

Conceptual framework for early health technology assessment of a new diagnostic concept

(Oxygen Delivery Index – ODIN)

A conceptual model of extracorporeal membrane oxygenation (ECMO) treatment for adult patients in refractory cardiogenic shock

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Abstract

Background: Treating refractory cardiogenic shock (RCS) adult patients with extracorporeal membrane oxygenation (ECMO) consumes considerable resources with questionable effectiveness. By assessing microcirculatory system of individual patients, a new health care technology oxygen delivery index (ODIN) may aid to increase the efficacy and efficiency of the costly ECMO treatment. The aim of this thesis was to build a conceptual framework for ECMO treatment that can be used to approach the early health technology assessment (HTA) of ODIN for RCS adult patients during ECMO treatment.

Method: A decision tree and a Markov model have been utilized to construct the conceptual model. It has been revised at every stage of the model development by systematic literature review and experts' opinion. After finalizing the conceptual model, suggestions for defining and obtaining parameter data and assumptions about how ODIN might affect parameter estimates were concluded using basic economic evaluation knowledge and experts' opinion.

Result: The conceptual model consists of a decision tree and a Markov model. It starts with a decision tree with the RCS patients receiving the ECMO treatment for the first time. There are four clinical responses: total or partial recovery, receiving more durable mechanical heart pump assistance, receiving heart transplant and death. The distribution of the responses was assumed to be affected by age, the clinical causes for receiving ECMO. All the patients who survived the therapy entered the Markov model. It included four described health states: the first remission, the relapse, the second remission, and death. Patients with different clinical responses have different transition probabilities in every health state. The key estimation parameters were: state cost, state utility, transition probability and discounting rate.

Conclusion: The conceptual frame developed in this thesis can be used to do early HTA of ODIN when more data become available. The conceptual model can also be used to guide the personalized care of ODIN and ECMO and to develop more specific and customized models for solving more problems.

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Abbreviations

CPB	Cardiopulmonary bypass
CEA	Cost effectiveness analysis
cLab	The Central Laboratory
CUA	Cost utility analysis
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal life support organization
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
LUC	Limited use criteria
LVAD	Left ventricular assist device
MCS	Mechanical circulatory support
mLab	The Microvascular Laboratory
ODIN	Oxygen delivery index
ProECMO	Prognostic value of microvascular assessments in patients treated with ECMO
QALY	Quality adjusted life years
RCS	Refractory cardiogenic shock
USD	United States dollar
VA-ECMO	Veno-arterial extracorporeal membrane oxygenation
VV-ECMO	Veno-venous extracorporeal membrane oxygenation
WTP	Willingness to pay

Chapter 1

Introduction

Cardiogenic shock is the severest acute heart failure. Cardiogenic shock patients who are refractory to conventional treatments are usually critically ill. Some are treated with extracorporeal membrane oxygenation (ECMO), a temporary artificial heart and lung machine which mechanically circulates the blood from a patient's body [1,2]. However, Refractory cardiogenic shock (RCS) patients who are treated with the ECMO face high risk of mortality and fatal complications [1]. The clinical benefits of the ECMO treatment are controversial and not rigorously proven. Additionally, the ECMO treatment requires considerable healthcare resources in the form of personnel, blood products and specialized locations. The ECMO treatment can be very costly with questionable effectiveness to treat RCS adult patients. Patients' selections for the ECMO (i.e. inclusion of the "right" patients who are most likely to benefit from the ECMO) by monitoring individual patients become more and more important in order to offer more cost-effective approaches to use the costly ECMO [2].

Current clinical monitoring techniques are limited and not capable of yielding reliable overall prognostic information. It is a challenge to monitor the irreversible damage to circulatory system soon after the ECMO therapy is started. Patients who have normal monitoring parameters with current monitoring tools often end up with fatal consequences after lengthy ECMO therapy, the average length of time on ECMO is about 10 days [2]. Compared with existing methods, more reliable diagnosis and prognosis may be made by monitoring the microcirculatory system, i.e. the transportation system of oxygen to the cells of the body [2, 3, 4]. By assessing the important microcirculatory system of individual patients, we can make the best use of the ECMO and conventional treatments while decreasing the total cost of overuse of ECMO and other futile therapy.

However, monitoring the microcirculation is a novel tool and not proven routinely in clinical practice due to the monitoring complexity, lack of applicable technologies and key opinion leaders' knowledge. Oxygen delivery index (ODIN) is a new health technology that could

make it possible to routinely assess the microcirculatory system of individual patients in clinical practice in the future to yield more favorable clinical outcomes for patients, and to better guide informed decisions and tailored therapies when utilizing the ECMO as a treatment [2].

The objective of this master thesis was to build a conceptual framework to guide and support the early health technology assessment of the ODIN to analyze whether using the ODIN and the ECMO together to support the treatment of refractory cardiogenic shock adult patients is cost-effective alternative compared to using the ECMO only. To achieve this objective, a conceptual model for the ECMO treatment was built.

There is limited good quality data and publications about clinical and economic facts of ECMO treatment. Only two randomized controlled clinical trials to analyze the prognostic value of microvascular assessments in patients treated with ECMO have been done. Only one trial's results are published. The trial only includes eight patients [3]. In addition, the ECMO treatment is difficult to study in a randomized controlled trial. Because the refractory cardiogenic shock adult patients are very ill and the decision to use the ECMO is usually made instantaneously, which makes it almost impossible to do research-specific procedures like randomization or informed consent [5]. This might be one of the reasons why only a few clinical or economic evaluation papers to assess the treatment of ECMO for cardiogenic shock adult patients were found during the systematic literature review. There is also very little information about the clinical pathway of current ECMO treatment, which makes it difficult to conceptualize the model. Therefore, at present, limited relevant and reliable data is available about the effectiveness and no previous relevant models are available to be used in economic evaluation to check the impact that the ODIN might have on the effectiveness and cost of the ECMO treatment.

The quality of data significantly affects the model's credibility, so as we cannot compromise the credibility of the model by adding the data with questionable quality. Even though the data, especially key parameters such as effectiveness of the intervention and diagnostic features, are key elements of a model, the conceptual framework of the health technology analysis model should be determined by the decision problem and research question instead of data availability or quality [6].

Furthermore, even though models play an important role in economic evaluation, it has been noted that the economic evaluation papers rarely report the model's structure, how and why the model is built in a particular way and what influence it has on the final results of the model. The development of their models in many healthcare economic papers might be hardest to undertake and least well understood [7, 8]. Most of the economic evaluation studies only focus on presenting the implementation of the final model with statistical analysis and technical evaluation methods. The readers commonly have little understanding of the credibility of the model because of lack of systematic reports and transparency, i.e. why certain parameters were selected for inclusion (and why others have been excluded), why and how the model structure has been determined etc [9]. *"Models should be subjected to rigorous verification. The verification methods should be described in the non-technical documentation of the model."* [10 p798]. So, another objective of this thesis is to give a systematic and detailed report of the development and verification of the conceptual model, so its credibility and validation can be checked and the results of the future health technology assessment of ODIN based on this conceptual model will be more reliable.

To my knowledge, this might be the first conceptual model for decision analytic modelling for the ECMO treatment in adult patients with refractory cardiogenic shock. I am not aware of any published conceptual models for VA-ECMO treatment for adult patients. Even though most of the data is not available, we can design the conceptual model based on the research problem itself, and then later we can use the model to guide the collection of data [11]. The conceptual model can be beneficial as guidance to select and collect appropriate evidence-based clinical and economic data for estimating benefits, costs and transitional probability for populating the model. In addition, since a large scale of economic studies are trial-based economic evaluation, the conceptual model might have reference value for clinical researchers to design randomized clinical trials which are very important to generate medical evidence for the evaluation of healthcare interventions and medical development.

Furthermore, conceptual model encompasses more general and complex evidence. When doing health technology assessment of the ODIN technology, the future researchers and policymakers can use the conceptual model as a reference or a foundation to construct more customized model for different specific modalities, settings and subpopulation. They can also do heterogeneity analysis which can guide personalized healthcare for individual

patients, which the ODIN is associated with. Besides, the results of economic evaluation hinge on the model whose structure is determined by its chosen perspective, choice of parameters, data collection etc. If a new health intervention was not considered cost-effective, we can check each element of the economic evaluation, especially the model, to find the major cause in order to provide a foundation to the future development of the technology and concept. Therefore, a conceptual model which represents the reality with important relevant factors included can not only be useful for economic evaluation but also for the development of the new healthcare intervention like the ODIN technology.

Therefore, the conceptual model for the ECMO treatment developed and discussed in this paper will assist public health experts, future researchers and policy-makers to perform economic evaluation of the ODIN technology and ECMO treatment, and support developers' decision about further development and assessment of this new medical technology, when more data become available.

The master thesis consists of seven chapters.

The second chapter is background which elaborated important medical and economic evidences such as cardiogenic shock, ECMO, microcirculation and ODIN.

The third chapter is method which explained in detail of the steps and methods that were taken to develop this conceptual framework.

The fourth chapter discussed the results in detail, which presented and explained the conceptual model and how it is developed, and what we can do to define certain parameters and collect data or assign value to them.

The fifth chapter is discussion mainly about what the early health technology assessment of the ODIN concept could achieve by populating the model when more data become available, and how the conceptual model could serve for guiding the personalized healthcare and how it could be modified to become more customized model for more specific problems.

The six chapter describes the limitations of the conceptual model.

The final chapter is the conclusion.

Chapter 2

Background

2.1 Cardiogenic shock and extracorporeal membrane oxygenation (ECMO)

Acute heart failure is defined as a quick onset or worsening of symptoms and signs of heart failure, which can be either a new-onset heart disease or an acute decompensation of chronic heart failure [12]. The most severe form of acute heart failure is cardiogenic shock. It is commonly defined as a condition with low cardiac output, sustained hypotension and organ hypoperfusion [2, 13-15]. It is a grave cardiac dysfunction. Even though less than 10 percent acute heart failure patients fulfill the criteria of cardiogenic shock, the average in-hospital mortality rates of the cardiogenic shock patients can be as high as 40% to 50% [16, 17, 18]. The mortality rate can reach to about 100%, if without proper and timely treatment [2].

The conventional treatment for cardiogenic shock is based on pharmacological therapy. It can optimize heart rhythm and contractility, adjust intravascular blood volume and pressure. [2, 19]. If the low cardiac output and hypotension persists with adequate pharmacological and volume treatments, a short-term mechanical circulatory support (MCS) can be used to stabilize the patients to gain more time to plan more definitive therapy, such as longer term MCS and heart transplant [2, 12].

Extracorporeal membrane oxygenation (ECMO) is a form of short-term MCS. It's a mechanical technology to temporarily support or replace the heart and lung function [2, 12]. There are two forms of ECMO: veno-arterial (VA) ECMO and veno-venous (VV) ECMO. VV-ECMO is used to treat respiratory failure only and do not provide cardiac support. VA-ECMO is used to treat acute heart failure and its corresponding lung failure [2, 20, 21]. The VA-ECMO uses extracorporeal technique to mechanically circulate the blood from a patient's body [12]. The blood is drained from the central vein before reaching the right side of the heart (right atrium) into an extracorporeal circuit. The blood stream then passes through a mechanical pump (artificial heart) and a membrane oxygenator (artificial lung) and is returned into the

body through a large artery. The blood pump creates the driving force for the circulation. The membrane oxygenator removes the carbon dioxide from the blood and adds oxygen into it [2]. This process is presented in diagram 1 and 2.

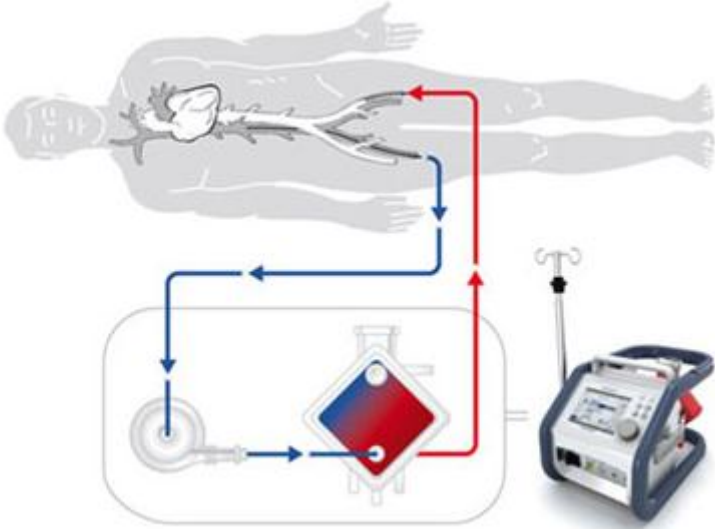


Diagram 1: VA-ECMO [22 p1].

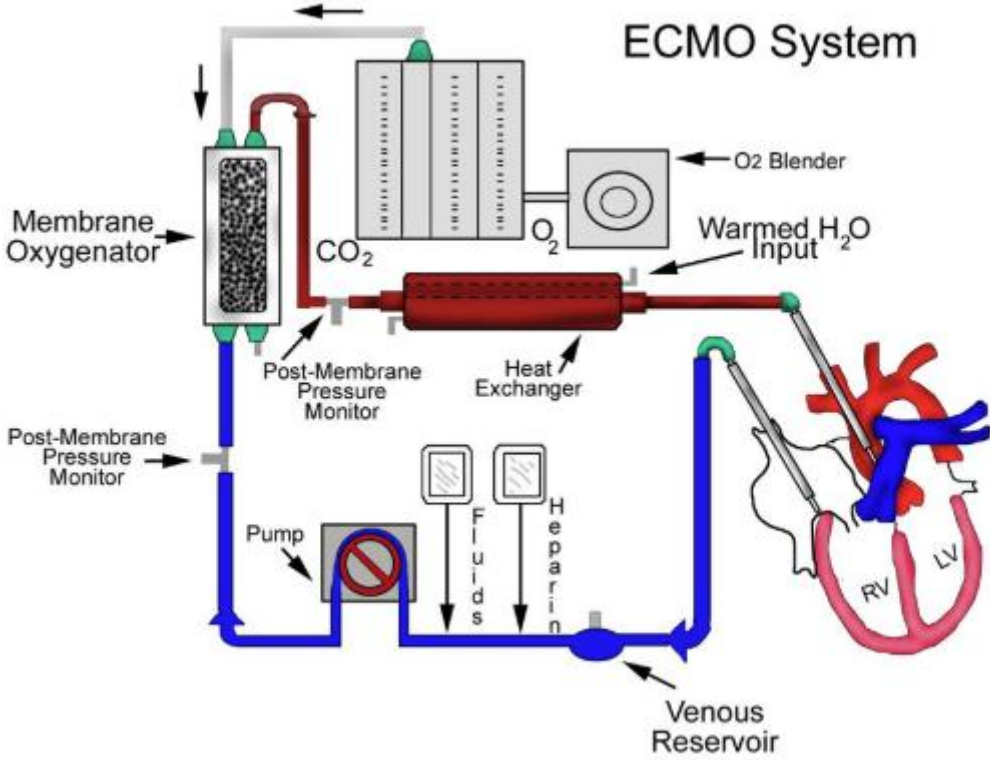


Diagram 2: VA-ECMO system [23 p1].

Cardiogenic shock is the most common indication to use the VA-ECMO. When patients who have cardiogenic shock are refractory to conventional pharmacological therapy, the VA-ECMO treatment can be considered to provide temporary mechanical cardiopulmonary support [2, 19]. The ECMO treatment usually lasts for up to one or two weeks until recovery of the heart function or death because of irreversible end organ failure [2, 12]. It also works as a “bridge to decision’ (BTD) to give time to do an assessment for the possibility of either a more durable MCS device or heart transplant [12].

Over the recent years, the ECMO technology has made progression and it became more commonly used to treat critically ill patients suffering from refractory cardiogenic shock. [2] However, the clinical outcome of the ECMO treatment is poor with severe complication and the costs of the ECMO treatment is quite high.

In a study of the use of ECMO for post cardiectomy heart failure (heart failure following open heart surgery) in 517 patients 63% were successfully weaned from ECMO, but only 25% of patients were discharged from the hospital alive [24]. Cumulative survivors were only 17.6% after 6 months, 16.5% after 1 year, and 13.7% after 5 years [24]. Other studies reported that the average survival rate among patients who received the VA ECMO ranged from 20% to 30%, which means about one of three cardiogenic shock patients can survive from ECMO treatment [1, 21].

In addition, many patients using ECMO experienced severe complications including life-threatening bleedings, end organ failure (e.g. renal failure) and neurological injury (e.g. stroke) [2, 24, 25]. And, the VA ECMO usually has more complications than the VV-ECMO and adult patients generally have more complications than the children do [1]. So, temporary MCS like ECMO is not recommended as a proven and efficacious treatment option for cardiogenic shock by official guidelines [9].

Further, the ECMO treatment is a resources-demanding procedure. The average of total in-hospital costs of ECMO treatment can be within the range from USD 42554 to 537554 in 2013 values [6]. In Norway, the estimated average total hospital costs were USD 213246 and the mean estimated cost for the ECMO procedure itself was USD 73122 in 2007 values, and the cost of the VA-ECMO treatment for an individual adult patient could be more than USD 400000, and the average cost of the VA-ECMO treatment for adult patients was about USD

235000[27]. The personnel costs contributed to the largest part of totally cost, since the ECMO treatment is a complicated procedure that is not easy to implement, which need additional resources and an experienced clinical team including physicians, perfusionists and nurses [26, 27].

Furthermore, most patients with heart failure are elderly patients. They account for 80% of total heart failure patients [28]. One of the dominant reasons of hospitalization in patients above the age of 65 years is the acute heart failure and thereby there is an increasing risk for individuals over 65 years old to get cardiogenic shock [28]. Just like many other European countries, Norway also faces an ageing population with increasing number of elderly citizens. More than 1/4 of inhabitants older than 67 years will be expected in 1/3 of Norwegian municipalities in 2030, and One of five people in Norway will be 70 years or older in 2060 [29, 30]. Therefore, the demand for using the expensive ECMO is expected to increase in the years to come.

The ECMO treatment might continue being a large consumption of healthcare resources. Therefore, it is important to use the VA-ECMO treatment in a cost-effective way. Patient selections is important since some patients might have better chance to survive after the ECMO treatment [15]. Techniques for patient monitoring during the ECMO treatment play important role for patient selection, which can optimize the outcome for the individual patient and thereby might make the ECMO treatment become more cost-effective.

The outcomes of cardiogenic shock patients who are treated with the support of ECMO is determined by three elements. The first one is how skilled and experienced the ECMO team is. The second is how good is the level of resources and support from other hospital, including supports from the blood bank, infections medicine department, etc. The third is how sick the patient is the moment he or she receive the support of ECMO [2, 32]. Currently, the severity of the heart failure and the accompanying circulatory failure of a cardiogenic shock patients is assessed by the medical history and findings during examination, including assessments of blood pressures(hemodynamics), biochemical examinations of blood samples, and specialized examinations with ultrasound and radiological techniques [2, 26]. However, even with the best equipment and supports handled by a very experienced and skilled ECMO team, the mortality rate of the ECMO treatment is still very high [2]. An explanation can be

that the information (such as blood pressures, biochemical examinations, etc) detected by the current monitoring devices used for selection of patients cannot precisely represent the true medical condition of the patients under the ECMO treatment and thereby cannot assess the efficacy of the treatment [2]. Therefore, patients with normal monitoring parameters detected by current monitoring devices may still die. A more precise monitoring device might offer more reliable parameters to guide the use of the ECMO treatment in a more cost-effective way.

2.2 Microcirculation and Oxygen Delivery Index

Microcirculation is the circulation of the blood in the smallest vessels in organ tissues [2,33]. The main function of the microcirculation is the delivery of oxygen and nutrients for the metabolism of the cells in the body [2,33]. Macrocirculation, in contrast, is the circulation of blood among the organs [33].

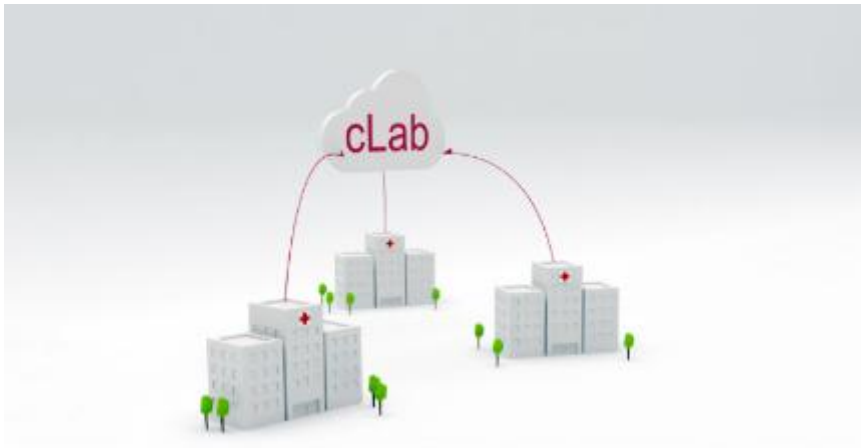
Cardiogenic shock causes damage in both microcirculatory and macrocirculatory system. It leads to reduced blood flow to the end organs and accordingly reduced blood supply to the microcirculation within organs [2]. The ECMO technology is used to improve the macrocirculatory function. The current devices used routinely in clinical practice can only monitoring the macrocirculatory system. Even with the normal monitoring parameters like blood pressure and cardiac output, the patients still die on the ECMO treatment. Maybe because the hemodynamic situation in the macrocirculation and microcirculation is not always coherent, that is to say, improvement or stabilization in macrocirculation in the ECMO treatments cannot guarantee an equal improvement in microcirculation [2,3,4]. And without a proper microcirculatory function, oxygen delivery for cell metabolism will be reduced, and cells function will deteriorate and eventually cells may die, leading to insufficient organ functions, and death of the patient [2].

Even though monitoring microcirculation might be more effective to assist the treatment and improve the clinical outcome of critically ill patients and to help allocate the healthcare resource in a more appropriate way, so far, no medical devices for direct assessments of the microcirculatory function is available for routine intensive care medicine [2]. The complexity of structure and lack of applicable technologies were the reasons [34].

Recently, a new technology, Oxygen Delivery Index, might have the potential to provide an assessment of the microcirculatory system of individual patients for bedside use [35]. It can be used to quantify the function of the microcirculatory system, make a prognosis of the condition of the patient (whether the dysfunction of the circulatory system is reversible or not), and to quantify and thereby assess the efficacy of the current treatments [2,35]. The ODIN technology mainly comprises two technological platforms. The first part is the Microvascular Laboratory, mLab (see picture 1). It is a noninvasive bedside technology to collect microcirculatory data, which can be done by trained clinical or technical personnel. Then the mLab software automatically encrypts and transfers the data to the second part of the ODIN technology, the Central Laboratory, cLab (see picture 2). It can conduct advanced analysis and assessment of the function of microcirculatory system of the individual patients by extracting a series of parameters from the data sent from the mLab. [35]



Picture 1: The Microvascular Laboratory, mLab, for getting data of microcirculatory system bedside. [35]



Picture 2: The Central Laboratory, cLab, for analyzing and assessing of the data from mLab to extract a set of parameters that can be used to evaluate the microcirculatory system. [35]

By assessing the microcirculation, the ODIN might be a very useful technological device which might be used routinely in clinical practice for the first time to assist individual patients' management. However, ODIN is a new technology that is under development. Whether it is a cost-effective way to improve the efficacy of the ECMO treatment for RCS adult patients, we can find out the answer by doing early health technology assessment (HTA).

2.3 The research objective

The objective of this master thesis was to develop a conceptual framework to guide the early HTA of the ODIN by building a conceptual model for ECMO treatment and giving suggestions about how to obtain important parameter estimates. When more data become available, by following this conceptual framework we will be able to populate the conceptual model to do early HTA more quickly to check what the impact that the ODIN will have on the efficacy and cost of the ECMO treatment for refractory cardiogenic shock patients.

Chapter 3

Method

Two steps are involved in building this conceptual framework to guide the early health technology assessment of the ODIN when more important parameter data become available.

The first and the more important step is to build a conceptual model. To prepare for populating the conceptual model to do the early HTA of the ODIN technology in the future, the second step is to discuss how we can collect data to estimate the value of important parameters (such as cost, utility and transition probability, discounting rate,), and how the ODIN can affect those parameter estimates by using basic economic evaluation knowledge.

3.1 Early health technology assessment (early HTA)

Early HTA plays an important role in development and diffusion of a new healthcare intervention [36]. Research and development (R&D) for a new health technology is expensive. Early HTA can be conducted along with phase I and II clinical trials to help design randomized clinical trial, guide market access and set acceptable price [37].

There are many definitions of early HTA. But early HTA is most frequently defined as a form of HTA to assess the potential cost-effectiveness of the new health technology under development and clinical assessment before its implementation in clinical practice by using the framework of economic evaluation [36]. Early stage health economic modelling is the most common method to conduct early HTA. Other methods, such as headroom analysis and stakeholder preference elicitation and multicriteria decision analysis also need be taken into consideration when doing an early HTA. Headroom analysis can discover the highest price of the technology based on the willingness to pay thresholds. Stakeholder preference elicitation and multicriteria decision analysis can be used to estimate value for certain parameters, such as transition probabilities and effectiveness in health economic model [36]. All these three methods are within the framework of economic evaluation.

3.2 Economic evaluation

Economic evaluation represents a comparative analysis of at least two health interventions by assessing the costs and benefits of the different health interventions. Healthcare resources are limited; thus, we need make decisions about allocating the resources by prioritizing the implementation of available healthcare interventions in order to maximize the health of the society while taken equity into consideration [11]. Economic evaluation provides a systematic framework to analyze the effectiveness and costs of healthcare interventions in order to offer information for decision makers to assess whether implementation of an intervention will be cost-effective utilization of the scare health resource [38].

Randomized clinical trials can provide good source of evidence for economic evaluation. It captures patient-level data. This data can identify patient heterogeneity, quantify the covariance between costs and effectiveness, and be reliable foundation to build and extrapolate models [61]. Trials can also help to guide economists to decide what types of resource use and information of effectiveness should be collected [61]. And the cost for adding an economic evaluation alongside a randomized clinical trial is relatively low [61]. However, economic evaluations that is only based on randomized clinical trials have certain weakness. Because most trials contain limited comparisons, short follow up and limited information to evaluate the dynamics in the health system. Even longest and largest clinical trial cannot offer all the important evidence needed to do economic evaluation [61]. So, the decision models that not only include relevant evidence and options from all existing trials but also from published studies, surveys, and other sources are preferable for economic evaluation [11].

Decision model is a schematic way to represent of all the clinical and economic evidence of a decision problem [11]. Economic evaluation focuses on expected costs and effects, and uncertainty in them [11]. Therefore, most models that are commonly used in economic evaluation are cohort models that offer mathematical approaches to capture the experience of the average patients. They usually contain decision alternatives, clinical and economic consequences and its sequence, and the likelihood of each consequence. The most common types of cohort models are the decision tree and the Markov model [11].

The decision tree usually consists of three main components. The first part is decision nodes, which is usually at the start of a tree and enumerates alternative options [11]. The second part is the chance nodes which indicate the possible consequences of a certain alternative option [11]. And the third part is the pathways which are mutually exclusive sequent consequences and the routes in the tree [11]. Each pathway has a certain probability which represents the likelihood of the alternatives and consequences [11].

For recurring remitting disease over a long time, a decision tree is not enough to reflect the complexity of the reality. The Markov model can be used to capture the larger number of possible consequences over a longer period [11]. It comprises several mutually exclusive health states and their transition probabilities, under the assumption that all patients in the same state having the same cost, the same utility and the same transition probabilities [11].

Cost in economic analysis is usually referred to opportunity cost: the benefit lost by giving up using those resources when using its best alternative instead [38]. Before collecting the data of cost, what type of perspective that the economic evaluation is based on can decide what type of resources is important to the study. Usually there are two types of perspective: healthcare payer perspective and societal perspective. When the societal perspective is chosen, all resource, including direct and indirect costs within and outside health care field, need to put into consideration. While the health care payer's perspective will only consider the direct healthcare costs which usually indicate in-hospital costs [40]. Direct costs include health care resources which usually contain staffing, consumables (e.g., drugs), overheads (e.g., administration, heat, light, cleaning which are usually shared by more than one program), capital (e.g. buildings and equipment), related services such ambulance services (e.g. for accident and emergency), etc. Indirect costs commonly consist of lost productivity due to morbidity (i.e. the days off work due to illness), premature mortality (i.e. foregone earnings due to early death. Societal perspective can be controversial. For example, the early death can also reduce health service costs) and other costs external to health services [38].

How to define and quantify the health benefits is important for economic evaluation. To decide in what way health outcomes should be measured can directly determine what kind of economic evaluation will be used to assess healthcare intervention [9]. There are generally three types of economic evaluation: cost effectiveness analysis (CEA), cost utility analysis

(CUA) and cost benefit analysis (CBA). CEA usually measures clinical outcomes in “natural units” such as life years gained that is usually based on survival results from studies, disability days avoided, or cases detected, etc. CUA’s consequences are usually measured in terms of preference-based measures of health that can combine quality of life with quantity of life (duration), such as quality adjusted life years (QALY) or disability adjusted life years. CUA is usually considered as a special case of CEA. CBA’s consequences are commonly valued in monetary units [9]. For this conceptual framework we choose quality adjusted life year to represent the state utilities, so the CUA will be used to do the economic evaluation when more data is available.

When we have the results of the costs and effectiveness of the new intervention and its comparator, we can measure the cost effectiveness by using the incremental cost-effectiveness ratio (ICER), where the incremental costs (cost of the new health technology minus the cost of the comparator that is usually the current best practice) is divided by the incremental effectiveness (effectiveness of the new health technology minus the effectiveness of the comparator) [10]:

$$\begin{aligned}
 \text{ICER} &= \frac{\text{Cost of the new intervention} - \text{Cost of the comparator}}{\text{Effectiveness of the new intervention} - \text{Effectiveness of the comparator}} \\
 &= \frac{\text{the incremental cost}}{\text{the incremental effectiveness}}
 \end{aligned}$$

Then we place the results of the ICER in the cost-effectiveness plane (it is presented in Figure 1), where the y-axis represents the incremental costs of the intervention under study and x-axis represents the incremental effectiveness. If the ICER is in the south-east quadrant, it means the new health intervention has higher effectiveness and lower cost, which means it dominates the comparator intervention and should be chosen by the decision maker. If the ICER falls in the north-west quadrant, it means the new intervention has lower effectiveness with higher cost, which will not be recommended to be used. If the ICER is in other two quadrants, decision maker might choose the intervention that has higher effectiveness with acceptably higher cost or the intervention that has lower costs with slightly lower effectiveness. The willingness to pay (WTP) threshold is usually used to represent the highest value of cost that the decision maker willing to pay for one additional year in perfect health (the effectiveness). If the ICER of the new intervention (it can be presented as the slope of the

straight line from the origin that passes through the point: the incremental effectiveness, the incremental cost.) is less than the acceptable threshold ratio (WTP threshold), the new treatment can be adopted by the decision maker [10].

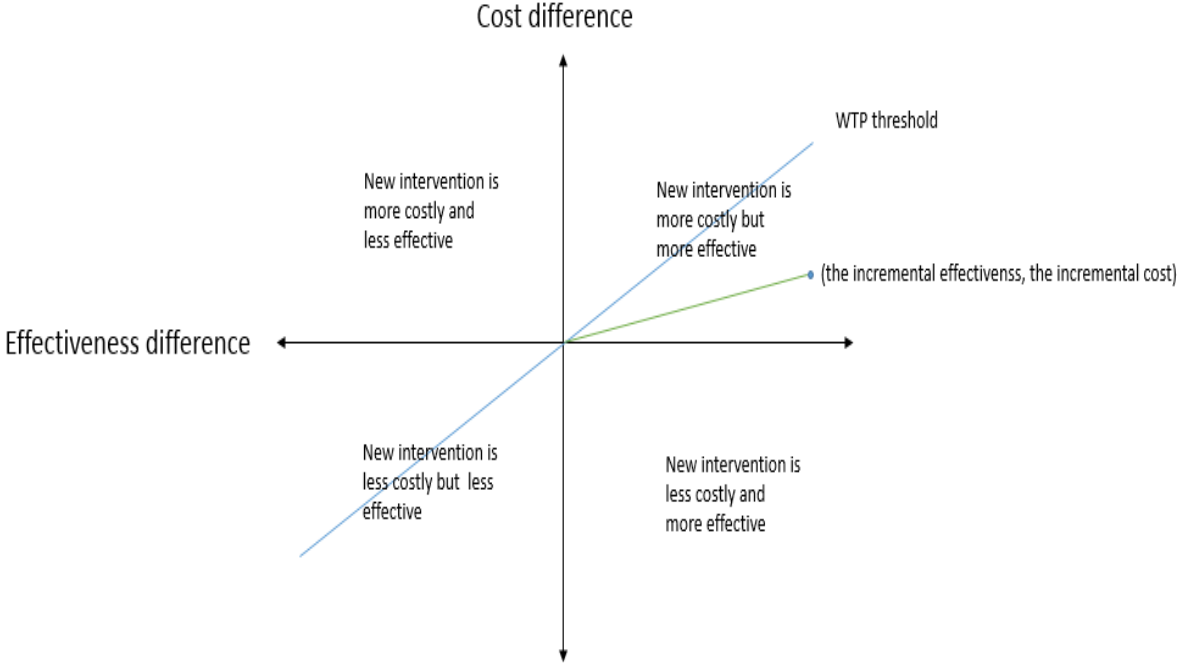


Figure 1: Cost effectiveness plane

All the outcomes, cost and effectiveness/utility, that have been discussed above for doing cost effectiveness analysis are expected value of outcomes, which is the sum of the outcomes of each consequence weighted by the probabilities of that consequence.

$$\text{Expected cost} = \sum_{k=1}^n (\text{cost})_k (\text{probability})_k$$

$$\text{Expected effectiveness} = \sum_{k=1}^n (\text{effectiveness})_k (\text{probability})_k$$

Probabilities represent the likelihood of an event occurring in the future which affect the health and costs of a health intervention. It can be shown as the proportion of homogenous patient cohorts expected to experience the event [11]. One of the most critical part of transition probability is to present how much time passes until an event occurs, i.e. the time spent in a certain health states, for example how long it lasts for refractory cardiogenic shock patients to stay in remission until their next relapse, how it affects the patient's survival if the patients stay in a certain state for a longer time, how the patients' heterogeneity can affect the time to events. We need to find out whether the transition probabilities vary according to the time [11]. There are generally two types of time dependency in transition probabilities in Markov models. One is probabilities that vary according to time in model where transition probabilities differs as the cohort ages. Another type is probabilities which change in line with the time a patient staying in a certain health state. To model a medical process where the current event will affect the future event, we can add more states to the model (too simplified model usually cannot reflect the time to event) and to add time dependency into transition probabilities [11]. We can estimate the relationship between the transition probability and time by obtaining patient-level data which usually come from clinical trial and cohort study with records of the time to one or more events for each patient by doing survival analysis or we can get the information directly from performed and published survival analysis [11].

Since many choices based on different sources and assumptions must be made to structure a model, every economic evaluation will contain some degree of uncertainty. One of the most important requirements for economic evaluation for decision making is to demonstrate the uncertainty in the available evidence and how it affects the decision uncertainty. [11]. Sensitivity analysis is a popular way to capture the uncertainty in the results of economic evaluations and to inform the impact of structural choices, which also helps to generalize the evaluation to other settings [10]. One-way simple sensitivity analysis (univariate analysis), multiway simple sensitivity analysis (scenario analysis) and probabilistic sensitivity analysis are commonly used in economic evaluation. When more data become available for this conceptual model, we can perform heterogeneity analysis to gain insight into how the results vary according to the variation of patients' characteristics. We can also do probabilistic sensitivity analysis by assigning certain probability distributions (usually including beta, di-

richlet, gamma, and the normal distribution) to certain type of parameters to check the effect of variations in parameter values on the cost effectiveness results [38]. And with a large sample of outcomes created by probabilistic sensitivity analysis, we can create a cost-effectiveness acceptability curves which can help to inform different stakeholders which healthcare intervention is most probably cost-effective under different willingness to pay thresholds. Probabilistic sensitivity analysis can also be used to find out the expected value of perfect information [11].

3.3 Conceptualize the model

A conceptual model needs adequately to capture all the key factors of a disease history and interventions' impact on the cost, effectiveness and other outcomes [11]. However, it is impossible to build a model that include all aspects of the treatment. Model is a simplified representation of the reality. The simplification and abstraction of the model makes it possible to observe the complex clinical real-world phenomenon. However, too simplified model affects the model's transparency which means to which extent that interested parties can review the structure, equations, parameter values, and assumptions of a model [41]. Besides, it affects face validity that means to which extent that an expert in relative field can confirm that a model including its assumption and application reflects current science and evidence [41]. Therefore, it leads to potentially wrong and misleading results about the cost effectiveness of certain healthcare intervention [11]. Credibility is always more important compared to simplicity [42]. *"Failure to account for the complexities of the decision problem may result in the development of models which are mathematically sophisticated but contextually naïve."* [43 p.6]. The conceptual model should display a certain degree of complexity to guarantee the credibility and keep the face validity to clinical expert, and can be further developed with more complexity to be used by policy makers for solving many problems [44].

According to "Conceptualizing a model a report of the ISPOR-SMDM modeling good research practices task force-2" and Briggs's book about decision modelling for health economic evaluation, the development and construction of this conceptual model generally consists of two parts [11, 44].

The first part is to conceptualize the research problem. It is done by first gaining knowledge of specific disease and health care intervention, such as refractory cardiogenic shock treated by ECMO and their specific clinical and economic characteristics. Afterwards, the information was transferred to represent the specific research problem and capture the key factors of the research problem. By doing this part, we can define the specific disease spectrum, the relevant analytic perspective, the target population, the alternative interventions including the new technology, the health outcomes, and how the costs and health outcomes can be expressed, and the time horizon, etc. [44]. The second part is to build the conceptual model by making the certain analytic model with their specific characteristics and attributes to meet the requirements of the research problem. [3, 44] For example, by doing the first part, I identified that certain characteristics, such as age, different causes of refractory cardiogenic shock, might have significant impact on the outcomes of ECMO treatment, so in the second part, I incorporated those factors in the conceptual model. Both parts have been revisited and modified in every stage of the model development.

It is usually not common to build a decision analytic model by gathering relevant medical and economic evidence from a single source. Evidence to inform their parameters are necessary in all decision analytic models, such as disease natural history and certain clinical events, resource utilization, treatment effects including health-related quality of life, survival and other time-to-event outcomes, and transitional probabilities. However, which parameters should be considered as relevant and important factor and how these parameters should be presented is very important evidence as well. Building a model requires to make many choices about what type of factors should be included in the model and how they are related to one another. Developing a useful mathematical decision analytic models need not only mathematical ability but also ability to capture the complexity of the process of the disease and to make choices to translating the understanding of complexity into the credible conceptual and mathematical model [45]. Those choices include choices about which events and their sequences, health states should be put into the model's structure, about which the intervention and its comparators, and about which evidence sources can be used to inform the model parameters, etc. Choices about what is relevant to the decision problem are usually based on subject judgements and limited evidence, which can be wrong because of ab-

sence of perfect information. So, the choices have close relation on the model's credibility and interpretation [45].

To make well-informed choices to develop a credible and valid conceptual model for the ECMO treatment for adult patients in refractory cardiogenic shock, systematic literature review and consultation with experts to gain more professional medical and economic opinion by meetings and emails were performed. As more information and evidence gathered through literature review, emails and meetings with experts, different choices were made at every stage during the process of the model development. The detailed process of the conceptual model development can be seen in the flow chart in Figure 2.

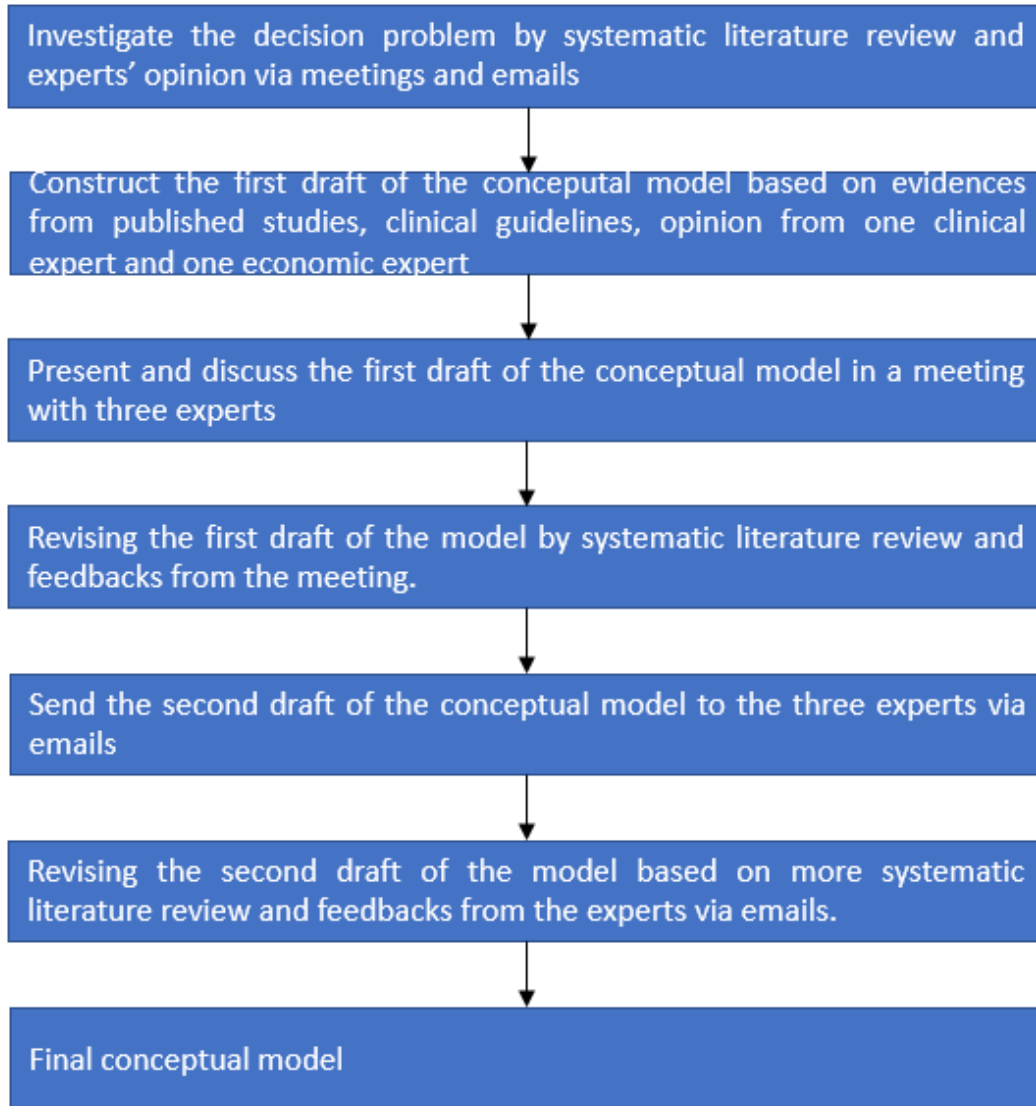


Figure 2: the flow chart of the development and construction process of the conceptual model

The first draft of the model was made during March 2018 by incorporate all the evidence I gathered through literature review and discussion with a clinical expert and a health economist via meetings and emails. Then I presented the first draft to the experts in April 2018 during a meeting. Afterwards I revised the first draft based on the opinions from the experts and more literature review. Then I sent the second draft to the experts by emails and revised it based on their feedbacks and more literature reviews to get the final conceptual model.

3.4 Gather information of relevant evidence

3.4.1 Literature review

A literature review was conducted to assist the construction and development of the conceptual model for refractory cardiogenic shock adult patients treated by ECMO. All the targeted literature searches were conducted online in search engine Google. The literature Searches were conducted during the period from January 2018 to April 2018. Only articles published in English language in the past 15 years (2003–2018) were selected into the literature review.

The literature search strategies can be divided into two parts: the clinical/medical part and the economic part, and they are developed and modified timely to meet the needs to offer adequate information to build the conceptual model. For clinical part, search terms such as “acute heart failure”, “cardiogenic shock”, “ECMO”, “microcirculation”, “macrocirculation”, “oxygen delivery index” , “ProECMO” and the different combination of them have been used in order to gain more understanding of the cardiogenic shock disease, microcirculation, the ECMO treatment and the ODIN by searching for clinical guidelines and medical literatures, and to identify the existing treatment pathways of refractory cardiogenic shock by obtaining available real world evidence in clinical studies and reviews. For the economic part, search terms such as “ECMO cost effectiveness”, “ECMO cost”, “ECMO economic evaluation”, “ECMO cost utility”, “cardiogenic shock economic evaluation” , “cardiogenic shock cost effectiveness” , “cardiac economic” and so on were used to find out the existing economic analyses of ECMO and cardiac disease. Most of the literatures that have been chosen to review were found through literature search strategies. Most literatures have a reference list. Several literatures that offer important information for developing this conceptual frame are also found in other articles’ reference list.

3.4.2 Expert opinion

During the process of the model development, one clinical expert, one health economists, and an expert in the pharmaceutical, biotechnology and clinical laboratory industries, were

consulted by emails and two meetings during the period from February 2018 to May 2018. One meeting was held in February 2018 and another one meeting was held in April 2018.

By consulting the experts, it is helpful to make choices about which part of reality should be considered to be relevant to the decision problem and be put into the model to appropriately represent the clinical process and characteristics of refractory cardiogenic shock treated by ECMO, and to gain face validity for the conceptual model to make sure that the model under development can be revised timely based on the input of the experts in order to ensure that the experts can understand how the conceptual model capture the nature of the problem and the impact of the ODIN on costs, utility and transition probabilities and to ensure that the model is good enough to address the decision problem.

By consulting with experts during March, the four clinical responses and the three medical causes of the VA-ECMO treatment for refractory cardiogenic shock adult patients were considered as important clinical characteristics that need to be put into the conceptual model to address the research question. I presented the first draft to the experts during the meeting in April and explained the structure of the conceptual model. We discussed the events included in the model on the short or long term and other topics that appeared after more systematic literature review. The model was revised based on the opinion of the experts. The second draft of the model was revised by the experts. Then the final model was built by revising the second draft based on their feedbacks.

Chapter 4

Results

Since the systematic literature reviews were conducted during the whole process of building the model, I didn't record the total number of all the literatures that I found, because new literatures with relevant information constantly appeared at every stage of the model development. But all the literatures that were used to develop this framework are listed in the reference.

The conceptual frame work consists of two parts: the conceptual model, and the suggestions for defining and collecting data of the key parameters and for the possible impacts that the ODIN technology could have on the value of the selected parameters.

4.1 The conceptual model

The conceptual model for the ECMO treatment is aimed to describe the experience of refractory cardiogenic shock patients treated by VA-ECMO. It can be applied to guide the early HTA of the ODIN technology. It consists of a decision tree model and a Markov model. By illustrating the demographic, clinical characteristics, and the possible clinical consequences over time of the refractory cardiogenic shock patients treated by ECMO, this model helps identify relevant therapeutic and economic endpoints and states.

The study perspective is healthcare payer perspective. Because the societal perspective can be controversial and previously raised in the method chapter. An example of this is, premature mortality can generate foregone earnings, however the early death can also reduce health service costs. The ECMO treatment is primary for critically ill patients who face high risk of premature mortality. Most of the published literatures about the ECMO cost took the healthcare payer perspective. it will be much easier to collect data for costs if we the chose healthcare payer perspective when we try to implement the model in the future [6].

Target population is adult patients with clinical characteristics of refractory cardiogenic disease. Since this model mainly aims to be used in health technology assessment in a healthcare perspective, the target population for this model is closed which means the patients can only get involved in the analysis at the beginning [44].

The health intervention of interest in this thesis is treating the refractory cardiogenic shock patients with the support of ECMO. This is the current best practice that can be offer for cardiogenic shock patients who are refractory to the conventional treatments.

The patients are assumed to receive the ECMO treatment temporarily the first time in their life at the beginning of the analysis. The conceptual model is evaluated in a lifetime horizon, modelling outcomes from the start of the healthcare intervention until the patient dies.

4.1.1 The first part of the ECMO treatment captured by the decision trees

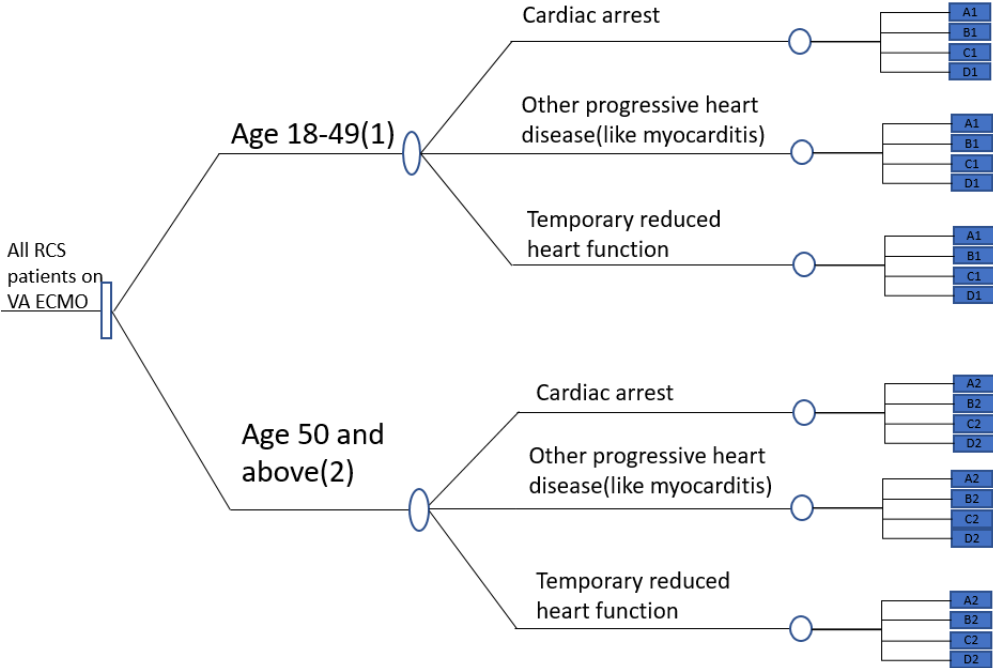


Figure 3: the draft of the decision tree that captures the important evidence of the first part of ECMO treatment.

The first part of the ECMO treatment is captured in the draft of decision tree that is presented in Figure 3. All RCS patients are assumed to receive the VA-ECMO treatment for the first time. They are likely to experience four clinical responses: total or partial recovery (denoted by A in the decision tree), more durable mechanical heart pump assist (denoted by B), and heart transplant (denoted by C), and death (denoted by D). The first part of ECMO treatment usually only lasts a few days to a few weeks. Decision trees are suitable for modeling problems with a short time horizon [11]. They can also outline and capture the constituents of the research problem. And they are easy to conceptual and modify [11].

The distribution of the four clinical responses are affected by patients' age, and their medical causes to use the ECMO treatment. There are two age groups that were identified, with group 1 being defined as age between 18 to 49 years old and group 2 being defined as age 50 and above. For each age group there are three clinical causes why the VA-ECMO initially treated the patients: Cardiac arrest, other progressive heart disease (like myocarditis), and temporary reduced heart function during open heart surgery.

After more literature review, communication with experts, presentation of the model draft in the second meeting, two parts of the decision tree were thus revised. Firstly, the third cause "temporary reduced heart function during open heart surgery" was replaced by "post cardiac surgery". Because ECMO is not used during open heart surgery but after surgery. A different but similar type of cardiopulmonary bypass (CPB) is usually used in the operating room [46]. During open heart surgery CPB is used routinely. This is because the heart is paralyzed (cardioplegia) to make the heart stand still for better working conditions for the surgeon, and because the surgeons often must open the heart to repair or replace [2]. This standard procedure with using CPB is used for valve surgery, coronary surgery (can be operated also without CPB), aortic surgery, heart transplant and for implanting a mechanical assist (LVAD) [2, 5]. CPB is usually used for hours during the heart operations, while the VA ECMO is usually used for days or weeks [2]. Secondly, patients with three different indications for using ECMO are further divided into two groups: with or without history of heart disease, because whether patients have a history of heart disease or not might influence the survival rate [2, 38]. Therefore, we got the second draft of the decision tree that is represented in Figure 4.

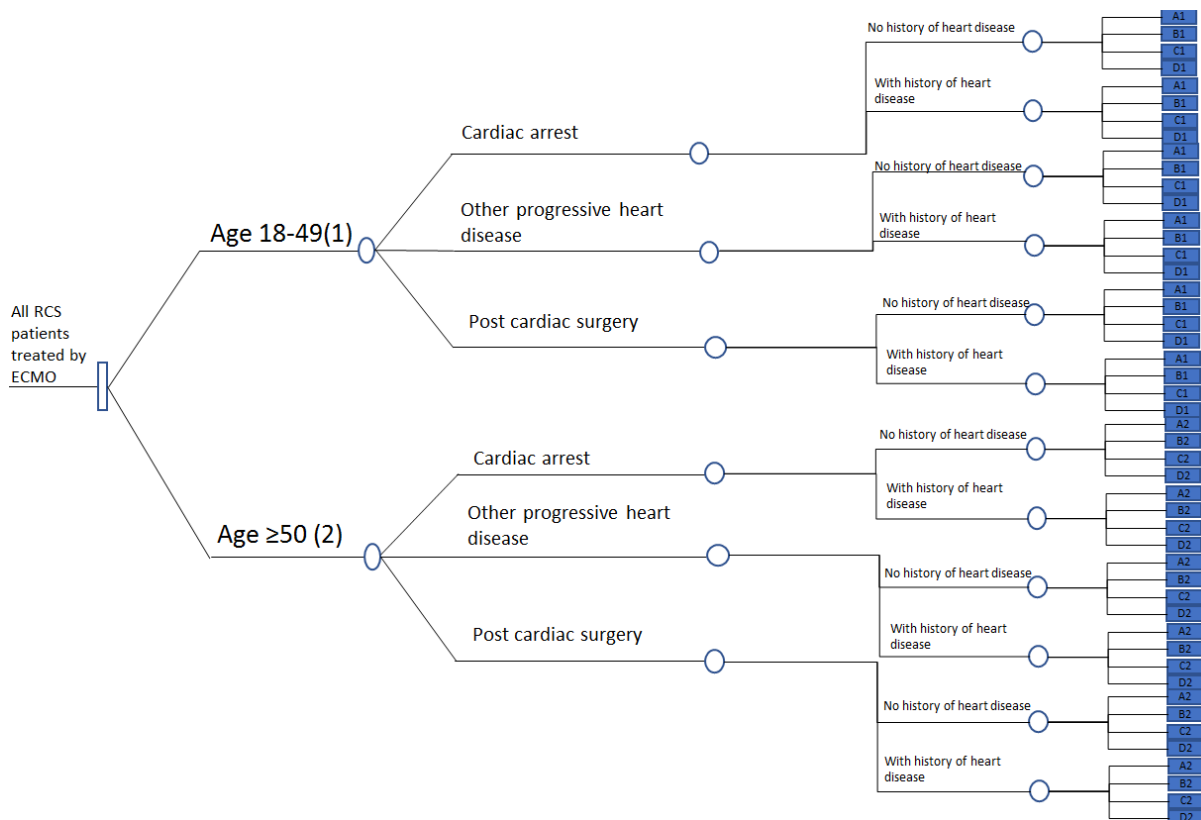


Figure 4: The second draft of the decision tree that captures the reality of important characteristics in the first part of the ECMO treatment for RCS adult patients.

However, the second revised draft of the decision tree became very bushy, based on expert's opinion, which might make it difficult to program and to present [11]. And the evidence to support the point that the history of heart disease has a significant impact on the outcomes was not strong and rigorously proven [2,38]. So, I decided to delete them from the decision tree and we got the final version of the decision tree that is presented in Figure 5.

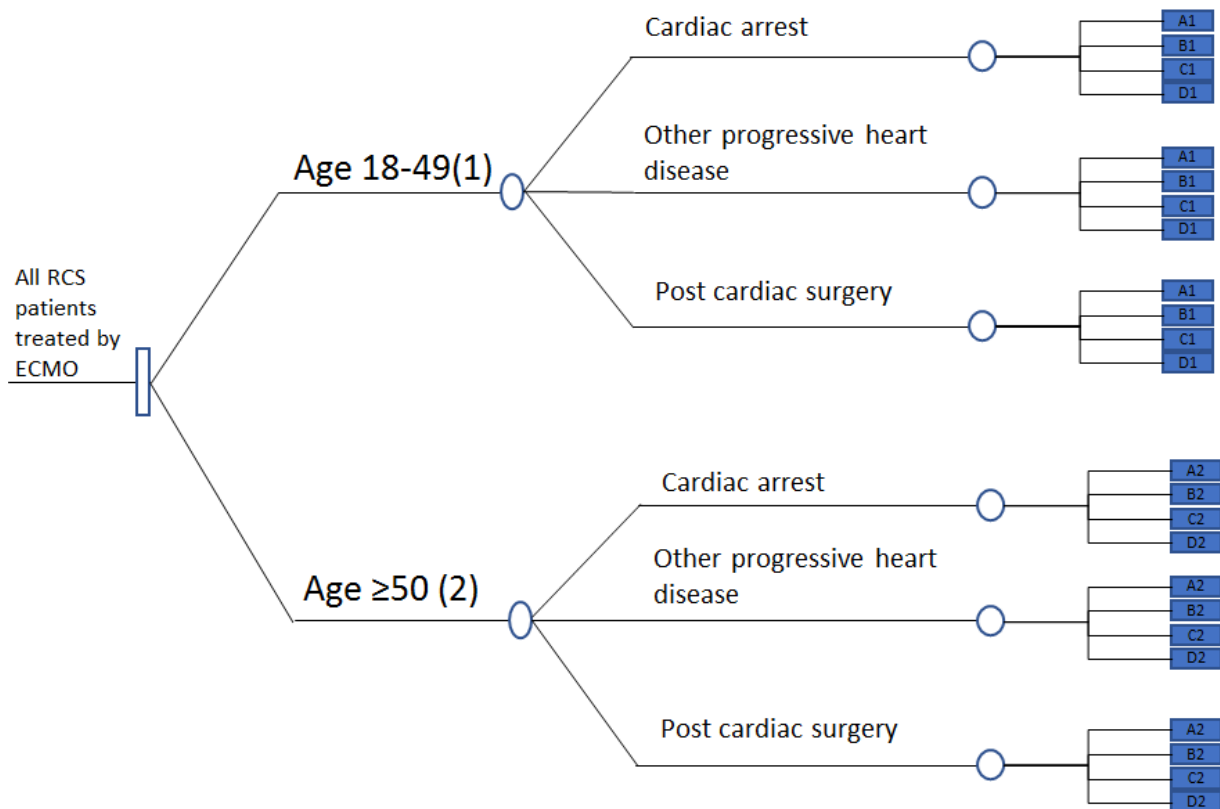


Figure 5: the final decision tree that captures the most important characteristics of the first part of the ECSO treatment.

The reasons why the final decision tree is structured this way is elaborated below in detail:

1. Arguments for dividing the patients into two age groups in the decision tree

Firstly, different age groups have different survival rate and different distribution of clinical outcomes. For patients treated by ECSO, there is a negative correlation between age and survival rate. The older the age the patient is, the lower survival rate the patient will have, and vice versa. In the Mathieu’s paper of SAVE score, it said younger age is a protective characteristic to predict the survival after the ECSO treatment for refractory cardiogenic shock, which means the younger the patient is, the higher survival rate the patient will have. The average hospital survival rate of a RCS patient in age 18 to 38 after ECSO can be higher than 75%, while the average hospital survival rate of a RCS patient who is older than 63 after

ECMO can be less than 42% [46]. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure also reported that older adults face a longer hospital length of stay and higher risk of mortality when admitted in hospital due to heart failure [12]. The clinical expert also confirmed that older patients might have higher probability of death and smaller chances to get more invasive management, such as heart transplantation, therefore young patients tend to have higher chance of having the clinical response heart transplant, compared to old patients, which leads to different distribution of outcomes [2].

Secondly different age groups are eligible for different treatment options and different distribution of treatment options, which leads to different cost. Usually older patients tend to have smaller chance of temporary ECMO treatment, heart transplantation, permanent LVAD and other open-heart surgery compared with younger patients [2]. And One of the important challenges for healthcare system is to increase the ability to select appropriate older patients for invasive management [48]. Besides comorbid conditions, cognitive impairment, frailty and limited social support, ageing also plays an important role in determining how complicated a heart failure management can be [12]. For example, drugs recommended for heart failure are often underused in the elderly patients (angiotensin converting enzyme inhibitors, beta-blockers and spironolactone are less frequently given to old patients), which shows a biased management for elderly patients with heart failure [28].

Lastly, the distributions of the three clinical causes for using ECMO to treat refractory cardiogenic shock vary among age groups [28]. This point was validated by the clinical expert during the second face to face meeting. When compared with younger patients, elderly patients usually present a distinct clinical profile and a more complicated course of disease because of some clinical features common in older population [28].

2. Arguments for three causes of the ECMO treatment.

All patients utilizing VA-ECMO as a means of providing mechanical circulatory support (MCS) only used it for threatening or established cardiogenic shock [2,5]. However, the underlying pathophysiologic etiology that causes refractory cardiogenic shock is different and can be identified and categorized as different causes for the VA-ECMO support.

Guidelines for Adult Cardiac Failure given by extracorporeal life support organization (ELSO) listed typical causes of cardiogenic shock for using ECMO that consist of acute myocardial infarction, myocarditis, peripartum cardiomyopathy, decompensated chronic heart failure, post cardiectomy shock [47]. One study suggests classifying the underlying reasons leading to the use of the VA-ECMO into seven categories as: cardiac arrest, acute decompensated congestive heart failure, acute on chronic congestive heart failure, myocardial infarction, acute PE, right ventricular failure (RVF) not secondary to acute pulmonary embolism (PE), and post-cardiectomy syndrome (PCS) [5]. In another study, cardiogenic shock patients were divided into twelve diagnostic groups: 'valvular heart disease', 'post-transplantation', 'congenital heart disease', 'aortic disease', 'other post-cardiectomy', 'acute myocardial infarction', 'chronic heart disease', 'fulminant myocarditis', 'pulmonary embolism', 'sepsis', and 'refractory ventricular tachycardia (VT) or ventricular fibrillation (VF)' [46]. However, none of the classifications of diagnostic causes in the studies are mutually exclusive, which makes them difficult to be use in a decision analytic model.

After discussing with the clinical expert by emails and meetings, it was decided to include three mutually exclusive clinical causes leading to refractory cardiogenic shock and utilization of the ECMO into the decision tree. They are 'cardiac arrest (ventricular fibrillation of systole)', 'other progressive heart disease' and 'post cardiac surgery'.

Cardiac arrest means a sudden failure of heart pump which causes loss of blood flow [49]. The other progressive heart disease comprises conditions like acute coronary syndrome, cardiac arrhythmic storm refractory to other measures, sepsis with profound cardiac depression, drug overdose/toxicity with profound cardiac depression, myocarditis, pulmonary embolism, isolated cardiac trauma, acute anaphylaxis, chronic cardiomyopathy [1]. They are usually treated with conventional therapies. If the patient in progressive heart disease have an established cardiogenic shock or in a process of deterioration anticipated to end up in a cardiogenic shock, they will be put on ECMO [2]. And patients who are through recent cardiac surgeries including coronary artery bypass grafting, valvar surgery, and heart transplantation and so on are usually supported by VA ECMO because they cannot be weaned from cardiopulmonary bypass in the operating room, or may get cardiogenic shock in the setting of post-operative course because of complications and other natural sequela of critical illness [2,5].

Different reasons leading to refractory cardiogenic shock which needs to be supported by ECMO differs with their typical treatments, which generates different costs [5]. Cardiac arrest (Ventricular fibrillation or asystole) is the most common form of acute heart failure with cardiogenic shock. When it happens, the patient might die within minutes, unless cardiopulmonary resuscitation (CPR) is started [2, 5]. Next treatment is to give an electrical shock to restart the normal heart rhythm. If all of them didn't work, ECMO treatment should be conducted within 40 minutes [2,50]. On the other hand, the treatment for the progressive heart disease can be very different. For example, myocarditis is an inflammation in the heart muscle caused by a virus. Medical treatment is directed towards reducing the inflammation and the virus infection (like steroids or chemotherapy (Metotrexat)) [2]. But myocarditis has the effect of harming the heart muscle function temporarily or permanently. The inflammation can at any stage increase and lead to increased heart failure. It might take weeks before refractory cardiogenic shock takes place. When it happens, the ECMO treatment might be used to partly or totally take over the pumping function of the heart [2].

The cost in Norway of the VA-ECMO treatment for an individual adult patient with one of the progressive heart disease cardiomyopathy was more than USD 400000, while the cost of the VA-ECMO treatment for an individual adult patient after heart transplant was much less, about USD 75000 [27]. Another study found out that in Taiwan the estimated total hospital cost was USD 43245 for average adult patients who had Postcardiotomy shock, which means they had shock after cardiac surgery, while the cost for other patients was much less, about USD 28266 [51]. A study conducted in the US found that the total charges for ECMO treatment was about USD 273429 for average adult patients postcardiotomy, about USD 722123 for patients post heart transplant, about USD 352559 for patients with other causes of cardiogenic shock [52].

And different causes of refractory cardiogenic shock treated by ECMO leads to different survival rates and distribution of the four clinical responses. The Mathieu's paper of predicting survival after ECMO for refractory cardiogenic shock points out that the underlying diagnosis of cardiogenic shock has significant impact on determining hospital survival [46]. According to the Extracorporeal Life Support Organization registry, survival rates of cardiac ECMO patients are ranging from 23% to 71%. The lowest survival rate is seen in patients who had cardiac arrest, and the highest survival rate is with myocarditis, which can be as high as 71%

[21]. Patients in cardiac arrest which is usually thought an extreme form of cardiogenic shock are reported with a worse survival compared to the other cardiogenic shock patients [5]. Patients getting ECMO treatment after getting a cardiac surgery generally face a poor survival rate compared to other causes of cardiogenic shock too [5]. In a study, 67% mortality rate was found for patients with refractory cardiogenic shock postcardiotomy [53]. A multicenter study in the USA found that the average in-hospital mortality rate of the ECMO treatment was 44.2% for adult patients postcardiotomy, 41.9% for adult patients post heart transplant, 64% for adult patients with other causes of the VA-ECMO treatment [52]. According to the guidelines for adult cardiac failure issued by ELSO, different reasons really generates different distribution of outcomes. For example, VA ECMO patients in acute MI after revascularization and myocarditis has higher chance to recover, while patients with unrevascularizable acute MI and chronic heart failure have higher probability to get heart transplant [47]. It is less likely for patients using ECMO after cardiac surgery to get an open-heart surgery later again either for LVAD or for heart transplant (corresponding to response B and C) compared to patients in other causes (cardia arrest and other progressive heart disease). All of information listed above indicates that there will be different distributions of the four clinical responses for different causes leading to refractory cardiogenic shock which needs the support of ECMO.

3. Arguments for the four clinical responses in the decision tree.

ECMO is a temporary device to take over the insufficient pumping capacity of the heart at the time when the ECMO is started. ECMO can be used to keep supporting the patient until the patient either recovers or partially recovers to gets a long-term ventricular assist device as a bridge to cardiac transplantation, under the assumption that the brain function is normal or only minimally damaged [1]. As a temporary mechanical circulatory support, the ECMO increases both the likelihood of recovery and the time to consider the choice of other treatment options, such as more durable mechanical heart pump assist (for example, a left ventricular assist device) or heart transplant [21]. ELSO's guidelines say that ECMO is a bridge to recovery, transplant and implantable circulatory support [47].

The clinical expert also confirms that there are generally four possibilities of clinical consequences after using ECMO to assist treatment for refractory cardiogenic shock patients:

A: Total or partial recovery of the heart function, and no need for heart transplant or a Mechanical pump (Left ventricular assist device - LVAD). ECMO is a bridge to recovery.

B: ECMO can be a bridge to a more durable mechanical heart pump assist such as LVAD.

C: ECMO can be a bridge to heart transplantation.

D: The patient can die on ECMO.

4.1.2. The second part of the ECMO treatment captured by the Markov model

For longer time horizon, more dynamic modelling methods such as state-transition Markov model is required. It can reflect a more complex prognosis. The Markov model contains a set of possible transition between the mutually exclusive health states over a series of discrete time periods (cycle) [11]. If we keep using decision tree to model all the possible consequences over a longer period, the decision tree will end up with a large quantity of pathways and nodes, which will make it difficult to present and program the research problems. So Markov model is a better choice to model the second part of the ECMO treatment [11].

I first started with one specific Markov model, and then revised it twice before I got the optimal model. Because I constantly gained more evidence and information about the key features of the disease and their clinical impact by systematic literature review, and emails and meetings with the experts when developing the models.

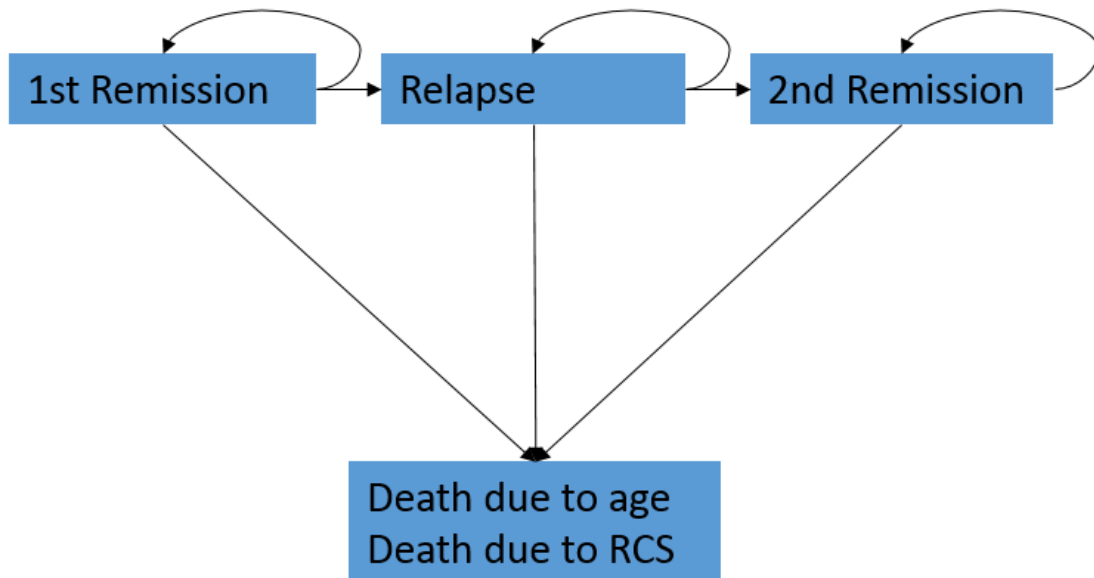


Figure 6: the first draft of the Markov model that captured the second part of the VA ECMO treatment.

The basic structure of the first draft of the Markov model is given in the Figure 6. It captures the possible clinical consequences over time in a life time horizon of the RCS patients in second part of VA ECMO treatment. After getting the first part of ECMO treatment, the patients who survive include patients who get total or partial recovery of the heart function (denoted as A in the decision tree), and patients who will receive a durable mechanical heart pump assist such as LVAD (denoted as B in the decision tree), and patients who will get a heart transplant (denoted as C in the decision tree). Patients who died in the first part of the ECMO treatment (denoted as D in the decision tree) will not be modelled in the Markov model. All the patients who survived from the first part of ECMO treatment will have three health states. They might stay in survive in the first remission, might get cardiogenic shock relapse to receive ECMO treatment again, and might die. Patients who get the ECMO treatment again might either survive to get the second remission (which means they might survive to get recovery, get LVAD or get a heart transplant), or stay in relapse or die. Patients who are in the second remission might either stay in the second remission or die. The death is usually caused by two reasons aging or the specific disease refractory cardiogenic shock.

Therefore, this draft contains four mutually exclusive health states including the first remission, relapse, the second remission and death. The total numbers of survived patients in response group A, B, C in the decision tree can be counted as the total patients in the state of the first remission. The model is evaluated over 20 years, because it is assumed that after 20 years most of the patients have already died, and modelling the experience of remaining patients is not going to have significant impact on the final results.

The cardiogenic shock can be a recurring-remitting disease over a period of many years. Refractory cardiogenic shock patients are usually very ill, and based on the feedbacks from the clinical expert: *“many patients may be admitted several times because of cardiogenic shock and treated each time with drugs, only a few patients are admitted to hospital to receive VA ECMO treatment several times because of refractory cardiogenic shock.”* [2]. I assume that they can only go through one relapse of refractory cardiogenic shock during their life time. And For patients in the response B and response C who received the VA ECMO to get a more durable mechanical circulatory support such as left ventricular assist device or as a bridge to heart transplant might have a higher possibility to use VA ECMO again (relapse) because post cardiac surgery is one of the three clinical causes in the decision tree to receive ECMO as temporary support, therefor they might have higher chance to have a relapse.

With more information from literature review and experts' opinion, I found that patients in group B who needs to receive a more durable mechanical circulatory support such as LVAD and group C who needs a heart transplant will move to cardiac surgery [2]. And in the long run, a proportion of the recovered and the partially recovered patients (denoted as A in the decision tree) might experience complication or progression of disease and will need to go through cardiac surgery to get more durable mechanical circulation device or to get a heart transplant. Some patients in group A will become patients in group B and C to get cardiac surgery. All of them might have higher chance to get first relapse to receive VA ECMO again due to complications or the natural sequela of critical illness after surgery, compared to other patients [5]. So, the transition probability of relapse from remission is higher for patients in group B and C, compared to the group A patients. The other transition probabilities might be different as well. Further, since B and C patients who will undergo cardiac surgery after getting ECMO, their quality of life in health state of remission and relapse might be different from other patients. Since Markov model is memoryless, and do not account for the pa-

tients' history of disease, we can relax the Markov assumption by adding additional health states. So, the first draft of the Markov model was revised and a second version was built. It is displayed in Figure 7.

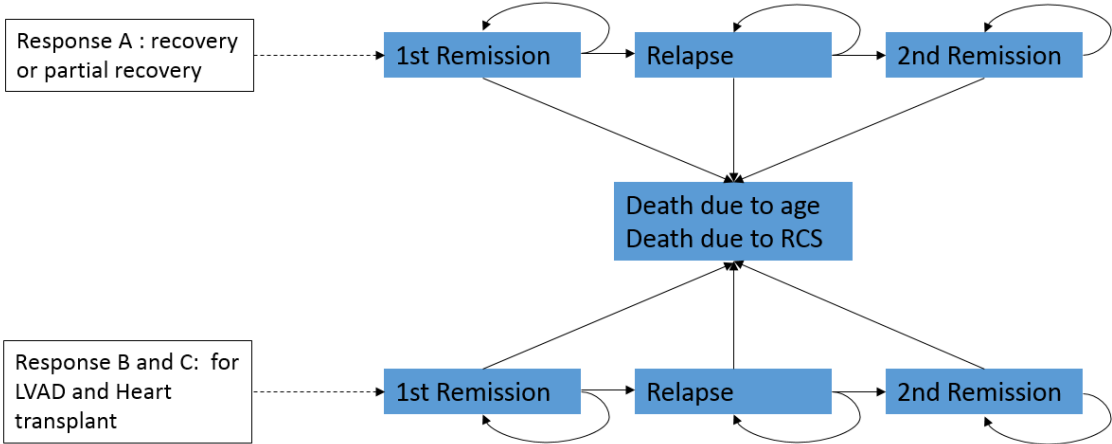


Figure 7: the second draft of the structure of the Markov model which captures the second part of the ECMO treatment. The dotted line indicates where the patients in the first remission initially come from. Becomes patients who have recovered or partially recovered (denoted as A in the decision tree) entering the second part of the ECMO treatment will have different transition probability and cost and utility for the four health states (the first remission, relapse, the second remission and death), compare to the patients who enter into Markov model for LVAD and heart transplant (patients in group denoted as B and C and a proportion of patients in group denoted as A in the decision tree.)

The additional health states have added to the second draft of the Markov model to help reflect the influence of patients' history on the future transition probability, costs and health-related quality of life. Because patients in Recovery group (Response A) and patients in the cardiac surgery group to get LVAD (Response B) or heart transplant (Response C) might have different transition probability, costs and utility for the four mutually exclusive health states that include the first remission from the first part of the ECMO treatment, the relapse to get the ECMO treatment again, and the second remission after the second ECMO treatment, and death. In this model, part of the patients in response group A will become patients in B and C, because the condition of the patients who recover from the ECMO

treatment might get worse, which might cause them to get relapse to receive the ECMO treatment again, or make them become patients in B and C group to get LVAD or heart transplant. And patients in group B and C, they might stay in the first remission before and after the cardiac surgery to get LVAD or heart transplant. They might get relapse to ECMO treatment again after the first remission, either before or after the cardiac surgery.

After getting more information from literature review, I found evidence that the time that patients in group B and C spend in waiting before they receive cardiac surgery might have a significant influence in the future transition probability, costs and utility of different health states. Patients with different response (to get LVAD or heart transplant) might have different time waiting for cardiac surgery. The waiting time for heart transplant is often more than six months. And all waiting times vary because of factors such as: blood type, geographic area, a shortage of donor hearts [54]. In addition, patients who need get heart transplant and patients who only need LVAD might have different level of severity of illness. If the difference of the waiting time for cardiac surgery and the difference of the degree of illness between group B (LVAD) and group C (heart transplant) is significant, and the transition probability and quality of life is highly dependent on how long the patient must wait before they get the surgery and severity of their illness, we can add more health states in the Markov model to reflect the difference between LVAD patients and heart transplant patients. Furthermore, as we know LVAD is also a bridge to heart transplantation, which means a proportion of patients in group B might become patients in group C to get heart transplant in the years to come [55]. To capture those difference and features, I revised the second draft in Figure 7 and get the modified final Markov model in figure 8 by adding more health states.

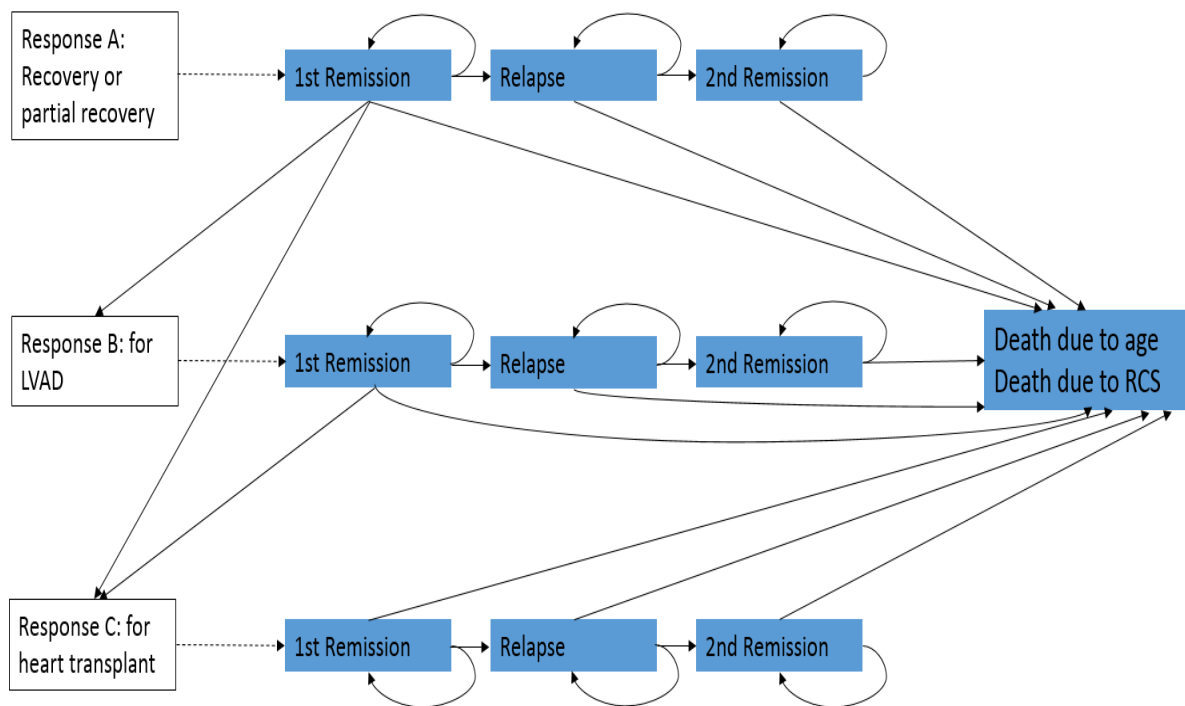


Figure 8: the final structure of the Markov model that captured the second part of the ECMO treatment for refractory cardiogenic shock adult patients treated by ECMO. The dotted line indicates where the patients in the first remission initially come from. Because patients that come from different response group (denoted as A or B or C in the decision tree) will have different transition probability, cost and utility for each health states, including the first remission, relapse, the second remission and death.

Model in the Figure 8 is the final Markov model which got modified on the basis of the second draft in Figure 7. The additional health states considered the details of the history of the patients and their influence for the future costs, utility and transition. Patients who used the first part of ECMO treatment as a bridge to LVAD (including patients in response group B and a proportion of patients in response group) might have different waiting time and severity of disease before they get the cardiac surgery to receive the LVAD, when compared to patients who used the first part of ECMO treatment as a bridge to heart transplant (including patients in response group C and a proportion of patients in group A and B from the decision tree). Therefore, they might have different transition probability for different health states, for example, probability to staying in the first remission before or after the surgery, and transi-

tion probability from the first remission to the relapse due to cardiogenic shock they got again before or after the surgery, etc. And they might generate different cost and have different quality of life in different health states.

4.2 Parameters

Before conducting an economic evaluation of ODIN by implementing the conceptual models, we need to collect data to estimate the effectiveness and costs associated with each part of the conceptual model. Parameters need to be estimated in all decision models. There are usually four categories of parameters involved to populate the model. They are state costs, state utilities in every health state in the conceptual model and transition probabilities (chance of moving from one health state to another or the likelihood of a certain outcome following an event.), and discounting rate [11]. Several suggestions and assumptions were made below for defining and collecting data for important parameters, and for the impact that ODIN might have on the parameters. Those suggestions and assumptions might be useful when we try to populate the conceptual model in the future. All the suggestions and assumptions were made by conforming to the basic principles of evidence based medicine and economic evaluation.

4.2.1 State cost

As discussed in the third chapter Method, societal perspective can be controversial, for example, premature mortality can generate foregone earnings, and however the early death can also reduce health service costs. ECMO treatment are mainly for critically ill patients who face high risk of premature mortality. And most of the published literatures about the ECMO cost took healthcare payer perspective [13]. It might be difficult to get data if we took the societal perspective. Since the perspective of the evaluation plays a crucial role in determining the necessary data that need to be collected to estimate both the utility and costs of the intervention, I suggest taking healthcare payer perspective for this conceptual framework. However, if we are more interested in production loss due to ECMO treatment and allocating resources in different sectors of the society for policy purpose and the total welfare of the society, societal perspective can be chosen.

After deciding the costing perspective, we need to find answers to questions like: what kinds of resources utilization are closely connected to the ECMO treatment of refractory cardiogenic patients, and how those types of resources can be assessed and valued. By examining the healthcare intervention process and by conducting a sensitivity analysis that can measure the costs in detail, we can gain insight into what kinds of resource utilization have significant influence on the change of the incremental and total costs and decide what cost units can be incorporated into the calculation of state cost. For example, in a hospital perspective, after examining the process of the refractory cardiogenic patient's treatment journey, we include costs of medications, ECMO support, ODIN, personnel resources, diagnostic and laboratory tests, radiology and operating room procedures, blood products, future medical charges for survivor post discharged and other overhead costs, etc [13,27]. Then we can conduct a sensitivity or other kinds of statistical analysis to assess the uncertainty related to the labelling of cost categories. This type of analysis can also be used to figure out how other factors such as the diagnosis category, setting and patients demographical characteristics affects the wide variation in the in-hospital cost of current VA ECMO and future ODINN treatment [6]. Then we can further filter out the most relevant categories of costs that can be included to calculate the total state costs and exclude the types of costs that are unlikely to have significant impact on the results of total costs. Commonly the largest resource utilization of health care resources is related to staffing costs [38]. By analyzing the cost of ECMO in Riskhospitalet University Hospital the writer found that on average personnel use comprise 82% of the cost for the total hospital stay [27]. The study in Taiwan also reported that the personnel use accounted for 41% of the total hospital cost [51]. Therefore, we can assume that personnel cost contributes as an important cost component of the ECMO treatment. However, it is very difficult to identify the other important cost components of the ECMO treatment by literature review. There is a wide variation in the types of cost that are included to calculate the total cost of the ECMO treatment in different published literatures [13, 27].

Current published papers didn't differentiate VV-ECMO and VA-ECMO and reported the total cost of the ECMO that included both types [13, 27]. The small number of papers about the cost of the ECMO treatment specifically for cardiac conditions are only about children. [56, 57, 58] The range of the total in hospital cost is very large from USD 42554 to USD 537554

[13]. The clinical expert confirms this large difference of cost between different type of ECMO treatments and between adult and children patients. *"Use of resources varies considerably among children and adults, and is different between VV-ECMO and VA-ECMO."* [2].

However, we could still estimate the cost of the VA-ECMO treatment specifically for adult patients with different clinical causes of cardiogenic shock with the results reported by three studies [27,52,53]. One study in Taiwan reported that, for patients with cardiogenic shock caused by post cardiac surgery, the estimated total hospital cost of the VA-ECMO treatment is about USD 43235, and the cost is about USD 28266 for patients with other clinical causes for VA-ECMO use [53]. A study in USA classified the patients using VA-ECMO into different groups based on the clinical causes (including postcardiotomy, heart transplant, lung transplant other cardiogenic shock), then it reported the total charges of each groups [52]. And we can also get rough cost data for the VA-ECMO treatment for individual patients from a study in Norway [27].

However, those papers might only have reference value when we try to assign value to the cost parameters. There is a large variation in the cost of ECMO among the three different studies. The variation might be caused by different settings, patents demographical characteristics, and cost perspective. The thesis is in Norwegian setting, however the study in Norway was conducted about 10 years and only contained 5 adult patients using VA-ECMO [27]. We need carefully exam the three studies, if we try to use their results to assign values to the cost parameters when we try to implement the models. We need specifically check the cost components, the cost perspective, data collection timeframe etc.

According to the systematic review of the in-hospital cost of ECMO around the world published in 2015, the latest paper about calculating the cost of ECMO was published in 2010 in Taiwan. And according to the systematic literature review, I didn't find any paper about the cost of the ECMO published recently within 5 years. The ECMO technology might have been developed a lot in last 8 years. Therefore, compared to the data in literatures, it might be more reliable to collect the current cost data of the VA ECMO treatment for adult patients from hospitals, health insurers or other clinical sources.

In early health technology assessment, since the new healthcare technology such as that of ODIN is not generally being used in clinical practice yet, we need make assumptions of the

ODIN's cost based on expert opinions. One of the functions of mathematical model is to generating results from one context to another [45]. The generalizability and transferability of the conceptual model must be checked. A detailed list of resources that are used in the health technology interventions modelled (such as the ODIN technology) can help decision makers to assess how the model can be used to do an economic evaluation of the intervention in another region or country and therefore increase the possibility of successful dissemination of the new technology. Therefore, it is suggested to have a clear list of the cost components of both ECMO treatment and the ODIN technology when we try to implement the models in the future.

The ODIN technology can identify the irreversible damage to circulatory system soon after ECMO is started [2]. Patients who have normal monitoring parameters given by current devices often end up with death, which leads to an overuse of the ECMO treatment and other clinical resources, usually for up to more than one week. ODIN might decrease the unit cost of ECMO treatment for the patients who will not be able to survive by avoiding futile treatments and decreasing the overuse of ECMO which is very resource demanding. By adding ODIN into the ECMO treatment for refractory cardiogenic shock patients, it will increase the total cost in short term. But we don't know to what extent the ODIN can increase the total cost, since the cost of ODIN has not been valued yet. But even though the additional cost of ODIN might be high, it might reduce the long-term cost in a life time horizon by less future subsequent hospital admissions of patients because of less chance of relapse and better quality of life achieved by better efficacy of treatments and prognosis with the help of ODIN. We can estimate the impact of the ODIN on the total cost of the ECMO treatment by using hospital register data about studies such as the ProECMO study in the future. Because it might be possible to get a detail list of the costs from hospitals in which the clinical trials are conducted.

4.2.2 Health related quality of life

Since many patients using VA ECMO frequently experience complications, such as bleeding, infection, which might lead to a long-term physical and psychological impairment and high mortality rate. And refractory cardiogenic shock patients are generally critically ill whose functional status and quality of life are usually bad with persistent physical and social prob-

lems even if they survive [59]. Therefore, the health-related quality of life of the cardiogenic shock patients treated with ECMO are expected very low. Clinical outcomes of the treatment should be both subjective (such as patients' quality of life) and objective (such as survival rate) and reflect the adverse consequences of the healthcare intervention under study. [44] Quality adjusted life years (QALYs) take account of the fact that a patient may care about both the quality of their life and the quantity of life [38]. Therefore, QALYs can better represent the effectiveness of the ECMO intervention for critically ill patients. The health state utility can be estimated and valued on a scale from 0 to 1, where 0 is equivalent to death and 1 is equivalent to perfect health. And the weighting of the QALYs can be done by time trade off, standard gamble, or visual analogue scale. [43]

We can estimate the QALYS to combine life years gained from ODIN and ECMO treatment under study that are usually estimated from data gathered from randomized clinical trial (such ProECMO study) or previously published studies with information on the quality of life years by collecting data that is estimated either by health care professionals, patients or society [38].

There are only a few published studies with good data about the VA-ECMO treatment. However, two studies might be able to be used when we estimate effectiveness of the ECMO treatment and collect data for populating the conceptual model. A study in Taiwan reported that the in-hospital survival rate of the postcardiotomy shock (after cardiac surgery) adult patients treated by the VA-ECMO was 52 %, the survival rate of non-postcardiotomy adult patients was 27% [51]. One study in the USA reported that in hospital survival rate for postcardiotomy adult patients was 55.8%, for heart transplant patients 58.1%, for lung transplant patients 46.0%, for other cardiogenic shock patients 36.0% [52]. However, both studies didn't report the survival rate of patients with cardiac arrest that usually has the lowest survival rate.

The study in the US is a very good data source for estimating the effectiveness of the VA-ECMO treatment in short term. It is a multicenter study by using a database which contains a large quantity of data, including 8753 patients [52]. However, it is difficult to find long-term clinical outcomes. The clinical expert also mentioned that it is hard to find good outcome data. One paper reported short and long term clinical results of the VA-ECMO treatment,

that 25% of patients were discharged from the hospital alive, Cumulative survivor were 17.6% after 6 months, 16.5% after 1 year, and 13.7% after 5 years [24]. However, this paper was specifically about the adult postcardiotomy cardiogenic shock patients. Since there might be significant difference of survival rate of patients with different causes of cardiogenic shock. This result cannot be used to populate this conceptual model which is focus on all the cardiogenic shock patients with different diagnosis treated by VA-ECMO. And based on the systematic literature review, no randomized clinical trial of VA-ECMO treatment for adult patients were found. Therefore, we need collect the data about the effectiveness of the VA - ECMO treatment for adult patients, especially the long-term clinical results, in the clinical trials conducted in the future and hospital register data.

The results of the proECMO study can be used when they are published in the future. The ODIN technology is used with 24 hours after the initial establishment of ECMO in the proECMO study. And following up studies might be done by doing ODIN examination every day on ECMO to test the stability of the ODIN and for securing optimal additional treatment such as medicine therapy while on ECMO [2]. And therefore, we can gather reliable data about the effectiveness of ECMO treatment supported by ODIN from these clinical trials.

4.2.3 Transition probability

The good data for transition parameters of the conceptual model that shows the possibility of a certain consequence following an event including the proportion of different age group, the probability of each clinical causes, clinical outcome in the decision tree and transition probabilities from one health state to another in Markov model are difficult to obtain from current published literature. The data might be able to be assumed by gain clinical experts' opinion. The clinical expert suggested to discuss which probabilities we can use to implement the model with more clinical experts and then send the results of the discussion to experts in other countries to gain more opinion when trying to implement the model [2]. And it might also be captured by the results of randomized clinical trials published in the future, such as ProECMO study. In addition, currently the clinical expert is trying to initiate a NorECMO database where all patients treated with the ECMO in Norway will be recorded with clinical data, microvascular data captured by the ODIN and possible health economic data. If the Norwegian university hospital agrees on creating this database in the future, we

can get very good data from this database to evaluate the effectiveness and costs of the ECMO treatment with or without the support of microcirculatory data offered by ODIN [2]. The large database with data from 1998 to 2009 that was used in the US study might have reference value or be used directly when we try to implement the model, if we are able to get access to it [52].

It can be expected that in general ODIN might increase the survival rate and quality of life for patients who receiving VA ECMO treatment by making a better diagnosis and assessing the efficacy of treatment. When using ODIN, cardiogenic shock patients treated by the VA-ECMO might not have to suffer extra physical and mental pain which is caused by unnecessary and futile treatments and patients might also have better survival rates and quality of life by receiving more effective treatment both in short term and in long term. The transition probability for the ODIN and ECMO treatment is based on adjustment to the values according to the treatment effect of ODIN and ECMO treatment relative to the only ECMO treatment. The treatment effect of ODIN will be represented as a relative risk which can be obtained from randomized clinical trials (such as ProECMO study). The relative risk of ODIN might reduce the transition probabilities from one state to any worse state in Markov model and influence the distribution of the probabilities of the four clinical response pathway including recovery, receiving heart transplant, receiving a more durable mechanical support, and death in the decision tree. The value of the relative risk is possible to be gained from experts' opinion, future published results from randomized controlled clinical trials, and hospital database.

4.2.4. Discounting rate

Discounting costs and utilities of healthcare interventions can occur at different times. For example, by using ODIN, the additional costs are incurred in short term whereas the increased utility may happen in the short term or in the long term. Individuals generally prefer to incur costs in the future, and receive benefits sooner. Given the fact of the time preference, the costs and utility seems to be less valuable in the future and therefore should be discounted [4]. The greater the preference is, the higher the discount rate is. When we try to do economic evaluation of ODIN, discounting rate for both cost and effectiveness can be 4% based on the Norwegian guidelines for health technology assessments advices [60].

Chapter 5

Discussion

This objective of the master thesis was to develop a conceptual frame work by building a conceptual model for the ECMO treatment and giving suggestion to assign value to key parameters to guide the implementation of the early HTA of the ODIN technology. By doing systematic literature review and obtaining experts' opinion, the conceptual model encompasses comprehensive key factors of the refractory cardiogenic shock disease treated by ECMO. It can be used to present the impact that the ODIN might have on the effectiveness, costs and other outcomes associated with the ECMO treatment. This conceptual model might make it useful for three purposes that are discussed below.

5.1 Do early HTA

When more data become available, by populating the conceptual model, we can find out whether the ODIN technology offers a cost-effective utilization of healthcare resource. Whether it is cost effective is determined by two factors: the given willingness to pay per QALY and the target patient group under study (an average patient group or a subgroup of patients with homogeneous characteristics such as age, diagnosis categories, etc.). As more and more data become available during the development of ODIN in the years to come, more analysis can be performed to test the impact of different assumptions on cost effectiveness of ODIN such as the extreme value analysis, threshold analysis. We can quantify the minimum effectiveness the ODIN should achieve and set the maximum costs for ODIN so that it can be cost effective. If the ODIN cannot offer the minimum effectiveness or if the cost of ODIN exceeds the maximum allowed cost, timely improvements of ODIN should be made in terms of costs and effectiveness [37]. It is also possible to calculate the potential minimum revenue on investments of ODIN by multiplying the expected sales of ODIN (simulating the number of patients per year and the speed of adoption of ODIN) with the difference in the proposed sales price and feasible maximum cost that is determined by the economic evaluation [61]. In addition to cost effectiveness analysis, a budget impact analysis

can also be done to estimate the financial consequences of adopting a new intervention like ODIN in the short term by multiplying the cost of the ODIN with the number of patients who are affected by the ODIN to inform the decision makers or the healthcare payers the total budget required to fund the ODIN in the future [37].

Different stakeholders (clinicians, healthcare payers, policy makers, and the developer of the ODIN) can benefit from the results of the early health technology assessment of ODIN by populating the conceptual model. All the stakeholders can be informed early about the existence of ODIN, its cost and its effectiveness [62, 63]. The results of early HTA can help the developer to make better market access strategy, attract more investment and to improve the development of the technology by adjusting its cost and effectiveness. Future clinical and legal guidelines for using ODIN can be created timelier and the clinicians may adopt the ODIN in clinical practice faster. And Healthcare payer can make timely policy and decision regarding to the future reimbursement for ODIN [62,63].

5.2 Guide personalized healthcare

Patient centered intervention is a hot topic in the healthcare industry. The ODIN technology is expected to be used successfully in the individual patients by opening for guiding individualized therapy with the function assessment of the microcirculatory system. The ODIN technology may have the potential to become a very useful tool to gather individual patient clinical data and help to offer personalized care [35].

This conceptual model classified the patient population under study into subgroups by age, clinical causes for getting refractory cardiogenic shock and receiving ECMO treatment, which can affect the effectiveness and costs and other outcomes of ECMO and ODIN treatment. Therefore, it could be useful to do heterogeneity analysis, a more personalized approach to analyze the cost effectiveness in the future when more data become available.

When being used with ECMO, ODIN might have big influence in decision to withdraw ECMO for patients who has no chance to recover and are not suitable to get long-term MCS or heart transplant (end life decision) [12]. Therefore, it usually elicits ethics issue. Heterogeneity analysis is useful tool to quantify and identify the efficiency/equity tradeoffs under a cer-

tain threshold, which can help allocate the ODIN and ECMO interventions to the optimal subgroup patients to increase the efficiency under a limited budget while equity and ethics issue are also well concerned. When doing heterogeneity analysis, limited use criteria (LUC) policy will be created. This LUC policy will offer a certain health intervention only to the patients who have the certain clinical or demographic characteristics or preference, because for only these patients the intervention is cost effective [64]. Usually the government and the patients will find it more acceptable when the LUC created is based on the clinical characteristics than on the patient demographics such as age or race [65]. ODIN offers additional clinical characteristic microcirculatory parameters to use to create the LUC which is more acceptable than age, weight, etc. With more clinical microcirculation data offered by ODIN and with the heterogeneity analysis, we can modify the conceptual model by adding microcirculatory parameter into it, so it can be more helpful to guide the personalized care of refractory cardiogenic shock adult patients, solve the problem of overuse and underuse of expensive VA-ECMO.

So far, this conceptual model only contains three types of patient heterogeneity. To do a more personalized evaluation of ODIN and ECMO, more types of patient heterogeneity can be put into the model in a more detailed way, for example, more demographics characteristics such as gender, weight etc. and clinical characteristics such as disease severity (e.g. how damaged the microcirculation system is), genetic profile, etc. And both age and clinical causes for ECMO utilization in the conceptual model can be future divided into more subgroups instead of just two age groups and three general causes. The damage of microcirculation individually tracked by ODIN can also be added into the model. When more characteristics and more levels of each characteristic become involved and if the risks of event are significantly affected by them, the patient-level simulation models will become more practical option to reflect the impact of the individual patient's history on the intervention's efficacy. (Intervention such as ECMO) [11, 44].

5.3 Develop more customized models that can be applied for more specific research problems.

Conceptual models tend to include more general and complex evidence which commonly get simplified or modified when put into practice. A model that can be implemented with specific clinical data is usually a subset of the conceptual model, which makes it easier to debate and justify the simplifications and abstractions represented in the specific model which is derived from the conceptual model. Furthermore, since the conceptual model yields a fully understanding of the complexities, patients' experience, clinical characteristics, and general process of the relevant disease that we are interested in, it can be utilized as a reference or a foundation to build a design-oriented model for more specific problems.

When more specific data for certain clinical characteristics is available, the conceptual model can be modified to be used in health technology assessment for ODIN and ECMO treating refractory cardiogenic shock patients with a more specific clinical feature, such as the severity of the damage of microcirculation, different diagnosis groups including cardiac arrest, heart transplant, etc. The existing papers doing economic evaluation of VA-ECMO are usually about very specific heart diseases, such as dilated cardiomyopathy, cardiac arrest for children [66,67]. This kind of additional specific economic study of the ODIN and the ECMO might be necessary to more accurately capture the impact of the technology on end-stage heart failure patients, which can help to identify the economic burden and clinical effectiveness of the technology and their associated drivers. There are good short-term and long-term data for both cost and effectiveness of the VA-ECMO treatment for the postcardiotomy adult patients, we might be able to start with modifying the conceptual model for this specific problem [24,51,52].

This conceptual model encompasses many key characteristics of the research problem, however, it cannot include every specific details. So future researchers and policymakers can modify the conceptual model to construct more customized model to do health technology assessment of the ODIN technology for different modalities and subpopulations.

Chapter 6

Limitations of the conceptual model

Since every model is simplification and an abstraction of reality based on several assumptions, there is no perfect model that do not need improvements. This conceptual model inevitably can be improved to some degree. And different researcher can explore out which part of the model needs to be improved by assessing the credibility of this model by evaluating the structural and methodological uncertainty retrospectively when more good quality data become available, and by checking the decisions and choices made in the process of constructing and developing this conceptual model prospectively.

Many decisions and assumptions have been made when conceptualizing a research problem and the conceptual model, every choice will affect the results. In order to identify and evaluate the impacts the assumptions might have on the conceptual model and their uncertainty, exploratory sensitivity and scenario analysis need conduct. Using early-stage health economic modeling to do early HTA requires relatively large amount of data. However, the data are very limited. Even though the conceptual model captures the nature of the decision problem and contains important characteristics of the refractory cardiogenic shock treated by EMCO and its clinical consequences, we need good data to help design and justify the model and its structure. But now it is also possible to do sensitivity analysis to test whether a model feature without available data has significant impact on the model's results by giving possible value to the feature's parameters [44]. Those parameter estimates are possible to be given by experts' guesses and assumptions. This process is time consuming, so it was not done in this thesis.

This conceptual model was built on the information gained from systematic literature review and expert opinion. Face validation of the model by expertise in the problem field who are neutral to the results of the analysis is very important part for the validation of a model. Only one clinical expert was involved during the development of the conceptual model. So, the credibility of this model to some degrees is highly affected by the clinical expert's experience and expertise, and the setting he has been in. The conceptual model has certain degree of

bias especially in terms of the clinical inputs. Beside his own experience and expertise, the clinical expert is the inventor of ODIN, it might also cause some degree of bias. Other factors, such as the geographic setting, my expertise, the time and resource and data that are available to build and construct the model, can also generate certain level of bias. Those potential biases should be taken into consideration when checking the credibility and the generalization of the model [45]. Further, I kept finding new and important literatures at every stage of the framework development. Therefore, I might miss some relevant literatures that might offer important evidence to address the research problem.

Another thing to discuss about the conceptual model is whether they can be used in other countries or in different regions within the same country. This conceptual model is built on evidence gathered in Norway. The scope for generalizability and transferability might be constricted when we try to adopt the conceptual model for every economic evaluation in different setting and different study population which has notable influence on the intervention and clinical process and its effect. The internal validity should be achieved to build a useful and credible conceptual model to fully represent the research problem in the setting of Norway. External validity related to generalizability and transferability of the model and its results to other settings should be also taken into consideration. Usually Internal validity and external validity cancel out each other. As internal validity gets stronger, the external validity becomes weaker, and vice versa [68]. Since this conceptual model is built in the setting of Norway, the balance between external and internal validity should be considered and further discussed if we try to assess the cost and the effectiveness of the ODIN technology by using the same model in other settings.

Another limitation is that it is lack of sufficient information about whether a patient will receive ECMO treatment at least two times in their life time. I built the conceptual model, assuming that patients will have at most one relapse which means they might receive VA ECMO treatment at least one time and most two times. But the clinical expert said there are very few if any patients that would be treated on two or several occasions with ECMO [2]. More clinical experts should be consulted to make sure whether the chance for a patient to get the second ECMO treatment is significantly small. If the likelihood for receiving the VA-ECMO treatment is significantly small for average patients, we need modify the Markov

model. We need delete the relapse and the second remission health states. The final Markov model will only have two health states, remission and death.

The conceptual model built in this thesis is a cohort model. It models the clinical experience of the average patients with same characteristic, such as diagnosis (clinical cause). Cohort models are commonly used in health economics and HTA. However, cohort models might not be able to capture the dynamics of the healthcare pathways of the VA-ECMO patients. The clinical expert said that the costs of adult VA-ECMO treatment varies a lot and the variation is not caused by different diagnosis categories or different patients demographical characteristics but caused by personalized treatments for individual patients [2]. And the ODIN is used to diagnose circulatory failure on an individual patient basis and guide the patient tailored ECMO treatment. If there is a significant cost variation among individual VA-ECMO patients who share the same clinical and demographical characteristics, patient-level simulation models such as discrete-event simulation might need to be used to model the individual dynamic treatment sequences for the health interventions and capture the variability between patients [69].

Chapter 7

Conclusion

The new healthcare technology ODIN has potential to increase the efficacy and decrease the total cost of the costly ECMO treatment for refractory cardiogenic shock patients. However, before its implementation in the clinical practice, it is essential to do an early HTA of it. The conceptual framework for ECMO treatment in this thesis contains a conceptual model, suggestions for defining key parameters and obtaining data for them, and assumptions about how the ODIN will affect the value of them. The conceptual framework can be used for the early HTA of ODIN when more data become available. It can also play an important role to guide personalized care of patients treated with the ODIN technology and the ECMO. Since the conceptual model contains more general and complex evidence, it can get simplified or modified when put into practice to develop customized model to solve more specific problems.

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