multiple prescribers, this means that imposing a strict prospective usage cap (as per VADs) would be impractical for pharmaceuticals. The difference between the two systems is the impact of the arrangements. The former is explicit rationing of medical devices and the latter is to control for uncertainty in patient numbers via leakage into other indications. Ventricular assist devices have recently been listed on the Australian Prostheses List [5]; thus, private health insurers must reimburse the cost of the device. Although private hospitals are rarely implanting VADs, patients being treated as a 'private patient' in a public hospital would be affected by this policy.

The situation that medical devices are funded through a mixture of local and national funding while pharmaceuticals are funded nationally is not unique to Australia and occurs globally. An observation of the Canadian healthcare system was that there is "variability in funding arrangements and decisions by jurisdictions, particularly for health technologies that are frequently funded by local hospitals or health regions, in contrast to drugs that are often funded at higher organisational levels (nationally, or by province)" [29]. This mix of funding sources may partially explain the inconsistency between pharmaceuticals and devices, as there may be a tendency for divided responsibility and cost shifting.

In Australia, the reason as to why VADs could not be funded solely at a national level is that the source of hospital funding is distinct between public and private hospitals [32]. Much of public hospital funding comes from federal or state/territory governments whilst for private hospitals, almost half of funding comes from private health insurance and 20% from the Australian Government in the form of Medical Services Advisory Committee reimbursement. Furthermore, any cost savings to a public hospital (state government funded) would not be realised in another setting, e.g. federal budget. The difference in hospital funding sources has implications on what services are performed in private hospitals. Liver, heart or lung transplants are only performed in public hospitals and consequently transplant services are never performed in private hospitals [33]. As VADs could be an alternative to HTxs, it is unlikely that the Medical Services Advisory Committee will reimburse VADs to be performed in private hospitals.

5 Reimbursement Options for High and Uncertain Cost-Effectiveness Ratios

Reimbursement agencies all face risk and uncertainty. Ventricular assist devices are a costly medical device involving surgery, which both represent large upfront costs. Patients may die during surgery or soon after, and

Table 2 Criteria for life-saving/life-extending pharmaceutical reimbursement programs

	Program and criteria	References
Australia	Life-Saving Drugs Program 1. There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the Therapeutic Goods Administration 2. The disease is identifiable with reasonable diagnostic precision 3. Epidemiological and other studies provide evidence acceptable to the PBAC that the disease causes a significant reduction in age-specific life expectancy for those with the disease 4. There is evidence acceptable to the PBAC to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug 5. The drug must be accepted as clinically effective, but rejected for PBS listing because it fails to meet the required cost-effectiveness criteria 6. There is no alternative drug listed on the PBS or available for public hospital in-patients, which can be used as life-saving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP 7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) that is recognised by medical authorities as a suitable and cost-effective treatment for this condition 8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a 1-y period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian	[41]
UK	NICE, appraising life-extending end-of-life treatments 2.1 This supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied: 2.1.1 The treatment is indicated for patients with a short life expectancy, normally less than 24 mo; and 2.1.2 There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 mo, compared to current NHS treatment; and 2.1.3 The treatment is licensed or otherwise indicated for small patient populations 2.2 When the conditions described in 2.1 are met, the Appraisal Committee will consider: 2.2.1 The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, and; 2.2.2 The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range 2.3 In addition, the Appraisal Committees will need to be satisfied that: 2.3.1 The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review), and; 2.3.2 The assumptions used in the reference case economic modelling are plausible, objective and robust	[35]
Canada, Ontario	Framework for assessing funding of drugs for rare diseases Eligibility criteria: (a) disease incidence rate of fewer than 1 in 150,000 live births or new diagnoses per year; (b) lack of availability or feasibility of adequately powered randomised controlled trials detecting clinically relevant outcomes, given the rarity of the disease The evaluation framework uses an evidence-based process. The framework consists of five steps: Assesses whether a submitted disease meets the framework's criteria of "rare" Gains an understanding of the natural history of the disease Assesses the potential effectiveness of the drug, based on the best available evidence Evaluates budget and cost impact Identifies whether any additional follow-up data are needed	[47]
Canada, Alberta	Rare Disease Drug Program Eligibility criteria: 1. A genetic lysosomal storage disorder occurring in < 1 in 50,000 Canadians, as determined by Alberta Health, Fabry disease, Pompe disease and Gaucher disease 2. Albertans with rare diseases, who have government-sponsored drug coverage and whose physician has applied for coverage 3. An individual or family must reside in Alberta for 5 years to be eligible for the program. The residency requirement will be waived for individuals moving to Alberta from another province in Canada if they were covered by that province's program for these drugs In addition, applicants must consent to the following conditions: Conditional initial and continued coverage are dependent upon clinical outcomes Ongoing clinical outcome monitoring is mandatory Inadequate patient response or deterioration, as defined by pre-established withdrawal criteria for a specific drug and/or as assessed by the program's clinical review panel, will dictate coverage discontinuation	[47]

Table 2 (continued)

	Program and criteria	References
Japan	National Registry of Designated Intractable Diseases Eligibility criteria: [1] rarity (affecting less than 0.1% of the population in Japan); [2] unknown aetiology; [3] lack of effective treatment; [4] necessity of long-term treatment; and [5] existence of objective diagnostic criteria and not necessarily equal to rare diseases in other countries In 2015, a major reform to the program was implemented, thus the number of diseases covered is now 306 rather than the initial 56 intractable diseases	[48]

LSDP Life-Saving Drugs Program, *NHS* National Health Service, *NICE* National Institute for Health and Care Excellence, *PBAC* Pharmaceutical Benefits Advisory Committee, *PBS* Pharmaceutical Benefits Scheme, *QALYs* quality-adjusted life-years

once implanted, withdrawal of therapy involves further surgery and a high likelihood of death. Conversely, if a pharmaceutical product is ineffective, it is possible to stop treatment and payment. It is more difficult to manage the risk associated with funding a high-cost medical device compared with a pharmaceutical product. In recent years, there have been a plethora of risk share arrangements (with or without coverage with evidence development) relating to pharmaceuticals [31], and it has been suggested that for situations where further evidence is required, VADs can be listed as 'only in research' or 'approval with research' [34]. The risk share arrangement between the sponsor and payer through a financial volume-based cap would depend on the type of risk. Sources of risk can include more patients being treated or VADs having less value (e.g. lower survival) than expected. However, the implementation of the arrangement would be difficult as there are different payers for the procedure (state government), the device (state and private health insurance) and the medication (federal government).

There are situations where even if the commonly acceptable cost-effectiveness thresholds are exceeded, a pharmaceutical may still be reimbursed based on life-extending or rarity criteria (Table 2). The National Institute for Health and Care Excellence (NICE) developed supplementary guidelines titled "Appraising life-extending, end of life treatments" in July 2009 [35] to assess high-cost pharmaceutical products that fulfilled these criteria. Clarke et al. noted that according to the current UK threshold of £20,000–£30,000/quality-adjusted life-year recommended by NICE, VADs cannot be considered cost effective [18]. However, at a higher willingness-to-pay threshold of £50,000/quality-adjusted life-year, it might be considered appropriate according to end-of-life criteria [18]. Clarke et al. cited the guidance by NICE for abiraterone (for prostate cancer) [36] and considered VADs to have a similar incremental cost-effectiveness ratio (ICER) along with fulfilling the criteria for consideration as a life-extending end-of-life treatment. Many cost-effectiveness studies of VADs draw parallels to the reimbursement of high-cost pharmaceuticals in discussing the high ICERs estimated in their analyses [18, 20, 23, 37].

Justification for the application of higher cost-effectiveness thresholds for life-extending treatment by NICE relates to the concept of the 'rule of rescue' [38]. The rule of rescue refers to the "imperative to rescue identifiable individuals facing avoidable death, without giving too much thought to the opportunity cost of doing so" [38]. However, the basis of the rule of rescue conflicts with the "standard logic underlying CEA" [38]. Under 'rule of rescue' considerations, Clarke et al. noted that it was possible that VADs as BTT were considered eligible for the life-extending treatment criteria despite the high ICER [18]. Additionally, a recent economic evaluation of the HeartMate II VAD in BTT patients vs. non-bridged HTx patients yielded ICERs above the generally accepted threshold for the UK of £30,000 [20]. The authors compared the HeartMate II VAD to the NICE criteria for increasing the established threshold and argued that it satisfied the first two criteria (short life expectancy of less than 24 months and treatment extends life by up to 3 months) [20]. Modelled survival data using the Seattle Heart Failure Score for a patient with a left VAD indicated that survival would be greatly increased fulfilling the second criteria [39]. However, Moreno et al. did not consider that the final criterion—indication for small patient populations — was satisfied because of the prevalence of end-stage heart failure [20].

In Australia, the Life-Saving Drugs Program (LSDP) funds pharmaceuticals that are not considered cost effective, but may be considered life saving for serious and rare medical conditions. The major difference between the NICE criteria and the LSDP is that NICE specified the treatment must be life extending by at least 3 months. Conversely, the LSDP only specifies that a "patient's lifespan will be substantially extended". Currently, the LSDP lists 14 medicines for nine conditions [40]. These include genetic conditions such as Gaucher disease, Fabry disease and infantile/late-onset juvenile/adult Pompe disease [41]. In a hypothetical comparison against the LSDP criteria, VADs satisfy each condition [42] (see Table 3).

Table 3 Evaluation of ventricular assist devices (VADs) to the Life-Saving Drugs Program (LSDP) Source: [41, 42, 55]

	LSDP criteria[a]	Current LSDP drugs listed	Example criteria response for VADs[a]
(A)	The drug must be found to meet each of the following criteria:		
1.	There is a rare but clinically definable disease for which the drug is regarded as a proven therapeutic modality, i.e. approved for that indication by the TGA	For the purpose of orphan drug registration, the Australian Therapeutic Goods Act defines a rare disease as one that has fewer than 2000 patients, which is approximated as a prevalence of 1 in 10,000 persons. Drugs currently listed are "≤1 per 100,000" [41]	HeartMate II is approved by the TGA for BTT, BTR and DT in patients with end-stage refractory left ventricular heart failure. While it is difficult to determine the prevalence of VAD-eligible end-stage refractory heart failure, the number of VAD-eligible patients would likely be similar to the number of patients who are eligible for HTx. At the end of 31 December, 2015, there were 59 people deemed 'active' on the wait list. These are small patient numbers It is difficult to determine the potential number of patients who are ineligible for HTx but would be eligible for VAD (i.e. DT patients) but it would a small proportion of patients with heart failure
2.	The disease is identifiable with reasonable diagnostic precision	In Australia, the LSDP included genetic conditions such as type 1 Gaucher disease, Fabry disease, infantile/late-onset juvenile/adult Pompe disease, mucopolysaccharidosis types I, II and VI, paroxysmal nocturnal haemoglobinuria and type I hereditary tyrosinaemia. Gaucher disease, for instance, is diagnosed via an enzyme activity test or DNA testing for the *GBA* gene	Medically refractive ESHF is identifiable using a number of classifications systems including the NYHA Functional Class and the ACC/AHA Stage classification. Eligibility to be added onto the HTx wait list can also be used
3.	Epidemiological and other studies provide evidence that the disease causes a significant reduction in age-specific life expectancy for those with the disease	For instance, in type 1 Gaucher disease in the USA, it was estimated that "life expectancy at birth for GD1 patients was approximately 9 years less than reference population", this equated to 68 y, instead of 77 years [49]	An RCT by Rose et al. (2001) indicated that the rates of survival at 1 year and 2 years were 25% and 8% with OMM, respectively [24]. This is substantially lower than the age-specific life expectancy. Recent INTERMACS 2016 registry data of VAD recipients indicate rates of survival at 1 year of 85% from 2013 to 2016
4.	There is evidence to predict that a patient's lifespan will be substantially extended as a direct consequence of the use of the drug	According to Cochrane Reviews, there was no RCT evidence of survival benefit using ERT for type 1 Gaucher disease [50] or Anderson–Fabry disease [51]	In an RCT by Rose et al. (2001), rates of survival at 1 year were 52% with pulsatile-flow LVADs and 25% in OMM ($p=0.002$); at 2 years, these were 23% and 8% ($p=0.09$), respectively [24]. The 1- and 2-yEAR survival with LVADs with continuous-flow pumps from 2008 to 2014 is 80% and 70% based on registry data, respectively [15]. The ROAD-MAP registry followed patients enrolled between 2011 and 2013 receiving OMM vs. VAD and the intention-to-treat analysis of 1-year survival was 81% and 82% ($p=0.93$), respectively [52]
5.	The drug must be accepted as clinically effective, but rejected for the PBS listing because it fails to meet the required cost-effectiveness criteria	A Dutch cost-effectiveness study indicated that the lifetime cost of treating a patient with type 1 Gaucher disease with ERT compared to standard medical care without ERT was €434,416 per QALY gained [53]	Nunes et al. found that VADs as BTT compared to medical management resulted in ICERs of "between $85,025 and $200,166" and for DT patients "between $87,622 and $1257,946" per QALY gained (2012 Canadian dollars per QALY) [29]. This would fail to meet Australian cost-effectiveness thresholds of $50,000 per QALY gained

Table 3 (continued)

LSDP criteria[a]	Current LSDP drugs listed	Example criteria response for VADs[a]
6. There is no alternative drug listed on the PBS or available for public hospital in-patients that can be used as life-saving treatment for the disease. However, the availability of an alternative drug under the LSDP does not disqualify the proposed drug from consideration for the LSDP	No other treatment options for enzyme diseases available on the PBS or LSDP for type 1 Gaucher disease	No other device within this indication exists that is currently being reimbursed by the Australian Government A totally artificial heart is rarely implanted and is not listed on the MBS or publicly funded
7. There is no alternative non-drug therapeutic modality (e.g. surgery, radiotherapy) that is recognised by medical authorities as a suitable and cost-effective treatment for this condition	No therapeutic options available for type 1 Gaucher disease	HTx is an option for some patients, but it is dependent on the supply of donor hearts. The criteria for HTx are more restrictive than for MCS. For those who are ineligible for HTx, there are no other options
8. The cost of the drug, defined as the cost per dose multiplied by the expected number of doses in a 1-y period for the patient, would constitute an unreasonable financial burden on the patient or his/her guardian	The enzyme replacement therapy imiglucerase Cerezyme® for Gaucher disease is priced at $US200,000 per patient per year in 2014 [54]	The average index admission for VAD costs $260,000 and subsequent admission costs $9000 per patient [45]. Cost of VAD was $100,000 [5]
(B) Consideration and advice will also be provided by the Pharmaceutical Benefits Advisory Committee, if applicable, on:		
1. The proposed price of the drug compared with the effective price of the drug in comparable overseas markets	N/A	The prosthesis list (August 2017) reports that the device (HeartWare and HeartMate II) is $100,000 with peripherals at an additional cost [5] A UK study reported the cost of a Heart Ware Device at £80,076 and HeartMate II at £89,830 in 2011 prices. Therefore, the cost of the device is similar to comparable overseas markets
2. The proposed cost of the drug compared with the cost of comparable drugs, if any, that are already funded through the LSDP	N/A	N/A

ACA/AHA American College of Cardiology/American Heart Association, *BTR* bridge to recovery, *BTT* bridge to transplant, *CF* continuous flow, *DT* destination therapy, *ERT* enzyme replacement therapy, *ESHF* end-stage heart failure, *HTx* heart transplant, *ICER* incremental cost–effectiveness ratio, *LVAD* left ventricular assist device, *MCS* mechanical circulatory support, *N/A* not applicable, *NYHA* New York Heart Association, *OMM* optimal medical management, *PBS* Pharmaceutical Benefits Scheme, *QALY* quality-adjusted life-year, *TGA* Therapeutic Goods Administration

[a]The sample evaluation criteria response is based on the hypothetical LSDP criteria for 'devices' rather than drugs

Based on the Australian LSDP criteria, it would appear logical and equitable that VADs should be considered eligible for reimbursement. The areas of contention relate to rarity (first LSDP criteria). Although heart failure is not rare, only in end-stage patients would VAD be considered a life-extending option. For instance, VAD as BTT requires that patients are eligible for an HTx, hence fewer than 100 patients, those that are currently on the HTx wait list, would be eligible for VAD each year [12]. For DT, of the estimated 500,000 patients with heart failure [43], those with contra-indicating co-morbidities must be excluded. There is a further interaction in the delivery of therapy with devices, through a comprehensive multidisciplinary team involving heart failure cardiologists, surgeons, nurse co-ordinators, social work and allied support services [44]. Provision of the therapy is dependent on referral to such units, resulting in smaller proportion implanted. However, an Australian costing study by Marasco et al. argued that the "potentially enormous pool of suitable patients is cause for concern to policy makers in healthcare" [45], which may explain the reluctance to fund VAD as DT. Therefore, if VADs were assessed under an analogous LSDP, it is possible it would be approved for HTx-eligible patients only.

6 Conclusion

The article highlights the differences in reimbursement of high-cost life-extending medical devices compared with pharmaceuticals. We use VADs in Australia to demonstrate that some of these issues are generalisable to other countries; however, some are specific to Australia. The reimbursement of high-cost innovative medical devices is challenging, with limited RCT evidence and a lack of incentives to perform cost-effectiveness analysis because of regulatory differences [7, 11]. In many jurisdictions, the funding arrangements for pharmaceuticals are simple with a single payer; however, funding arrangements for implantable medical devices are complex with multiple purchasers, shared funding responsibilities and the opportunity to cost shift. These reasons may explain the differences in the reimbursement of devices and pharmaceuticals.

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Compliance with Ethical Standards

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Data Availability Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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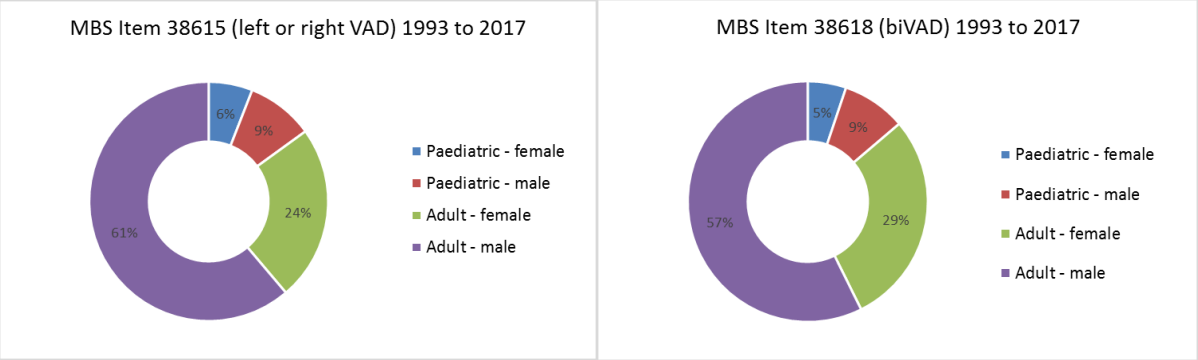
8.1.2 VAD reimbursed through Medicare by age and gender

Figure 8-1: VAD Medicare Benefit Item by age and gender



Note: Paediatric patients are aged 0 to 14 and adults were aged 15 and over. MBS Item 38615 = 286 and MBS Item 38618 = 232.
Source: Medicare Statistics, Medicare Item Reports

8.2 Appendix 2: Model structure guidance in ESHF

Table 8-1: Issues and guidance on choice of model structure and comparison to ESHF model

	Issue	Example	Choice of Model	*ESHF model*
I.1	Does the decision-maker require knowledge of variability to inform the decision?	Effects of intervention are small and variable over time	Need for stochastic output (columns B–D)	*Not a requirement.*
I.2	Is the decision-maker uncertain about which sub-groups are relevant and likely to change his/her mind?	Decision maker may want to sub-divide the risk groups or test new interventions	Individual level models are more flexible to further covariates or changed assumptions (columns C–D)	*Yes, patient selection and sub-groups of patients drives the outcomes.*
I.3	Is Probabilistic Sensitivity Analysis (PSA) required?	Decision maker uses cost-effectiveness acceptability curves or expected value of information	Deterministic model may be preferred (column A) but need for PSA should not drive model structure decisions	*Not a requirement.*
I.4	Do individual risk factors affect outcome in a non-linear fashion?	Effects of age, history of disease, co-morbidity	Need to subdivide states in an aggregate model. Need to consider individual level modelling if the number is large. (columns C–D)	*Yes, prognosis of ESHF is based on many factors.*
I.5	Do covariates have multiple effects, which cause interaction?	Co-morbidities in diabetes affect renal failure and retinopathy	Individual level modelling likely to be necessary. (columns C–D)	*Yes, prognosis of ESHF based on co-morbidities.*
I.6	Are times in states non-Markovian?	Poor survival after an operation, moving from one age group to another, length of stay in hospital	Need to use 'fixes' in Markovian models or use non-Markovian models (columns D)	*Yes, previous events such as LVAD would impact on time to HTx.*
I.7	Is the dimensionality too great for a cohort approach?	Large number of risk factors and /or subdivision of states to get over non-Markovian effects	Individual level modelling likely to be necessary. (columns C–D)	*Yes, prognosis of ESHF is based on many factors.*
I.8	Do states 'recycle'?	Recurrence of same illness (e.g. heart attack, stop responding to drugs)	Decision tree approach is probably not appropriate (rows 2 to 4)	*Yes, patients cycle in states such as alive with 'VAD'*
I.9	Is phasing or timing of events decisions important?	In smokers, if lung cancer occurs before bronchitis, then patient may die before bronchitis occurs	Possible to have different branches in the decision tree but Markov model or simulation may be necessary. (rows 2 to 4)	*Yes, timing of surgery has implications for outcomes.*

	Issue	Example	Choice of Model	*ESHF model*
I.10	Is there interaction directly between patients?	Infectious disease models	Models with interaction (rows 3, 4)	*Yes, interactions between donor hearts match with patients.*
I.11	Is there interaction due to constrained resources?	Models with resource constraints	Models with interaction (rows 3, 4)	*Yes, restricted supply of donor hearts.*
I.12	Could many events occur in one time unit?	Disaster, outbreak of infection, risk of co-morbidities (e.g. diabetes)	Need for small time intervals or continuous time models (row 4)	*Yes, surgery could have immediate complications.*
I.13	Are interactions occurring in small populations?	Use in hospital catchments area rather than nationally	Need to consider individual level modelling because of the inaccuracies in using fractions of individuals (columns C, D, rows 3, 4)	*Yes, few patients per year with four transplant units in Australia.*
I.14	Are there delays in response due to resource constraints which affect cost or health outcome	Rapid treatment with angioplasty and stents after a myocardial infarction	Need for stochastic output and interaction (columns C, D, rows 3, 4)	*Yes, if on HTx wait list, patients condition may deteriorate.*
I.15	Is there non-linearity in system performance when inherent variability occurs?	A marginal change in parameters produces a non-linear change in the system ICU is suddenly full and newly arriving patients must transfer elsewhere	DES useful	*Yes, one HTx surgery has a large impact on the rest of the cardiology unit.*

Abbreviations: DES, Discrete event simulation; ESHF, End-Stage Heart Failure; HTx, Heart Transplant; ICU, intensive care unit; VAD, Ventricular Assist Device.
Source: adapted from Table 2, p.1304-1305, Brennan et al. (2006)(27).

8.3 Appendix 3: Economic literature review for LVADs

8.3.1 Search strategy results for economic literature review for VADs vs. comparator

Search strategy adapted from Nunes et al. 2016(90) for Medline Ovid.

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present. BIOSIS Previews. Embase.

1. heart assist device/
2. assisted circulation/
3. ((ventric* or biventric* or heart or cardiac) adj assist*).mp.
4. (lvad* or lvas* or rvad* or bivad*).mp.
5. ((vad or vads) and (heart or cardiac)).mp.
6. (HeartMate or HeartWare).mp.
7. or/1-6
8. economic evaluation/ or 'cost benefit analysis'/ or 'cost effectiveness analysis'/ or 'cost utility analysis'/
9. (cost adj2 (benefit* or effect* or utility or analys*)).mp.
10. (economic adj (evaluation* or analysis or analyses)).mp.
11. (cost* or economic*).ti.
12. or/8-11
13. 7 and 12
14. limit 13 to (english or french or german or italian or portuguese or spanish)
15. limit 14 to yr='2014 -Current'
16. limit 15 to humans

Note: MP - multiple field search.

Medline == 47
Embase == 166

PubMed

(((((((heart assist device) OR assisted circulation) OR (((ventric* or biventric* or heart or cardiac) AND assist*))) OR (((lvad* or lvas* or rvad* or bivad*)))) OR (((vad or vads) and (heart or cardiac)))) OR (((HeartMate or HeartWare))))) AND ((((((economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis'))) OR (((cost) AND (benefit* or effect* or utility or analys*)))) OR (((economic) AND (evaluation* or analysis or analyses)))) OR (((cost*[Title] OR economic*)[Title]))))) == 1712

Filters activated: Publication date from 2014/01/01 to 2017/06/27, Humans, English, French, German, Italian, Portuguese, Spanish. == 319

EBSCO Host – CINAHL and EconLit

heart assist device == 1598
assisted circulation == 174
((ventric* or biventric* or heart or cardiac) AND assist*) == 6753
(lvad* or lvas* or rvad* or bivad*) == 523

(vad or vads) and (heart or cardiac) == 181
(HeartMate or HeartWare) == 153
S1 OR S2 OR S3 OR S4 OR S5 OR S6 == 6920
(economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') == 30237
(cost AND (benefit* or effect* or utility or analys*)) == 180279
(economic AND (evaluation* or analysis or analyses)) == 360843
TI (cost* or economic*) == 194831
S8 OR S9 OR S10 OR S11 == 589231
S7 AND S12 == 305
S7 AND S12 Limiters Published Date: 20140101-20171231 == 71

Cochrane database:

- Cochrane Reviews – Cochrane Database of Systematic Reviews (CDSR),
- Other Reviews - Database of Abstracts of Reviews of Effects (DARE),
- Technology Assessments – Health Technology Assessment Database (HTAD),
- Economic Evaluations – NHS Economic Evaluation Database (NHSEED).

heart assist device
assisted circulation
((ventric* or biventric* or heart or cardiac) and assist*):ti,ab,kw
(lvad* or lvas* or rvad* or bivad*):ti,ab,kw
(vad or vads) and (heart or cardiac):ti,ab,kw
(HeartMate or HeartWare):ti,ab,kw
#1 or #2 or #3 or #4 or #5 or #6
(economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis')
(cost and (benefit* or effect* or utility or analys*)):ti,ab,kw
(economic and (evaluation* or analysis or analyses)):ti,ab,kw
(cost* or economic*):ti
#8 or #9 or #10 or #11
#7 and #12
#7 and #12 Online Publication Date from Jan 2014
#7 and #12 Limits: Online Publication Date from Jan 2014, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations

N=115.

Tufts CEA Registry

'Ventricular assist device'
Returned 4 articles from 2014 onwards.

8.3.2 Inclusion criteria for full-text review

The inclusion criteria used were adapted from those used by Nunes et al. (2016)(90).

Table 8-2: Inclusion criteria for cost-effectiveness studies of VADs

	Question	Yes/No
1a	Was the study presented as a full manuscript in a peer-review journal?	
1b	Was the article published in English	

1c	Does the article contain original research (i.e. primary data)
	Population:
2	Was the population mostly adults - always
2	Was the population mostly adults - other (e.g means)
2	Was the population mostly adults - not reported
	Indication:
3	Did the study population have end-stage heart failure with an indication for mechanical circulatory support? Bridge to transplant
3	Did the study population have end-stage heart failure with an indication for mechanical circulatory support? Bridge to myocardial recovery
3	Did the study population have end-stage heart failure with an indication for mechanical circulatory support? Long-term mechanical support
3	Did the study population have end-stage heart failure with an indication for mechanical circulatory support? Bridge to Decision
3	Did the study population have end-stage heart failure with an indication for mechanical circulatory support? Other? Specify
	Alternatives:
4a	Did at least one arm of the study receive a mechanical circulatory support? LVAD
4a	Did at least one arm of the study receive a mechanical circulatory support? RVAD
4a	Did at least one arm of the study receive a mechanical circulatory support? Biventricular assist
4b	Did at least one other arm of the study receive one of the following? Medical Management or Heart Transplant
4b	Did at least one other arm of the study receive one of the following? Another type of mechanical circulatory support
	Outcomes:
5a	Were relevant health care costs reported? Inpatient Costs?
5a	Were relevant health care costs reported? Inpatient Costs? Outpatient Costs?
5b	Were relevant outcomes of effectiveness reported? QALYS or LY (mortality)?
5b	Were relevant outcomes of effectiveness reported? Other HYE?
	Study Design:
6	Were benefits divided by costs? ICER (cost-effectiveness)
6	Were benefits divided by costs? ICUR (cost-utility)
6	Were benefits divided by costs? Other (cost-utility)
	Final decision:
7	Should this study be included in the next stage? Yes
7	Should this study be included in the next stage? No
7	Should this study be included in the next stage? Unsure

Source: adapted from Nunes et al. (2016)(90)

8.4 Appendix 4: Economic literature review for heart transplant

8.4.1 Search strategy for economic literature review for HTx

Table 8-3: Databases searched for economic evaluation literature review of HTx

Database	Dates searched	Date of search	Results returned
Ovid MEDLINE	2012 – Current	30/10/2017	496
Ovid Embase	2012 – Current	30/10/2017	
CINAHL via EBSCO Host	20120101-20171231	30/10/2017	42
EconLit via EBSCO Host	20120101-20171231	30/10/2017	
PubMed	2012/01/01 to 2017/06/27	5/10/2017	131
Cochrane Database of Systematic Reviews	Jan 2012 – Oct 2017	30/10/17	267
Database of Abstracts of Reviews of Effects	Jan 2012 – Oct 2017	30/10/17	
Health Technology Assessment Database	Jan 2012 – Oct 2017	30/10/17	
NHS Economic Evaluation Database	Jan 2012 – Oct 2017	30/10/17	
Tufts Cost Effectiveness Analysis Registry	2012 – current	30/10/17	5

Table 8-4: Search terms for economic literature review for HT

Type	Terms (Medline)	Terms (PubMed/EBSCO host)	Terms Cochrane Database
Cost-effectiveness of HT	• (heart or cardiac) and transplant*) • *heart transplantation • [limit to human only]	• (heart OR cardiac) AND transplant*).ti.ab • (heart transplant*).ti.ab • *heart transplantation • [limit to human only]	• ((heart or cardiac) and transplant*):ti,ab,kw (Word variations have been searched) • *heart transplantation
Economic	• economic evaluation/ or 'cost benefit analysis'/ or 'cost effectiveness analysis'/ or 'cost utility analysis'/ • (cost adj2 (benefit* or effect* or utility or analys*)).mp. • (economic adj (evaluation* or analysis or analyses)).mp. • (cost* or economic*).ti.	• (economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') • (cost AND (benefit* or effect* or utility or analys*)) • (economic AND (evaluation* or analysis or analyses)) • TI (cost* or economic*)	• (economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') • (economic and (evaluation* or analysis or analyses)):ti,ab,kw • (cost* or economic*):ti
Restrictions	• english or french or german or italian or portuguese or Spanish • human only	• Limiters Published Date: 20140101-20171231	• Online Publication Date from Jan 2012 to Oct 2017

Source: adapted from Sutcliffe et al. (2013)(52)

Search strategy for economic literature review for HTx vs. no VAD

Search strategy adapted from Sutcliffe et al. (2013)(52).

MedlineOvid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

((heart or cardiac) and transplant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
*heart transplantation/
1 or 2
economic evaluation/ or 'cost benefit analysis'/ or 'cost effectiveness analysis'/ or 'cost utility analysis'/
(cost adj2 (benefit* or effect* or utility or analys*)).mp.
(economic adj (evaluation* or analysis or analyses)).mp.
(cost* or economic*).ti.
4 or 5 or 6 or 7
3 and 8
limit 9 to (humans and yr='2012 -Current')
limit 11 to english language
Medline = 136 articles
Embase = 264 articles

PubMed

(((((((heart[Title/Abstract] OR cardiac)[Title/Abstract] AND transplant*[Title/Abstract]))) OR *heart transplantation) AND ((((((economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis'))) OR (((cost AND (benefit* or effect* or utility or analys*))))) OR

(((economic AND (evaluation* or analysis or analyses))))) OR ((TI (cost* or economic*))))) AND ('2012/01/01'[PDat] : '2017/10/05'[PDat]) AND Humans[Mesh]) ==207
Filters activated: Publication date from 2012/01/01 to 2017/12/31, Humans, English, Adult: 19+ years ==207

(((((((heart[Title/Abstract] OR cardiac) title/abstract AND transplant*[Title/Abstract]))) OR *heart transplantation) AND ((((((economic evaluation OR 'cost benefit analysis' OR 'cost effectiveness analysis' OR 'cost utility analysis'))) OR (((cost AND (benefit* OR effect* OR utility OR analys*))))) OR (((economic AND (evaluation* OR analysis OR analysis))))) OR ((TI (cost* OR economic*))))) AND ('2012/01/01'[PDAT] : '2017/10/05'[PDAT]) AND Humans[Mesh])

EBSCO Host – CINAHL and EconLit

AB (heart OR cardiac) AND transplant*) == 3097
(heart transplant*). == 3623
*heart transplantation == 3264
S1 OR S4 OR S5 == 4759
(economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis') == 30381
(cost AND (benefit* or effect* or utility or analys*)) == 184891
(economic AND (evaluation* or analysis or analyses)) == 372021
TI (cost* or economic*) == 197872
S8 OR S9 OR S10 OR S11 == 604299
S13 AND S14 == 141
S13 AND S14 Published Date: 20120101-20171231 == 39

Cochrane database:

- Cochrane Reviews – Cochrane Database of Systematic Reviews (CDSR),
- Other Reviews - Database of Abstracts of Reviews of Effects (DARE),
- Technology Assessments – Health Technology Assessment Database (HTAD),
- Economic Evaluations – NHS Economic Evaluation Database (NHSEED).

((heart or cardiac) and transplant*):ti,ab,kw (Word variations have been searched)
*heart transplantation
(economic evaluation or 'cost benefit analysis' or 'cost effectiveness analysis' or 'cost utility analysis')
(cost and (benefit* or effect* or utility or analys*)):ti,ab,kw
(economic and (evaluation* or analysis or analyses)):ti,ab,kw
(cost* or economic*):ti
#1 or #2
#3 or #4 or #5 or #6
#7 and #8
#7 and #8 Limits: Online Publication Date from Jan 2012 to Oct 2017, in Cochrane Reviews (Reviews and Protocols), Other Reviews, Technology Assessments and Economic Evaluations
Returned 114 articles.

Tufts CEA Registry

'Heart Transplant'
Returned 16 papers from 1985 onwards and 5 published from 2012 onwards.

2015-01-17868 2015 Am J Transplant Cost-Effectiveness of Pediatric Heart Transplantation Across a Positive Crossmatch for High Waitlist Urgency Candidates.
2014-01-16979 2014 Circ Heart Fail Comparative survival and cost-effectiveness of advanced therapies for end-stage heart failure.
2014-01-16083 2014 Circ Heart Fail Cost-effectiveness of routine surveillance endomyocardial biopsy after 12 months post-heart transplantation.
2014-01-15148 2014 J Heart Lung Transplant Comparative cost-effectiveness of the HeartWare versus HeartMate II left ventricular assist devices used in the United Kingdom National Health Service bridge-to-transplant program for patients with heart failure.
2014-01-15004 2014 Int J Cardiol Cost-effectiveness of left ventricular assist devices (LVADs) for patients with advanced heart failure: analysis of the British NHS bridge to transplant (BTT) program.

8.5 Appendix 5: Published effectiveness of VADs and heart transplant

8.5.1 Search strategy for LVAD and HTx published clinical data

A purposive literature review of the clinical effectiveness of LVADs and HTx was conducted. This analysis used the same strategy as Sutcliffe et al. (2013) of online resources of regulatory bodies, health services research agencies and professional societies.(52)[45] The current review included prospective registry data reported in national repositories for Australia, the USA and Europe. The current search strategy excluded search terms relating to device brands and the term 'heart pump' was added (Table 8-5). Only RCTs including an LVAD (durable MCS) were included. Excluded papers were review articles, trials of inappropriate intervention (e.g. IABP) and inappropriate population (e.g. paediatric). This search was conducted on 1 March 2019 in PubMed. Inclusion criteria for RCTs: minimum of 50 participants (aged ≥ 16 years) in the approved VAD group; second-generation axial CF pumps and third-generation CF pumps; LVADs, RVADs and BiVADs currently approved by the FDA and/or CE and in current clinical use. Comparators included MM and HTx or two different VADs.

Table 8-5: Search results in PubMed for VAD RCTs

Search	Query	No. Items
#6	Search ((*Heart-Assist Devices/ AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) AND (((((((lvad or biVAD or bvad or vad or vads or rvad).)) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) OR ((((heart pump or ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*))) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat])) Filters: Clinical Trial; Publication date from 2012/01/01	125
#5	Search ((*Heart-Assist Devices/ AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) AND (((((((lvad or biVAD or bvad or vad or vads or rvad).)) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) OR ((((heart pump or ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*))) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat])) Filters: Publication date from 2012/01/01	5591
#4	Search (((((lvad or biVAD or bvad or vad or vads or rvad).)) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat]))) OR ((((heart pump or ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*))) AND ('2012/01/01'[PDat] : '3000/12/31'[PDat])) Filters: Publication date from 2012/01/01	8823
#3	Search ((heart pump or ventricular support or biventricular support or ventric* assist device* or ventric* assist system* or biventricular assist device* or ventricular assistance or heart assist device*)) Filters: Publication date from 2012/01/01	5814
#2	Search ((lvad or biVAD or bvad or vad or vads or rvad).) Filters: Publication date from 2012/01/01	5553
#1	Search *Heart-Assist Devices/ Filters: Publication date from 2012/01/01	6042

[45] 1) HTA organisations (including the National Institute for Health Research and the National Research Register Archive); 2) INTERMACS; 3) NHS Blood and Transplant (including the Cardiothoracic Transplant Advisory Group); 4) Ventricular Assist Device Forum, National Specialised Commissioning Team; 5) The International Society Heart & Lung Transplantation; 6) Eurotransplant; 7) Scandiatransplant; 8) US Transplant; 9) The Transplantation Society; 10) British Transplantation Society; 11) Medicines and Healthcare products Regulatory Agency; 12) US FDA52.

8.5.2 Registry – INTERMACS description

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) enrolled patients with MCS from the US. The INTERMACS 8th Annual Report included 22,866 patients receiving from 180 hospitals from 2006 to 2016.(51) The registry includes Food and Drug Administration (FDA)-approved devices including those as part of a trial. Of the 18,987 implanted devices for left sided support, the majority have CF pumps for both LVAD and/or RVAD (93%, n=17,634), and the remaining devices are PF (5%, n=957) and TAH (2%, n=396).

8.5.3 Registry – IMACs description

The International Society for Heart and Lung Transplantation (ISHLT) Mechanically Assisted Circulatory Support (IMACS) Registry includes individual medical hospitals outside the US that have an active mechanical circulatory support device program. Australian hospitals including SVHS contribute data. The first IMACS Registry report was published in 2016(160) and included 5,942 patients from 31 countries[46]. Since then the 2nd Registry Report was published in 2018 (161) and included 14,062 patients from 35 countries.

Table 8-6: Patient demographics and pre-implant characteristics (Jan 2013-Dec 2014)

IMACs patient characteristic	No. (%) (N=5,942)
Age, years	
19-39	733 (12)
40-59	2,508 (42)
60-79	2,662 (45)
≥ 80	29 (0.6)
Gender	
Female	1,250 (21)
Male	4,633 (78)
Unspecified/missing	59 (1)
Device strategy	
Bridge to transplant, listed	1,719 (29)
Bridge to candidacy	1,762 (30)
Destination therapy	2,364 (40)
Other (bridge to recovery, rescue, etc.)	97 (1)

Abbreviations: IMACS, International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support
Source:(160)

[46] The reporting centres that contributed to IMACS were from INTERMACS, the European Registry for Patients with Mechanical Circulatory Support (EUROMACS), the Japanese registry for Mechanical Assisted Circulatory Support (JMACS) and the UK Registry by NHS Blood and Transplant. The EUROMACS registry enrols patients using MCS from Austria, Azerbaijan, Belarus, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Kazakhstan, Netherlands, Norway, Poland, Spain, Switzerland and Turkey as of 31 December 2016.(242) Participation in the JMACS is mandatory for device manufactors in Japan. The first Report for JMACS has now been published with data from June 2010 to April 2015 consisting of 476 patients from 31 hospitals.(80)

8.5.4 Registry - ANZCOTR description

The Australia and New Zealand Cardiothoracic Organ Transplant Registry (ANZCOTR) is a registry of Australian and New Zealand patients with heart and or lung transplant data collected since February 1984.(70, 149, 162, 181) The participating units in Australia are The Prince Charles Hospital in Brisbane, The Alfred Hospital and The Royal Children's Hospital, both in Melbourne, St Vincent's Hospital in Sydney (the coordinating centre) and Fiona Stanley Hospital in Perth. Data from New Zealand was provided from Auckland City Hospital. HTx recipient data include demographics, waiting times, factors which may affect survival such as blood group, gender, pre-transplant symptom status, and age.

Table 8-7: Recipient and donor details – 1984-2016

Variable	Recipients	Donors
Age, mean (min-max), years	45.17 (1-73)	32.68 (1-66)
Gender, male (%)	N=2,596 1,970 (76)	N=2,684 1,818 (68)
State of origin	N=2683 ACT=46, 1.7%; NT=5, 0.2%; NSW=811, 30.2%; QLD=440, 16.4%; VIC=672, 25%; SA=111, 4.1%; WA=212, 7.9%; TAS=68, 2.5%; NZ=318, 11.9%;	N=2685 ACT=62, 2.3%; NT=24, 0.9%; NSW=684, 25.5%; QLD=509, 19%; VIC=585, 21.8%; SA=250, 9.3%; WA=192, 7.2%; TAS=50, 1.9%; NZ=329, 12.3%;

Abbreviations: ACT, Australian Capital Territory; IDCM, idiopathic dilated cardiomyopathy; NSW, New South Wales; NZ, New Zealand; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia;
Source: (149)

Table 8-8: Pre-transplant status for HTx recipients (all ages, OHT and HHT) in Australia and NZ

Year	2010	2011	2012	2013	2014	2015	2016	2017	2018
N	76	76	84	86	95	102	124	117	141
NYHA III%	30	28	46	35	58	50	58	64	82
NYHA IV%	7	8	13	7	6	6	11	8	11
Inotropic support %	4	9	2	7	0	3	8	13	7
IABP %	0	1	0	1	0	0	1	1	1
VAD %	28	29	35	4	31	43	43	31	39
TAH %	1	1	1	0	0	0	0	0	1

Abbreviations: IABP, intra-aortic balloon pump; NYHA, New York Heart Association; TAH, total artificial heart; VAD, ventricular assist device.
Source:(70, 149)

8.5.5 Registry - ISHLT description

The International Society for Heart and Lung Transplantation (ISHLT) reports a registry of heart and lung transplants from 457 heart transplant centres, 253 lung transplant centres and 177 heart-lung transplant centres from around the world(80, 163). Most of the data are from North America and Europe. Australia reports to the registry via ANZCOTR. Between 1 July 2015 and 30 June 2016 there were 4,763 heart transplant performed, of which 4,119 were conducted in adults.(80)

8.6 Appendix 6: Quality of life extraction from published data

A generic QoL instrument is a tool that can be used across a range of disease areas such as the EuroQol EQ-5D (EQ-5D).(243) Utility ranges from 0 to 100 and is used to estimate a quality-adjusted life year (QALY). In addition to generic instruments there are disease specific instruments such as the Kansas City Cardiomyopathy Questionnaire (KCCQ) (244), with scores ranging from 0 to 100 (higher scores indicate better QoL). Quality of life captured in MOMENTUM and INTERMACS via EQ-5D-3L domains does not link to the total score and hence cannot be used to estimate utilities. The EQ-5D-VAS scores are not preference based and may bias the utility results unlike the total score.

8.6.1 Quality of life in MOMENTUM 3 and INTERMACS

Secondary endpoints of QoL and functional status were measured from baseline to 24 months. There were no significant differences between the groups for or QoL assessed with the EQ-5D-5L (Table 8-9), EQ-5D VAS and KCCQ. However, there were improvements from baseline to 6 months in scores for KCCQ, EQ-5D-5L and EQ-5D VAS, which remained stable from 6 months onwards.

Table 8-9: EQ-5D-5L Total score over time

	Centrifugal flow pump		**Axial-Flow pump**	
	N	EQ-5D-5L score	N	EQ-5D-5L score
Baseline	180	11.2	160	11.4
3 month	162	8.9	146	8.6
6 month	156	8.4	129	8.6
12 month	138	8.3	111	8.6
18 month	118	8.3	89	8.6
24 month	112	8.4	81	8.9

Note: p<0.0001 for treatment over time. No statistically significant difference between treatment arms over time (p=0.47).
Source: adapted from Mehra et al. (2018)(245)

In INTERMACS, the EQ-5D-VAS at baseline, 3 months, 6 months, 12 months, 18 months and 24 months with an improvement from baseline (35) to around 70 from 3 months onwards.(51)

8.7 Appendix 7: Statistical methods for time-to-event analysis

8.7.1 Time-to-event analyses: Cox Proportional Hazard

The Cox Proportional Hazard (CPH) regression model (166) is a simple regression model for time-to-event data. The hazard is the instantaneous rate of the event, with explanatory variables x_1, x_2 and x_3 modelled as:

$$\text{Log}\{h(t; x_1, x_2, x_3)\} = \log\{h_0(t)\} + \beta_1 * x_1 + \beta_2 * x_2 + \beta_3 * x_3$$

Where h0(t) is the baseline hazard (the hazard for a reference person), and β_1 is the log hazard-ratio (HR) associated with one-unit difference in xi. This additive model on the log-hazard scale corresponds to a multiplicative model on the hazard scale:

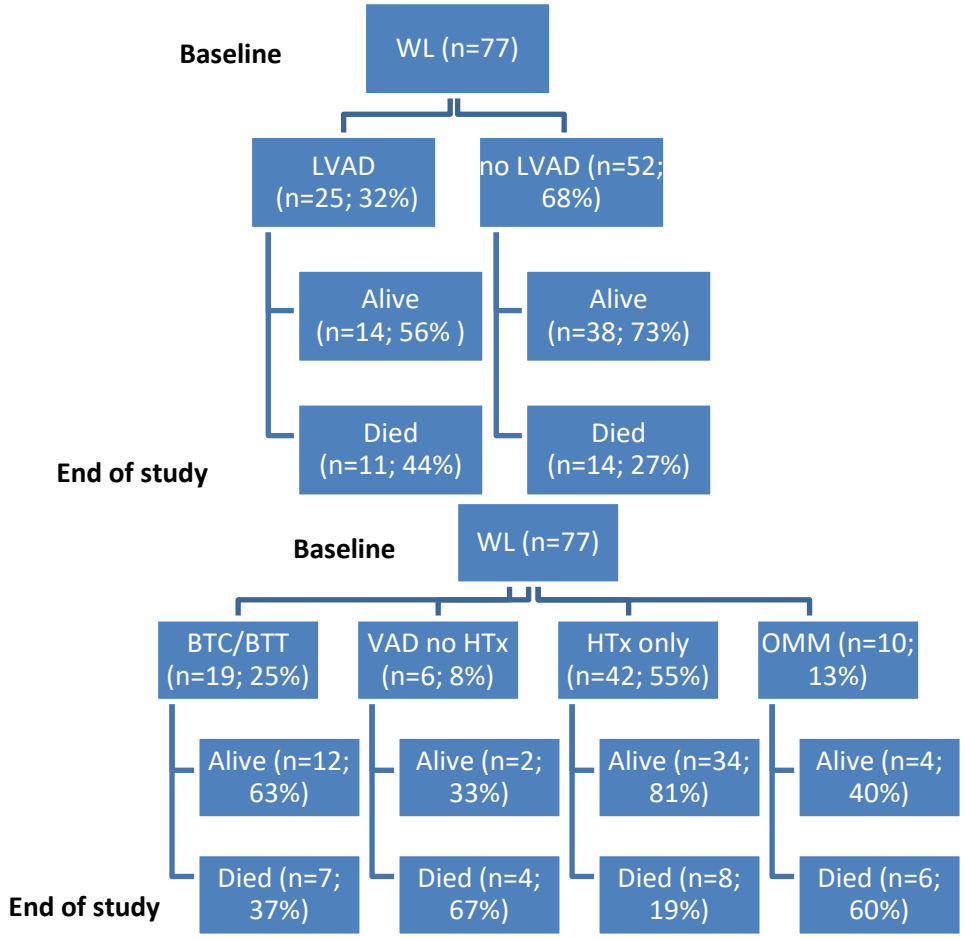
$$h(t; x_1, x_2, x_3) = h_0(t) * HR_1^{X1} * HR_2^{X2} * HR_3^{X3}$$

One of the central assumptions is the assumption of proportionality, that is, that the hazard ratio associated with each covariate is constant over time. The proportional hazards assumption is critical and the methods employed to assess the assumption regarding the distance between the two curves (should be equidistant). The log-(-log) of the within-group Kaplan-Meier estimator of the survivorship versus log-time are plotted and if the plot has parallel curves.(167)

8.8 Appendix 8: St. Vincents Hospital Sydney Add Value dataset analyses

8.8.1 Add Value cohort subgroup

Figure 8-2: Add Value, number deaths of patients with LVAD (top) and subgroups (bottom)



Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; HTx, heart transplant; OMM, optimal medical management; VAD, ventricular assist device; WL, waiting list

8.8.2 Add Value demographic and prognostic data by subgroup

Table 8-10: Summary table of demographics and prognostic data by treatment strategy at baseline

Characteristics	Sub-category	BTT/BTC (n=19)	VAD no HTx (n=6)	HTx only (n=42)	OMM (n=10)	p-value†
Sex	**Male n (%)**	13 (68)	5 (83)	28 (67)	7 (70)	ns

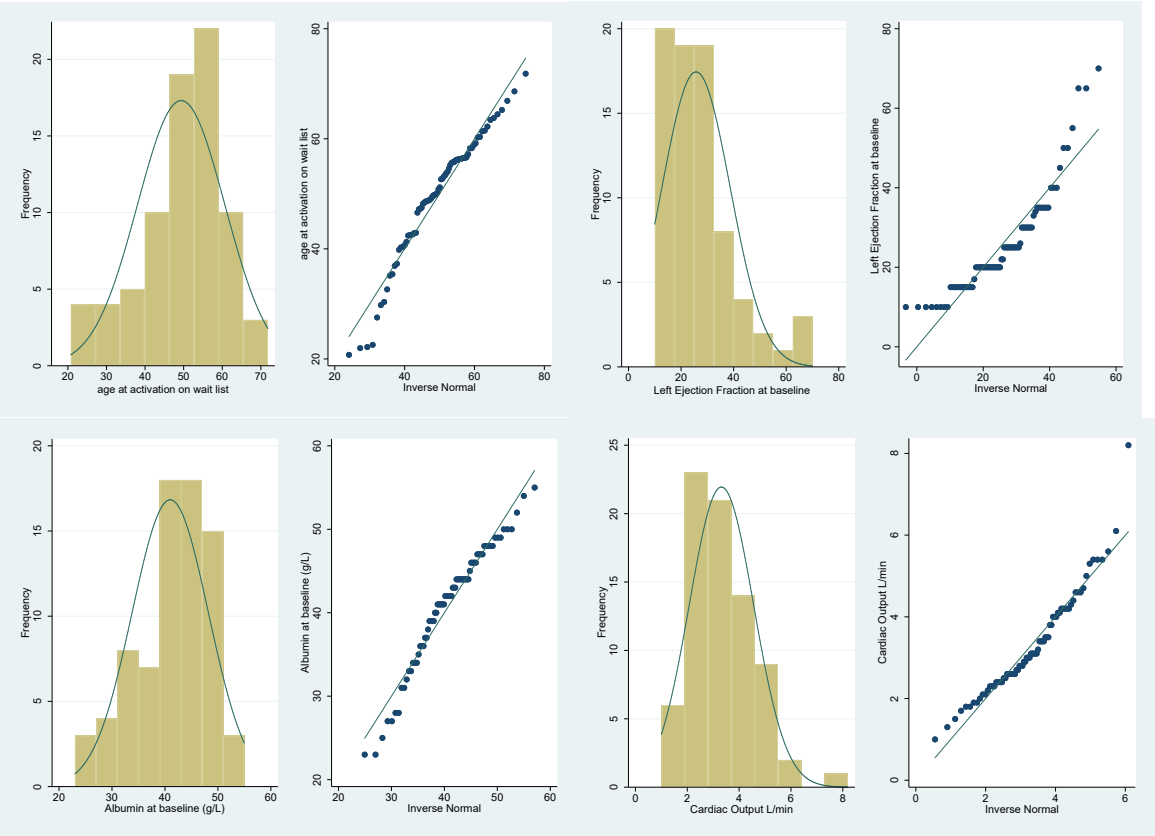
	Female n (%)	6 (32)	1 (17)	14 (33)	3 (30)	
Age (year)	**Mean (SD)**	46.93 (13.30)	48.77 (16.16)	49.78 (10.16)	52.48 (9.57)	ns
	Median	48.67	51.46	51.80	51.30	
	Min-Max	20.74-68.61	21.96-65.24	27.52-71.83	36.91-66.89	
NYHA at baseline	**I n (%)**	0 (0)	0 (0)	0 (0)	0 (0)	p<0.001
	II n (%)	0 (0)	0 (0)	9 (24)	2 (22)	
	III n (%)	0 (0)	0 (0)	20 (54)	6 (67)	
	IV n (%)	19 (100)	6 (100)	8 (22)	1 (11)	
	Missing	0	0	5	1	
IMACs at baseline	**1 n (%)**	7 (37)	1 (17)	0 (0)	0 (0)	p<0.001
	2 n (%)	11 (58)	5 (83)	0 (0)	0 (0)	
	3 n (%)	1 (5)	0 (0)	1 (7)	0 (0)	
	4 n (%)	0 (0)	0 (0)	2 (14)	0 (0)	
	5 n (%)	0 (0)	0 (0)	0 (0)	0 (0)	
	6 n (%)	0 (0)	0 (0)	4 (29)	0 (0)	
	7 n (%)	0 (0)	0 (0)	6 (43)	2 (67)	
	NA n (%)	0 (0)	0 (0)	1 (7)	1 (33)	
	Missing	0	0	28	7	
LVEF (%)	**Mean (SD)**	21.39 (8.54)	20 (4.47)	28.31 (14.26)	26.00 (15.78)	ns
	Median	20.00	20.00	25.00	20.00	
	Min-Max	10.00-35.00	15.00-25.00	10.00-70.00	15.00-65.00	
	Missing	1	0	0	0	
Albumin (g/L)	**Mean (SD)**	37.00 (5.28)	38.80 (9.15)	42.40 (7.30)	43.80 (6.53)	p<0.05
	Median	37.00	44.00	43.50	44.00	
	Min-Max	28.00-46.00	25.00-47.00	23.00-55.00	28.00-50.00	
	Missing	0	1	0	0	
Cardiac Output (L/min)	**Mean (SD)**	3.16 (1.10)	3.68 (1.16)	3.21 (1.33)	3.83 (1.12)	ns
	Median	3.00	3.30	3.05	4.10	
	Min-Max	1.00-5.60	2.60-5.40	1.30-8.20	2.10-5.30	
	Missing	1	0	0	0	
Ischaemic Heart Disease	**No**	12 (63)	6 (100)	36 (88)	9 (90)	ns
	Yes	7 (37)	0 (0)	5 (12)	1 (10)	
	Missing	0	0	1	0	
Biventricular pacing at baseline	**No**	14 (74)	4 (67)	23 (58)	6 (67)	ns
	Yes	5 (26)	2 (33)	17 (43)	3 (33)	
	Missing	0	0	2	1	
ICD at baseline	**No**	5 (26)	2 (33)	4 (10)	2 (22)	ns
	Yes	14 (74)	4 (67)	37 (90)	7 (78)	
	Missing	0	0	1	1	
IABP at baseline	**No**	10 (53)	3 (50)	40 (98)	9 (100)	p<0.001
	Yes	9 (47)	3 (50)	1 (2)	0 (0)	
	Missing	0	0	1	1	
IV inotropic medicine at baseline	**No**	0 (0)	0 (0)	27 (79)	4 (80)	p<0.001
	Yes	13 (100)	4 (100)	7 (21)	1 (20)	
	Missing	6	2	8	5	

Note: †Comparison between groups of patients.
Abbreviations: IABP, intra-aortic balloon pump; ICD, Implantable Cardioverter Defibrillator; LVEF, left ventricular ejection fraction (%); min, minimum; max, maximum; n, number of observations; N, Number of sample; SD, standard deviation.

8.8.3 AddValue demographic and clinical variables tests for normality assumption

Plots to assess normality assumption of variables at baseline are presented in Figure 8-3. The variables age, albumin and cardiac output are normally distributed; however, left ejection fraction does not appear to be normally distributed.

Figure 8-3: Graphical test for normality, histogram and standardized normal probability plot Age at activation onto waitlist, left ejection fraction, albumin and cardiac output at baseline



8.8.4 Add Value New York Heart Association analyses

Table 8-11: Change in NYHA between baseline and followup, all patients

		NYHA at follow-up				
		I	II	III	IV	Total
NYHA at baseline	I	0	0	0	0	0
	II	0	5	3	3	11
	III	0	1	20	5	26
	IV	6	9	1	13	29
	Total	6	15	24	21	66

Note: NYHA_1 = 71 at baseline and NYHA_2 = 65 at follow-up, cross-tab, whole Add Value sample

Change in NYHA score in subgroups

The cross-tabulations in the subgroups (see Table 8-12 to Table *8-15*) have small sample sizes, so caution should be used when drawing conclusions on the impact of interventions. The variation in timing of follow-up measurements limits the usefulness of these finding. For patients who received an LVAD followed by a HTx, there were 15 patients with both baseline and follow-up NYHA data. At baseline (pre-LVAD) all 15 patients were in NYHA IV; however, at follow-up post-HTx, only 1 patient was in NYHA IV and the rest had improved.

Table 8-12: Change in NYHA at baseline and follow-up in HTx recipients bridged with a VAD

	NYHA at follow-up				
	I	II	III	IV	Total
NYHA at baseline I	0	0	0	0	0
NYHA at baseline II	0	0	0	0	0
NYHA at baseline III	0	0	0	0	0
NYHA at baseline IV	6	8	0	1	15
NYHA at baseline Total	6	8	0	1	15

tab nyha_1 nyha_2 if lvad==1 & htx_excl==1

For LVAD only recipients, 6 patients all started in NYHA IV; however, at follow-up, 2 patients had improved their status (Table 8-13).

Table 8-13: Change in NYHA at baseline and follow-up in LVAD only

	NYHA at follow-up				
	I	II	III	IV	Total
NYHA at baseline I	0	0	0	0	0
NYHA at baseline II	0	0	0	0	0
NYHA at baseline III	0	0	0	0	0
NYHA at baseline IV	0	1	1	4	6
NYHA at baseline Total	0	1	1	4	6

Note: tab nyha_1 nyha_2 if lvad==1 & htx_excl==2

Table 8-14: Change in NYHA at baseline and followup in HTx patients

	NYHA at follow-up				
	I	II	III	IV	Total
NYHA at baseline I	0	0	0	0	0
NYHA at baseline II	0	4	3	2	9
NYHA at baseline III	0	0	18	2	20
NYHA at baseline IV	0	0	0	7	7
NYHA at baseline Total	0	4	21	11	36

Note: tab nyha_1 nyha_2 if lvad==2 & htx_excl==1

Table 8-15: Change in NYHA at baseline and follow-up in OMM patients

	NYHA at follow-up				
	I	II	III	IV	Total
NYHA at baseline I	0	0	0	0	0
NYHA at baseline II	0	1	0	1	2
NYHA at baseline III	0	1	2	3	6
NYHA at baseline IV	0	0	0	1	1
NYHA at baseline Total	0	2	2	5	9

Note: LVAD==2; htx_excl==1

8.8.5 Time–to-event - Study entry to LVAD

Table 8-16: Cox Proportional Hazard model – time from waitlist activation to VAD all VAD

Variable	Single
Age_act	HR: 0.98; p=0.281
Gender	HR: 1.12; p=0.798

Note: Breslow method for ties.

Figure 8-4: KM plots for time from VAD to waitlist activation in BTC patients by gender (left) and HTx (right)

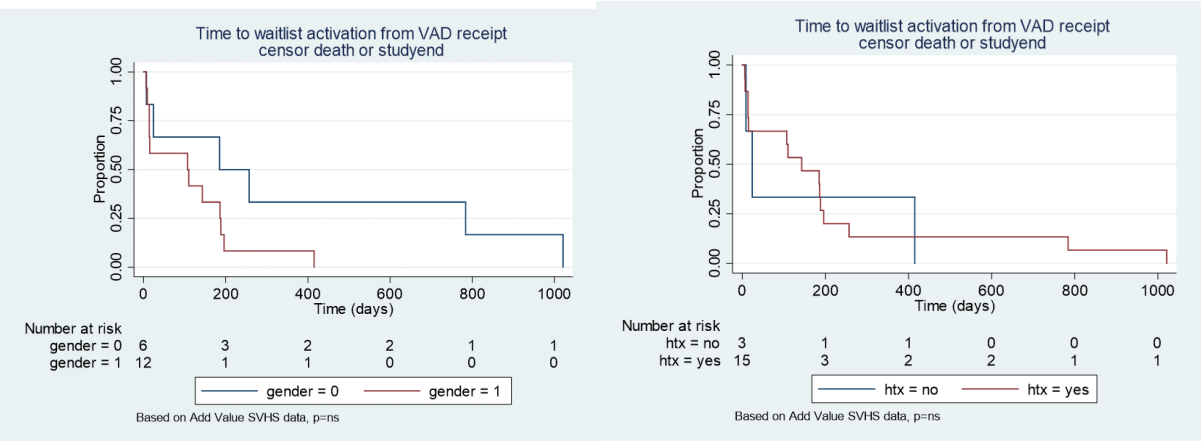


Table 8-17: Cox Proportional Hazard model – time from VAD to waitlist activation for BTC

Variable	Single
Age_act	HR: 0.98; p=0.583
Gender	HR: 3.12; p=0.103
HTx	HR: 1.07; p=0.927

Note: Breslow method for ties.

Figure 8-5: KM plots from waitlist to VAD in BTT by gender (left) and HTx (right)

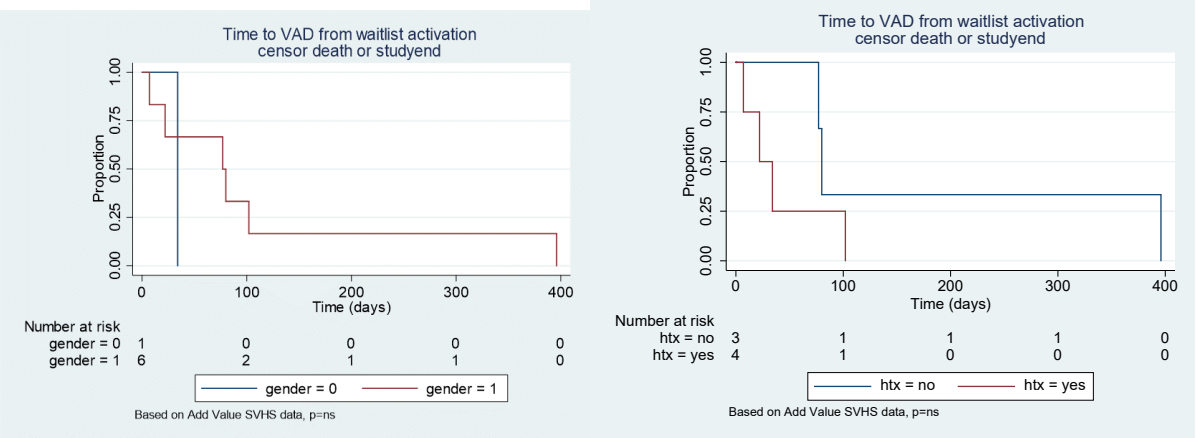


Table 8-18: Cox Proportional Hazard model – time from waitlist activation to VAD for BTT

Variable	Single
Age_act	HR: 0.88; p=0.33
Gender	HR: 3.62; p=0.58
HTx	HR: 8.93; p=0.23

8.9 Appendix 9: Costs in linked administrative APDC and EDDC from Add Value

8.9.1 Descriptive statistics for APDC variables

Table 8-19: Descriptive statistics of APDC variables

Variable	Options	Obs	Sample
Demographic variables			
Patient identifier	AV or PPN	1,983	77 patients

Variable	Options	Obs	Sample
Age	Years	1983	Mean 49.6 (SD 12.18), Median 51.84 (Min-Max 19.6-73.8)
Sex	1 = male; 2=female; 9 = unspecified.	1,983	1: 1,801 (67%) 2: 886 (33%) 9:1 (0.04%)
Hospital variables			
Area identifier	15 different area identifiers in the sample. X690, St Vincent's Health Network; X770, Central Coast LHD; X710, South Western Sydney LHD; X720, South Eastern Sydney LHD; X730, Illawarra Shoalhaven LHD; X740, Western Sydney LHD; X750, Nepean Blue Mountains LHD; X760, Northern Sydney LHD; X770, Central Coast LHD; X800, Hunter New England LHD; X810, Northern NSW LHD; X820, Mid North Coast LHD; X830, Southern NSW LHD; X840, Murrumbidgee LHD; X850, Western NSW LHD	1,983	X700: 133 (6.71%) X710: 219 (11.05%) X720: 160 (8.07%) X730: 26 (1.31%) X740: 193 (9.74%) X750: 33 (1.66%) X760: 505 (25.48%) X770: 149 (7.52%) X800: 220 (11.1%) X810: 50 (2.52%) X820: 39 (1.97%) X830: 97 (4.89%) X840: 140 (7.06%) X850: 17 (0.86%) X980: 1 (0.05%)
Hospital Type	1=Public hospital, 2=Private hospital	1983	Public 1665 (84%) Private 318 (16%)
Unit Type on admission	The designation of each bed, in terms of type of care or group of patients, which the patient is accommodated in during his/her stay in hospital.	1982	
	1 General-mixed		1: 873 (44.05%)
	2 Rehabilitation		2: 52 (2.62%)
	15 General Intensive Care		15: 8 (0.4%)
	17 Emergency Department-Level 3 and Above		17: 462 (23.31%)
	19 unknown		19: 32 (1.61%)
	25 Hospital in the Home - General		25: 5 (0.25%)
	29 Collaborative Care Service Provider - General		29: 4 (0.2%)
	33 Coronary Care		33: 204 (10.29%)
	34 High Dependency Care		34: 1 (0.05%)
	39 Same Day Renal Dialysis		39: 114 (5.75%)
	46 Medical		46: 24 (1.21%)
	47 Surgical		47: 8 (0.4%)
	58 Emergency Department - Level 1 and 2		58: 34 (1.72%)
	67 Operating Theatre/Recovery		67: 2 (0.1%)
	72 Sleep Disorder (<24 hour care)		72: 4 (0.2%)
	75 Same Day Not Elsewhere Classified		75: 13 (0.66%)
	76 Transit Lounge		76: 1 (0.05%)
	81 Same Day Surgical		81: 7 (0.35%)
	87 Medical Asessment Unit		87: 1 (0.05%)
	99 Lodger / Boarder		99: 133 (6.71%)
Facility Type	The category of the facility through which the health service is delivered.	1983	
	C Public Hospital, Privately Managed under Contract		C: 1 (0.05%)
	D Private Day Procedure Centre		D: 55 (2.77%)
	H Public hospital, Recognised (Non-Psych), NSW		H: 1659 (83.66%)
	M Public Multi-Purpose Service, Admitting Entity		M: 6 (0.3%)
	P Private hospital, Admitting Entity		P: 261 (13.16%)
	Z Private Sleep Disorder Centre, Admitting Entity		Z: 1 (0.05%)
Facility identifier	The specific hospital, nursing home or day procedure centre reporting the inpatient episode of care.	1983	
	A208 Royal Prince Alfred		A208: 17 (0.86%)
	A209 Sacred Heart		A209: 41 (2.07%)

Variable	Options		Obs	Sample
	A212	St. Vincent's - Public		A212: 1193 (60.16%)
	A237	Concord		A237: 5 (0.25%)
	B202	Gosford		B202: 24 (1.21%)
	B206	Wyong		B206: 9 (0.45%)
	B210	Hornsby		B210: 3 (0.15%)
	B212	Manly		B212: 6 (0.3%)
	B214	Mona Vale		B214: 10 (0.5%)
	B218	Royal North Shore		B218: 32 (1.61%)
	B224	Ryde		B224: 4 (0.2%)
	B226	NSCCAHS Acute and Post-acute Centre (APAC)		B226: 3 (0.15%)
	C208	Prince of Wales		C208: 7 (0.35%)
	C213	St. George		C213: 6 (0.3%)
	C214	Sutherland		C214: 8 (0.4%)
	D201	Auburn		D201: 3 (0.15%)
	D203	Blacktown		D203: 10 (0.5%)
	D206	Fairfield		D206: 3 (0.15%)
	D209	Liverpool		D209: 24 (1.21%)
	D210	Nepean		D210: 12 (0.61%)
	D215	Campbelltown		D215: 24 (1.21%)
	D218	Mount Druitt		D218: 3 (0.15%)
	D224	Westmead (all)		D224: 31 (1.56%)
	D227	Bankstown/Lidcombe		D227: 6 (0.3%)
	H201	Ballina		H201: 6 (0.3%)
	H208	Coffs Harbour		H208: 10 (0.5%)
	H214	Lismore		H214: 4 (0.2%)
	H272	Port Macquarie		H272: 1 (0.05%)
	J216	Tamworth		J216: 9 (0.45%)
	J225	Manning		J225: 7 (0.35%)
	L201	Bathurst		L201: 3 (0.15%)
	M215	Tumbarumba		M215: 6 (0.3%)
	N201	Batemans Bay		N201: 11 (0.55%)
	N215	Queanbeyan		N215: 3 (0.15%)
	P202	Bulli		P202: 1 (0.05%)
	P205	Milton-Ulladulla		P205: 1 (0.05%)
	P207	Shoalhaven		P207: 1 (0.05%)
	P211	Shellharbour		P211: 1 (0.05%)
	PRIV	PRIVATE		PRIV: 318 (16.04%)
	Q206	Maitland		Q206: 3 (0.15%)
	Q209	Muswellbrook		Q209: 4 (0.2%)
	Q211	Newcastle Mater		Q211: 2 (0.1%)
	Q214	Belmont		Q214: 1 (0.05%)
	Q216	Scone Scott Memorial		Q216: 2 (0.1%)
	Q230	John Hunter		Q230: 38 (1.92%)
	R205	Griffith		R205: 14 (0.71%)
	R215	Narrandera		R215: 12 (0.61%)
	R218	Tumut		R218: 3 (0.15%)
	R219	Wagga Wagga		R219: 25 (1.26%)
	R221	Cootamundra		R221: 13 (0.66%)
Acute Flag	Indicates whether or not the patient received the service at an acute facility. N = No; Y=yes		1983	 N= 362 (18%) Y= 1,621 (82%)
Peer Group[47]	Facility Peer Grouping		1665	
	A1	Principal Referral		A1: 1166 (70.03%)
	A1a	Principal Referral Group A		A1a: 210 (12.61%)
	A1b	Principal Referral Group B		A1b: 18 (1.08%)
	A3	Ungrouped Acute		A3: 2 (0.12%)

[47] Categorisation of hospitals into groups with similar characteristics (size, location etc. to allow comparisons).

Variable	Options		Obs	Sample
	B	Major Metropolitan or Major Non-Metropolitan		B: 63 (3.78%)
	B1	Major Metropolitan		B1: 30 (1.8%)
	B2	Major Non-Metropolitan		B2: 12 (0.72%)
	BM	Major Metropolitan		BM: 22 (1.32%)
	BNM	Major Non-Metropolitan		BNM: 15 (0.9%)
	C1	District Group 1		C1: 21 (1.26%)
	C2	District Group 2		C2: 29 (1.74%)
	D1a	Community with surgery		D1a: 27 (1.62%)
	D1b	Community without surgery		D1b: 3 (0.18%)
	F3	Multi-Purpose Services (current)		F3: 6 (0.36%)
	F4	Multi-Purpose Services (future)		F4: 41 (2.46%)
Local Health District 2010 code	X700	Sydney LHD	1982	X700: 133 (6.71%)
	X710	South Western Sydney LHD		X710: 219 (11.05%)
	X720	South Eastern Sydney LHD		X720: 160 (8.07%)
	X730	Illawarra Shoalhaven LHD		X730: 26 (1.31%)
	X740	Western Sydney LHD		X740: 193 (9.74%)
	X750	Nepean Blue Mountains LHD		X750: 33 (1.66%)
	X760	Northern Sydney LHD		X760: 505 (25.48%)
	X770	Central Coast LHD		X770: 149 (7.52%)
	X800	Hunter New England LHD		X800: 220 (11.1%)
	X810	Northern NSW LHD		X810: 50 (2.52%)
	X820	Mid North Coast LHD		X820: 39 (1.97%)
	X830	Southern NSW LHD		X830: 97 (4.89%)
	X840	Murrumbidgee LHD		X840: 140 (7.06%)
	X850	Western NSW LHD		X850: 17 (0.86%)
	X980	Australian Capital Territory		X980: 1 (0.05%)
Referral or Separation				
Mode of separation	1	discharged by hospital	1983	1: 1680 (84.72%)
	2	discharged at own risk		2: 4 (0.2%)
	5	transferred to other hospital		5: 182 (9.18%)
	6	died (autopsy)		6: 6 (0.3%)
	7	died (no autopsy)		7: 13 (0.66%)
	8	transferred other accommodation		8: 3 (0.15%)
	9	type change separation		9: 6 (0.3%)
	10	discharge on leave		10: 6 (0.3%)
	11	transferred to palliative care unit/hospice		11: 83 (4.19%)
AR-DRG mode of separation for private	Private hospitals. Status at separation of person (discharge / transfer / death) and place to which the person is released (where applicable). Mode of separation has been re-coded by removing the leading zero from values 0-9.		318	1: 39 (12.26%) 4: 3 (0.94%) 5: 1 (0.31%) 9: 275 (86.48%)
	1	discharged by hospital		
	4	transferred to psychiatric hospital		
	5	transferred to other hospital		
	9	type change separation		
Facility transfer from	The hospital, nursing home or day procedure centre the patient was transferred from.		251	
	A209	Sacred Heart		A209: 55 (21.91%)
	A212	St. Vincent's - Public		A212: 67 (26.69%)
	B202	Gosford		B202: 8 (3.19%)
	B206	Wyong		B206: 3 (1.2%)
	B210	Hornsby		B210: 1 (0.4%)
	B214	Mona Vale		B214: 1 (0.4%)
	B218	Royal North Shore		B218: 4 (1.59%)
	B224	Ryde		B224: 1 (0.4%)
	B753	Royal Rehabilitation - Weemala Nursing Home		B753: 1 (0.4%)
	C208	Prince of Wales		C208: 4 (1.59%)
	C213	St. George		C213: 1 (0.4%)
	C214	Sutherland		C214: 1 (0.4%)
	D201	Auburn		D201: 1 (0.4%)

Variable	Options		Obs	Sample
	D203	Blacktown		D203: 3 (1.2%)
	D206	Fairfield		D206: 1 (0.4%)
	D209	Liverpool		D209: 4 (1.59%)
	D215	Campbelltown		D215: 3 (1.2%)
	D224	Westmead (all)		D224: 6 (2.39%)
	H201	Ballina		H201: 1 (0.4%)
	H208	Coffs Harbour		H208: 4 (1.59%)
	H214	Lismore		H214: 1 (0.4%)
	J216	Tamworth		J216: 3 (1.2%)
	J225	Manning		J225: 4 (1.59%)
	M215	Tumbarumba		M215: 3 (1.2%)
	N201	Batemans Bay		N201: 1 (0.4%)
	PRIV	Private		PRIV: 40 (15.94%)
	Q209	Muswellbrook		Q209: 2 (0.8%)
	Q214	Belmont		Q214: 1 (0.4%)
	Q216	Scone Scott Memorial		Q216: 1 (0.4%)
	Q230	John Hunter		Q230: 2 (0.8%)
	R215	Narrandera		R215: 5 (1.99%)
	R219	Wagga Wagga		R219: 8 (3.19%)
	R221	Cootamundra		R221: 5 (1.99%)
	T202	Unknown		T202: 5 (1.99%)
Facility transfer to	The hospital, nursing home or day procedure centre the patient was transferred to.		260	
	A209	Sacred Heart		A209: 84 (32.31%)
	A212	St. Vincent's - Public		A212: 60 (23.08%)
	B202	Gosford		B202: 4 (1.54%)
	B206	Wyong		B206: 1 (0.38%)
	B214	Mona Vale		B214: 1 (0.38%)
	B218	Royal North Shore		B218: 4 (1.54%)
	C208	Prince of Wales		C208: 6 (2.31%)
	C213	St. George		C213: 2 (0.77%)
	D206	Fairfield		D206: 1 (0.38%)
	D209	Liverpool		D209: 2 (0.77%)
	D210	Nepean		D210: 1 (0.38%)
	D215	Campbelltown		D215: 2 (0.77%)
	D224	Westmead (all)		D224: 1 (0.38%)
	H201	Ballina		H201: 1 (0.38%)
	H214	Lismore		H214: 1 (0.38%)
	H222	St. Vincent's Rehab Lismore*		H222: 1 (0.38%)
	L222	St Vincent's Community Hospital		L222: 2 (0.77%)
	PRIV	Private		PRIV: 60 (23.08%)
	Q211	Newcastle Mater		Q211: 1 (0.38%)
	Q230	John Hunter		Q230: 2 (0.77%)
	R215	Narrandera		R215: 1 (0.38%)
	R218	Tumut		R218: 3 (1.15%)
	R219	Wagga Wagga		R219: 16 (6.15%)
	T202	Unknown		T202: 2 (0.77%)
	T207	Unknown		T207: 1 (0.38%)
Contract_status_ public	An indication whether or not the admitted patient service being provided during this stay in hospital is being performed under a contractual agreement with another facility or health service.		1665	
	0	Single Facility Admitted Patient Care		0: 1503 (90.27%)
	2	Not a Contract Service Provided at this Facility		2: 66 (3.96%)
	3	Full Care Purchased from a Private Facility		3: 2 (0.12%)
	4	Part Care Purchased from a Private Facility		4: 5 (0.3%)
	5	Part Care Obtained from another Public Facility		5: 13 (0.78%)
	7	Part Care Provided for another Public Facility		7: 45 (2.7%)
	8	Part Care Provided for a Private Facility		8: 15 (0.9%)
	E	Unknown		E: 8 (0.48%)

Variable	Options		Obs	Sample
	O	Unknown		O: 3 (0.18%)
	P	Unknown		P: 1 (0.06%)
	R	Community Residential		R: 4 (0.24%)
Contract status Private	1	Contract Service Provided at this Facility	318	1: 6 (1.89%)
	2	Not a Contract Service Provided at this Facility		2: 312 (98.11%)
Source of referral	The source from which the person was referred to the hospital. Source of referral has been re-coded, by adding a leading zero to values 0-9.		1,983	
	1	Emergency Department		1: 466 (23.5%)
	2	Community Health		2: 1 (0.05%)
	3	Outpatients		3: 756 (38.12%)
	4	Hospital in same Health Service		4: 151 (7.61%)
	5	Other Hospital/Day Procedure Centre		5: 94 (4.74%)
	6	Nursing Home/ Residential Aged Care Facility		6: 1 (0.05%)
	7	Medical Practitioner other than Private Psychiatric Practice		7: 393 (19.82%)
				8: 90 (4.54%)
	8	Other Agency		9: 6 (0.3%)
	9	Type Change Admission		13: 1 (0.05%)
	13	Relative		14: 12 (0.61%)
	14	Self		15: 3 (0.15%)
	15	Unknown		33: 9 (0.45%)
	33	Code unknown		
Episode of care				
Episode start date	The date on which an admitted patient completes an episode of care, by either a formal discharge from the hospital or by a statistical type change to a subsequent episode.		1983	Various
Episode end date	The time on which an admitted patient completes an episode of care, by either a formal discharge from the hospital or by a statistical type change to a subsequent episode.		1983	Various
Episode day stay length of stay	Hours. The number of hours a patient who is admitted and separated on the same day is admitted to the hospital.		1983 950 if excl. 0	Mean, 1.6 (2.46), min 0 and max 17 Excl. 0 (same-day), mean 3.44 (2.55), min 1 and max 17
Episode length of stay	The number of days the patient spends in the hospital i.e. the number of days between the episode start date and episode end date (inclusive) minus the number of leave days i.e. los = episode end date –episode start date – leave day.		1983 811 if excl 1	Mean 5.85 (SD 12.56); min 1 and max 178 Excl. 1. Mean 12.84, (SD 17.40); min 2 and max 178.
Cost_weight_a	Public hospitals. The estimated value of the relative resource requirements for a given separation, where the total costs are calculated based upon the current cost of care standards.		1665	Various
AR-DRG	AR-DRG code applied to each episode of care.		1983	Various.
Major Diagnostic code	1	Nervous System	1,983	1: 51 (2.57%)
	2	Eye		2: 18 (0.91%)
	3	Ear, Nose and Throat		3: 16 (0.81%)
	4	Respiratory System		4: 116 (5.85%)
	5	Circulatory System		5: 863 (43.52%)
	6	Digestive System		6: 94 (4.74%)
	7	Hepatobiliary System and Pancreas		7: 12 (0.61%)
	8	Musculoskeletal System and Connective Tissues		8: 16 (0.81%)
	9	Skin, Subcutaneous Tissue and Breast		9: 26 (1.31%)
	10	Endocrine,Nutritional and Metabolic		10: 18 (0.91%)
	11	Kidney and Urinary Tract		11: 167 (8.42%)
	12	Male Reproductive System		12: 2 (0.1%)
	13	Female Reproductive System		13: 5 (0.25%)
	14	Pregnancy,Childbirth and the Puerperium		14: 3 (0.15%)
	16	Blood & Blood Forming Organs & Immunity		16: 17 (0.86%)
	17	Myeloproliferative Disorders & Poorly Differentiated Neoplasms		17: 13 (0.66%)

Variable	Options	Obs	Sample
	18 Infectious and Parasitic Diseases		18: 47 (2.37%)
	19 Mental Diseases and Disorders		19: 6 (0.3%)
	20 Substance Use & Substance Induced Organic Mental Disorders		20: 1 (0.05%)
	21 Injury,Poisoning and Toxic Effects of Drugs		21: 20 (1.01%)
	23 Factors Influencing Health Status & Other Contacts with Health Services		23: 472 (23.8%)
Clinical Codeset	An identifier to identify the current classification scheme a procedure or diagnosis has been mapped to	1983	ICD10V6 =460 (23%) ICD1-V7= 1,375 (69%) ICD10V8= 148 (7%)

Note: Major Diagnostic coding has been simplified and does not separated the Pre-MDC codes or 'unrelated operating room DRGs'.
Abbreviations: SD, standard deviation.

8.9.2 Categorising admissions by VAD or HTx date

Admissions were divided into the following categories for those who received an LVAD and/or HTx; 1) pre-intervention with two groups; 2) intervention, and 3) post-intervention into three groups. There were six groups in total for patients who received VAD followed by HTx ('post-VAD and pre-HTx'), or no HTx ('post-VAD no HTx') and patients who received neither intervention during the study period ('OMM').

Table 8-20: Categorisation of APDC observations

Category	No. of patients	No. of admissions	Average admissions per patient
Pre-LVAD	25	209	8
Post-LVAD (no-HTx)	5	40	8
Post-LVAD and pre-HTx	19	123	6
Pre-HTx (no LVAD)	42	399	10
Post-HTx (bridged and not bridged)	62	1,068	17
OMM	10	144	14

Abbreviations: HTx, heart transplant, OMM, optimal medical management, VAD, ventricular assist device.
Note: Categorised using episode start date, episode end date from APDC and AR-DRG code A10Z (VAD implant), A05Z (heart transplant)

8.9.3 Estimating the cost of an admission

Admissions were costed using the cost weights for the ARDRG codes as provided by the National Hospital Cost Data Collection (NHCDC). The cost weight are the estimated value of the relative resource requirements for a given separation, where the total costs are calculated based upon the current cost of care standards. Cost groups are split into direct and overhead: imaging, allied health, pharmacy, critical care, operating rooms, emergency departments, supplies, special procedure suites. The average component costs consist of prostheses, on-costs, hotel and depreciation. The national cost weight for the average AR-DRG is equal to 1.00, with more costly AR-DRGs having a cost weight greater than 1.00 and vice versa.

The AR-DRG codeset for public hospitals was Version 6 (2010/2011). Private admissions (n=318) cost weights were taken from Round 18 private sector (2013/13) national consolidation cost weight tables(246). On average, these cost-weights were slightly higher than public cost weights for the same AR-DRG. The reference cost weight, i.e. cost weight=1.00 in 2015/2016 NHCDC Cost Report for AR-

DRG version 8.0 was $5,198.70 (2016 Australian dollars)(170). The reference cost ($) was multiplied to both public and private hospital admissions AR-DRG cost weights. Admission in private hospitals reported '.' for cost_weight_a (n=49 observations) requiring private sector cost weights.

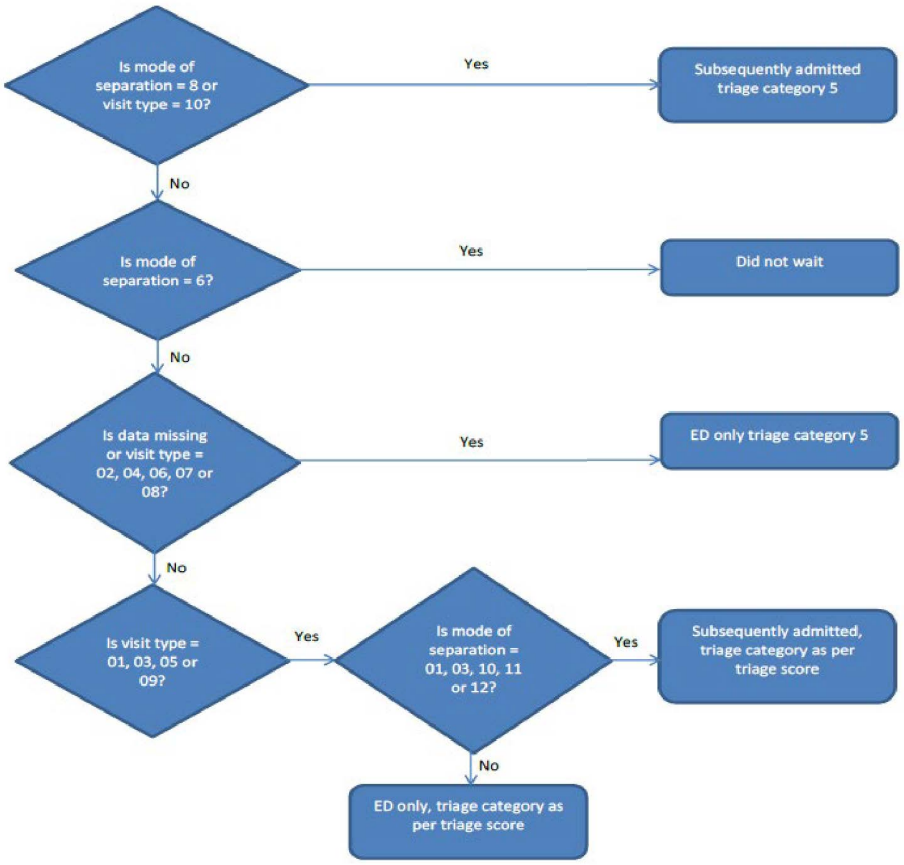
Table 8-21: Total costs of all admitted patient episodes of care

	Obs.	Mean	SD	Median	Min	Max
Total	1983	$15,465	$40,551	$3,160	$416	$377,020
Public	1665	$15,453	$41,780	$3,062	$416	$377,020
Private	318	$15,525	$33,557	$3,206	$698	$234,754
VAD admission	25	$260,654	$39,552	$245,119	$229,185	$377,020
HTx admission	61	$126,333	$54,928	$103,080	$96,379	$355,440

Note: cost weight for VAD is 50.14 and HTx is 24.30.

8.9.4 Urgency and Disposition Group class allocation for ED cost weights

Figure 8-6: Urgency and Disposition Group class allocation for ED cost weights



Source: CHERE Working paper, 2014(179)

8.9.5 Descriptive statistics of EDDC variables

Table 8-22: Summary of EDDC variables, all consented patients

Variable	Options	All consented % (N=705)	All admitted % (N=245)
Triage category	1 Resuscitation	1=19 (3%)	1=2 (0.8%)
	2 Emergency	2=179 (25%)	2=44 (18%)

Variable	Options	All consented % (N=705)	All admitted % (N=245)
	3 Urgent	3=333 (47%)	3=87 (36%)
	4 Semi urgent	4=118 (17%)	4=73 (30%)
	5 Non urgent	5=56 (8%)	5=39 (16%)
	U Any or none	U=0	U=0
ED Visit Type	01 Emergency presentation	01=663 (94%)	01=236 (96%)
	02 Return visit - planned	02=4 (0.6%)	02=2 (0.8%)
	03 Unplanned return visit for continuing condition	03=5 (0.7%)	03=1 (0.4%)
	04 Outpatient clinic	04=3 (0.4%)	04=3 (1.2%)
	05 Privately referred, non-admitted person	05=1 (0.1%)	05=0 (0%)
	06 Pre-arranged admission: without ED workup	06=20 (2.8%)	06=0 (0%)
	07 Code unknown	07=1 (0.1%)	07=1 (0.4%)
	08 Pre-arranged admission: with ED workup	08=7 (1.0%)	08=1 (0.4%)
	09 Person in transit	09=0	09= 0 (0%)
	10 Dead on arrival	10=1 (0.1%)	10=1 (0.4%)
	11 Disaster	11=0	11=0 (0%)
Mode of separation	1 Admitted: To ward/inpatient unit, not a critical care ward	1 =197 (28%)	1 =0
	2 Admitted and discharged as inpatient within ED	2 =38 (5.4%)	2 =0
	3 Admitted: Died in ED	3 = 2 (0.3%)	3 = 0
	4 Departed: Treatment completed	4 =225 (31.9%)	4 =225 (92%)
	5 Departed: Transferred to hospital without being admitted to hospital transferred from	5 =5 (0.7%)	5 =5 (2%)
	6 Departed: Did not wait	6=7 (1.0%)	
	7 Departed: Left at own risk	7=3 (0.4%)	6=7 (3%)
	8 Dead on arrival	8=1 (0.1%)	7=3 (1%)
	9 Departed: For other clinical service location	9=4 (0.6%)	8=1 (0.4%)
	10 Admitted: To critical care ward (including HDU/CCU/NICU)	10=202 (28.7%)	9=4 (1.6%)
	11 Admitted: Via operating suite	11=7 (1.0%)	10=0
	12 Admitted: Transferred to another hospital	12=13 (1.8%)	11=0
	13 Admitted: Left at own risk	13=1 (0.1%)	12=0
			13=0

8.9.6 Estimating the cost of an ED presentation

Table 8-23: Emergency Department cost weights by Urgency and Disposition Group

udg	Urgency and Disposition Group (UDG)	Cost weight	Freq.	Percent	$ Mean
1	Subsequently Admitted, Triage 1	2.96	15	2.13	1197.38
2	Subsequently Admitted, Triage 2	1.78	124	17.59	720.06
3	Subsequently Admitted, Triage 3	1.53	209	29.65	618.92
4	Subsequently Admitted, Triage 4	1.33	35	4.96	538.01
5	Subsequently Admitted, Triage 5	0.91	12	1.7	368.11
6	ED Only, Triage 1	1.62	4	0.57	655.32
7	ED Only, Triage 2	1.24	55	7.8	501.60
8	ED Only, Triage 3	1.08	102	14.47	436.88
9	ED Only, Triage 4	0.81	77	10.92	327.66
10	ED Only, Triage 5	0.50	65	9.22	202.26
11	Did not wait	0.18	7	0.99	72.81
Total			705	100	

Abbreviations: udg = urgency and disposition group
Source: Table 3; p.18 (171)

Table 8-24: Cost of ED visits, all observations

	Obs.	Mean	Median	SD	Min	Max
Total	705	$529.80	$538.01	$191.13	$72.81	$1,197.38
Subsequently admitted	395	$657.84	$618.92	$130.14	$368.11	$1,197.38
ED only	305	$366.64	$436.88	$118.19	$72.81	$655.32

It was not possible to discern if the ED visit was linked to the patient's HF; hence, all visits are included in the analysis, which may overestimate the costs.

Table 8-25: Number of observations and patients in each hospitalisation group

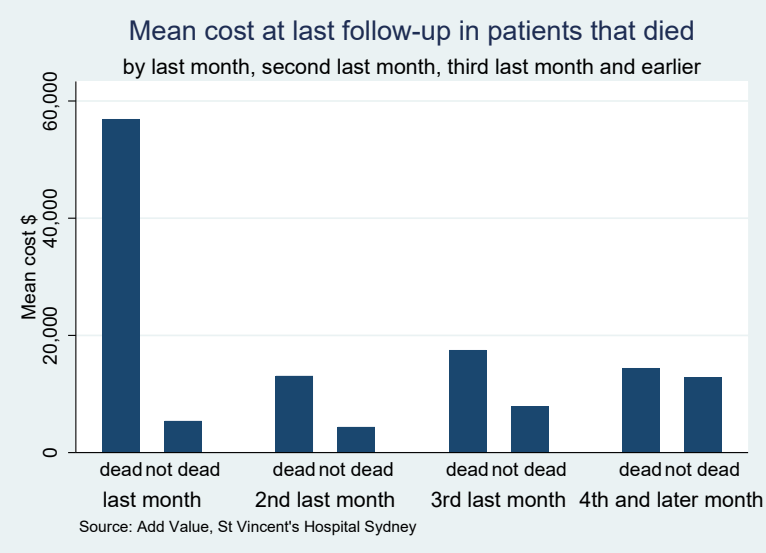
	Patient no.	Total sample	Admitted APDC episodes	ED only, included	Obs (Total)	Health state
Group	N	Obs	Obs	Obs	Obs	
1: pre-VAD	24	301	184	33	217	Wait list
2: intervention-VAD	25	29	26	0	26	Alive with VAD
3: post-VAD and no HTx	4	77	51	5	56	Alive with VAD
4: post-VAD and pre-HTx	18	158	108	20	128	Alive with VAD
5: pre-HTx no VAD	42	616	393	96	489	Wait list
6: intervention HTx	61	104	61	1	62	Alive with HTx
7: post-HTx	56	1207	1019	78	1,097	Alive with HTx
8: omm	10	196	141	12	153	Wait list/ Not eligible
		2688	1983	245	2,228	

Abbreviations: APDC, Admitted Patient Data Collection; ED, emergency department; HTx, heart transplant, Obs, observation; omm, optimal medical management; VAD, ventricular assist device

8.9.7 Mean costs in last months of follow-up in those that died vs. those that did not

The final episode of care was higher in those that died compared to those that did not (Figure 8-7).

Figure 8-7: Mean hospitalisations costs in last months of follow-up in patients that died



8.10 Appendix 10: SVHS 'Mechanical Circulatory Support' dataset analyses

8.10.1 Variables in MCS dataset

Table 8-26: Demographic, prognostic variables and device details at baseline in MCS Registry

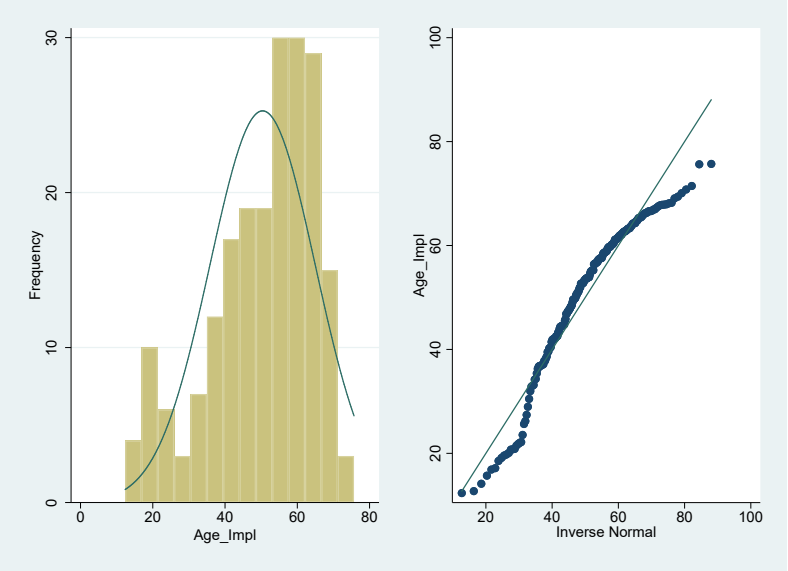
Type	Variable
Demographic	Age, gender
Prognostic	INTERMACS at baseline

Pre-operative support	Intraortic balloon pump use, Extracorporeal membrane oxygenation and ventilation
Device Type	Type of flow, Device, Configuration, indication
Surgical Details	Concomitant surgery, RVAD site (if applicable), LVAD outflow
Surgical Outcomes	Venopulmonary arterial ECMO post-implant, cause of death

Abbreviations: ECMO, extra-corporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, Right ventricular assist device.

8.10.2 Mechanical Circulatory Support variable tests for normality

Figure 8-8: Graphical test for normality, histogram and standardized normal probability plot Age at implant



8.10.3 Demographics for CF vs. non-CF devices

Table 8-27: Demographic and prognostic variables in MCS – full sample and by CF device

Characteristics	Sub-category	All (n=204)	CF (n=161)	Non-CF (n=43)	p-value[a]
Sex	Male n (%)	162 (79)	128 (80)	34 (79)	ns
	Female n (%)	42 (21)	17 (20)	9 (21)	
Age (year)	Mean (SD)	50.40 (14.58)	51.76 (14.17)	45.30 (15.09)	p<0.01
	Median	53.67	54.80	51.00	
	Min-Max	12.34 – 75.70	12.34 – 75.70	12.72 – 64.80	
IMACs at baseline	1 n (%)	68 (33)	49 (30)	19 (44)	ns
	2 n (%)	113 (56)	90 (56)	23 (53)	
	3 n (%)	23 (11)	22 (14)	1 (2)	
IABP at baseline	No n (%)	150 (74)	111 (69)	39 (91)	p<0.01
	Yes n (%)	54 (26)	50 (31)	4 (9)	
ECMO at baseline	No n (%)	180 (88)	139 (86)	41 (95)	ns
	Yes n (%)	24 (12)	22 (14)	2 (5)	
Ventilation at baseline	No n (%)	174 (85)	141 (88)	33 (77)	ns
	Yes n (%)	30 (15)	20 (12)	10 (23)	

Abbreviations: CF, continuous-flow; ECMO, extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; IMACS, International Society for Heart and Lung Transplantation Registry for Mechanically Assisted Circulatory Support; SD, standard deviation
[a].Comparison between CF vs. non-CF

Table 8-28: Details of LVAD implant and surgery – included patients

Variable	Sub-category	Included (n=137)
LVAD Device	HVAD n (%)	104 (76)
	MVAD n (%)	2 (1)

	VentrAssist n (%)	31 (23)
Configuration	LVAD n (%)	135 (98)
	MVAD n (%)	2 (1)
Indication	BTC n (%)	2 (1)
	BTT n (%)	127 (93)
	Destination n (%)	8 (6)
LVAD outflow	Aorta n (%)	134 (98)
	Subclavian n (%)	3 (2)
Venopulmonary arterial ECMO post-implant	Yes n (%)	11 (8)
	No n (%)	126 (92)
Outcome	Alive on pump n (%)	18 (13)
	Transplanted n (%)	77 (56)
	Died on pump n (%)	41 (30)

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; ECMO, extra-corporeal membrane oxygenation; HVAD, HeartWare™ HVAD™ System; LVAD, left ventricular assist device; MVAD, HeartWare® Miniaturized Ventricular Assist Device (MVAD®).

8.10.4 Time to event -VAD to death

Figure 8-9: Kaplan-Meier plots of survival for days alive on pump, by Gender (top left), INTERMACS (top right) and ECMO (bottom left), event death

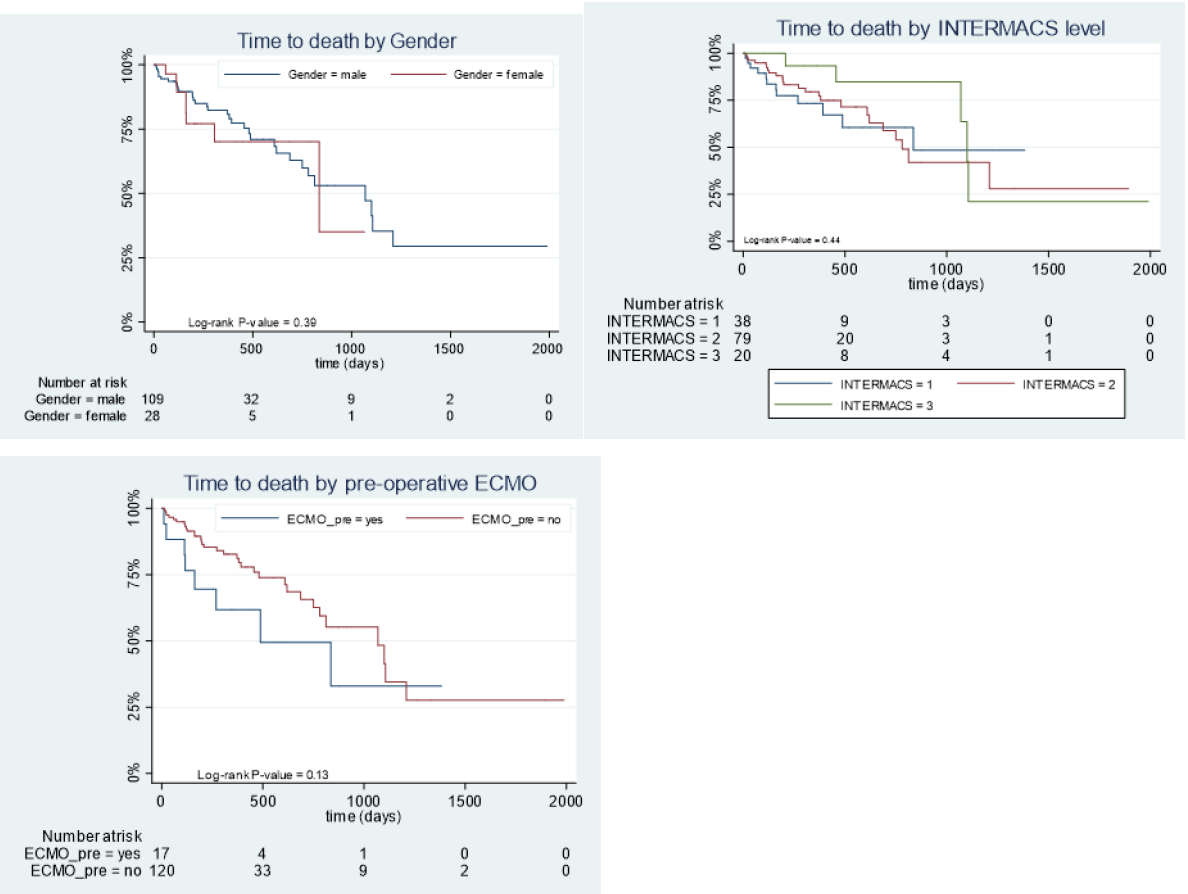


Table 8-29: Cox Proportional Hazard Model – VAD to death in MCS

Variable	HR; p-value
Age_Impl	HR: 1.01; p=0.27
Gender	HR: 1.28; p=0.53
ECMO_pre	HR: 0.55; p=0.13

INTERMACS	HR: 0.77; p=0.27

Breslow model for ties.
Note: Gender: 1 = male; 2 = female. INTERMACS 1 to 3, with 3 being less severe.

8.11 Appendix 11: SVHS 'CPR-CHF' dataset analyses

8.11.1 Time to event – waitlist to HTx in CPR

Table 8-30: Cox Proportional Hazard Model – waitlist to death - CPR

	Time to HTx	Time to Death
Variable	HR; p-value	HR; p-value
VAD	HR: 0.14; p=0.000	HR: 6.91; p=0.099

8.11.2 Time to event – VAD to HTx with competing risk of death

Table 8-31: Summary statistics of time from VAD to HTx or Death

Time to HTx	Failure HTx	Failure death
Subjects, n	28	28
Failures, n	4	3
Survival time: 25%, 50%; 75%	744; NE; NE	NE; NE; NE
10% remaining at risk; SE (95% CI)	6; 2.98 (0.001, 19)	32; NE (32,368)

Figure 8-10: Kaplan-Meier plots of survival with VAD, event HTx (left) or death (right)

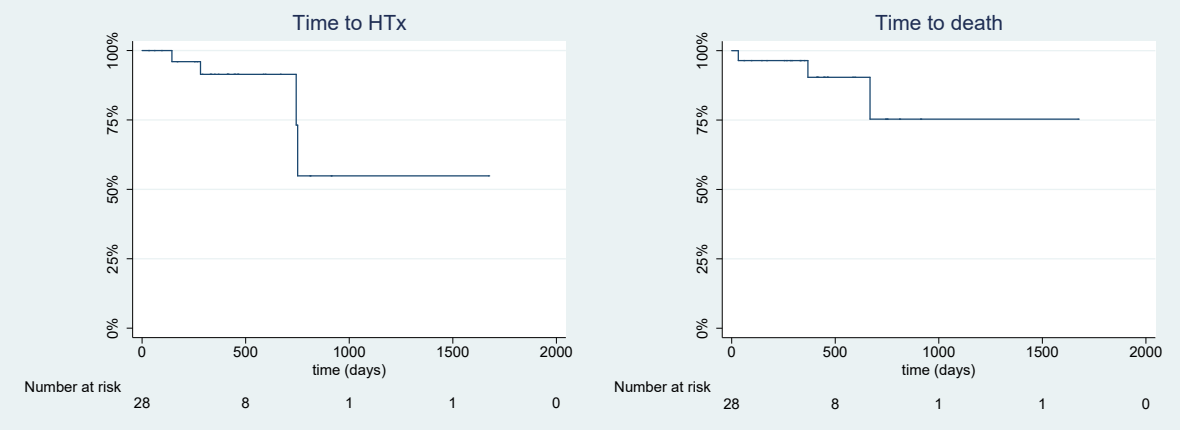
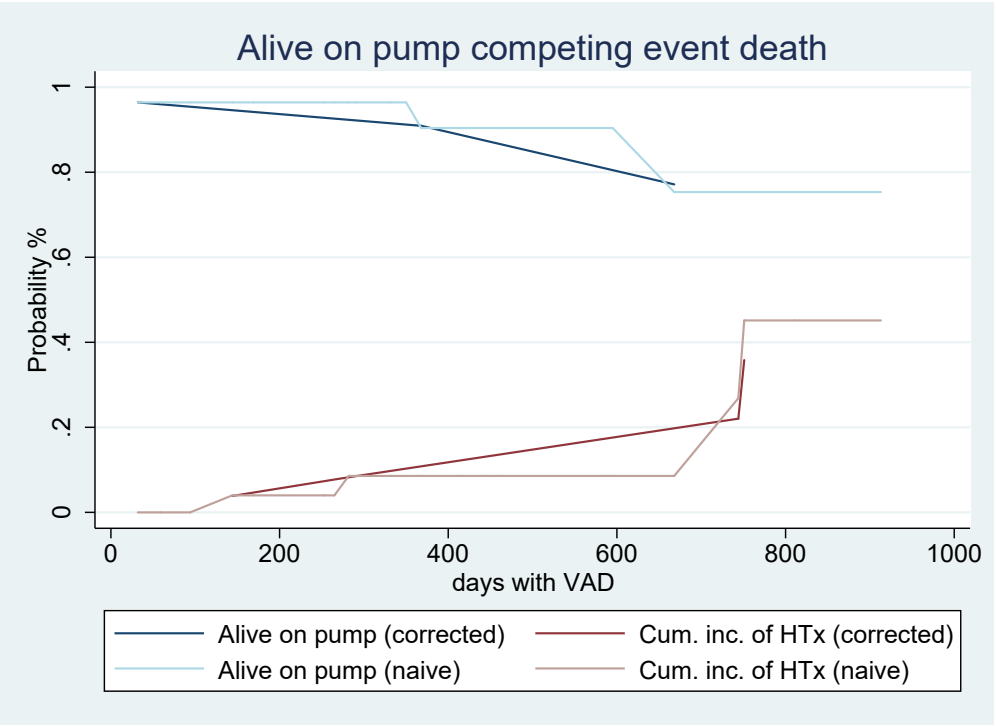


Figure 8-11: Alive with pump waiting for HTx with competing risk death



8.12 Appendix 12: Technical appendix for digitisation and extrapolation of published survival curves

8.12.1 Parameterisation of distributions for extrapolation

The distributions fitted in the model are presented in Table 8-32. In the Weibull model, alpha is the scale parameter which determines the fitted hazard rate (and hence transition probabilities) are increasing or decreasing over time. A scale parameter (α or λ) > 1 means increasing hazard; α < 1 means decreasing hazards and α = 1 produces a constant hazard which produces a constant hazard which is equivalent to an exponential model. The beta (β or γ) is the shape parameter and determines the fitted slope of the curve, this is also known as the gamma (γ). The Weibull model also nests the exponential as a special case when gamma = 1 with the formula: $tp(t_{\mu}) = 1 – exp(\lambda(t-\mu)^{\gamma}-\lambda t^{\gamma})$ (200).

Table 8-32: Distributions

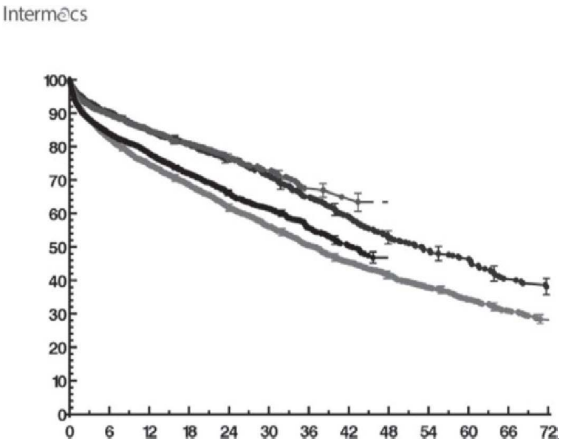
	Hazard function	Parameter	Nonzero initial hazard	Nonmonotonic increasing/ decreasing hazard	Location param.	PH/AFT	Notes
Exponential	λ	$\lambda > 0$	Yes	No	Rate	PH	Constant hazard
Weibull	$\lambda\gamma t^{\gamma-1}$	$\lambda > 0$ (scale) $\gamma > 0$ (shape)	No	No	Rate	AFT	$\gamma > 1$, hazard rate monotonically ↑ with time. $\gamma < 1$, hazard rate monotonically ↓ with time. $\gamma = 1$, hazard is flat. When γ = 0, Weibull is equivalent to exponential.
Log-normal	$\varphi(\ln(t) - \frac{\mu}{\sigma})/\sigma t[1 - \varphi(\ln(t) - \frac{\mu}{\sigma})$	μ (scale) σ (shape)		Yes	Meanlog	AFT	Log of event time is normally distributed
Log-logistic	$\left[\left(\frac{\beta}{\alpha}\right)\left(\frac{t}{\alpha}\right)^{\beta-1}\right]/[1 + \left(\frac{t}{\alpha}\right)^{\beta}]$	$\alpha > 0$ (scale) $\beta > 0$ (shape)	Yes	Yes	Scale	AFT	Monotonic change followed by gradual decreasing
Gompertz	$\alpha e^{\beta t}$	$\alpha > 0$ (scale) $\beta > 0$ (shape)	Yes	No	Rate	PH	Monotonically increasing or decreasing
Generalised gamma	$\exp(-\ln(\sigma t) + \ln\lvert\kappa\rvert + \kappa^{-2}\ln(\kappa^{-2}) + \kappa^{-2}\left(\kappa * \ln(t) - \frac{\mu}{\sigma} - \exp\left(\kappa * \ln(t) - \frac{\mu}{\sigma}\right)\right) - \ln\lvert\Gamma(\kappa^{-2}, t)\rvert)$ / S(t)	μ (scale) σ (shape) κ (sign)		Yes	Mu	AFT	

Abbreviations: AFT, accelerated failure time; param; PH, proportional hazards
Φ is the cumulative standard normal distribution.
Source: https://cran.r-project.org/web/packages/flexsurv/flexsurv.pdf; http://installers.treeagesoftware.com/treeagepro/PDF/Parameterization-STATA-SAS-R.pdf; (30)

8.12.2 How to generate survival curves from published Kaplan-Meier curves for the purpose of extrapolating and use in a Markov model

1. Paste image of published Kaplan-Meier curve into Enguage Digitizer®.

Figure 8-12: Pasted into Enguage Digitizer (left) and published in Kirklin et al. (2017) (right)



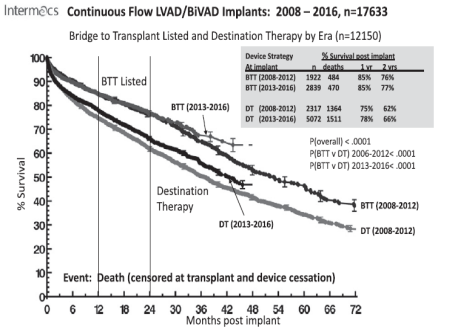
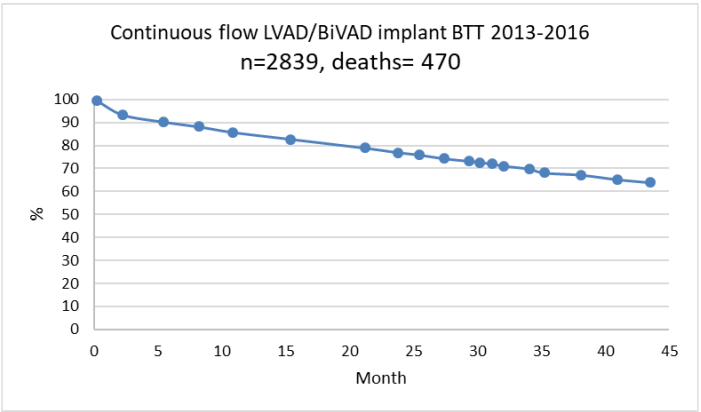


Figure 9 Kaplan-Meier survival curves, stratified by device strategy and era. Depiction is as in Figure 3. LVAD, left ventricular assist device; BiVAD, biventricular assist device.

Source: (51)

2. Define axes (0,0; x-axis and y-axis).
3. Click on segment fill and manually click on sections to connect using blue crosshairs.
4. Export data as a csv. Should have x-values and y-values.
5. Create a scatter plot to check against published plot (*Figure 8-13*). This chart does not report numbers at risk at various time intervals.

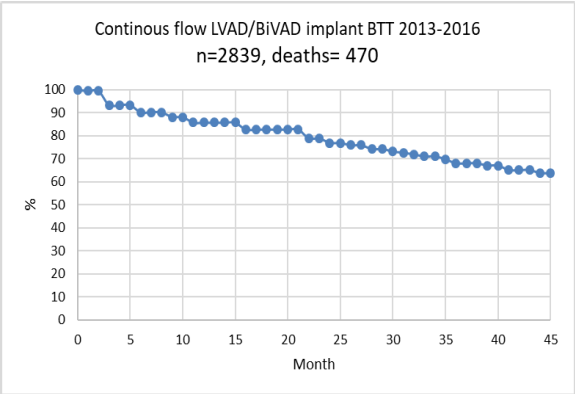
Figure 8-13: Digitised survival curve of INTERMACS Kaplan-Meier data



Source: Figure 9, Kirklin 2017(51)

6. The x-values (time) from Engauge Digitizer will not be in discrete months as they when events occurred. Use the VLOOKUP function in Excel to apply linear interpolation to generate the y values that correspond to the x (time/month) values in discrete monthly intervals. The expression in Excel =VLOOKUP('column time','matrix of x and y values','column 2').

Figure 8-14: Digitised survival curve from INTERMACS Kaplan-Meier data and linear interpolation



Note: digitised from Figure 9, Kirkin 2017(51).

7. Access Hoyle and Henley Excel Excel spreadsheet.(201) The spreadsheet has a built in template to add in the digitised empirical survival probability in the sheet titled 'Number events & censored'. The sheet includes start time from 0 to 18, in 0.75 increments, ensure that linear interpolation of y-values are for these x-values.
8. Estimated the numbers at risk as they were not reported in the published Kaplan-Meier curve. Hoyle and Henley Excel spreadsheet recommended the use of Tierney et al. (2007) spreadsheet.(202) Instructions are: the numbers at risk are not provided, fill in the Start Time (column B) in worksheet 'Number events & censored' and paste the expected numbers of events and censorships from the Tierney et al. (2007) spreadsheet into columns K and N. In column H, Number at risk R(t) has available cells to input the number at risk at certain time points.
9. Using the Tierney et al. (2007) spreadsheet, use the '(2a)_Curve_Data' sheet and add start-time (3/4 months) as this corresponds with the cells available for data in the Hoyle and Henly Excel spreadsheet. Add in survival probability at the start of time defined. Add in study size, e.g. n=2,839 and expected events, e.g. 470 reported from the Kirklin 2017 paper (52). The published Kaplan-Meier curve reported that there were 470 deaths (event defined as censored at transplant and device cessation). From the estimated data so far, the total number of events at the end of 24 months was 446. Therefore, underestimated by 24 deaths (5.11% difference [(470-446)/470]. Finally, in cell M5 of sheet '(2a)_Curve_Data' reports the final survival proportion for patients ($S_r(t_s)$ at the end of the study and the corresponding chart. Chose to fit the first 24 months of data. The Tierney et al. (2007) spreadsheet estimated the number event-free at start of t, effective no. at risk and effective no. censored (Table 8-33).

Table 8-33: Estimated number at risk, events and censored from INTERMACS digitised Kaplan-Meier data using Tierney et al. (2007)

Month	Survival prob at start of t (%)	Effective number event-free at start of t	Effective number at risk during t	Effective number of events during t	Effective number censored during t
ts	Sr(ts)	Rr(ts)	Rr(t)	Dr(t)	Cr(t)
0	100	2839	2795	16	44
0.75	99	2779	2734	0	45
1.5	99	2734	2688	165	46
2.25	93	2524	2480	0	44
3	93	2480	2436	0	44
3.75	93	2436	2391	0	45
4.5	93	2391	2345	0	46
5.25	93	2345	2298	76	47
6	90	2222	2175	0	46
6.75	90	2175	2128	0	47
7.5	90	2128	2080	48	48
8.25	88	2032	1983	0	48
9	88	1983	1934	0	50
9.75	88	1934	1883	0	51
10.5	88	1883	1830	50	52
11.25	86	1780	1728	0	52
12	86	1728	1674	0	54
12.75	86	1674	1618	0	56
13.5	86	1618	1560	0	58
14.25	86	1560	1500	0	60
15	86	1500	1438	50	63
15.75	83	1388	1324	0	63
16.5	83	1324	1258	0	66
17.25	83	1258	1188	0	70
18	83	1188	1114	0	74
18.75	83	1114	1034	0	80
19.5	83	1034	948	0	86
20.25	83	948	853	0	95
21	83	853	747	35	107
21.75	79	712	593	0	119
22.5	79	593	445	0	148
23.25	79	445	223	6	223
24	77	217	217	0	0.00

10. From the Hoyle and Henley spreadsheet, save the sheet titled 'R data' as a CSV (*Table 8-34*). Titled 'VAD survival'. The start_time_event and end_time_event represents the start time and end time period for the number of events in 0.75 months. The start_time_censor and end_time_censor represents the time period for the number of censorings in 0.75 months. The method assumed that the maximum end time was 10,000 months meaning that by the end of the time period, all patients would have been censored.

Table 8-34: The R data from Hoyle and Henley et al. (2011)

start_time_event	start_time_censor	end_time_event	end_time_censor	n_events	n_censors
0.0001	0.375	0.7499	10000	16	45
0.75	1.125	1.5	10000	0	45
1.5	1.875	2.25	10000	162	45
2.25	2.625	3	10000	0	45
3	3.375	3.75	10000	0	46

3.75	4.125	4.5	10000	0	46
4.5	4.875	5.25	10000	1	46
5.25	5.625	6	10000	76	46
6	6.375	6.75	10000	0	49
6.75	7.125	7.5	10000	0	49
7.5	7.875	8.25	10000	47	49
8.25	8.625	9	10000	0	49
9	9.375	9.75	10000	0	53
9.75	10.125	10.5	10000	0	53
10.5	10.875	11.25	10000	49	53
11.25	11.625	12	10000	0	53
12	12.375	12.75	10000	0	59
12.75	13.125	13.5	10000	0	59
13.5	13.875	14.25	10000	0	59
14.25	14.625	15	10000	0	59
15	15.375	15.75	10000	48	69
15.75	16.125	16.5	10000	0	69
16.5	16.875	17.25	10000	0	69
17.25	17.625	18	10000	0	69
18	18.375	18.75	10000	0	92
18.75	19.125	19.5	10000	0	92
19.5	19.875	20.25	10000	0	92
20.25	20.625	21	10000	0	92
21	21.375	21.75	10000	29	123
21.75	22.125	22.5	10000	0	123
22.5	22.875	23.25	10000	2	123
23.25	23.625	24	10000	7	123
24	24.375	24.75	10000	0	54

Note: event is death, censor is alive at time-point

11. Open R Studio.
12. Parametric model fitting analysis (247) was conducted using the 'estimated' patient-level data. Using the 'R code' from Henly and Hoyle to run the model using different functional forms(201). The choice of the most appropriate survival distribution for long-term projections was based on the relative goodness-of-fit of these distributions using Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), the lower the number the better the fit.(248) Collect intercept and log_scale which can be used to calculate shape and scale parameters.
13. Amend and run the provided R code for exponential distribution. Text with # preceding are notes. Text in green are specific to the current example. Additional explanatory notes added from R help documentation.

```
#set-up dataset

rm(list=ls(all=TRUE))

library(survival)
# Update directory name and text file name in line below (make sure directory has two backslashes or one forward slash)

setwd('F:\\Users\\SS\\PhD\\DES Project\\Model\\ESHF\\Model Inputs Literature\\Survival curves')
data<- read.csv('vadsurvival_20180217.csv')
attach(data)
data
```

```
#generating time variables; c function to combine values into a vector or list; rep function to replicate elements of vectors and lists
times_start <-c(  rep(start_time_censor, n_censors), rep(start_time_event, n_events) )
times_end <-c(  rep(end_time_censor, n_censors), rep(end_time_event, n_events)  )
#  adding times for patients at risk at last time point; at last time point number at risk (not applicable if none at risk)
times_start <- c(times_start, rep(24,54))
times_end <- c(times_end, rep(10000,54))
#   Step 5. choose exponential function forms  (one of 5, see below for code)
model  <-  survreg(Surv(times_start,  times_end,  type='interval2')~1,  dist='exponential')     # Exponential  function,  interval censoring
#   Compare AIC values
n_patients <- sum(n_events) +  sum(n_censors)
-2*summary(model)$loglik[1] + 1*2   #  AIC for exponential distribution
-2*summary(model)$loglik[1] + 1*log(n_patients)   #  BIC exponential distribution
intercept <- summary(model)$table[1]   # intercept parameter
log_scale <- summary(model)$table[2]   # log scale parameter
```

14. Run code for Weibull distribution.

```
rm(list=ls(all=TRUE))
library(survival)
setwd('F:\\Users\\SS\\PhD\\DES Project\\Model\\ESHF\\Model Inputs Literature\\Survival curves')
data<- read.csv('vadsurvival_20180217.csv')
attach(data)
data
times_start <-c(  rep(start_time_censor, n_censors), rep(start_time_event, n_events) )
times_end <-c(  rep(end_time_censor, n_censors), rep(end_time_event, n_events)  )
model <- survreg(Surv(times_start, times_end, type='interval2')~1, dist='weibull')   # Weibull function, interval censoring
#fit statistics for other functional forms
n_patients <- sum(n_events) +  sum(n_censors)
-2*summary(model)$loglik[1] + 2*2   #  AIC for 2-parameter distributions
-2*summary(model)$loglik[1] + 2*log(n_patients)   #  BIC for 2-parameter distributions
#  output for the example of the Weibull distribution
lambda <- 1/ (exp(intercept))^ (1/exp(log_scale))    # l for Weibull, where S(t) = exp(-lt^g)
gamma <- 1/exp(log_scale)     # g for Weibull, where S(t) = exp(-lt^g)
(1/lambda)^(1/gamma) * gamma(1+1/gamma)    # mean time for Weibull distrubtion
```

15. Run code for lognormal and log-logistic distribution (see below). The function survreg does not support Gompertz or Generalised Gamma. The function flexsurvreg supports these

flexible functional forms. Installed new package in R by typing install.packages ('flexsurv') [insert ref: ftp://cran.r-project.org/pub/R/web/packages/flexsurv/flexsurv.pdf].

```
model <- survreg(Surv(times_start, times_end, type='interval2')~1, dist='lognormal')   # Lognormal, interval censoring
model <- survreg(Surv(times_start, times_end, type='interval2')~1, dist='loglogistic')   # Loglogistic, interval censoring
```

16. Present the AIC and BIC to choose the model with the best fit. Lower AIC and BIC is preferable, intercept, log_scale, parameter 1 and 2 (if applicable). The models for Generalised Gamma and Gompertz not converging with flexsurvreg in R due to interval censoring. However, managed to get log-likelihoods and can consequently estimate the AIC and BIC.

Table 8-35: INTERMACS VAD survival for 45 months, fit statistics and parameters for distributions

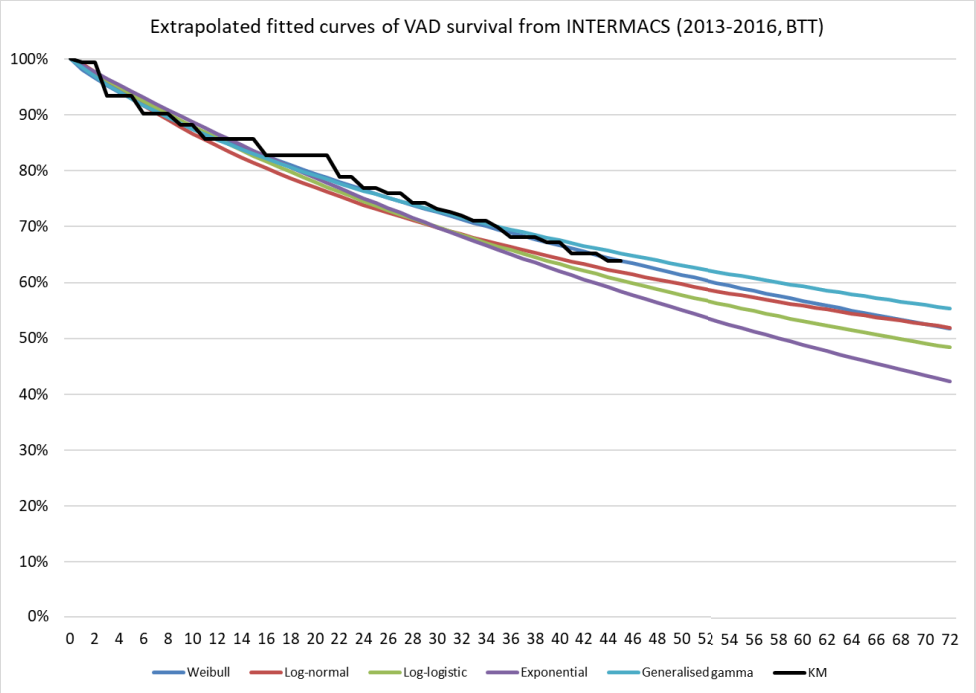
	Weibull	Log-normal	Log-logistic	Exponential	Generalised gamma
Log-likelihood	-2487.45	-2499.93	-2509.40	-2497.78	-2481.61
AIC	4978.90	5003.866	5022.814	4997.551	4969.227
BIC	4990.655	5015.619	5034.568	5003.427	*4978.98*
_cons	4.784	4.368	4.214	4.428	4.788
Parameter 1	0.195	0.620	-0.037	4.243	1.696
Parameter 2					0.473

Abbreviations: AIC, Akaike's information criterion; BIC, Bayesian information criterion.

17. Calculate the transition probability of mortality as a function of time in Excel. PDeath(t) = 1 – EXP(lambda*(T^gamma – (T+1)^gamma))[48]. Estimate the probability of survival using Weibull Estimated Survival (S(t) = exp(-lambda*(T^gamma)).(240)
18. Estimating discrete time transition probabilities from instantaneous hazard rates.(200) The baseline transition probability of the event of interest defined as one minus the ratio of the survivor function at the end of the interval to the survivor function at the beginning of the interval(200): $tp(t_u) = 1 - S(t)/S(t\text{-}u)$ which is equivalent to $1 - \exp\{H(t\text{-}u)\text{-}H(t)\}$ where H is the culmulative hazard function. The extrapolated transition probabilities using the different distributions were plotted over time (*Figure 8-15*).

[48] https://mbounthavong.com/blog/2018/3/15/generating-survival-curves-from-study-data-an-application-for-markov-models-part-1-of-2

Figure 8-15: Extrapolated survival analysis of VAD survival data from INTERMACS(51)



Abbreviations: BTT, bridge to transplant; KM, Kaplan-Meier.

8.13 Appendix 12: Markov model inputs

8.13.1 Transition probability Australian Bureau of Statistics Life Table

This life table was used to inform the transitions probabilities for the following health states:

- *'Ineligible'* to *'Death (Other)'*
- *'Waiting list'* to *'Death (Other)'*
- *'Removed'* to *'Death (Other)'*
- *'Alive Post-HTx'* to *'Death (Other)'*
- *'Alive Post-VAD'* to *'Death (Other)'*

Table 8-36: Australian Bureau of Statistics Life Table 2015-2017 and Add Value weighted cohort

Age	males	females	weighted	lower	upper	SE	α	β
50	0.00298	0.00184	0.0026	0.003	0.003	0.000	65798	25036101
51	0.00321	0.002	0.0028	0.003	0.003	0.000	71009	25030890
52	0.00347	0.00217	0.0031	0.003	0.003	0.000	76815	25025084
53	0.00378	0.00234	0.0033	0.003	0.003	0.000	83480	25018419
54	0.00412	0.00252	0.0036	0.004	0.004	0.000	90737	25011162
55	0.00448	0.00272	0.0039	0.004	0.004	0.000	98493	25003406
56	0.00486	0.00292	0.0042	0.004	0.004	0.000	106590	24995309
57	0.00527	0.00315	0.0046	0.005	0.005	0.000	115434	24986465
58	0.00573	0.00341	0.0050	0.005	0.005	0.000	125368	24976531
59	0.00622	0.00368	0.0054	0.005	0.005	0.000	135892	24966007
60	0.00676	0.00396	0.0059	0.006	0.006	0.000	147348	24954551
61	0.00732	0.00425	0.0063	0.006	0.006	0.000	159219	24942680
62	0.00792	0.00457	0.0069	0.007	0.007	0.000	172005	24929894
63	0.00857	0.00494	0.0074	0.007	0.007	0.000	186030	24915869
64	0.00929	0.00538	0.0080	0.008	0.008	0.000	201789	24900110
65	0.0101	0.0059	0.0088	0.009	0.009	0.000	219701	24882198
66	0.01099	0.00653	0.0096	0.010	0.010	0.000	239822	24862077
67	0.012	0.00725	0.0105	0.010	0.011	0.000	262675	24839224
68	0.01317	0.00805	0.0115	0.011	0.012	0.000	288858	24813041
69	0.01449	0.00891	0.0127	0.013	0.013	0.000	318037	24783862
70	0.01602	0.00988	0.0140	0.014	0.014	0.000	351607	24750292
71	0.01776	0.01098	0.0155	0.015	0.016	0.000	389706	24712193
72	0.01972	0.01223	0.0172	0.017	0.017	0.000	432636	24669263
73	0.02191	0.01367	0.0192	0.019	0.019	0.000	480848	24621051
74	0.0243	0.0153	0.0213	0.021	0.021	0.000	533803	24568096
75	0.02699	0.01717	0.0236	0.024	0.024	0.000	593539	24508360
76	0.03006	0.01931	0.0264	0.026	0.026	0.000	661581	24440318
77	0.03358	0.02179	0.0295	0.029	0.030	0.000	739564	24362335
78	0.03758	0.02467	0.0330	0.033	0.033	0.000	828346	24273553
79	0.04216	0.028	0.0370	0.037	0.037	0.000	929849	24172050
80	0.04752	0.0319	0.0418	0.042	0.042	0.000	1048121	24053778
81	0.05366	0.03646	0.0472	0.047	0.047	0.000	1183583	23918316
82	0.06054	0.04178	0.0532	0.053	0.053	0.000	1336023	23765876
83	0.06828	0.04793	0.0601	0.060	0.060	0.000	1507571	23594328
84	0.07722	0.05503	0.0679	0.068	0.068	0.000	1704149	23397750
85	0.08735	0.06311	0.0767	0.077	0.077	0.000	1925167	23176732
86	0.09862	0.07221	0.0864	0.086	0.087	0.000	2169397	22932502
87	0.1109	0.08258	0.0970	0.097	0.097	0.000	2435797	22666102
88	0.12427	0.09437	0.1086	0.108	0.109	0.000	2725809	22376090
89	0.13867	0.10778	0.1211	0.121	0.121	0.000	3038909	22062990
90	0.15409	0.1229	0.1344	0.134	0.135	0.000	3374479	21727420
91	0.17078	0.13957	0.1488	0.149	0.149	0.000	3733967	21367932

92	0.18851	0.15789	0.1639	0.164	0.164	0.000	4113342	20988557
93	0.20688	0.17768	0.1794	0.179	0.180	0.000	4504500	20597399
94	0.22531	0.19844	0.1950	0.195	0.195	0.000	4895314	20206585
95	0.23916	0.21042	0.2056	0.205	0.206	0.000	5161627	19940272
96	0.25101	0.23459	0.2180	0.218	0.218	0.000	5472048	19629851
97	0.26474	0.25393	0.2300	0.230	0.230	0.000	5773551	19328348
98	0.28313	0.27387	0.2444	0.244	0.245	0.000	6134916	18966983
99	0.31095	0.29699	0.2641	0.264	0.264	0.000	6628262	18473637
100	0.34231	0.31683	0.2842	0.284	0.284	0.000	7134206	17967693

Note: Australian population in September 2018 N = 2510900(249), weighted from Add Value gender distribution of male (69%): female (31%)
Source:(203)

8.13.2 Transition probability 'ineligible' to VAD', Add Value

Table 8-37: Add Value, time-to-event 'ineligible' to 'VAD' BTC, N=18

Month	Year	Survival function	% with VAD	Trans prob	Lower	Upper	SE	α	β
0	50.00	1.000	0.000	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
1	50.08	0.611	0.389	0.389	0.179	0.623	0.115	6.611	10.389
2	50.17	0.611	0.389	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
3	50.25	0.611	0.389	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
4	50.33	0.500	0.500	0.222	0.065	0.441	0.098	3.777	13.223
5	50.42	0.444	0.556	0.100	0.010	0.276	0.071	1.701	15.299
6	50.50	0.444	0.556	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
7	50.58	0.222	0.778	0.286	0.105	0.514	0.106	4.857	12.143
8	50.67	0.222	0.778	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
9	50.75	0.167	0.833	0.067	0.003	0.220	0.059	1.132	15.868
10	50.83	0.167	0.833	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
11	50.92	0.167	0.833	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
12	51.00	0.167	0.833	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
13	51.08	0.167	0.833	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
14	51.17	0.111	0.889	0.063	0.002	0.213	0.057	1.063	15.937
15	51.25	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
16	51.33	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
17	51.42	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
18	51.50	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
19	51.58	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
20	51.67	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
21	51.75	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
22	51.83	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
23	51.92	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
24	52.00	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
25	52.08	0.111	0.889	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
26	52.17	0.056	0.944	0.059	0.002	0.206	0.055	0.999	16.001
27	52.25	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
28	52.33	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
29	52.42	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
30	52.50	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
31	52.58	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
32	52.67	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
33	52.75	0.056	0.944	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
34	52.83	0.000	1.000	0.056	0.001	0.200	0.054	0.945	16.055

8.13.3 Transition probability 'wait list' to 'Removed', CPR

Table 8-38: CardioPulomary Registry, time-to-event – 'Waitlist' to 'Removed', N = 102

Year	Month	Survival Function	Trans Prob	Lower	Upper	SE	α	β
50.00	0	1	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
50.08	1	0.9699	0.0301	0.01	0.07	0.02	3.04	97.96
50.17	2	0.9583	0.0120	0.00	0.04	0.01	1.21	99.79
50.25	3	0.9583	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
50.33	4	0.9445	0.0144	0.00	0.04	0.01	1.45	99.55
50.42	5	0.9132	0.0331	0.01	0.08	0.02	3.35	97.65
50.50	6	0.9132	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
50.58	7	0.8777	0.0389	0.01	0.08	0.02	3.93	97.07
50.67	8	0.8053	0.0825	0.04	0.14	0.03	8.33	92.67
50.75	9	0.7856	0.0245	0.00	0.06	0.02	2.47	98.53
50.83	10	0.7638	0.0277	0.01	0.07	0.02	2.80	98.20
50.92	11	0.7188	0.0589	0.02	0.11	0.02	5.95	95.05
51.00	12	0.6708	0.0668	0.03	0.12	0.02	6.74	94.26
51.08	13	0.6201	0.0756	0.03	0.13	0.03	7.63	93.37
51.17	14	0.5366	0.1347	0.08	0.21	0.03	13.60	87.40
51.25	15	0.5366	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
51.33	16	0.5366	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
51.42	17	0.477	0.1111	0.06	0.18	0.03	11.22	89.78
51.50	18	0.477	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
51.58	19	0.4452	0.0667	0.03	0.12	0.02	6.73	94.27
51.67	20	0.4452	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
51.75	21	0.4452	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
51.83	22	0.4081	0.0833	0.04	0.14	0.03	8.42	92.58
51.92	23	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.00	24	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.08	25	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.17	26	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.25	27	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.33	28	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.42	29	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.50	30	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.58	31	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.67	32	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.75	33	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.83	34	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
52.92	35	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.00	36	0.4081	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.08	37	0.3498	0.1429	0.08	0.22	0.03	14.43	86.57
53.17	38	0.3498	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.25	39	0.3498	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.33	40	0.3498	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.42	41	0.2915	0.1667	0.10	0.24	0.04	16.83	84.17
53.50	42	0.2915	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.58	43	0.2915	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.67	44	0.2915	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.75	45	0.2332	0.2000	0.13	0.28	0.04	20.20	80.80
53.83	46	0.2332	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
53.92	47	0.2332	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
54.00	48	0.2332	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
54.08	49	0.1749	0.2500	0.17	0.34	0.04	25.25	75.75
54.17	50	0.1749	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!
54.25	51	0.1166	0.3333	0.25	0.43	0.05	33.67	67.33
54.33	52	0.1166	0.0000	0.00	0.00	0.00	#DIV/0!	#DIV/0!

8.13.4 Transition probability 'wait list' to 'Alive Post-HTx', CPR

Table 8-39: CardioPulomary Registry, time-to-event – 'Waitlist' to 'Alive post-HTx', N = 53

Year	Month	Survival function	% on WL	Trans prob	Lower	Upper	SE	α	β
50.00	0	0	1	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
50.08	1	0.120	0.880	0.1202	0.048	0.220	0.045	6.250	45.750
50.17	2	0.192	0.808	0.0812	0.024	0.168	0.038	4.220	47.780
50.25	3	0.273	0.727	0.1013	0.036	0.196	0.041	5.267	46.733
50.33	4	0.325	0.675	0.0713	0.019	0.154	0.035	3.706	48.294
50.42	5	0.389	0.611	0.0939	0.031	0.186	0.040	4.884	47.116
50.50	6	0.399	0.601	0.0176	0.000	0.066	0.018	0.914	51.086
50.58	7	0.432	0.568	0.0537	0.011	0.129	0.031	2.790	49.210
50.67	8	0.467	0.533	0.0620	0.014	0.141	0.033	3.224	48.776
50.75	9	0.467	0.533	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
50.83	10	0.505	0.495	0.0721	0.019	0.156	0.036	3.750	48.250
50.92	11	0.545	0.455	0.0808	0.024	0.168	0.037	4.200	47.800
51.00	12	0.574	0.426	0.0637	0.015	0.143	0.034	3.310	48.690
51.08	13	0.589	0.411	0.0353	0.004	0.099	0.025	1.833	50.167
51.17	14	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.25	15	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.33	16	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.42	17	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.50	18	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.58	19	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.67	20	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.75	21	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.83	22	0.589	0.411	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.92	23	0.649	0.351	0.1459	0.065	0.253	0.048	7.585	44.415
52.00	24	0.649	0.351	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
52.08	25	0.680	0.320	0.0891	0.029	0.179	0.039	4.633	47.367
52.17	26	0.680	0.320	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!

8.13.5 Transition probability 'wait list' to 'Alive Post-VAD', Add Value

Table 8-40: Transition probabilities – 'waiting list' to 'Alive post-VAD' in Add Value, N=7

Year	Month	Survival function	% with VAD	Trans Prob	Lower	Upper	SE	α	β
0	50.00	1	0	0.000	0	0	0	0	#DIV/0!
1	50.08	0.7143	0.2857	0.286	0.286	0.034	0.668	0.171	1.714
2	50.17	0.5714	0.4286	0.200	0.200	0.010	0.568	0.151	1.200
3	50.25	0.2857	0.7143	0.500	0.500	0.147	0.853	0.189	3.000
4	50.33	0.1429	0.8571	0.500	0.500	0.147	0.853	0.189	2.999
5	50.42	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
6	50.50	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
7	50.58	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
8	50.67	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
9	50.75	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
10	50.83	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
11	50.92	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
12	51.00	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
13	51.08	0.1429	0.8571	0.000	0	0	0	0	#DIV/0!
14	51.17	0	1	1.000	1.0	#DIV/0!	#DIV/0!	0.0	#DIV/0!

8.13.6 Transition probability 'VAD' to 'Removed', CPR

Table 8-41: Transition probabilities – 'Alive Post-VAD' to 'Removed' in CPR, N=28

Year	Month	Survival Function	%Removed	Trans prob	Lower	Upper	SE	α	β
50.00	0	0	1	0	0.00	0.00	0.00	0.00	#DIV/0!
50.08	1	0	1	0.000	0.00	0.00	0.00	0.00	#DIV/0!
50.17	2	0.037	0.963	0.037	0.04	0.00	0.13	0.04	1.00
50.25	3	0.037	0.963	0.000	0.00	0.00	0.00	0.00	#DIV/0!
50.33	4	0.074	0.926	0.039	0.04	0.00	0.14	0.04	1.04
50.42	5	0.074	0.926	0.000	0.00	0.00	0.00	0.00	#DIV/0!
50.50	6	0.113	0.887	0.042	0.04	0.00	0.14	0.04	1.13
50.58	7	0.113	0.887	0.000	0.00	0.00	0.00	0.00	#DIV/0!
50.67	8	0.113	0.887	0.000	0.00	0.00	0.00	0.00	#DIV/0!
50.75	9	0.190	0.810	0.087	0.09	0.01	0.22	0.05	2.35
50.83	10	0.230	0.770	0.050	0.05	0.00	0.16	0.04	1.35
50.92	11	0.311	0.689	0.105	0.11	0.02	0.24	0.06	2.84
51.00	12	0.352	0.648	0.059	0.06	0.01	0.17	0.04	1.59
51.08	13	0.352	0.648	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.17	14	0.482	0.519	0.200	0.20	0.07	0.37	0.08	5.40
51.25	15	0.529	0.471	0.091	0.09	0.02	0.22	0.05	2.45
51.33	16	0.623	0.377	0.200	0.20	0.08	0.37	0.08	5.40
51.42	17	0.623	0.377	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.50	18	0.623	0.377	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.58	19	0.623	0.377	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.67	20	0.717	0.283	0.250	0.25	0.11	0.43	0.08	6.75
51.75	21	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.83	22	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
51.92	23	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.00	24	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.08	25	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.17	26	0.717	0.283	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.25	27	0.811	0.189	0.333	0.33	0.17	0.52	0.09	8.99
52.33	28	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.42	29	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.50	30	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.58	31	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.67	32	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.75	33	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.83	34	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
52.92	35	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.00	36	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.08	37	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.17	38	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.25	39	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.33	40	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.42	41	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.50	42	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.58	43	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.67	44	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.75	45	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.83	46	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
53.92	47	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.00	48	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.08	49	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.17	50	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.25	51	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.33	52	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.42	53	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!

54.50	54	0.811	0.189	0.000	0.00	0.00	0.00	0.00	#DIV/0!
54.58	55	1.000	0.000	1.000	1.00	#DIV/0!	#DIV/0!	0.00	#DIV/0!

8.13.7 Transition probability 'VAD' to 'HTx', INTERMACS

Table 8-42: Transition probabilities 'Alive post-VAD' to 'Alive - Post HTx'

		INTERMACS		IMACS		MOMENTUM 3				Add Value		MCS	
Year	Month	%	Trans prob.	%	Trans prob.	% centrifugal	% axial	Trans prob. centrifugal	Trans prob. axial	%	Trans prob.	%	Trans prob.
50.0	0	0	0	0	0	0	0	0	0	0.00	0.00	0.00	0.00
50.1	1	0.01	0.01	0.00	0.00	0.00	0.01	0.00	0.01	0.00	0.00	0.00	0.00
50.2	2	0.03	0.02	0.02	0.02	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0.01
50.3	3	0.05	0.02	0.02	0.00	0.01	0.01	0.01	0.01	0.00	0.00	0.01	0.01
50.3	4	0.10	0.05	0.05	0.03	0.02	0.01	0.01	0.00	0.00	0.00	0.04	0.02
50.4	5	0.14	0.04	0.09	0.03	0.02	0.05	0.00	0.04	0.00	0.00	0.06	0.02
50.5	6	0.17	0.04	0.09	0.00	0.03	0.06	0.01	0.00	0.08	0.08	0.11	0.05
50.6	7	0.21	0.04	0.17	0.08	0.05	0.07	0.02	0.01	0.12	0.04	0.16	0.06
50.7	8	0.24	0.03	0.17	0.00	0.06	0.07	0.01	0.01	0.24	0.12	0.20	0.04
50.8	9	0.27	0.02	0.21	0.05	0.08	0.10	0.02	0.02	0.24	0.00	0.23	0.03
50.8	10	0.30	0.03	0.24	0.03	0.10	0.11	0.03	0.02	0.24	0.00	0.23	0.00
50.9	11	0.32	0.02	0.26	0.02	0.10	0.12	0.00	0.01	0.24	0.00	0.29	0.06
51.0	12	0.33	0.01	0.28	0.02	0.10	0.12	0.00	0.00	0.32	0.08	0.32	0.03
51.1	13	0.35	0.02	0.28	0.00	0.12	0.14	0.02	0.02	0.36	0.04	0.35	0.03
51.2	14	0.38	0.02	0.31	0.03	0.13	0.16	0.01	0.01	0.40	0.04	0.38	0.03
51.3	15	0.39	0.01	0.31	0.00	0.14	0.16	0.01	0.00	0.44	0.04	0.40	0.03
51.3	16	0.40	0.01	0.33	0.02	0.17	0.18	0.03	0.02	0.48	0.04	0.44	0.03
51.4	17	0.42	0.02	0.34	0.01	0.17	0.20	0.00	0.02	0.52	0.04	0.44	0.00
51.5	18	0.43	0.01	0.36	0.02	0.17	0.20	0.00	0.00	0.52	0.00	0.44	0.01
51.6	19	0.44	0.01	0.36	0.00	0.17	0.22	0.00	0.02	0.56	0.04	0.46	0.02
51.7	20	0.45	0.01	0.39	0.02	0.19	0.22	0.02	0.00	0.60	0.04	0.48	0.02
51.8	21	0.46	0.01	0.39	0.00	0.19	0.24	0.00	0.02	0.60	0.00	0.49	0.01
51.8	22	0.48	0.01	0.40	0.01	0.20	0.24	0.01	0.00	0.64	0.04	0.49	0.00
51.9	23	0.48	0.00	0.40	0.00	0.21	0.24	0.01	0.00	0.64	0.00	0.50	0.01
52.0	24	0.48	0.00	0.42	0.02	0.21	0.24	0.00	0.00	0.64	0.00	0.51	0.01
52.1	25			0.43	0.01					0.64	0.00	0.52	0.01
52.2	26			0.44	0.02					0.64	0.00	0.54	0.02
52.3	27			0.44	0.00					0.69	0.05	0.56	0.03
52.3	28			0.44	0.00					0.69	0.00	0.57	0.01
52.4	29			0.46	0.02					0.69	0.00	0.60	0.03
52.5	30			0.46	0.00					0.69	0.00	0.60	0.00
52.6	31			0.46	0.00					0.69	0.00	0.61	0.01
52.7	32			0.46	0.00					0.69	0.00	0.61	0.00
52.8	33			0.47	0.01					0.69	0.00	0.61	0.00
52.8	34			0.47	0.00					0.69	0.00	0.61	0.00
52.9	35			0.49	0.02					0.69	0.00	0.62	0.01
53.0	36			0.49	0.00					0.77	0.08	0.62	0.00
53.1	37			0.50	0.01					0.77	0.00	0.62	0.00
53.2	38			0.50	0.00					0.77	0.00	0.62	0.00
53.3	39			0.51	0.01					0.77	0.00	0.62	0.00
53.3	40			0.51	0.00					0.77	0.00	0.62	0.00
53.4	41			0.52	0.01					0.77	0.00	0.62	0.00
53.5	42			0.52	0.00					0.77	0.00	0.63	0.01
53.6	43			0.52	0.00					0.77	0.00	0.63	0.00
53.7	44			0.52	0.00					0.64	0.01	0.64	0.01
53.8	45			0.53	0.01					0.64	0.00	0.64	0.00

53.8	46	0.53	0.00	0.65	0.01	0.65	0.01
53.9	47	0.53	0.00	0.65	0.00	0.65	0.00
54.0	48	0.53	0.00	0.65	0.00	0.65	0.00

Source: Digitised from Figure 5, Kirklin 2017(51), Figure A3, Kirklin 2018(161) and S11 Mehra 2018

Table 8-43: Transition probabilities 'Alive post-VAD' to 'Alive - Post HTx', SVHS MCS, N=137

Year	Month	% transplanted	Trans Prob	Lower	Upper	SE	α	β
50.00	0	0.000	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
50.08	1	0.000	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
50.17	2	0.007	0.007	0.000	0.027	0.007	0.993	135.007
50.25	3	0.015	0.007	0.000	0.027	0.007	0.993	135.007
50.33	4	0.037	0.022	0.005	0.053	0.013	3.052	132.948
50.42	5	0.060	0.023	0.005	0.054	0.013	3.121	132.879
50.50	6	0.106	0.046	0.018	0.087	0.018	6.271	129.729
50.58	7	0.161	0.055	0.023	0.099	0.019	7.488	128.512
50.67	8	0.201	0.040	0.014	0.078	0.017	5.382	130.618
50.75	9	0.233	0.032	0.009	0.067	0.015	4.333	131.667
50.83	10	0.233	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
50.92	11	0.291	0.058	0.026	0.103	0.020	7.954	128.046
51.00	12	0.316	0.025	0.006	0.057	0.013	3.409	132.591
51.08	13	0.350	0.034	0.011	0.070	0.015	4.622	131.378
51.17	14	0.376	0.025	0.006	0.058	0.013	3.467	132.533
51.25	15	0.401	0.025	0.006	0.058	0.013	3.467	132.533
51.33	16	0.436	0.035	0.011	0.071	0.016	4.725	131.275
51.42	17	0.436	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.50	18	0.445	0.009	0.000	0.030	0.008	1.213	134.787
51.58	19	0.463	0.018	0.003	0.046	0.011	2.462	133.538
51.67	20	0.481	0.018	0.003	0.047	0.011	2.498	133.502
51.75	21	0.490	0.009	0.000	0.031	0.008	1.249	134.751
51.83	22	0.490	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
51.92	23	0.500	0.009	0.000	0.031	0.008	1.249	134.751
52.00	24	0.509	0.009	0.000	0.031	0.008	1.249	134.751
52.08	25	0.518	0.009	0.000	0.031	0.008	1.249	134.751
52.17	26	0.536	0.018	0.003	0.047	0.011	2.498	133.502
52.25	27	0.564	0.028	0.007	0.061	0.014	3.746	132.254
52.33	28	0.573	0.009	0.000	0.031	0.008	1.249	134.751
52.42	29	0.601	0.028	0.007	0.061	0.014	3.746	132.254
52.50	30	0.601	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
52.58	31	0.610	0.009	0.000	0.031	0.008	1.249	134.751
52.67	32	0.610	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
52.75	33	0.610	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
52.83	34	0.610	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
52.92	35	0.619	0.009	0.000	0.031	0.008	1.249	134.751
53.00	36	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.08	37	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.17	38	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.25	39	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.33	40	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.42	41	0.619	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.50	42	0.628	0.009	0.000	0.031	0.008	1.249	134.751
53.58	43	0.628	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.67	44	0.637	0.009	0.000	0.031	0.008	1.249	134.751
53.75	45	0.637	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
53.83	46	0.647	0.009	0.000	0.031	0.008	1.249	134.751
53.92	47	0.647	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!
54.00	48	0.647	0.000	0.000	0.000	0.000	#DIV/0!	#DIV/0!

8.13.8 Transition probability 'VAD' to 'Death', INTERMACS

Table 8-44: Transition probabilities 'Alive post-VAD' to 'Death', INTERMACS, base, N=2,839

Year	Survival function	Trans Prob	Lower	Upper	SE	α	β	Survival MCS (n=137)
50.0	1.00	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	1.000
50.1	0.99	0.0056	0.003	0.009	0.001	16.01	2821.99	0.964
50.2	0.99	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.949
50.3	0.93	0.0613	0.053	0.070	0.005	174.01	2663.99	0.942
50.3	0.93	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.904
50.4	0.93	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.896
50.5	0.90	0.0332	0.027	0.040	0.003	94.29	2743.71	0.873
50.6	0.90	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.842
50.7	0.90	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.842
50.8	0.88	0.0231	0.018	0.029	0.003	65.61	2772.39	0.826
50.8	0.88	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.826
50.9	0.86	0.0275	0.022	0.034	0.003	78.04	2759.96	0.817
51.0	0.86	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.817
51.1	0.86	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.792
51.2	0.86	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.792
51.3	0.86	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.783
51.3	0.83	0.0348	0.028	0.042	0.003	98.88	2739.12	0.775
51.4	0.83	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.766
51.5	0.83	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.766
51.6	0.83	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.766
51.7	0.83	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.766
51.8	0.83	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.748
51.8	0.79	0.0463	0.039	0.054	0.004	131.40	2706.60	0.748
51.9	0.79	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.738
52.0	0.77	0.0250	0.020	0.031	0.003	70.96	2767.04	0.738
52.1	0.77	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.729
52.2	0.76	0.0132	0.009	0.018	0.002	37.40	2800.60	0.720
52.3	0.76	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.711
52.3	0.74	0.0215	0.017	0.027	0.003	61.12	2776.88	0.702
52.4	0.74	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.702
52.5	0.73	0.0144	0.010	0.019	0.002	40.88	2797.12	0.702
52.6	0.73	0.0077	0.005	0.011	0.002	21.82	2816.18	0.702
52.7	0.72	0.0093	0.006	0.013	0.002	26.41	2811.59	0.702
52.8	0.71	0.0125	0.009	0.017	0.002	35.60	2802.40	0.702
52.8	0.71	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.702
52.9	0.70	0.0174	0.013	0.023	0.002	49.47	2788.53	0.702
53.0	0.68	0.0250	0.020	0.031	0.003	71.07	2766.93	0.692
53.1	0.68	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.674
53.2	0.68	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.674
53.3	0.67	0.0140	0.010	0.019	0.002	39.85	2798.15	0.674
53.3	0.67	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	0.665
53.4	0.65	0.0294	0.023	0.036	0.003	83.37	2754.63	
53.5	0.65	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	
53.6	0.65	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	
53.7	0.64	0.0199	0.015	0.025	0.003	56.40	2781.60	
53.8	0.64	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	
53.8	-	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	
53.9	-	0.0000	0.000	0.000	0.000	#DIV/0!	#DIV/0!	
54.0	-	0.0090†	0.006	0.013	0.002	25.54	2812.46	

Source:† (96).(51), SVHS MCS data based on 137 individuals, assumptions as in base case.
Note: Assume post 4 years, annual probability of death is 3% p.a.

Table 8-45: Transition probabilities 'Alive post-VAD' to 'Death', INTERMACS, extrapolated, N=2,839

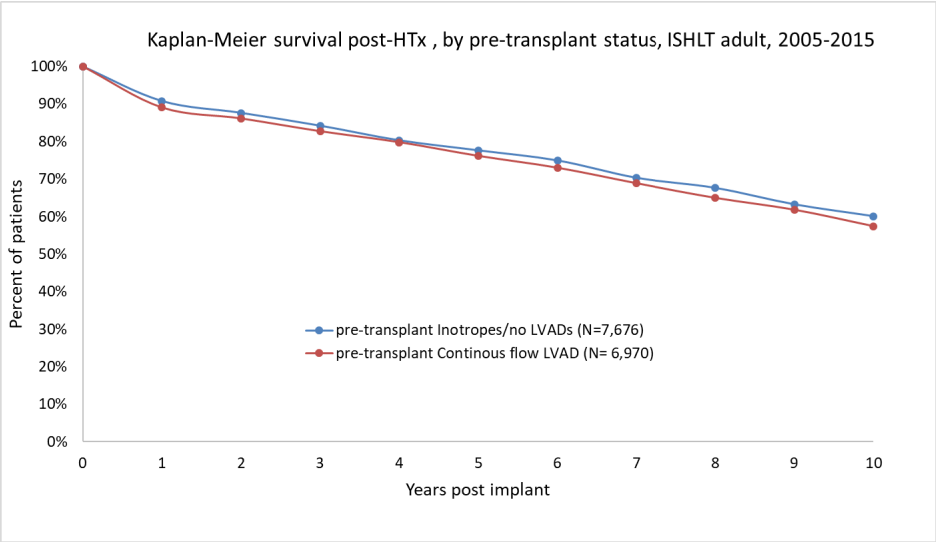
Age	% survival	Observed	Weibull	Log-normal	Log-logistic	Exponential	Generalised gamma	obs+wei
50.0	100.0%	0.000	0.000	0.000	0.000	0.000	0.000	0.000
50.1	99.4%	0.006	0.019	0.009	0.012	0.012	0.016	0.006
50.2	99.4%	0.000	0.015	0.015	0.013	0.012	0.016	0.000
50.3	93.3%	0.061	0.014	0.016	0.013	0.012	0.015	0.061
50.3	93.3%	0.000	0.013	0.016	0.013	0.012	0.014	0.000
50.4	93.3%	0.000	0.012	0.015	0.013	0.012	0.013	0.000
50.5	90.2%	0.033	0.012	0.015	0.013	0.012	0.013	0.033
50.6	90.2%	0.000	0.011	0.015	0.013	0.012	0.012	0.000
50.7	90.2%	0.000	0.011	0.014	0.013	0.012	0.012	0.000
50.8	88.2%	0.023	0.011	0.014	0.013	0.012	0.012	0.023
50.8	88.2%	0.000	0.011	0.013	0.013	0.012	0.011	0.000
50.9	85.7%	0.027	0.011	0.013	0.012	0.012	0.011	0.027
51.0	85.7%	0.000	0.010	0.013	0.012	0.012	0.011	0.000
51.1	85.7%	0.000	0.010	0.012	0.012	0.012	0.010	0.000
51.2	85.7%	0.000	0.010	0.012	0.012	0.012	0.010	0.000
51.3	85.7%	0.000	0.010	0.012	0.012	0.012	0.010	0.000
51.3	82.7%	0.035	0.010	0.012	0.012	0.012	0.010	0.035
51.4	82.7%	0.000	0.010	0.011	0.012	0.012	0.010	0.000
51.5	82.7%	0.000	0.010	0.011	0.012	0.012	0.009	0.000
51.6	82.7%	0.000	0.010	0.011	0.012	0.012	0.009	0.000
51.7	82.7%	0.000	0.009	0.011	0.011	0.012	0.009	0.000
51.8	82.7%	0.000	0.009	0.010	0.011	0.012	0.009	0.000
51.8	78.9%	0.046	0.009	0.010	0.011	0.012	0.009	0.046
51.9	78.9%	0.000	0.009	0.010	0.011	0.012	0.009	0.000
52.0	76.9%	0.025	0.009	0.010	0.011	0.012	0.009	0.025
52.1	76.9%	0.000	0.009	0.010	0.011	0.012	0.008	0.009
52.2	75.9%	0.013	0.009	0.010	0.011	0.012	0.008	0.009
52.3	75.9%	0.000	0.009	0.009	0.011	0.012	0.008	0.009
52.3	74.3%	0.022	0.009	0.009	0.011	0.012	0.008	0.009
52.4	74.3%	0.000	0.009	0.009	0.010	0.012	0.008	0.009
52.5	73.2%	0.014	0.009	0.009	0.010	0.012	0.008	0.009
52.6	72.7%	0.008	0.009	0.009	0.010	0.012	0.008	0.009
52.7	72.0%	0.009	0.009	0.009	0.010	0.012	0.008	0.009
52.8	71.1%	0.013	0.009	0.009	0.010	0.012	0.008	0.009
52.8	71.1%	0.000	0.009	0.008	0.010	0.012	0.008	0.009
52.9	69.8%	0.017	0.009	0.008	0.010	0.012	0.007	0.009
53.0	68.1%	0.025	0.008	0.008	0.010	0.012	0.007	0.008
53.1	68.1%	0.000	0.008	0.008	0.010	0.012	0.007	0.008
53.2	68.1%	0.000	0.008	0.008	0.010	0.012	0.007	0.008
53.3	67.1%	0.014	0.008	0.008	0.010	0.012	0.007	0.008
53.3	67.1%	0.000	0.008	0.008	0.010	0.012	0.007	0.008
53.4	65.2%	0.029	0.008	0.008	0.009	0.012	0.007	0.008
53.5	65.2%	0.000	0.008	0.008	0.009	0.012	0.007	0.008
53.6	65.2%	0.000	0.008	0.008	0.009	0.012	0.007	0.008
53.7	63.9%	0.020	0.008	0.007	0.009	0.012	0.007	0.008
53.8	63.9%	0.000	0.008	0.007	0.009	0.012	0.007	0.008
53.8	0.0%	0.000	0.008	0.007	0.009	0.012	0.007	0.008
53.9	0.0%	0.000	0.008	0.007	0.009	0.012	0.007	0.008
54.0	0.0%	0.000	0.008	0.007	0.009	0.012	0.007	0.008
54.1	0.0%	0.000	0.008	0.007	0.009	0.012	0.007	0.008
54.2	0.0%	0.000	0.008	0.007	0.009	0.012	0.006	0.008
54.3	0.0%	0.000	0.008	0.007	0.009	0.012	0.006	0.008
54.3	0.0%	0.000	0.008	0.007	0.009	0.012	0.006	0.008
54.4	0.0%	0.000	0.008	0.007	0.009	0.012	0.006	0.008
54.5	0.0%	0.000	0.008	0.007	0.008	0.012	0.006	0.008
54.6	0.0%	0.000	0.008	0.007	0.008	0.012	0.006	0.008
54.7	0.0%	0.000	0.008	0.007	0.008	0.012	0.006	0.008

54.8	0.0%	0.000	0.008	0.007	0.008	0.012	0.006	0.008
54.8	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
54.9	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.0	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.1	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.2	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.3	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.3	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.4	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.5	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.6	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.7	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.8	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.8	0.0%	0.000	0.008	0.006	0.008	0.012	0.006	0.008
55.9	0.0%	0.000	0.008	0.006	0.007	0.012	0.006	0.008
56.0	0.0%	0.000	0.008	0.006	0.007	0.012	0.006	0.008

Source: Digitised from Figure 9, Kirklin 2017

8.13.9 Transition probability 'HTx' to 'death'

Figure 8-16: Kaplan-Meier survival post-HTx, bridged with CF-LVAD and not-bridged



Note: p-value = not significant.
Source: (163)

Table 8-46: Cutler-ederer survival recipient 50-59 years all hearts (1984 to 2018) in ANZCOTR, N=1,021

Year	% Survival	% death	Trans prob	Lower	Upper	SE	α	β
50	100%	0%	0.000	0.000	0.000	0.000	0.00	0.00
51	88%	12%	0.123	0.104	0.144	0.010	125.46	894.54
52	85%	15%	0.029	0.019	0.040	0.005	29.08	990.92
53	84%	16%	0.019	0.011	0.028	0.004	19.15	1000.85
54	81%	19%	0.036	0.025	0.048	0.006	36.60	983.40
55	79%	21%	0.019	0.011	0.028	0.004	18.98	1001.02
56	76%	24%	0.037	0.026	0.049	0.006	37.40	982.60
57	73%	27%	0.039	0.028	0.052	0.006	40.16	979.84
58	70%	30%	0.040	0.029	0.052	0.006	40.41	979.59
59	67%	33%	0.041	0.030	0.054	0.006	42.08	977.92
60	64%	36%	0.050	0.038	0.065	0.007	51.45	968.55
61	62%	38%	0.034	0.024	0.046	0.006	35.06	984.94
62	57%	43%	0.074	0.059	0.091	0.008	75.92	944.08

63	54%	46%	0.052	0.040	0.067	0.007	53.50	966.50
64	50%	50%	0.079	0.064	0.097	0.008	80.92	939.08
65	46%	54%	0.076	0.061	0.093	0.008	77.68	942.32
66	43%	57%	0.076	0.060	0.093	0.008	77.44	942.56
67	39%	62%	0.096	0.079	0.115	0.009	98.17	921.83
68	36%	64%	0.065	0.051	0.081	0.008	66.23	953.77
69	33%	67%	0.089	0.072	0.107	0.009	90.67	929.33
70	30%	70%	0.095	0.077	0.113	0.009	96.40	923.60
71	28%	72%	0.061	0.047	0.076	0.007	61.82	958.18
72	24%	76%	0.136	0.116	0.158	0.011	138.92	881.08
73	21%	79%	0.145	0.124	0.167	0.011	148.13	871.87
74	19%	81%	0.073	0.058	0.090	0.008	74.27	945.73
75	18%	82%	0.047	0.035	0.061	0.007	48.06	971.94
76	15%	85%	0.181	0.158	0.206	0.012	184.95	835.05
77	14%	87%	0.094	0.077	0.113	0.009	95.84	924.16
78	14%	87%	0.000	#DIV/0!	#DIV/0!	0.000	#DIV/0!	#DIV/0!
79	14%	87%	0.000	#DIV/0!	#DIV/0!	0.000	#DIV/0!	#DIV/0!

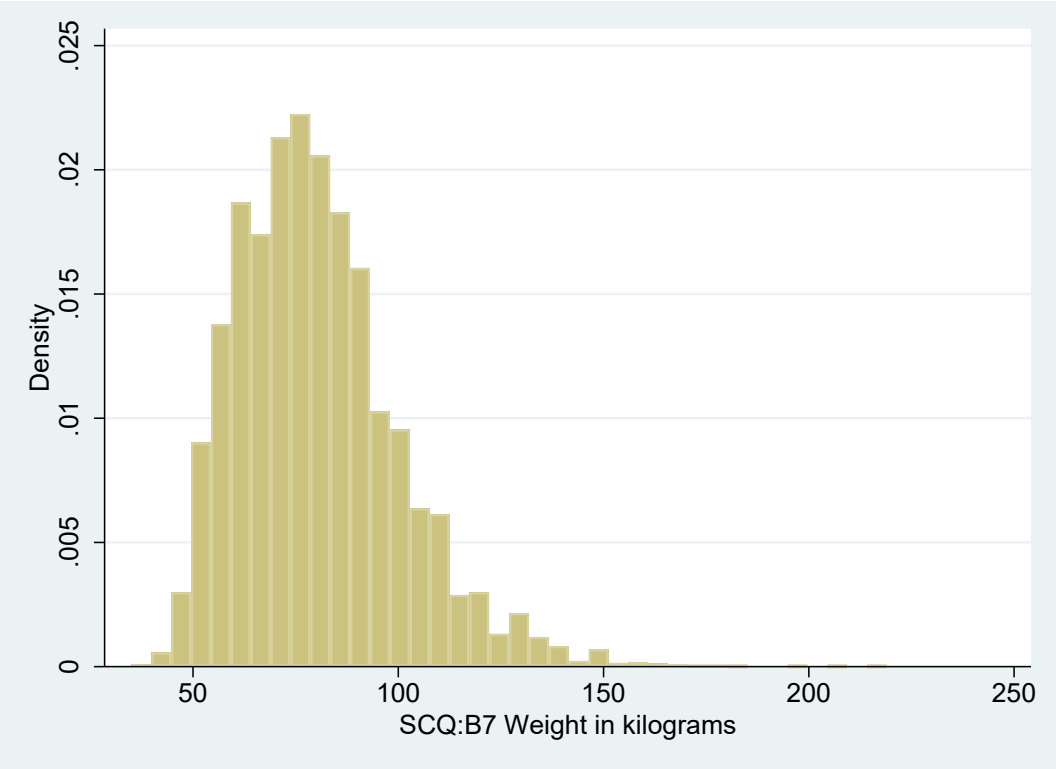
Source: (70)

8.14 Appendix 13: Discrete event simulation inputs

8.14.1 Patient attribute – weight

The frequency of weight from HILDA is presented in Figure 8-17.

Figure 8-17: Frequency of weight distribution in persons aged 15 to 50 years in HILDA



Abbreviations: SCQ = self-completed questionnaire.
Source: analysed using HILDA data Wave 18.

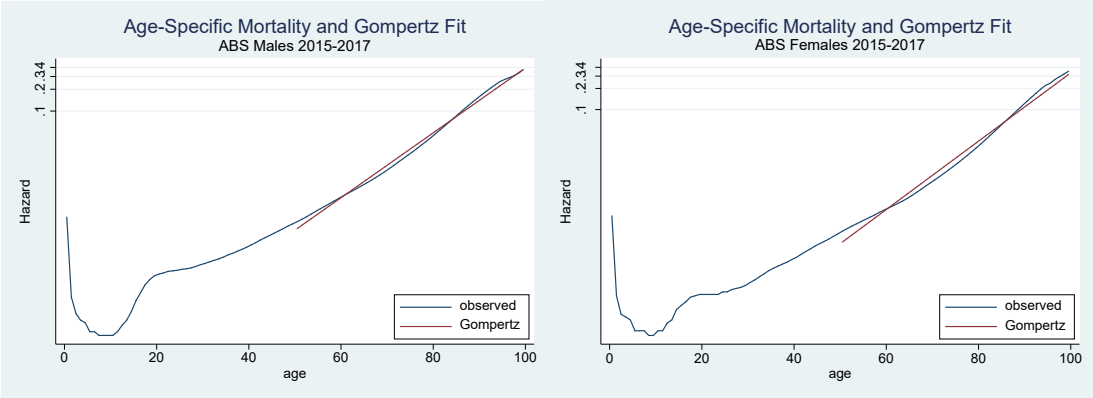
8.14.2 Gompertz distribution for Australian age-related mortality

Mortality was estimated using a Gompertz mortality function (250) using STATA code.[49] In this analysis, custom empirical distributions were utilised in AnyLogic for age-related mortality and post-HTx survival. The implication of not using the Gompertz was that extrapolation over the time horizon was not possible; however, given ABS data is up to 100 years old this was unlikely to be a problem. The Gompertz distribution for age-related mortality are presented in Table 8-47 and Figure 8-18.

Table 8-47: Gompertz distribution for age-related mortality for age 50 years and over, by Gender

		Male	Female
_Cons	Shape	-6.084982	-6.704759
Parameter_1	Scale	0.1030622	0.1121725

Figure 8-18: Age-related mortality fitted with Gompertz distribution males (left) and females (right)



8.14.3 Gompertz distribution for Cutler-Ederer survival curves post-HTx

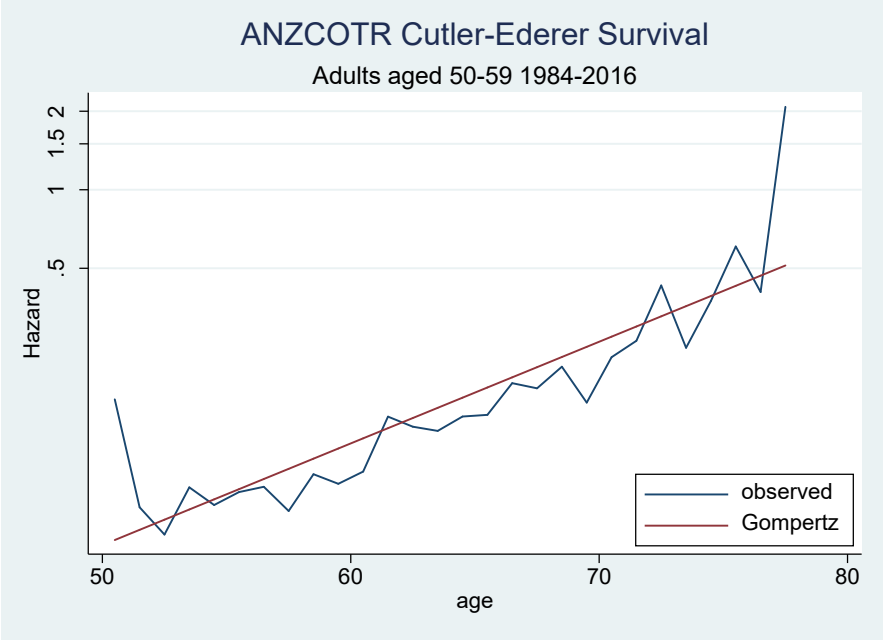
The Gompertz distribution for HTx survival are presented in Table 8-48 and Figure 8-19*Table 8-47*, data was available to 25 years post-HTx from ANZCOTR so not applying Gompertz is unlikely to be a problem.

Table 8-48: Gompertz distribution for ANZCOTR Cutler-Ederer survival curves aged 50 years and over

		All adults
_Cons	Shape	-3.136763
Parameter_1	Scale	.0897521

[49] https://data.princeton.edu/eco572/us2002gompertz

Figure 8-19: Post-HTx survival fitted with Gompertz distribution



8.14.4 Parameterisation of time-to-event curves for DES

The sample size for the transitions to the '*Removed*' health states from 'Alive post-VAD' and 'Waiting List' were 28 (Table 8-49) and 102 respectively from the SVHS CPR dataset. Due to the small number of events a custom empirical distribution using the Kaplan-Meier curves were used instead of applying parametric distributions.

Table 8-49: Parametric distributions of time-to-event 'Alive post-VAD' to 'Removed'

	Weibull	Log normal	Log logistic	Ggamma	Exponential	Gompertz
loglikelihood	-29.144489	-28.758602	-28.277399	-28.527968	-31.362244	-30.547377
AIC	62.288978	61.517204	60.554798	61.055936	66.724488	65.094754
BIC	64.95338702	64.18161302	63.21920702	63.72034502	69.38889702	67.75916302
_cons	-9.706339	6.153376	-6.156123	6.281792	-6.510102	0.0010963
parameter_1	1.496594	0.8194502	0.4446909	0.7543578		0.0007866
parameter_2				0.385898		

The parameterisation of the time-to-event transition from 'Waiting List' to 'Removed' resulted in poorly fitting curves (*Table 8-50*). The lowest AIC and BIC was from the generalised gamma model, and compared to the KM data, there should be a distinct change in rate before Month 4.

Table 8-50: Parametric distributions of time-to-event 'Waiting List' to 'Removed'

	Weibull	Log normal	Log logistic	Ggamma	Exponential	Gompertz
loglikelihood	-78.918902	-88.123967	-81.723328	-78.409401	-79.257571	-78.508058
AIC	161.837804	180.247934	167.446656	**160.818802**	162.515142	161.016116
BIC	167.087749	185.4978796	172.6966016	**166.0687476**	167.7650876	166.2660616
_cons	-7.492811	6.545189	-6.438503	6.934593	0.001084	0.0009034
parameter_1	1.103681	1.647176	0.7373046	0.7792934		0.0003714
parameter_2				1.379948		

The parameterisation of 'Ineligible' to 'Alive post-VAD' or the BTC transition was based on 18 patients and resulted in poorly fitting curves; the best fit based on visual inspection were Weibull and Exponential (Table 8-51). Overall, Generalised Gamma produced the lowerst AIC and BIC but did not fit the data well based on visual inspection; between Weibull and exponential, Weibull had the lower AIC and BIC. A custom empirical distribution was applied.

Table 8-51: Parametric distributions of time-to-event 'Ineligible' to 'Alive post-VAD' - BTC

	Weibull	Log normal	Log logistic	Ggamma	Exponential	Gompertz
loglikelihood	-34.212	-34.157	-35.043	-34.051	-36.204	-35.320
AIC	72.425	72.314	74.086	**72.102**	76.408	74.639
BIC	74.206	74.095	75.866	**73.883**	78.189	76.420
_cons	0.0264	4.309	4.375	4.666	0.00489	0.00676
parameter_1	0.7126	1.614	0.988	1.553		-0.00135
parameter_2				0.445		

The transition from 'Alive post-VAD' to 'Alive post-HTx' was based on the 3,642 patients in IMACs dataset (Table 8-52). A custom empiricial distribution was applied in the cross-validation model. The lowest AIC and BIC was based on the log-normal distribution and, based on visual inspection, it was a good fit; however, the AnyLogic software does not support this distribution. Similarly, the log-logistic model appeared to fit the data well. The exponential model appeared to overestimate the KM data at every timepoint. Therefore, the sensitivity analysis was based on the Weibull distribution.

Table 8-52: Parametric distributions of time-to-event 'Alive post-VAD' to 'Alive post-HTx'

	Weibull	Log-normal	Log-logistic	Ggamma	Exponential	Gompertz
Log-likelihood	-2487.45	-2499.93	-2509.40	-	-2497.78	-
AIC	8507.342	**8398.988**	8456.77	-	8590.098	-
BIC	8519.742577	**8411.388577**	8469.170577	-	8602.498577	-
_cons	3.498827	3.279199	3.232385	-	3.739294	-
Parameter 1	-0.2856126	0.1423775	-0.428587	-	0.03421975	-
Parameter 2						

Note: Generalised gamma and gompertz distribution would not converge in R.

The parameterisation of 'Alive post-VAD' to 'Death' transition was based on a sample of 2,839 patients from INTERMACS Table 8-53. Although the Generalised Gamma distribution had the lowest AIC and BIC, the Weibull distribution resulted in the best visual fit. The use of Weibull distribution extrapolated to 6 years was applied in Chapter 5 and in this model was applied in the sensitivity analysis. The base case model relied on a custom empirical distribution.

Table 8-53: Parametric distributions of time-to-event 'Alive post-VAD' to 'Death'

	Weibull	Log-normal	Log-logistic	Ggamma	Exponential	Gompertz
Log-likelihood	-2487.45	-2499.93	-2509.40	-2481.61	-2497.78	-
AIC	4978.90	5003.866	5022.814	**4969.227**	4997.551	-
BIC	4990.655	5015.619	5034.568	**4978.98**	5003.427	-
_cons	4.783948	4.367869	4.214219	4.787800	4.428038	-
Parameter 1	0.195002	0.620416	-0.036568	1.695500	4.243435	-
Parameter 2				0.473		-

Note: Gompertz distribution would not converge in R.

The parameterisation of 'Waiting List' to 'Alive post-VAD' was based on a sample of 102 patients from SVHS CPR Table 8-54. Based on visual inspection, the Weibull, log-normal, log-logistic and generalised gamma curve appears to overestimate the KM data from Month 5 onwards. Both exponential and Gompertz overestimate the risk of HTx for the entire period. Therefore, a custom empirical distribution was applied.

Table 8-54: Parametric distributions of time-to-event 'Waiting List' to 'Alive-Post HTx'

	Weibull	Log-normal	Log-logistic	Ggamma	Exponential	Gompertz
Log-likelihood	-163.73341	-167.972	-162.50336	-163.48736	-179.94041	-162.96537
AIC	331.46682	339.944	**329.00672**	330.97472	363.88082	329.93074
BIC	336.7167656	345.1939456	**334.2566656**	336.2246656	369.1307656	335.1806856
_cons	-3.731273	5.857969	-5.747179	6.339797	-6.339377985	0.0039453
Parameter 1	0.5762122	2.726135	1.345783	1.890209		-0.0032829
Parameter 2				6.339797		

Given the poor fit of the distributions based on the sample size of 7 for the BTT analysis (Table 8-55), none of the parametric distributions were applied in the sensitivity analysis. A custom empirical distribution was applied.

Table 8-55: Parametric distributions of time-to-event 'Waiting List' to 'Alive-Post VAD'

	Weibull	Log-normal	Log-logistic	Ggamma	Exponential	Gompertz
Log-likelihood	-11.444592	-11.12768	-11.248237	-11.122229	-11.518384	-11.367903
AIC	26.889184	**26.25536**	26.496474	26.244458	27.036768	26.735806
BIC	26.7810043	**26.1471803**	26.3882943	26.1362783	26.9285883	26.6276263
_cons	0.0163111	3.985076	4.006449	4.052074	0.0097493	0.0120881
Parameter 1	0.8999527	1.186171	0.6827007	1.182725		-0.0018867
Parameter 2				0.1130535		

8.14.5 Survival probability Australian Bureau of Statistics Life Table

Table 8-56: Australian Bureau of Statistics Life Table 2015-2017, Add Value weighted cohort for DES

Age	% Death	Lower	Upper
18	0.000392	0.000384	0.0004
19	0.000436	0.000428	0.000445
20	0.000464	0.000456	0.000472
21	0.000478	0.000469	0.000486
22	0.000491	0.000483	0.0005
23	0.000508	0.0005	0.000517
24	0.000518	0.000509	0.000527
25	0.000528	0.000519	0.000537
26	0.000545	0.000536	0.000554
27	0.000562	0.000553	0.000571
28	0.000586	0.000576	0.000595
29	0.000613	0.000603	0.000622
30	0.00065	0.00064	0.00066
31	0.00069	0.000679	0.0007
32	0.000726	0.000716	0.000737
33	0.000776	0.000765	0.000787
34	0.000823	0.000812	0.000834

35	0.00088	0.000868	0.000892
36	0.000937	0.000926	0.000949
37	0.000991	0.000979	0.001004
38	0.001055	0.001042	0.001068
39	0.001132	0.001119	0.001146
40	0.001223	0.001209	0.001237
41	0.001327	0.001313	0.001341
42	0.001435	0.00142	0.001449
43	0.001552	0.001537	0.001567
44	0.001672	0.001656	0.001688
45	0.001797	0.00178	0.001813
46	0.001944	0.001927	0.001962
47	0.002095	0.002078	0.002113
48	0.002256	0.002238	0.002275
49	0.00243	0.002411	0.00245
50	0.002621	0.002601	0.002641

Note: Australian population in September 2018 N = 2510900(249), weighted from Add Value gender of male (69%): female (31%)
Source:(203)

8.14.6 Survival probabilities 'ineligible' to 'VAD', Add Value

Table 8-57: Add Value, time-to-event 'ineligible' to 'VAD' BTC, N=18

Month	% Implant	Lower	Upper
0	0	0	0
1	0.3889	0.179409	0.623134
2	0.3889	0.179409	0.623134
3	0.3889	0.179409	0.623134
4	0.5	0.272235	0.727765
5	0.5556	0.323103	0.775705
6	0.5556	0.323103	0.775705
7	0.7778	0.559239	0.935012
8	0.7778	0.559239	0.935012
9	0.8333	0.629336	0.964245
10	0.8333	0.629336	0.964245
11	0.8333	0.629336	0.964245
12	0.8333	0.629336	0.964245
13	0.8333	0.629336	0.964245
14	0.8889	0.70743	0.986678
15	0.8889	0.70743	0.986678
16	0.8889	0.70743	0.986678
17	0.8889	0.70743	0.986678
18	0.8889	0.70743	0.986678
19	0.8889	0.70743	0.986678
20	0.8889	0.70743	0.986678
21	0.8889	0.70743	0.986678
22	0.8889	0.70743	0.986678
23	0.8889	0.70743	0.986678
24	0.8889	0.70743	0.986678
25	0.8889	0.70743	0.986678
26	0.9444	0.800201	0.998758
27	0.9444	0.800201	0.998758
28	0.9444	0.800201	0.998758
29	0.9444	0.800201	0.998758
30	0.9444	0.800201	0.998758
31	0.9444	0.800201	0.998758
32	0.9444	0.800201	0.998758
33	0.9444	0.800201	0.998758
34	1	1	1

8.14.7 Survival probability 'Waiting list' to removed, CardioPulmonary Registry

Table 8-58: Waiting List to Remove, n=102

Month	% Remove	Lower	Upper
0	0	0	0
1	0.0301	0.0064	0.0710
2	0.0417	0.0121	0.0882
3	0.0417	0.0121	0.0882
4	0.0555	0.0200	0.1075
5	0.0868	0.0404	0.1486
6	0.0868	0.0404	0.1486
7	0.1223	0.0662	0.1925
8	0.1947	0.1239	0.2769
9	0.2144	0.1404	0.2991
10	0.2362	0.1590	0.3233
11	0.2812	0.1983	0.3723
12	0.3292	0.2414	0.4234
13	0.3799	0.2882	0.4761
14	0.4634	0.3675	0.5607
15	0.4634	0.3675	0.5607
16	0.4634	0.3675	0.5607
17	0.5230	0.4258	0.6193
18	0.5230	0.4258	0.6193
19	0.5548	0.4575	0.6500
20	0.5548	0.4575	0.6500
21	0.5548	0.4575	0.6500
22	0.5919	0.4950	0.6853
23	0.5919	0.4950	0.6853
24	0.5919	0.4950	0.6853
25	0.5919	0.4950	0.6853
26	0.5919	0.4950	0.6853
27	0.5919	0.4950	0.6853
28	0.5919	0.4950	0.6853
29	0.5919	0.4950	0.6853
30	0.5919	0.4950	0.6853
31	0.5919	0.4950	0.6853
32	0.5919	0.4950	0.6853
33	0.5919	0.4950	0.6853
34	0.5919	0.4950	0.6853
35	0.5919	0.4950	0.6853
36	0.5919	0.4950	0.6853
37	0.6502	0.5551	0.7397
38	0.6502	0.5551	0.7397
39	0.6502	0.5551	0.7397
40	0.6502	0.5551	0.7397
41	0.7085	0.6166	0.7925
42	0.7085	0.6166	0.7925
43	0.7085	0.6166	0.7925
44	0.7085	0.6166	0.7925
45	0.7668	0.6800	0.8436
46	0.7668	0.6800	0.8436
47	0.7668	0.6800	0.8436
48	0.7668	0.6800	0.8436
49	0.8251	0.7456	0.8924
50	0.8251	0.7456	0.8924
51	0.8834	0.8144	0.9381
52	0.8834	0.8144	0.9381

8.14.8 Survival probability 'wait list' to 'Alive Post-VAD', Add Value

Table 8-59: Waiting List to VAD, n=7

Month	%Implant	Lower	Upper
0	0	0	0
1	0.2857	0.033985	0.66814
2	0.4286	0.101231	0.800241
3	0.7143	0.33186	0.966015
4	0.8571	0.513777	0.997479
5	0.8571	0.513777	0.997479
6	0.8571	0.513777	0.997479
7	0.8571	0.513777	0.997479
8	0.8571	0.513777	0.997479
9	0.8571	0.513777	0.997479
10	0.8571	0.513777	0.997479
11	0.8571	0.513777	0.997479
12	0.8571	0.513777	0.997479
13	0.8571	0.513777	0.997479
14	1	1	1

8.14.9 Survival probability 'wait list' to 'Alive Post-HTx', CPR

Table 8-60: Waiting List to Heart Transplant, n=53

Month	%Transplant	Lower	Upper
0	0	0	0
1	0.120202	0.047508	0.220359
2	0.191599	0.097711	0.307892
3	0.273475	0.162424	0.401018
4	0.325249	0.206139	0.457091
5	0.388622	0.262051	0.523312
6	0.399365	0.27177	0.534297
7	0.431595	0.301323	0.566855
8	0.466833	0.334298	0.601786
9	0.466833	0.334298	0.601786
10	0.505283	0.371055	0.639126
11	0.545241	0.410106	0.677078
12	0.574192	0.438948	0.704027
13	0.589203	0.454088	0.717816
14	0.589203	0.454088	0.717816
15	0.589203	0.454088	0.717816
16	0.589203	0.454088	0.717816
17	0.589203	0.454088	0.717816
18	0.589203	0.454088	0.717816
19	0.589203	0.454088	0.717816
20	0.589203	0.454088	0.717816
21	0.589203	0.454088	0.717816
22	0.589203	0.454088	0.717816
23	0.649125	0.515831	0.771553
24	0.649125	0.515831	0.771553
25	0.680389	0.548924	0.798712
26	0.680389	0.548924	0.798712

8.14.10 Survival probability 'VAD' to 'Remove', CardioPulmonary Registry

Table 8-61: VAD to Remove, n= 28

Month	% Remove	Lower	Upper
0	0	0	0
1	0	0	0
2	0.037	0.000969	0.132202
3	0.037	0.000969	0.132202
4	0.0741	0.009464	0.19641
5	0.0741	0.009464	0.19641
6	0.1127	0.025205	0.253538
7	0.1127	0.025205	0.253538
8	0.1127	0.025205	0.253538
9	0.1898	0.068452	0.354379
10	0.2303	0.095266	0.403024
11	0.3113	0.154806	0.494245
12	0.3519	0.187093	0.537484
13	0.3519	0.187093	0.537484
14	0.4815	0.299289	0.666309
15	0.5286	0.343261	0.709922
16	0.6229	0.436409	0.792143
17	0.6229	0.436409	0.792143
18	0.6229	0.436409	0.792143
19	0.6229	0.436409	0.792143
20	0.7172	0.537043	0.866936
21	0.7172	0.537043	0.866936
22	0.7172	0.537043	0.866936
23	0.7172	0.537043	0.866936
24	0.7172	0.537043	0.866936
25	0.7172	0.537043	0.866936
26	0.7172	0.537043	0.866936
27	0.8114	0.6471	0.932306
28	0.8114	0.6471	0.932306
29	0.8114	0.6471	0.932306
30	0.8114	0.6471	0.932306
31	0.8114	0.6471	0.932306
32	0.8114	0.6471	0.932306
33	0.8114	0.6471	0.932306
34	0.8114	0.6471	0.932306
35	0.8114	0.6471	0.932306
36	0.8114	0.6471	0.932306
37	0.8114	0.6471	0.932306
38	0.8114	0.6471	0.932306
39	0.8114	0.6471	0.932306
40	0.8114	0.6471	0.932306
41	0.8114	0.6471	0.932306
42	0.8114	0.6471	0.932306
43	0.8114	0.6471	0.932306
44	0.8114	0.6471	0.932306
45	0.8114	0.6471	0.932306
46	0.8114	0.6471	0.932306
47	0.8114	0.6471	0.932306
48	0.8114	0.6471	0.932306
49	0.8114	0.6471	0.932306
50	0.8114	0.6471	0.932306
51	0.8114	0.6471	0.932306
52	0.8114	0.6471	0.932306
53	0.8114	0.6471	0.932306
54	0.8114	0.6471	0.932306
55	1	1	1

8.14.11 Survival probability 'VAD' to 'HTx, INTERMACS

Table 8-62: VAD to HTx, n=3642

Month	% Transplant	Lower	Upper
0	0.00	0.00	0.00
1	0.00	0.00	0.01
2	0.02	0.02	0.02
3	0.02	0.02	0.02
4	0.05	0.05	0.06
5	0.09	0.08	0.10
6	0.09	0.08	0.10
7	0.17	0.16	0.18
8	0.17	0.16	0.18
9	0.21	0.20	0.23
10	0.24	0.23	0.26
11	0.26	0.25	0.27
12	0.28	0.27	0.30
13	0.28	0.27	0.30
14	0.31	0.30	0.33
15	0.31	0.30	0.33
16	0.33	0.32	0.35
17	0.34	0.33	0.36
18	0.36	0.35	0.38
19	0.36	0.35	0.38
20	0.39	0.37	0.40
21	0.39	0.37	0.40
22	0.40	0.38	0.41
23	0.40	0.38	0.41
24	0.42	0.40	0.43
25	0.43	0.41	0.44
26	0.44	0.43	0.46
27	0.44	0.43	0.46
28	0.44	0.43	0.46
29	0.46	0.44	0.47
30	0.46	0.44	0.47
31	0.46	0.45	0.48
32	0.46	0.45	0.48
33	0.47	0.46	0.49
34	0.47	0.46	0.49
35	0.49	0.48	0.51
36	0.49	0.48	0.51
37	0.50	0.48	0.52
38	0.50	0.48	0.52
39	0.51	0.49	0.53
40	0.51	0.49	0.53
41	0.52	0.50	0.53
42	0.52	0.50	0.53
43	0.52	0.50	0.53
44	0.52	0.51	0.54
45	0.53	0.52	0.55
46	0.53	0.52	0.55
47	0.53	0.52	0.55
48	0.53	0.52	0.55

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