Operations Research Models for Investigation and Improvement of the Hyperacute Stroke Care System

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship. I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis/project is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

Mahsa Keshtkaran

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Dedicated to my inspiring parents Firoozeh and Mohsen,

for their unconditional love, guidance, and support.

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Abstract

Stroke is the third most common cause of death and the sixth major cause of disability around the world with ischemic stroke accounting for around 80% of all strokes. It has been clinically indicated in treating ischemic stroke patients that maximum benefits can be achieved with the speediest arterial recanalization by effective and fast application of existing acute therapies. These therapies comprise either (1) dissolving the blood clot using Intravenous Tissue Plasminogen Activator (IV tPA) treatment or (2) physically removing the clot from the artery using endovascular thrombectomy treatment. These treatments should be performed within the hyperacute time window of 6 hours from stroke onset.

For nearly two decades until late 2014, the intravenous thrombolysis delivered to patients was the most effective treatment for stroke patients. This was administrated within a maximum of 4.5 hours from stroke onset. In early 2015, results of five clinical trials from different parts of the world demonstrated the effectiveness of the endovascular thrombectomy therapy. This was provided within 6 hours of stroke onset for the eligible stroke patients who already have received thrombolysis treatment.

Research presented in this thesis is the first attempt to quantify the link between the earlier treatment and long-term benefits for the hyperacute stroke patients. Moreover, with the gradual emergence of new evidence about effectiveness of the endovascular thrombectomy treatment in the hyperacute stroke care systems, new questions were raised in the clinical literature since not all hospitals have the expertise and equipment required for delivering the endovascular thrombectomy treatment. Some of the most burning questions were formulated in an *Editorial* article published in the *Journal of the American Medical Association (JAMA)* by Warach and Johnson (2016). These questions mainly concern the issue of treatment pathway selection between two groups of hospitals with different facilities and expertise to support new investigations in the hyperacute stroke care system by comparing the long-term benefits for individual patients.

This research demonstrates how Operations Research (OR) models can be used to answer these and other questions in the hyperacute stroke care system. It is specifically focused on OR models for *investigation and improvement* to provide better understanding of the complex decisions arising in the hyperacute stroke care system. The main aimof this thesis is to investigate the issue of *design, development and validation of OR models used for investigation and improvement of the hyperacute stroke care system*. Thus, this work

addresses very recent and important questions in the field to support more effective and efficient provision of the services to stroke patients.

Three OR models for investigation and improvement are designed and validated in this thesis: (1) *'IV tPA'* model, (2) *'Endovascular Thrombectomy'* model, and (3) *'Individual Patient'* model. The first two OR models are used to provide an understanding of the long-term *population benefits* of faster access to stroke treatment interventions. Based on the first two OR models, one minute earlier of IV tPA and endovascular thrombectomy interventions respectively on average provide 1.8 days and 3.2 extra days of healthy life for the stroke patients. The third OR model is used to provide assistance with maximizing the individual patient's life-time benefits over two pathways of the hyperacute stroke care system. Finally, we present a novel validation framework that is used to validate all three OR models developed in this thesis.

This research contributes to OR/MS literature by design, development and validation of OR models used to provide an improved understanding of the long-term population and individual patient's benefits due to faster delivery of stroke treatment interventions in the hyperacute stroke care system. A discussion on the validation of OR models is also novel and further addresses the existing gaps in OR/MS literature.

List of publications arising

Following is the list of publications arising from this research:

1. Meretoja, A., Keshtkaran, M., Saver, J.L., Tatlisumak, T., Parsons, M.W., Kaste, M., Davis, S.M., Donnan, G.A. and Churilov, L., 2014. Stroke thrombolysis: save a minute, save a day. *Stroke*, 45(4), pp.1053-1058.
2. Keshtkaran, M., Hearne, J., Abbasi, B. and Churilov, L., 2015, December. Stroke care systems: can simulation modeling catch up with the recent advances in stroke treatment? In *Winter Simulation Conference (WSC), 2015* (pp. 1379-1390). IEEE.
3. Keshtkaran, M., Churilov, L., Hearne, J., Abbasi, B. and Meretoja, A., 2016. Validation of a decision support model for investigation and improvement in stroke thrombolysis. *European Journal of Operational Research*, *253*(1), pp.154-169.
4. Meretoja, A., Keshtkaran, M., Tatlisumak, T., Donnan, G.A. and Churilov, L., 2017. Endovascular therapy for ischemic stroke, save a minute – save a week. Accepted for publication in *Neurology* at the time of submitting this thesis.

Please note that although the presented research work was collaborative between the clinical research team at the Florey Institute of Neuroscience and Mental Health and operations research team at RMIT University, the candidate's substantial contribution is reflected in the authorship of the published articles: the candidate is the first author for the two operations research- related papers, while she is the second author for the two clinical articles resulting from this research.

Chapter 1: Introduction

Chapter 1 serves as an introduction to this research by first outlining the research gaps in the application of Operations Research (OR) models to assist with understanding of the hyperacute stroke care system. To address the identified research gaps, we present the aim of this research to investigating the issues of *design, development and validation of OR models for investigation and improvement of hyperacute stroke care systems*. To achieve this aim, we formulate three research questions and present the relevant outcomes. We then describe the research settings, outline and contribution of this research.

1.1 Background to hyperacute stroke care system

Stroke is the third most common cause of death and the sixth major cause of disability around the world with ischemic stroke accounting for 80% of all stroke types (Feigin, et al., 2014). It has been clinically indicated that maximum benefits in treating ischemic stroke patients can be achieved by effective and fast application of existing acute therapies. These therapies are aimed at dissolving the blood clot using Intravenous Tissue Plasminogen Activator (IV tPA) (Emberson, et al., 2014; Fransen, et al., 2016), or physically removing the clot from the artery by using a clinical procedure known as Intra-arterial (IA) endovascular thrombectomy treatment (Saver, et al., 2016). An eligible ischemic stroke patient can either only receive IV tPA therapy within a maximum of 4.5 hours from stroke onset, or first receive IV tPA and then undergo the endovascular thrombectomy treatment with usually not more than 6 hours from stroke onset. This category of stroke patients who present in the stroke care unit within 6 hours from stroke onset are known as *hyperacute stroke patients*, with the care system being referred to as the *hyperacute stroke care system*.

Even though clinical research has shown that maximum benefits in treating hyperacute stroke patients can be achieved by effective and fast application of existing acute therapies (Saver, 2006; Saver, et al., 2016), the effect of faster treatment for different treatment interventions on patient's lifetime outcomes was not quantified prior to this research. Moreover, in reality, not all hospitals are capable of delivering the intra-arterial treatment to stroke patients. Therefore, delivering the right treatment intervention to the right group of patients within prescribed time-window has become a challenging issue for the clinicians in the field of hyperacute stroke care system. With recent and gradual emergence of new evidence about the effectiveness of the endovascular thrombectomy treatment in the hyperacute stroke care systems, new questions were raised in clinical literature. Some of the

most burning questions were formulated in an *Editorial* article published in *Journal of the American Medical Association (JAMA)* in 2016 as follows: "*Should primary stroke centres be bypassed to transport patients to comprehensive centres, even if it means delaying the start of IV tPA? How much delay in bypass is acceptable? How much of a delay to start IV tPA would eliminate the benefit of earlier thrombectomy*? (Warach & Johnston, 2016, p. 1266)". By addressing these research questions, clinicians can obtain the necessary insights for more effective and efficient provision of the stroke care services.

1.2 Research gaps

Despite a growing body of application of OR tools to the general domain of health care operations (Cooper, Brailsford, Davies, & Raftery, 2006; Fries, 2013; Osorio, Brailsford, & Smith, 2015), there is a clear research gap in the use of OR models to assist with understanding of the hyperacute stroke care systems, in particular:

- There is a lack of OR models to understand the long-term benefits of faster access to different stroke treatment interventions on patients' life-time outcomes.

This is an important topic to address, since even though the benefits of faster treatment of the hyperacute stroke care patients have been demonstrated in the clinical literature, there is no OR model used to quantify the *population benefits* for the hyperacute stroke patients due to faster delivery of treatment interventions.

- There is a lack of OR models to assist with hyperacute stroke care system pathway selection based on the individual patients' life-time outcomes.

With emergence of new evidence about the effectiveness of endovascular thrombectomy treatment in late 2014, new questions were raised by clinicians about how individual patients can maximize their long-term benefits in choosing different pathways of the hyperacute stroke care system.

- There is a lack of reported knowledge about practical aspects of how to validate an OR model for investigation and improvement in the context of health systems and service operations.

Proper validation of OR models used for *investigation and improvement* leads to an increased credibility of the model and its outcomes. Therefore, it is crucial to systematically address the issue of validation of such models.

1.3 Research aim and research questions

The aim of this research is to address the identified research gap and to contribute to Operations Research/ Management Science (OR/MS) literature by investigating the issue of *design, development and validation of OR models used for investigation and improvement of the hyperacute stroke care system*. Following is a list of objectives and relevant research questions:

- *Objective 1:* to design and validate OR models for better understanding of earlier treatment benefits for two different treatment interventions in hyperacute stroke care system;

  Research question 1: How OR models can be designed, developed, and validated to provide an improved understanding of the earlier treatment benefits on patients' life-time outcome for two different treatment interventions in hyperacute stroke care system?
- *Objective 2*: to design and validate an OR model used to assist with maximizing the individual patients' life-time benefits over two pathways of the hyperacute stroke care system;

  Research question 2: How OR models can be designed, developed, and validated to assist with maximizing the individual patients' life-time benefits over two pathways of the hyperacute stroke care system?
- *Objective 3*: to demonstrate how comprehensive validation of a complex OR model for investigation and improvement in the context of health systems and service operations can be conducted using the case of hyperacute stroke care.

  Research question 3: What are the conceptual and application issues of conducting comprehensive validation of an OR model for investigation and improvement in the context of health systems and service operations using the case of hyperacute stroke care?

Outcomes of this research achieved by addressing these research questions are outlined in the next section.

1.4 Research outcomes

This research has produced the following outcomes:

1. Two validated OR models for understanding of the long-term effects of faster access to two different treatment interventions on stroke patients' life-time outcomes in the hyperacute stroke care system.
2. A validated OR model that can be used to assist with maximizing the individual patients' life-time benefits over two pathways of the hyperacute stroke care system.
3. Generic and structured set of validation techniques used to validate complex OR models in the hyperacute stroke care system with wide applicability for validating OR models in both health and non-health contexts.

By generating these outcomes, this research contributes to OR/MS literature by design, development and validation of OR models used to provide an improved understanding of the long-term population and individual patient's benefits due to faster delivery of stroke treatment interventions in the hyperacute stroke care system. A discussion on the validation of OR models used for investigation an improvement provided in this thesis is also novel and contributes further to existing OR/MS literature.

1.5 Research settings of thesis

This research was an industry-based project supported by the *Florey Institute of Neuroscience and Mental Health*, the largest neuroscience research institute in the Southern Hemisphere. The *Florey Institute of Neuroscience and Mental Health* has wide range of research projects on neuroscience-related diseases such as stroke, epilepsy, Alzheimer's disease, depression, and spinal cord injury. The scope of the research presented in this thesis is limited to *design, development and validation of OR models used for investigation and improvement of the hyperacute stroke care system*. Strong research connections between the *Florey Institute of Neuroscience and Mental Health* and other clinical centers both locally and globally, facilitated the use of information obtained from different databases to develop the OR models in this thesis. Moreover, during the model building and validating stages we were working closely with many clinicians at *Florey Institute of Neuroscience and Mental Health* to further increase the accuracy and credibility of this research.

1.6 Outline of thesis

Discussion in this research is organized as follows:

Chapter 2 provides a background to hyperacute stroke care system, followed by a discussion on the application of OR models with different intended use to address different problem areas in the stroke care system. This chapter also reports on literature review conducted to

investigate the OR applications published in the research and professional literature to address different problems of the hyperacute stroke care systems.

Chapter 3 discusses challenges of validating OR models for investigation and improvement in the context of health systems and service operations. It then demonstrates how generic methods and approaches of validation as reported in OR/MS literature can be used to develop a generic framework of validation.

Chapter 4 is dedicated to design, development, and validation of two novel OR models in the context of hyperacute stroke care system. These OR models are used for the first time to investigate the effect of time delays on population benefits for the stroke patients in the hyperacute stroke care system. Discussion on the validation of these models is provided in the same chapter.

Chapter 5 reports on design, development, and validation of a novel OR model used to investigate the effect of time delays on individual patient's life time outcomes over two pathways of the hyperacute stroke care system. Discussion on validation of this model is provided in the same chapter.

Chapter 6 summarizes the findings, novelty and contributions, and limitations of the study as an indication to conduct future research in addressing the three research questions of this thesis.

1.7 Contribution of thesis

The contribution to knowledge of the research presented in this thesis is graphically presented in Figure 1-1. This can be summarized as five main points as listed below:

1. **Current use of OR interventions in stroke care system**: In Chapter 2 of this thesis, we adopt a conceptual framework by Churilov and Donnan (2012) to classify the stroke-related OR studies found as a result of a literature review conducted in the same chapter, thus reporting on current use of OR interventions to address different problems of the stroke care system. Discussion on this topic was partially published in the *Proceedings of Winter Simulation Conference* in 2015, titled "*Stroke care systems: can simulation modelling catch up with the recent advances in stroke treatment?"* (Keshtkaran, Hearne, Abbasi, & Churilov, 2015)
2. **Current state of art of validating OR models**: In Chapter 3 of this thesis, we conduct a literature review to investigate and report on current state of art of

validating OR models as reported in OR/MS literature. Discussion on this topic was partially published in the *European Journal of Operational Research* in 2016, titled *"Validation of a decision support model for investigation and improvement in stroke thrombolysis"* (Keshtkaran, Churilov, Hearne, Abbasi, & Meretoja, 2016)

3. **Generic framework for OR model validation**: In Chapter 3 of this thesis, we propose a generic validation framework used to validate complex OR models in the context of hyperacute stroke care system with potential wide applicability for validating OR models in non-health contexts. Discussion on this topic was partially published in the *European Journal of Operational Research* in 2016, titled *"Validation of a decision support model for investigation and improvement in stroke thrombolysis"* (Keshtkaran, et al., 2016)
4. **Development and validation of OR models to estimating the population benefits**: In Chapter 4 of this thesis, we develop and validate the *'IV tPA'* and '*Endovascular Thrombectomy'* OR models used for the first time to provide understanding of the long-term effects of faster access to two different treatment interventions on stroke patients' life-time outcomes in the hyperacute stroke care system. A discussion on the validation of these two models contribute to OR/MS literature by demonstrating how comprehensivevalidation of a complex OR model for investigation and improvement in the context of health systems and service operations can be conducted using the case of hyperacute stroke care. The content of this chapter is partially based on three journal articles:

   (1) article published in *Stroke* in 2014, titled *"Stroke thrombolysis; save a minute, save a day"*(Meretoja, et al., 2014);

   (2) article published in the *European Journal of Operational Research* in 2016, titled *"Validation of a decision support model for investigation and improvement in stroke thrombolysis"* (Keshtkaran, et al., 2016); and

   (3) article accepted for publication in *Neurology* at the time of submitting this thesis, titled *"Endovascular therapy for ischemic stroke; save a minute – save a week"(Meretoja, Keshtkaran, Tatlisumak, Donnan, & Churilov, 2017).*
5. **Development and validation of an OR model to assist with maximizing the individual patient's benefits**: In Chapter 5 of this thesis, we develop and validate the *'Individual Patient'* OR model used for the first time to assist with maximizing the individual patient's life-time benefits over two pathways of the hyperacute stroke care system. A discussion on the validation of this OR model contributes to OR/MS literature by demonstrating how comprehensive validation of a complex OR model for investigation and improvement in the context of health systems and service operations can be conducted using the case of hyperacute stroke care.

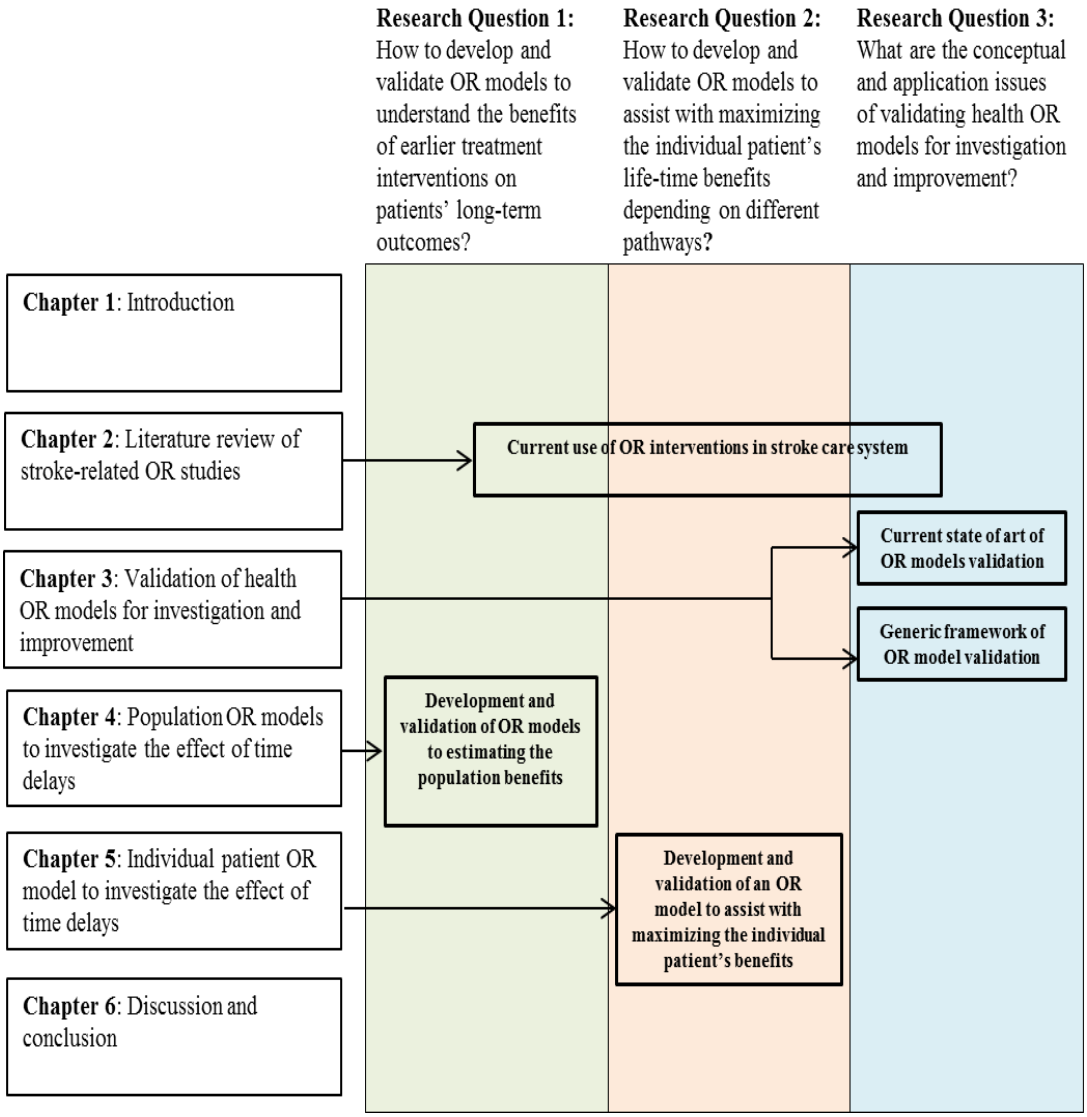

Figure 1-1 Summary of contributions of different chapters of this thesis

1.8 Summary and conclusion

This chapter laid the groundwork for all the other chapters in this thesis by identifying the problem areas in the hyperacute stroke care system, research gaps, objectives, questions, and outcomes. The contribution of this thesis to OR/MS literature is novel since for the first time it discusses the process of design, development and validation of OR models used to address some of the most current questions raised in clinical literature with the recent treatment advances in the hyperacute stroke care system since early 2015.

Chapter 2: Review of the OR applications to stroke care systems

Introduction

Discussion provided in different sections of this chapter addresses all the three research questions proposed earlier in Chapter 1. Topics discussed in Section 2.1 serve as an introduction to problem domain of this research by providing a background to hyperacute stroke care system and reviewing the stroke care processes as reported in key policy documents for stroke care by four English-speaking countries.

In Section 2.2, we discuss application of OR models with different intended use and interventions to address different problem areas in the hyperacute stroke care system. This includes discussing the link between the intended use of the model and model validation. This is an important topic as it provides background to third research question of this thesis: *'What are the conceptual and application issues of conducting* comprehensive *validation of an OR model for investigation and improvement in the context of health systems and service operations?'*

We then conduct a literature review in Section 2.3 to investigate the published OR applications in research and professional literature used to address different problems of the hyperacute stroke care system as reported in OR/MS literature. This assist us in better appreciation of the importance of research questions and objectives proposed in this research to address the existing knowledge gaps in OR/MS literature. Finally, in last section, summary of the findings of this chapter is provided.

The content of this chapter is partially based on the conference paper "*Stroke care systems: can simulation modelling catch up with the recent advances in stroke treatment?"* published in the *Proceedings of Winter Simulation Conference* in 2015 (Keshtkaran, et al., 2015).

2.1 Background to hyperacute stroke care system

In this section, we provide a background to hyperacute stroke care system, focusing on stroke burden, stroke types, existing acute interventions, and challenges regarding administration of different interventions. In Section 2.1.1, we expand our discussion by describing the stroke care processes as reported in key policy documents from four English-speaking countries; USA, UK, Canada, and Australia.

In 2016, stroke was ranked as the second most common cause of death in people aged above 60 years and the second most common cause of disability worldwide (World Health Federation, 2017). According to latest statistics, in 2015 there were more than 50,000 new and recurrent strokes in Australia with one stroke occurring every 10 minutes. Moreover, 65% of stroke victims are affected by long-term disability for the rest of their lives (Stroke Foundation - Australia, 2017). Financially, stroke accounts for more than 2-4% of total health-care costs and more than 4% of direct health-care costs in industrialised countries. This amount has been estimated to be around AUS$2.14 billion in Australia (Donnan, Fisher, Macleod, & Davis, 2008; Economics, 2013).

There are two major types of strokes: ischemic stroke and hemorrhagic stroke. Ischemic stroke happens when a blood clot or plaque blocks a blood vessel cause the brain cells become deprived of the oxygen and eventually stop functioning normally. If the vessel occlusion continues, after few minutes the brain cells may get damaged permanently, often leading to a significant long-term disability. This type of stroke accounts for 80% of all stroke types, while hemorrhagic stroke refers to the cases where an artery ruptures or breaks, causing bleeding in the brain (Feigin, et al., 2014).

Existing acute therapies and interventions for ischaemic stroke are aimed at the speediest possible *arterial recanalization*, where a blood clot that has blocked a blood vessel is either removed or dissolved (Emberson, et al., 2014; Fransen, et al., 2016; Saver, et al., 2016). These proven acute interventions are used to help with restoring the cerebral blood flow in ischaemic stroke patients. Up until very recently, tissue plasminogen activator or IV tPA was the most effective treatment for ischemic stroke patients which is used to dissolve the blood clot formed in the artery (Wahlgren, et al., 2008). In early 2015, the results of five randomized controlled trials from different parts of the world were published in the New England Journal of Medicine, with all demonstrating that the intra-arterial clot removal is even more effective in treating the ischemic stroke patients when used in addition to IV tPA treatment comparing to IV tPA alone (Berkhemer, et al., 2015; Campbell, et al., 2015; Goyal, et al., 2015; Jovin, et al., 2015; Saver, et al., 2015). This new intervention is used to remove the blood clot from the artery using a clot retrieval device.

As evidenced by the results of the modelling by Saver (2006), a typical stroke patient loses 1.9 million neurons for each minute in which stroke is untreated. Compared with the normal rate of neuron loss in brain aging, this results in the ischemic brain ages 3.6 years for each hour without treatment (Saver, 2006). As a result, for patients experiencing acute ischemic stroke, and for the physicians and allied health personnel treating them, every second counts.

Existing evidence demonstrates that the earlier treatment in both interventions, leads to the higher chance of effective outcome in ischemic stroke patients (Emberson, et al., 2014; Fransen, et al., 2016), while the upper time limit to receive IV tPA treatment and endovascular thrombectomy is respectively set to 270 and 360 minutes according to majority of the clinical guidelines (Emberson, et al., 2014; Saver, et al., 2016). In medical terms, an ischaemic stroke patient presents in a hospital with stroke care unit within 6 hours of stroke onset time, is referred to as a *hyperacute stroke patient*. This group of patients can be categorized to those who are eligible to receive IV tPA treatment and then undergo the process of receiving the endovascular therapy, or only receive the IV tPA treatment (Saver, et al., 2016). In addition to the time eligibility of the patients to receive appropriate treatment, the clinical eligibility of the stroke patients to receive IV tPA and endovascular therapy is specified by the neurologist teams in the treating centres.

With this introduction to hyperacute stroke care system and existing treatment interventions, in next section we discuss how different countries use different strategies and policies to address the problems in the system, thus improving the efficiency and the effectiveness of the services.

2.1.1 Stroke care processes as reported in key policy documents

With time being the most important factor in existing therapies for the ischemic stroke patients, different countries promote various strategies and policies for more effective and efficient management of the hyperacute stroke care system. The aim of this section is to provide a summary of the key recommendations by the public policy documents from USA, UK, Canada, and Australia in the field of stroke care systems. The first summary review of these documents were originally reported in a paper by Churilov and Donnan (2012). In this section, if available we report on the updated version of these documents; otherwise we refer to the original document as reported in the article by Churilov and Donnan (2012). The key findings of these policy documents are as follows:

1. *American Heart Association Public Policy Agenda 2010-14 report* (American Heart Association/American Stroke Association, 2014):

   According to American Heart Association (AHA), there are six major components for the Establishment of Stroke Systems of Care as listed by the AHA's task force on the Development of Stroke Systems. These include: Primordial and Primary Prevention, Notification and Response of Emergency Medical Services for Stroke, Acute Treatment for Stroke, Sub-Acute Stroke Care and Secondary Prevention for Stroke, Rehabilitation

of Stroke Patients, and Continuous Quality Improvement Initiatives (American Heart Association/American Stroke Association, 2014).

2. *Department of Health: National Stroke Strategy for England* (Department of Health, 2008)

The National Stroke Strategy suggests following points to be considered by stroke service providers in order to improve their services: stroke awareness, stroke prevention, involvement of the patients in the stroke care process, Transient Ischaemic Attack (TIA) and acting on the warnings, stroke as a medical emergency, stroke unit quality, rehabilitation and community support, participation, workforce, and service improvement (Department of Health, 2008). Another relevant source to obtain information about treatment guidelines for stroke and transient ischemic attack in UK is the National Institute for Health and Care Excellence (NICE) which provides consistent recommendations with that of the Department of Health (National Institute for Health and care Excellence, 2017).

3. *Canadian Stroke Strategy (CSS) Core Performance Indicators 2010 report* (CSS information and evaluation working group, 2010)

This document categorizes and presents the core indicators associated with stroke best practices into two groups of *system indicators* and *clinical indicators*. The first category consists of 6 main indicators which are used for population level planning and system coordination, while the second category consists of 21 indicators used which are directly linked to quality of care for stroke patients (CSS information and evaluation working group, 2010).

4. *Australian National Stroke Foundation Clinical Guidelines for Stroke Management* (National stroke foundation, 2010)

According to this Guideline, there are nine areas to improve the stroke care management, these include: organization of care services, stroke recognition and pre-hospital care, early assessment and diagnosis, acute medical and surgical management, secondary prevention, rehabilitation, management of the complications, community participation and long-term recovery, social and financial issues (National stroke foundation, 2010).

All the above public policy documents have been issued to address different challenges of the hyperacute stroke care system in the origin country. Therefore, strategies suggested by a

document from one country might not be directly applicable to another country. However, all these documents have been produced with the common objective of designing an efficient and effective system of care capable of addressing the time-sensitive treatment needs of the stroke patients.

Churilov and Donnan (2012), have presented a list of ten broad problem areas of the stroke care system, specified by reviewing the above policy documents. In Section 2.3.3, we use these problem areas for classifying the stroke related OR studies. Following is the list of these problem areas:

1. Stroke prevention: effective evaluation and management of risk factors and increasing the public awareness on lifestyle and available treatment options;

2. Pre-hospital stroke care: increasing the number of eligible patients to receive tPA treatment by reducing the stroke-to-hospital delay times;

3. Improving Information support for stroke patients;

4. Appropriate and timely management of Transient Ischaemic Attack (TIA);

5. Stroke unit care: patients suffering from stroke should have immediate access to required facilities and services within the stroke unit care;

6. Rehabilitation: patients should have access to post-stroke rehabilitation services for as long as they need;

7. Social and community care: to support the long-term needs of the stroke patients and their families;

8. Stroke networks: to connect the key stakeholders across the stroke care system;

9. Appropriate stroke care expertise: to facilitate the implementation of new therapeutic strategies;

10. Financial viability: Cost-effectiveness analysis of different stroke care models to financially support people affected by stroke.

The models developed in this thesis provide insights on the long-term impacts of faster access to treatment interventions for stroke patients, thus addressing the third, fifth, and ninth problem areas listed above.

Later in this chapter, we adopt these problem areas to classify the stroke-related OR studies found as a result of literature review conducted in Section 2.3.2. In the next section, we will provide a discussion on taxonomy of model use by Pidd (2010) and how OR models with different intentions can be used to address the above mentioned problem areas of the stroke care system.

2.2 OR models with different intended use

Pidd (2003) in his paper *Why modelling and model use matter* defines the model as "*an external and explicit representation of part of reality as seen by the people who wish to use that model to understand, to change, to manage and to control that part of reality*. This definition by Pidd (2003) describes important aspects of model which can be seen in any type of OR model. The first characteristic is its *external* representation as it attempts to build an artificial replica of the real-world problem. Second, he refers to the model as an *explicit* entity since we can explicitly distinguish between different components of the model once we design it. Third, the model developers will attempt to only model *part of reality*, thus calling explicitly for system boundaries of the phenomena being modelled. Fourth, model is a subjective artefact, where different modellers tend to develop different types of models based on their particular point of views (Pidd, 2010). Finally, OR models are developed with different intended use, which are models to understand, to change, to manage and to control.

Pidd (2010), in his classification for different archetypes of model use has introduced four categories. Models for *decision automation*, models for *routine decision support*, models for *investigation and improvement*, and models to *provide insight*. Models belong to each of these categories are different in nature and therefore have different needs in terms of model *validation*. Since one of the objectives of this thesis is to address the conceptual and application issues of conducting comprehensive validation of OR models for investigation and improvement in the context of health systems, in this section we discuss how models with different intended use have different needs in terms of model validation.

The category of *decision automation* refers to model use that is "frequent and routine, with in general no need to prepare the model for each use" (Pidd, 2010, p. 16). In such models, there is usually very little tolerance for any type of error, since decisions made based on the results of the model on a continuous basis in a less supervised environment. In terms of data requirements, these models often need extensive and representative data as model builders/users only rely on decisions made by the model and therefore data insufficiency will affect models functionality. Therefore, in terms of model validity all the model assumptions,

parameters, outputs, and their relationships should be examined critically before using the model in a decision making context (i.e. during the model-building stage) (Pidd, 2010).

The second category is models for *routine decision support* which refer to models "used to assist, but not replace, people making routine, repeated decisions" (Pidd, 2010, p. 17). Similar to models for decision automation, in this type of models there is a high demand for large and detailed data which is not usually easy to acquire. Therefore, it has been suggested by literature to expand the model and revise the model parameters as higher quality data become available. In validation of these models, the focus is on assuring that combination of a decision proposed by a model and that made by a decision-maker will lead to a better overall decision outcome (Pidd, 2010).

Third category of model use is modelling for *investigation and improvement* which refers to models used to "support investigations that are relatively unique, which may involve system design, system improvement or just an attempt to gain understanding of a very complex situation" (Pidd, 2010, p. 18). For this type of models, it is quite common to have very limited amount of historical data or even none at all, thus model developers are often unable to conduct an empirical "output-based" validation. As a result, validation of such models involves examining different components of the model, including model inputs, assumptions, and parameters to provide an improved understanding of the limitations of the model (Pidd, 2010).

The fourth category is modelling to *provide insight* where models are "not would-be representations of the real-world, but are rather attempts to understand and represent how different stakeholders and interest groups see the world" (Pidd, 2010). In models developed for providing insight, data is often much less demanding when compared to other model archetypes and it is usually in form of qualitative data based on different perceptions of various stakeholders of the model (Pidd, 2010). Validation of such models is very difficult and often involves the use of qualitative methods, rather than mathematical models to present viewpoints of different individuals and stakeholders.

Models with different intended use can be employed by model developers to represent real-world systems. A key concept here, is that these models often have different requirements and limitations in terms of input data and validation; thus, it is important to identify the nature of model intention, so the process of data acquisition and model validation is performed with the aim of providing enough confidence to decision makers to use the outcomes generated by the model.

For stroke care systems, Churilov and Donnan (2012) proposed four main categories of intended use of OR models used to address different problems in the hyperacute stroke care system. These are as follows:

1. *Stroke care operations improvement:* (1.1) processes design and performance, risk, and quality measurement; (1.2) scheduling and workforce planning; (1.3) stroke specialist workload models; (1.4) stroke services utilization models; (1.5) social and support care services planning and utilization models; (1.6) ambulance service models; (1.7) equipment planning; (1.8) stroke units and thrombolysis facility location and layout; and (1.9) clinical and management decision support systems.

2. *Economic analysis*: (2.1) imaging and surgical equipment evaluation and selection models; (2.2) optimal pricing and costing models; (2.3) stroke demand forecasting and planning models; (2.4) impact of prevention and knowledge dissemination policies on stroke care demand; and (2.5) long term evaluation of stroke burden and implications of various intervention strategies.

3. *Public policy*: (3.1) stroke national and regional planning and network models; (3.2) stroke unit treatment access and availability population models; (3.3) stroke prevention and risk factors management models; and (3.4) risk screening subsequent to TIAs.

4. *Clinical applications*: (4.1) stroke risk assessment and analysis; (4.2) stroke clinical decision support; (4.3) disease modelling at individual level; (4.4) drug selection and interaction models for stroke prevention; and (4.5) optimal therapy dose selection models.

Each of these categories employ different modelling methodologies such as optimization modelling, analytical/statistical modelling, and simulation modelling to address different problems of the hyperacute stroke care system. These can be models used for decision automation, used for routine decision support, used for investigation and improvement, or used to provide insight. In next section, we provide a literature review to investigate the stroke related OR studies as reported in OR/MS literature.

2.3 Evidence from literature

In literature review conducted in this section, two search methodologies are used to identify the number of stroke related OR studies. In Section 2.3.2, we provide a short description of the studies found as a result of this literature review. In Section 2.3.3, we classify these

studies based on both the specific part of the stroke care system (problem area) being addressed and the nature and purpose of the modelling intervention.

2.3.1 Literature search methodologies

For the first search methodology, the stroke related OR studies were identified from the sources listed in Table 2-1.

Database	
PubMed (no specific starting date before 2016 was fixed for this database)	
Conference Proceedings	
Winter Simulation Conference (1971–2015)	
EURO (2007–2015)	
Journal Title	
Operations Research (1957–2016)	Antimicrobial Agents and Chemotherapy (1963–2016)
Management Science (1929–2016)	Journal of Operations Management (1980–2016)
European Journal of Operational Research (1978–2016)	Omega (1973–2016)
Computers and Operations Research (1978–2016)	Annals of Operations Research (1996–2016)
Operations Research for Health Care (2012–2016)	Decision Support System (1989–2016)
The Journal of the Operational Research Society (1978– 2016)	Chemosphere (1933–2016)
International Journal of Simulation and Process Modelling (2005–2016)	Preventive Veterinary Medicine (1982–2016)
Pharmacoeconomics (1992–2016)	Vaccine (1929–2016)
Applied Health Economics and Health Policy (2002– 2016)	Simulation: Transactions of The Society for Modelling and Simulation International (1963–2016)
Medical Decision Making (1981–2016)	Health Policy (1984–2016)
Current Medical Research and Opinion (1972–2016)	American Journal of Public Health (1954–2016)
Journal of Simulation (2006–2016)	Clinical Pharmacokinetics (1976–2016)
Risk Analysis (1981–2016)	IIE Transactions (1982–2016)
Health Economics (1988–2016)	International Journal of Nursing Studies (1965–2016)
Human and Ecological Risk Assessment (1998–2016)	Decision Analysis (1977–2016)

Table 2-1 List of different sources used for the selection of stroke studies in the first search methodology

The search was conducted in two stages. At the first stage, we used different combinations of the terms "stroke", "simulation", and "simulation model*" as string search criteria in the article's title, abstract or keywords. As a result, we found 149 articles which titles and abstracts were further screened to exclude both duplicates (n=9) and irrelevant studies (n=53). In the second stage, we screened the full text of the 87 remaining articles to include those which specifically addressed the stroke care system as a focus of the study or as a full illustrative example, as opposed to the studies not specifically focusing on stroke. This stage resulted in 40 studies being identified for the subsequent in-depth analysis. The summary of the search process is graphically presented in Figure 2-1.

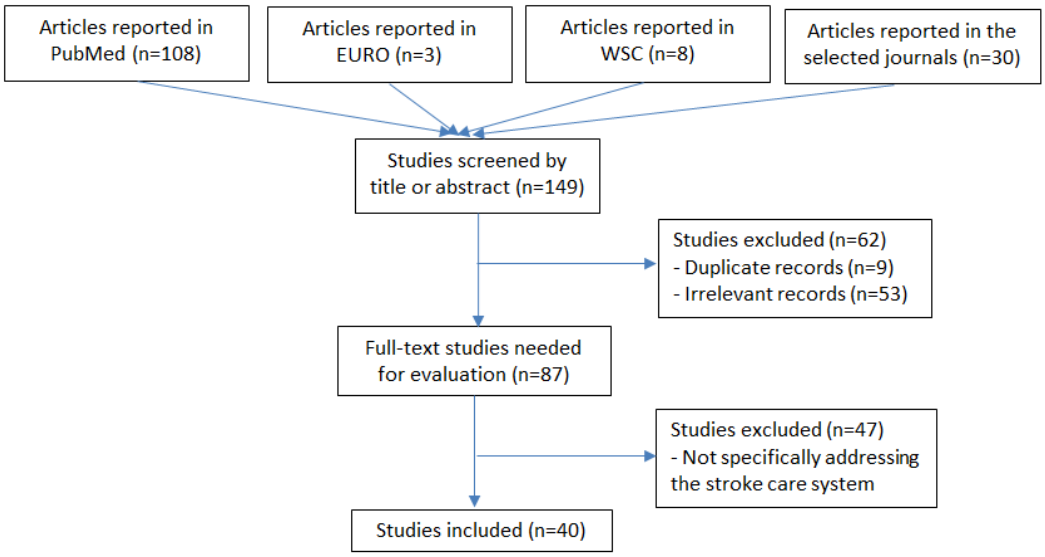

Figure 2-1 Flow diagram of the first search methodology for selection of the stroke related OR studies

For the second search methodology, the stroke related OR studies we used "stroke" and "operations/operational research" as string search criteria in the full text of the articles published in *Scopus* database to find stroke related OR studies used to address different problems in the stroke care system. In total, we found 46 articles, which were further screened to exclude both duplicates (n=25) and the irrelevant studies (n=14). As a result, we included 11 articles which were specifically addressing the stroke care system as a focus of the study. The summary of the search process is graphically presented in Figure 2-2.

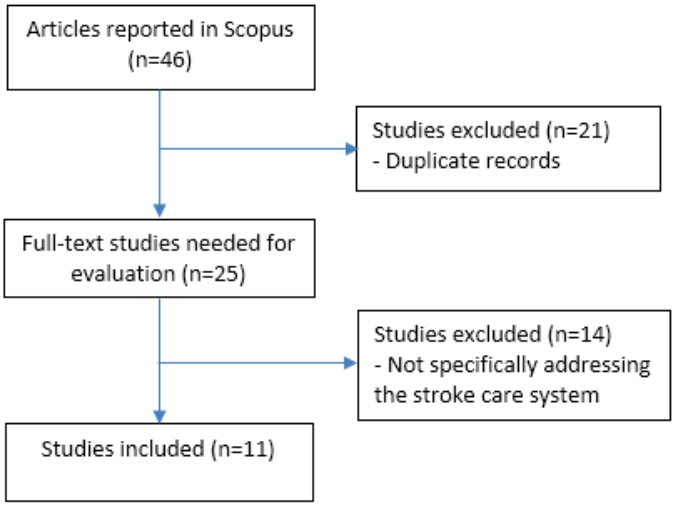

Figure 2-2 Flow diagram of the second search methodology for selection of the stroke related OR studies

2.3.2 Literature search results

In this section, we provide a summary of OR applications to stroke care systems as reported in OR/MS and clinical literature, identified as a result of the literature review conducted in previous section.

We provide a reference number (in square brackets) for every study discussed to facilitate the future discussion in Section 2.3.3, as we classify these studies in relation to both the problem areas of the stroke care system and OR modelling interventions.

[1] Parmigiani, et al. (1997) used both the Bayesian inference and resampling methods to quantify the cost uncertainty, effectiveness measures, and marginal cost-effectiveness ratios for a complex stroke prevention policy model.

[2] Matchar, et al. (1997) used a Duke Stroke Policy Model, a continuous-time simulation model, to investigate the cost-effectiveness of the alternative therapies compared with placebo for secondary prevention of recurrent ischemic stroke patients.

[3] Ozcan, Watts, Harris, and Wogen (1998) applied Data Envelopment Analysis (DEA) to investigate if there is any link between technical efficiency and care provider experience. The results of the study show that there is a relationship between technical efficiency, provider experience, and expenses.

[4] Lee , Vasilakis, Kearney, Pearse, and Millard (1998) used English Hospital Episode Statistics database to investigate the effect of weekends and public holidays on top of patients' characteristics on admission and discharge patterns of aged stroke patients.

[5] Heinrichs, Beekman, and Limburg (1999) used data from The Netherlands to model a patient flow in a stroke unit. Due to the high variability of admission rates for stroke patients, the model was used as a decision support tool to assist with the capacity planning and optimization in the stroke unit.

[6] Jørgensen, Nakayama, Kammersgaard, Raaschou, and Olsen (1999) reported on using a mental simulation model to predict the impact of tPA on prognosis of general population of stroke patients.

[7] Matchar and Samsa (1999) used a Stroke Prevention Policy Model, a semi-Markov simulation model, to identify the best treatment alternative for the prevention of stroke. This model factors the viewpoints of different stakeholders, incorporates the best evidence from multiple sources, and performs sensitivity analysis to assess the effect of uncertainty in the model parameters on the model outcomes.

[8] Samsa, et al. (1999) described a simulation model used to perform the cost-effectiveness analysis of randomized controlled trials to provide a link between the short-term and long-term effects of different treatment alternatives for the acute ischemic stroke patients. The authors concluded that treatment alternatives with moderate improvements in the health benefits for patients are more likely to be cost-effective.

[9] Quaglini, Caffi, Cavallini, Micieli, and Stefanelli (2001) described a simulation model used to represent the careflow system for treating patients with ischemic stroke in a Stroke Unit (SU), adopted from both the process and organisational model. The simulation model was developed based on a database for 100 patients and was applied for identifying the bottlenecks in the workflow processes to optimize the recourse utilization within the stroke unit.

[10] Sackley and Pound (2002) reported on the process of a panel of 12 members using the Nominal Group Technique, a decision making technique to conduct a formal priority-setting project for stroke patients of the nursing home care. This group of experts agreed on a discharge plan as evidenced by different experiments for the stroke patients in the nursing home care.

[11] Sundberg, Bagust, and Terént (2003) developed a model to estimate the costs associated with stroke services. The model was implemented by running simulations and comparing the results for three stages of stroke prevention, treatment and rehabilitation using a Swedish data. The authors concluded that the costs associated with stroke services can be reduced significantly by implementing a policy consists of all the three stages of stroke care.

[12] Stahl, Furie, Gleason, and Gazelle (2003) presented the results of the cost-effectiveness analysis of implementing a protocol compliant with National Institute of Neurological Disorders and Stroke (NINDS) recommendations for ischemic stroke patients. The authors use Discrete Event Simulation (DES) to model the stroke care pathways from onset-to-treatment time. Having obtained data for process times, performance of computed tomography, health outcomes, and cost estimates from literature, a "base-case" strategy was developed and compared with that of NINDS-compliant strategy based on the cost-effectiveness analysis of the outcomes followed up by a sensitivity analysis. The authors conclude that applying NINDS-compliant strategy is cost-effective.

[13] In a paper by Lee, Wang, Yau, and Somerford (2003) , the authors employed a zero-truncated negative binomial mixed regression model to investigate how different patients' characteristics at the index stroke can affect the number of readmissions. The findings of this study were further used to provide insight on the effect of number of readmissions on resource consumption, and planning of the rehabilitation and stroke care services.

[14] Marshall and McClean (2004) used Coxian phase-type distributions to model the length of stay for different groups of elderly patients (including stroke patients). The result of this study was expected to provide useful implications for the care providers and clinicians in service planning and bed allocation of the hospital wards.

[15] Matchar, Samsa, and Liu (2005) used a continuous-time simulation model to investigate the cost-effectiveness of the alternative therapies using a dataset for male patients with non-disabling stroke to measure the Quality-adjusted Life Years (QALYs), costs, and costs per QALYs for the patients.

[16] Vasilakis and Marshall (2005) used different analytical and simulation modelling techniques to analyse the length of stay for stroke patients who were discharged from English hospitals over a 1-year period. The authors then provide a summary of the alternative methods and their similarity in terms of the parameters used to estimate the patient flow as calculated by the phase-type distribution and compartmental modelling techniques.

[17] Sullivan, Arant, Ellis, and Ulrich (2006) reported on using a semi-Markov Monte Carlo simulation model to investigate the cost-effectiveness of a medication used to prevent stroke, specifically in old patients with high risk of stroke. The model was built based on an Arterial Fibrillation (AF) trial and a Medical Expenditure Panel Survey over 10-year time horizon to estimate the cost and QALYs for the patients.

[18] Kongnakorn, et al. (2009) used Discrete Event Simulation (DES) to investigate the cost-effectiveness of a medication used for prevention of stroke based on a trial. The simulation model generates two groups of patients one for those who only receive the usual care and one for those that also receive the medication under study. The simulation model was used to estimate the cost within a 5-year period and QALYs for the patient's lifetime.

[19] Geng, Augusto, Xie, and Jiang (2009) employed a stochastic programming model to assist with a faster service planning of Magnetic Resonance Imaging (MRI) examination used for stroke patients. In another paper, the authors reported on the effect of advance cancellation on system performance improvements for MRI examinations.

[20] Garg, McClean, Meenan, El-Darzi, and Millard (2009) used stroke patients' length of stay data obtained from the English Hospital Episode Statistics database and proposed an idea for a combined distribution using different components of Gaussian mixture and Coxian phase type distributions models.

[21] Bayer, Petsoulas, Cox, Honeyman, and Barlow (2010) described a prototype model to support integrative planning for local stroke services by using DES to map the pathways for stroke patients. The authors concluded that simulation modelling provides a systematic approach to further understand the impact of service change and improvements within the system.

[22] Bredno, Olszewski, and Wintermark (2010) used a brain perfusion simulation model to represent the physiological mechanisms associated with secondary stroke prevention.

[23] Rivero-Arias, et al. (2010) reported on using both Ordinary least squares regression method and multinomial logistic regression with a Monte Carlo simulation approach to map the Modified Rankin Scale Measurement into a Generic Health Outcome. The study compared the performance of each of the mentioned models based on the magnitude of their predicted-to-actual mean health outcome tariff difference, their mean absolute and means squared errors, and associated 95% confidence intervals.

[24] Mar, Arrospide, and Comas (2010) reported on using a DES model to estimate the budget impact of thrombolysis on the prevalence rate of stroke-related disability in Spain and its consequent hospital and social costs. The results of this study suggest a decreased rate of dependent patients and financial savings on social communities' budgets after 6 years.

[25] Gillespie, et al. (2011) proposed a model associated with treating the stroke patient in a healthcare facility using a mixture of Coxian phase type model with multiple absorbing states. In the same paper, the authors also investigated whether benefits due to increase in the administration rate of thrombolysis would balance against its associated costs.

[26] Hwang, Lee, and Shin (2011) designed a study in which two Korean Hospitals participated to investigate the effect of layout design and process improvement on the efficiency of the emergency departments for stroke patients. One of the participated hospitals employed a structured-oriented approach while the other one used a process-oriented approach. By comparing data before and after changes in both hospitals, the authors concluded that the implemented changes were effective in both hospitals, thus suggesting a combination of a structure-oriented and process-oriented strategy for further improvements in the hospitals.

[27] Gantner-Bär, Djanatliev, Prokosch, and Sedlmayr (2011) and [28] Djanatliev, German, Kolominsky-Rabas, and Hofmann (2012) used a technology assessment approach developed in Germany to assess the effects of using Mobile Stroke Units (MSUs) within the stroke care system in the metropolitan Berlin. The authors used both the System Dynamics (SD) and the Agent Based Simulation (ABS) to investigate the effect of using this new technology from perspective of different stakeholders before its implementation. The paper concludes that stroke patients benefit about 18% more from thrombolysis therapy by using the MSU technology.

[29] Pitt, et al. (2012) used Monte Carlo Simulation (MCS) to investigate the effect of extended time window for thrombolysis treatment on stroke patients' data form UK. The results of the study showed that, despite the benefits of the increased number of the treated patients due to the extended time window, the absolute benefit from thrombolysis were reduced by delayed treatments.

[30] Monks, Pitt, Stein, and James (2012) used DES to investigate the stroke patients benefits from both reducing the in-hospital delays and extending the treatment time window from 3 to 4.5 hours. The study concluded that the patients' benefits can be maximized when the two mentioned interventions are used to gather in the hospitals.

[31] Garg, McClean, Barton, Meenan, and Fullerton (2012) applied phase-type distribution methods to data of the stroke patients admitted to Belfast City Hospital for better hospital capacity planning.

[32] AlMuhanna, et al. (2012) used a linear circuit simulation model to represent the anatomical mechanisms associated with the occurrence of ischemic stroke, and [33] Clemens, et al. (2012) used a pharmacokinetic model to investigate the effect of a medication dose on prevention of stroke in patients with Arterial Fibrillation (AF).

[34] Barton, et al. (2012) used Irish data to investigate the benefits of investing on thrombolysis provision for the eligible stroke patients. The study used the results of survival analysis based on the length of stay and discharge destinations for stroke patients to create different groups of patients to form the basis of a DES model used to explore both the benefits on patient's quality of life and the cost-effectiveness of increasing thrombolysis provision in the hospital, community rehabilitation and social services.

[35] Davidson, Husberg, Janzon, Oldgren, and Levin (2013) reported on using a Markov-based simulation model to compare the cost-effectiveness of dabigatran compared to warfarin used for stroke prevention. Data for Swedish patients were obtained to investigate the outcomes on the number of strokes prevented, life years gained, and Quality-adjusted Life Years (QALYs) gained. The study concluded that dabigatran is a cost-effective treatment in Sweden.

[36] Geng, Xie, and Jiang (2013) reported on the results of using new capacity reservation strategies to decrease the waiting times for MRI examinations for stroke patients.

[37] Lahr, van der Zee, Vroomen, Luijckx, and Buskens (2013) reported on using a DES to reorganize the pre- and in-hospital pathways in community hospitals adopted from the organizational model performance achieved by centralized stroke care centres. The study investigated the number of patients treated with thrombolysis, and patient outcome at 90 days for stroke onset to treatment time.

[38] Lahr, van der Zee, Luijckx, Vroomen, and Buskens (2013) used a three-step simulation-based approach to improve utilization of Tissue Plasminogen Activator (tPA) therapy for patients with acute brain infarction. Having identified the barriers and solutions to those barriers from literature and expert consultation, the authors used DES to test the solutions identified for Dutch acute stroke pathway. The results of this study showed that the tPA treatment rates and efficacy of thrombolysis can be increased by using a scoop-and-run

protocol for ambulance personnel and point-of-care diagnostic device instead of laboratory technician.

[39] Churilov, et al. (2013) used a DES model to show how multi-factorial interventions in prehospital acute care system will impact the eligibility of acute stroke patients to receive thrombolysis treatment.

[40] Yang, Chen, Chitkara, and Xu (2014) used a Markov simulation model to compare the long-term effect of three medications (aspirin, clopidogrel, and clopidogrel plus aspirin) used for prevention of stroke or transient ischemic attack (TIA) in patients with intracranial artery stenosis, demonstrating that an increased benefit of treatment with clopidogrel plus aspirin.

[41] Ghijben, Lancsar, and Zavarsek (2014) used a Discrete Choice Experiment to investigate the patients' preferences with different medications used for stroke prevention in patients with AF. The study used data for seventy-six participants, who completed the study followed up by an interview to check whether patients had moderate-to-high risk of stroke. Following the simulation-based sensitivity analysis, the study concluded that new medications are more cost-effective when compared to the currently most used medications.

[42] Lich, et al. (2014) described a SD model to investigate the effect of different scenarios of prevention and rehabilitation interventions on reducing the burden of disease for stroke patients using the US Veteran population data. Different outcomes reported in this study were QALYs, stroke prevented, stroke fatalities prevented, and the number-needed-to-treat per QALY gained.

[43] Aronsson, et al. (2015) presented the results of the cost-effectiveness analysis of screening patients with atrial fibrillation (AF) using an analytic Markov simulation decision support model. In this study, data was generated for 1000 individual patients, whom matched population data from STROKESTOP study.

[44] Vidyanti and Basurto-Davila (2015) used a MCS model to investigate the cost-effectiveness of policies involve reducing the level of dietary sodium on prevention of the hearth disease and stroke for residents of the Los Angeles County.

[45] Mobbs, Boness, and Polden (2015) reported on using a DES to review the efficiency of service provision in the East of England Ambulance Service Trust (EEAST). Subsequent to the review, the authors assessed the potential gains for different stakeholders of the system by providing higher levels of performance.

[46] Micieli, Wijeysundera, Qiu, Atzema, and Singh (2016) used a patient-level Markov micro-simulation decision support model to assess the cost-effectiveness of two new medications compared to a commonly used medication for stroke patients with atrial fibrillation.

[47] Monks, et al. (2016) used DES model as a tool to predict the number of patients at different stages of stroke care system from admission time in a stroke care unit through to rehabilitation services and patients' discharge. The model can be used as a Decision Support (DS) tool for capacity planning of the stroke care pathways with an increased precision compared to previous methods published in literature.

[48] Hoffmeister, et al. (2016) presented the results of the DES used to model the effect of an increased rate of thrombolysis administration on the prevalence of disability at population level for stroke patients. The authors conclude that the minimum rate of tPA to have an increased benefit for the stroke population is 12%.

[49] Pandya, et al. (2016) used a microsimulation model to investigate how mismatch information obtained from two MRI techniques can be used to estimate the stroke onset time for ischemic stroke patients with unknown time of stroke onset.

[50] Kypridemos, et al. (2016) presented the results of a microsimulation study to investigate the effect of universal screening on disease burden and related social and economic factors for cardiovascular disease, specifically focussing on heart attacks and strokes. The authors also compared their selected strategy with other feasible strategies.

[51] Islek, et al. (2016) reported on using a Markov model to predict the effect of ischaemic stroke treatment on deaths associated with Stroke and Ischemic Heart Diseases, while comparing this strategy with system level policies for a population in Turkey.

By reviewing the studies presented in this section, it can be concluded that the application of OR tools and techniques to address different problems in stroke care system has been long the interest of many researchers and OR practitioners. In next section, we adopt a conceptual framework proposed by Churilov and Donnan (2012) to classify these studies in relation to both the specific part of the stroke care system being addressed and the nature of the OR modelling intervention.

2.3.3 Classification of OR studies in stroke care

Table 2-2 summarizes the positioning of the stroke related OR studies reviewed above in relation to both the specific part of the stroke care system (problem area) being addressed and the nature and purpose of the modelling intervention as per Churilov and Donnan (2012). In this table, we use the reference numbers (in square brackets) of studies reported in Section 2.3.2 to refer to each study.

Interventions		Problem areas									
		Stroke prevention	Pre-hospital stroke care	Improving information support	Transient Ischaemic Attack	Stroke unit care	Rehabilitation	Social and community care	Stroke networks	Stroke care expertise	Financial viability
Operations improvement	1.1	[37], [38], [12], [39], [28], [27]			[29], [37], [30], [38], [12], [9], [5], [16], [42]	[12], [21], [19], [26], [36]	[12], [21]	[21]			
	1.2		[37], [12], [21], [28], [27]			[37], [12], [9], [5], [21]	[12], [21]	[12], [21]	[21]		
	1.3					[12], [9], [5]	[12]	[12]			
	1.4		[37], [38], [28], [27]			[29], [2], [7], [37], [30], [38], [34], [24], [12], [9], [5], [16], [4], [14], [19], [31], [36]	[2], [7], [34], [24], [12]	[2], [7], [34], [24], [12], [4], [31]			
	1.5	[42]	[21]			[21], [4], [31]	[21], [42]	[21], [42], [4], [10], [31]	[21]		
	1.6		[37], [38], [39], [21], [28], [27], [45]			[37], [12], [21], [4]	[12], [21]	[12], [21]	[21]		
	1.7		[37], [21], [28], [27]			[37], [12], [9], [21], [4], [14], [19], [36]	[12], [21]	[12], [21], [4]	[21]		
	1.8					[26]					
	1.9		[37], [38], [39], [21], [28], [27], [45]			[29], [37], [38], [12], [9], [5], [16], [21], [47]	[12], [21], [47]	[12], [21]	[21]		

Economic analysis	2.1										
	2.2		[28], [27]			[25]					[25]
	2.3		[21]			[9], [21], [13], [20], [47]	[21], [3], [13], [47]	[21], [3]	[21]	[3]	[3]
	2.4	[11], [51]					[11]				[11]
	2.5	[35], [2], [7], [8], [17], [41], [1], [18], [42], [33], [11], [44], [46], [50], [51]			[43]	[15], [2], [7], [8], [17], [41], [1], [34], [24], [12], [18], [25], [48]	[15], [2], [7], [8], [17], [41], [1], [34], [24], [12], [18], [42], [11]	[15], [2], [7], [8], [17], [41], [1], [34], [24], [12], [18], [42]		[15]	[23], [11], [25], [43]
Public policy	3.1	[42]	[37], [21]			[37], [21], [42]	[21], [42]	[21], [42]	[21]		
	3.2		[39], [21], [28], [27]			[37], [21], [48]	[21]	[21]	[21]		
	3.3	[40], [35], [15], [2], [7], [8], [17], [41], [1], [18], [42], [33], [50], [51]		[40]	[15], [2], [7], [8], [17], [41], [1], [18]	[15], [2], [7], [8], [17], [41], [1], [18], [42]	[15], [2], [7], [8], [17], [41], [1], [18], [42]				
	3.4										

Clinical application	4.1										
	4.2		[28], [27]			[29], [30], [34], [24], [12], [6], [49]	[34], [24], [12]	[34], [24], [12]			
	4.3	[7], [8], [1], [32], [22]				[2], [7], [1]	[2], [7], [1]	[2], [7], [8], [1]			
	4.4	[40], [35], [15], [17], [41], [18], [44], [46]			[40]	[15], [17], [41], [18]	[15], [17], [41], [18]	[15], [17], [41], [18]			
	4.5	[33]									

Table 2-2 OR modelling studies in stroke care by problem areas and the purpose of the modelling.

As the result, we found that the following interventions have been addressed more actively than others: stroke care process design and performance, stroke team scheduling and workforce planning, stroke services planning and utilization models, long term evaluation of stroke burden, stroke prevention and risk factors management models, and stroke clinical and management decision support models. On the other hand, there was a lack of attention to interventions such as stroke units and thrombolysis facility location and layout, imaging and surgical equipment evaluation and selection models, optimal pricing and costing models for stroke care and insurance, impact of prevention and knowledge dissemination policies on stroke care demand, risk screening subsequent to TIAs, stroke risk assessment and analysis, and optimal therapy dose selection models.

With regard to different problem areas, stroke prevention, pre-hospital, stroke unit care, rehabilitation and social and community care parts were identified as the most addressed areas; while information and support for stroke patients, appropriate management of TIAs, appropriate stroke care expertise, and financial viability were addressed least in the literature. The models developed in this thesis provide insights on the long-term impacts of faster access to treatment interventions for stroke patients, thus addressing the problems in the pre-hospital stroke care, stroke unit care, and appropriate stroke care expertise problem areas.

2.4 Summary and conclusions

In this chapter, we first provided a background to hyperacute stroke care system followed by reviewing the stroke care processes as reported in key policy documents by different countries. These is served as an introduction to the problem domain of this thesis, thus providing a background to first and second research questions proposed earlier in Chapter 1.

Given the background to hyperacute stroke care system, we then discussed how we can use OR models with different intended use and interventions to address different problems in the hyperacute stroke care system. The key message here was that models with different intended use have different needs in terms of data requirements and validation. Discussion on this topic eventually provided a background to third research question of this research.

In last section, we reported on methodology and results of a literature review conducted to demonstrate how OR models can be used to address different problems of the stroke care system. We then classified the stroke-related OR studies found as a result of this literature

search in relation to both the specific part of the stroke care system (problem area) being addressed and the nature and purpose of the OR modelling intervention as per Churilov and Donnan (2012). Although we found that problem areas in the field of pre-hospital and stroke unit care have been now addressed for many years by different OR modelling interventions, with recent advances in the hyperacute stroke care system, there is a need for OR models to further address the new questions raised by the clinicians in these areas. OR models developed in this thesis are used to address some of these questions.

Chapter 3: Validation of health OR models for investigation and improvement

Introduction

In this chapter, we address the third research question of this thesis: '*What are the conceptual and application issues of conducting* comprehensive *validation of an OR model for investigation and improvement in the context of health systems and service operations?'*

In Chapter 2 of this thesis we discussed that OR models for investigation and improvement are used to "support investigations that are relatively unique, which may involve system design, system improvement or just an attempt to gain understanding of a very complex situation" (Pidd, 2010, p. 18). According to Schlesinger, et al. (1979, p. 3), model validation is referred to as the "substantiation that a model within its domain of applicability possesses a satisfactory range of accuracy consistent with the intended application of the model". According to Sargent (2013), *validation* of Operations Research (OR) decision models should be performed by model developers to increase the credibility of the model and its results before using the model's recommendations to assist with decision making. In the context of health systems, OR models have often very complex nature as they rely on wide variety of data sources and parameters obtained from clinical literature, and thus validation of such models involves systematically validating different aspects of the model. Additionally, as discussed in Chapter 2, there is a relationship between the intended use of the model and its validation, which suggests using appropriate validation methods and techniques for models with different intended use to ensure that model can be used confidently by model users within its specified domain.

In this chapter, we discuss validation of health OR models used for investigation and improvement as follows: In Section 3.1, we discuss different conceptual and application issues (e.g. lack of empirical data to validate model behaviour, using multiple sources to obtain model inputs) of validating complex OR models used for investigation and improvement in the context of health systems. We then dedicate Section 3.2 to the review of general approaches to model validation proposed in OR/MS literature by different authors. These general approaches are used later in this chapter to design and develop a generic validation framework. By developing this framework, we contribute to OR/MS literature by demonstrating how structured set of validation techniques adopted from literature in the four categories of *data validation*, *conceptual model validation*, *computational model verification*, and *operational validation* can be used to validate complex OR models. Since this validation framework is developed by reviewing the general validation approaches

reported in OR/MS literature, this framework is generic and can be applied to both health and non-health OR models. In Chapters 4 and 5 of this thesis we use this framework to systematically address different validation aspects of three health OR models in the context of hyperacute stroke care system, thus demonstrating how comprehensive validation of a complex OR model for investigation and improvement in the context of health systems and service operations can be conducted.

The content of this chapter is partially based on the paper *"Validation of a decision support model for investigation and improvement in stroke thrombolysis"*, published in the *European Journal of Operational Research* in 2016 (Keshtkaran, et al., 2016).

3.1 Validation of the models for investigation and improvement

As discussed in Chapter 2, OR models with different intended use can be employed by model users to explicitly represent specific parts of different systems (Pidd, 2010). According to Pidd (2010), OR models can be used for decision automation, models for routine decision support, models for investigation and improvement, and models to provide insight.

OR models used for investigation and improvement, can be employed to provide better understanding of a new real-world system which may not even physically exist or may be in the process of being designed. For this type of models, often there is very limited amount of empirical data available on the system behaviour, or even none at all (OR models developed in Chapter 4 and 5 of this thesis are of this type); therefore, empirical validation of the model is very challenging. In models for investigation and improvement, the accuracy needed is usually obtained by critically testing all the parameters and assumptions used to build the conceptual model, thus providing an improved understanding of the model boundaries; while the "output-based" validation of the model is not usually possible.

Validation of OR models used for investigation and improvement in the context of health systems and service operations is even more challenging, due to wide variety of data sources and parameters used for model development. While often various elements used to develop such models are obtained from clinical literature and other relevant sources, there is more complexity in health OR models due to interactions between different modelling elements. These interactions often exist between different parameters and model inputs obtained from multiple sources. Therefore, it is important to use structured set of validation techniques and methods for systematically addressing different aspects of model validation. This ensures

that model and its results have enough credibility to be used within their specified domain by the users.

In the next section, we provide review of the four general categories of model validation as reported in OR/MS literature: *data validity*, *conceptual model validity*, *computational verification*, and *operational validity*.

3.2 General approaches to model validation

According to Schlesinger, et al. (1979, p. 3), validation is the "substantiation that a model within its domain of applicability possesses a satisfactory range of accuracy consistent with the intended application of the model". Other notions used in OR/MS literature are *validation*, *verification*, *acceptability*, *and credibility*, which are mainly used to address the confidence of model developers/users in using an OR model for its proposed application (Pidd, 2003). There is a strong link between these concepts, while the differences are often subtle: for example, the terms *validation* and *verification* are frequently used together, where verification is understood as the process of ensuring that a computerized model has implemented accurately to represent a conceptual model (Sargent, 2013; Schlesinger, et al., 1979). *Acceptability* "usually refers to the entire study, which includes the model and is also clearly a reflection of the relationship between the modeller(s) and the user or client" (Pidd, 2003, p. 298). Finally, Robinson (2002) describes *credibility* as the confidence of the model users and clients in using a model and its results. In this research we use the terms *validity* and *validation* to refer to this broad spectrum of related concepts and relevant techniques and methods used for assessing OR models.

It is important to mention that while many authors repeatedly refer to different categories of model validation and corresponding techniques since early 1970s, it was Gass (1977, 1983) and Sargent (1979, 2013) who comprehensively summarized different categories of validation techniques. In the context of simulation model development, Sargent (1979, 2013) proposed a "development process" (2013, p.14) based on four categories of validation activities as well as a generic structure for model validation documentation (2013, p.22). Gass (1983) clearly outlined different categories of model validity and provided comprehensive discussion of specific technical steps involved in decision model validation.

In this research we utilize both Sargent's (2013) approach and that of Gass (1983) and categorize our subsequent review of the OR models' validation into following four categories: *data validity* (Balci, 1989; Gass, 1977; Oral & Kettani, 1993; Sargent, 2013), *conceptual model validity* (Balci & Nance, 1985; Gass, 1983; Oral & Kettani, 1993; Sargent,

2013), *computational verification* (Adrion, Branstad, & Cherniavsky, 1982; Chattergy & Pooch, 1977; Deutsch, 1981; Dunn, 1987; Gass, 1983; Myers, 1978; Sargent, 2013; Schlesinger, et al., 1979; Whitner & Balci, 1989; Williams & Sikora, 1991), and *operational validity* (Boehm, Brown, & Lipow, 1976; Gass, 1977; Sargent, 2013).

3.2.1 Data validation

The purpose of data validation is to ensure that "*the data necessary for model building, model evaluation and testing, and conducting the model experiments to solve the problem are adequate and correct*" (Sargent, 2013, p. 14). Balci (1989) describes data validation as assuring that both input data and model parameters have the required *accuracy*, *completeness*, *impartiality* and *appropriateness* for the proposed objectives of the model. Historically, empirical disciplines such as health and social sciences emphasize examining the *accuracy*, *consistency*, and *completeness* of the study data (Rothman, Greenland, & Lash, 2008). Oral & Kettani (1993) proposes a number of goals for a data validation procedure – these include ensuring data *sufficiency*, *accuracy*, *appropriateness*, *availability*, *maintainability*, *reliability*, as well as the *feasible cost* of data collection and manipulation. For the OR/MS models, Gass (1983) distinguishes between raw data and structured data, i.e. the raw data that has undergone some types of manipulation. Three desirable properties for raw data validation are then recommended: *accuracy*, defined as "*the ability to correctly identify, obtain, and measure what is desired", impartiality*, i.e. "*the assurance that the data are recorded correctly*", and *representativeness*, namely "*the assurance that the universe from which any sample data are drawn is properly identified and the sample was random*"(Gass, 1983, p. 612). For the structured data validation, the emphasis should be placed on the auditing of every step of data manipulation before the data are used as a part of the OR model (Gass, 1983).

Although there is a broad consensus in OR/MS literature as to *what* constitutes data validity, the recommendations in the literature as to *how* to perform data validation for an OR model are much less frequent. Empirical disciplines, including health sciences, emphasize the procedures of obtaining data and empirical estimates from accredited data sources and published research (Biau, Kernéis, & Porcher, 2008; Ellenberg, 1994). There is a strong emphasis on sampling procedures and sample size estimations to ensure that the precision and applicability of the outputs are adequate for the intended purpose of the study (Biau, et al., 2008). The recommendations also include screening the data for any unspecified outliers and missing values which might have been developed during the sampling process, or while raw data are being transformed to any type of structured data (Balci, 1989; Sargent, 2013).

According to Liu, Cheng, and Wu (2002) outliers either relate to *measurement errors* or *phenomena of interest*. Two methods that can be applied to locate outliers are the *outlier identification* and *outlier accommodation* (Lin & Brown, 2006). In the *outlier identification* the goal is to detect the outliers and decide whether they should be accepted or rejected (Hawkins, 1980), while in *outlier accommodation,* the researchers try *"to develop some robust estimates that are insensitive to the existence of outliers"* (Lin & Brown, 2006). Lastly, it is important to ensure that we document both raw input and parameters data, as well as all data modifications properly (Balci, 1989; Gass, 1983; Sargent, 2013; Williams & Sikora, 1991).

In summary, variety of data validation approaches have been suggested by different authors in OR/MS literature which should be selected and utilized for model validation based on its intended use. For models used for investigation and improvement, data validation is especially very important while the "output-based" validation of the model is not often possible and thus, it is important to validate all the model inputs and parameters used to develop the model.

3.2.2 Conceptual model validity

Compared to the discussions on data validity, various aspects of conceptual model validity are studies in OR/MS literature in greater detail. Sargent (2013) defines the goals of the conceptual model validation as to ensure that the assumptions and theories used to build the model are correct, as well as that there is a "reasonable" logical, mathematical and causal relationship in place for the intended use of the model. Gass (1983) describes three main groups of assumptions that should be examined to achieve conceptual model validity as follows:

- *mathematical assumptions* about the model structure;
- *content assumptions* that are used to define terms and variables of the model; and
- *causal assumptions* that reflect the hypothesized relationships between terms and variables.

In addition, to ensure logical and mathematical validity, Gass (1983) suggests to check the accuracy of the mathematical and numerical calculations, to check the accuracy of the logical flow of data and relevant results, and to ensure that none of the essential variables in the model or their relationships have been neglected. The role of the conceptual model validation, according to Oral & Kettani (1993), is in examining the "*appropriateness of the process of obtaining and using mental data bases*". Following a similar line of thought, Balci

and Nance (1985, p. 16) refer to the “formulated problem” verification as "*substantiation that the formulated problem contains the actual problem in its entirety and is sufficiently well structured to permit the derivation of a sufficiently credible solution*".

According to OR/MS literature, different procedures can be used to validate the conceptual model. Balci (1994) and Sargent (1986) suggest the application of the graphical models (e.g. Event Graphs (Schruben, 1983), Data Flow Diagrams (Batini, Nardelli, & Tamassia, 1986)) to provide better understanding of the conceptual model and its specifications. The choice of these graphical models often depends on the required level of representation by the conceptual model.

“Face validation” or “expert opinion” is another validation technique suggested by different authors (Balci, 1994; Hermann, 1967; Oral & Kettani, 1993; Williams & Sikora, 1991). Sargent (2013) refers to this as systematic investigation of the subjective opinions of individuals working on the model in order to examine whether the model and its behaviour are logical. Similarly, Gass (1983, p. 611) points out to the question of whether “*the initial impression of the model’s realism is positive when reviewed by decision makers who know the system being modelled*.” Finally, “structured walkthrough” – i.e. the process of explaining the model by the model developer to a peer group, is used to obtain the level of the accuracy of the conceptual model required for the intended use of the model (Balci, 1994; Sargent, 2013). As discussed in Chapter 2, for OR models used for decision automation and routine decision support, there is often very little tolerance for the errors in the model outcomes, while for the models used for investigation and improvement the results generated by the model are often an approximation and design and development of more precise methods is necessary to increase the precision of the outcomes generated by the model.

Another group of tests are techniques used to verify the logical behaviour of the model and all of its sub-models (Balci, 1989; Gass, 1983; Oral & Kettani, 1993; Schellenberger, 1974; Williams & Sikora, 1991). Such techniques are “tracing” where the logical behaviour of a model entity is checked to verify its correctness and accuracy (Balci, 1994; Sargent, 2013), the “degeneracy test” by verifying that inputs and internal parameters have reasonable values (Gass, 1983; Sargent, 2013), and the “data relationship correctness” test, to ensure that all data in the model have the “*proper values regarding relationships that occur within a type of data, and between and among different types of data*” (Sargent, 2013, p. 16). While some of these techniques can only be applied for conceptual model validation, validation tests such as “data relationship correctness” and “degeneracy test” can be used to ensure both data

validation and conceptual model validity. Lastly, it is also suggested to apply appropriate mathematical and statistical methods (e.g. mean, median, prediction intervals) to test the main theories and assumptions of the model to ensure that the logical behaviour of the model is correct (Balci, 1994; Gass, 1983; Schellenberger, 1974).

As reviewed in this section, different techniques can be used by model developers to ensure that the conceptual model has enough accuracy for its intended use. For models used for investigation and improvement the conceptual model validation is especially very important to ensure that the assumptions and logical behaviour of the model are accurate enough within the scope of model use. In the next section, we discuss how computational model verification tests can be utilized for correct implementation of the conceptual model.

3.2.3 Computational model verification

The purpose of the computational model verification is to check the logic of the computer program and to ensure that all the numerical and data procedures based on the conceptual model have been implemented correctly (Gass, 1983). Not surprisingly, this topic has attracted major attention in the computer and computational science literature (Adrion, et al., 1982; Chattergy & Pooch, 1977; Deutsch, 1981; Dunn, 1987; Myers, 1978; Sargent, 2013; Schlesinger, et al., 1979; Whitner & Balci, 1989; Williams & Sikora, 1991).

In one of the earliest articles in this subject, Fairly (1976) suggests two main approaches to computational model verification: *static* and *dynamic* testing. Static testing is aimed to verify the correctness of the computer code of the computational model; while in dynamic testing the computer code is executed under different scenarios, and the outcomes are used to identify whether the code and its execution are correct. Balci (1994) and Balci and Nance (1985) suggest different techniques for validation, verification, and testing (VV&T) of the computational models. Some of these include *debugging*, *walkthrough* and *execution tracing*. Debugging is the process of locating the errors, correcting them and checking the computer program of the computational model to confirm the code correctness (Whitner & Balci, 1989). Although debugging is usually a long and non-trivial task, it is an inevitable part of the computational model verification process (Dunn, 1987).

While both *tracing* and *walkthrough* techniques were mentioned in previous section as part of methods used for validation of the conceptual models, they can also be used for obtaining the computational verification of the OR models. The term *walkthrough* refers to “an effort to locate the flaws in the design and/or source code” by the model development team (Whitner & Balci, 1989, p. 7). Different authors refer to this as “structured walkthrough”

(Adrion, et al., 1982; Deutsch, 1981; Myers, 1978; Sargent, 2013), with Yourdon (1979) identifying seven different roles for this task which usually can be performed by a group of three members. Finally, *execution tracing* can be used with debugging to help the model builder with isolating the identified errors in the code script and is described as "locating model defects by *watching* the line-by-line execution activity of the model" (Whitner & Balci, 1989, p. 22).

In summary, the literature on computational model verification shows variety of tests and techniques suggested by different authors which should be selected and utilized for OR models verification based on their intended use. In some cases, the choice of computational verification technique depends on the computer program used to build the model. For instance, for simulation models model developers often use dynamic techniques such as simulation animation for *execution tracing* of the model, while static techniques can be often used for computational verification of both simulation and non-simulation computer Software.

3.2.4 Operational validity

Operational validity refers to the accuracy of the model's outputs being sufficient for the model's intended use (Boehm, et al., 1976). Gass (1983) sees the role of operational validity as that of justifying the use of the model based on the observed and expected errors of the model. Similarly, Sargent (2013) defines the operational validity of an OR model as the degree to which the model's outputs satisfy the accuracy requirements based on the intended use of the model and its applicability.

Specific techniques and tests employed to examine the operational validity of the model include *model output analysis*, *robustness analysis*, *comparison to the results produced by other models*, and *tests to validate an appropriate application of the model* (Boehm, et al., 1976; Gass, 1983; Pidd, 2010; Sargent, 2013).

For output analysis, different types of visual graphs (e.g. histograms, pie charts, Venn diagrams) and analytical techniques (e.g. mean, median, prediction intervals, confidence intervals range) are usually employed to verify the accuracy of the model's output (Balci, 1994; Gass, 1983; Sargent, 2001). Gass (1983) and Boehm et al. (1976) advocate the use of *robustness* test through checking the model's behaviour while changing parameters and inputs of the model. Whitner and Balci (1989), Balci (1994) and Sargent (2013), refer to *extreme conditions test* for testing the credibility of the model structure and output for any extreme value of the internal parameters, similar to the "degeneracy test" described earlier in

this chapter used to validate the conceptual model. Similarly, Myers, Sandler, and Badgett (2011) suggest application of *boundary analysis* technique which is used to observe the changes in model behaviour while changing the model inputs in specified manners.

Wherever possible, it is important that the results of the developed OR model are compared to the results of other previously validated models (Williams & Sikora, 1991). Within the context of simulation models, this comparison can be made between two validated simulation models (Sargent, 2013). Finally, as suggested by Pidd (2010) and (Gass, 1983), the decisions made based on the model outputs should be verified in terms of the intended use of the model.

In summary, the importance of model validation for OR models, as well as the specific methods and techniques for model validation, have been extensively addressed in the OR/MS literature with some techniques applicable to more than one area (e.g. tracing, walkthrough, data relationship correctness). At the same time, most of the effort in OR/MS model validation literature has been limited to broad descriptive articles and only little is reported on the specific cases of comprehensive validation of individual OR models in OR/MS literature.

3.3 Systematic review of specific examples of validating OR models in Health OR/MS literature

In this section, we conduct a systematic literature review to demonstrate the limited extent of studies reporting on comprehensive validation of OR models as found in OR/MS literature. In this chapter we explicitly limit the scope of the search to non-simulation OR models. Reasons for such a choice are as follows: firstly, the domain of simulation modelling within OR/MS is well known for its careful attention to detailed model validation (Balci, 1989; Sargent, 2001, 2013; Whitner & Balci, 1989), and secondly, as discussed by Brailsford and Vissers (2011), the domain of health care simulation modelling applications is expanding by the rate of up to 30 papers per day and conducting a comprehensive review of such a body of literature deserves its own special focus (such as in, e.g., (Fone, et al., 2003) and (Karnon & Afzali, 2014) and would have been impossible within the scope of this research. Lastly, although in this research we rely on numerical simulation for OR models used for investigation and improvement of the hyperacute stroke care system, none of the models developed in this thesis belong to the well-recognized classes of the simulation conceptual models including Discrete Event Simulation (DES), System Dynamics (SD), and Agent Based Simulation (ABS).

3.3.1 Literature search methodology

To illustrate the extent of comprehensive model validation studies of OR models reported in health OR/MS literature, in December 2016 we conducted a systematic search of online journal archives of the following ten most popular OR/MS and DS journals: *Health Care Management Science, Operations Research, Management Science, Journal of Operations Management, European Journal of Operational Research, Omega, Computers and Operations Research, Journal of the Operational Research Society, Annals of Operations Research, Operations Research for Health Care, and Decision Support Systems*.

The search was conducted in two stages. At the first stage, we used the "health*" & "model" & "valid*" strings as the search criteria in the full text of the online archives of the mentioned journals, initially identifying 1247 articles. These articles were then screened to ensure that only non-simulation studies that have reported on comprehensive validation of an OR model in the context of health systems and services applications are included. This resulted in inclusion of 148 articles for further study.

At the second stage, the "valid", "validated", "validity" and "validation" strings were used as the search criteria to search the contents of the remaining 148 articles for the description of the validation tasks undertaken in this research. Four broad validation categories described in Section 3.2 of this chapter (*data validation*, *conceptual model validation*, *computational model verification*, and *operational validation*), formed a classification system and we classified each identified paper as belonging to one or more of these validation categories based on the reported validation activities performed in that paper.

3.3.2 Literature search results

The non-simulation health OR studies selected for this review were identified from ten most popular OR/MS and DS journals. Table 3-1, presents the number of studies identified in each of these journals from the first stage of literature search.

Year	Publication title	Number of articles from keyword search
1998- 2016	Health Care Management Science	160
1971-2016	Operations Research	25
1971-2016	Management Science	61
1980-2016	Journal of Operations Management	81
1977-2016	European Journal of Operational Research	330
1973-2016	Omega	116
1974-2016	Computers and Operations Research	90
1971-2016	The Journal of the Operational Research Society	111
1984-2016	Annals of Operations Research	100
2012-2016	Operations Research for Health Care	20
1985-2016	Decision Support System	153
Total Number		1087

Table 3-1 Summary of a systematic review of specific examples of Validating OR models in Health Operations Research/Management Science literature

As the result, we identified 12 studies that reported on performing some data validation only, 53 studies reporting elements of conceptual model validation only, and 28 articles reporting some operational validation as the only validation approaches applied or discussed in the study. Eight studies reported some aspects of both data and conceptual model validation, 29 studies included elements of both conceptual and operational validation, and further five studies reported addressing data as well as operational validation issues. Finally, as presented in Figure 3-1 only 13 articles simultaneously address some aspects of data, conceptual model, and operational validation. Below we presents some examples of these articles:

- Blake and Carter (2002) in the "*A goal programming approach to strategic resource allocation in acute care hospitals*" paper where authors report on using the linear goal programming models for strategic resource allocation in health services;
- Zanakis et al. (2007) in the "*Scio-economic determinants of HIV/AIDS pandemic and nations efficiencies*" paper where the authors investigate the effect of epidemic HIV/AIDS socio-economic determinants across different countries;
- Junglas et al. (2009) in the "*Mobile technology at the frontlines of patient care: understanding fit and human drives in utilization decisions and performance*"

paper employ both qualitative and quantitative techniques to report on medical staff decisions on using mobile technologies in healthcare centres;

- Duque, Castro, Sörensen, and Goos (2015) in the "*Home care service planning. The case of Landelijke Thuiszorg*" paper report on using an optimization decision support model used to provide assistance in service planning for a "social profit" organization;
- Gardner, Boyer, and Gray (2015) in the "*Operational and strategic information processing: complementing healthcare IT infrastructure*" paper use different methods to examine the Healthcare Information Technologies and their impacts on patient satisfaction;
- Kortbeek, Braaksma, Smeenk, Bakker, and Boucherie (2015) in the "*Integral resource capacity planning for inpatient care services based on bed census predictions by hour*" paper use an analytical approach to investigate the effect of strategic, tactical, and operational decisions on bed occupancy in medical care units; and
- Keshtkaran, et al. (2016) in the "*Validation of a decision support model for investigation and improvement in stroke thrombolysis*" paper demonstrate how a complex decision support model for investigation and improvement in the context of hyperacute stroke care system can be systematically validated.

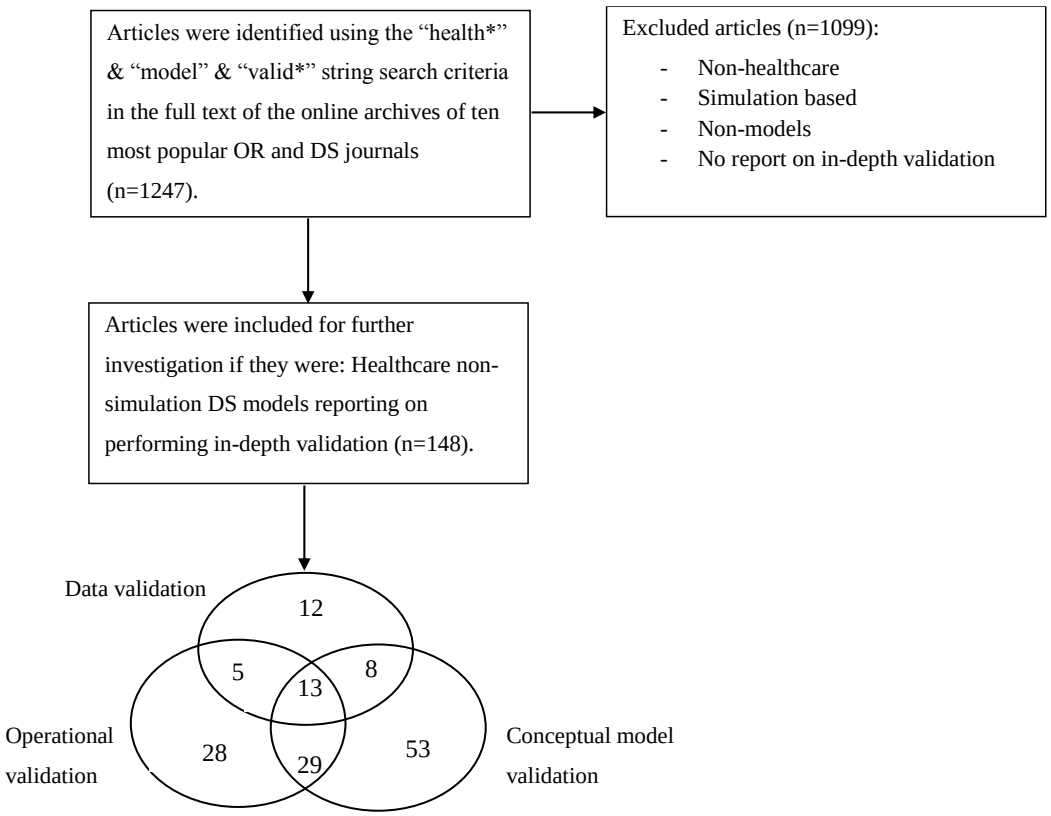

Figure 3-1 The process of identifying specific cases of OR model validation in Health OR/MS

The true extent to which various studies have reported validation issues of the OR models varied broadly, with the majority of the studies only claiming the *fact of the application* of one or more validation techniques or tests without providing sufficiently detailed information regarding the validation procedures or their results. One of the rare exceptions to this trend is the study by Blake and Carter (2002) in which the authors have provided an extensive section on theoretical, data and predictive validity of the model using a three-phase validation approach proposed by Schellenberger (1974). Another example is a study by Mason, Denton, Shah and Smith (2014) who employed a Markov decision process model to identify the optimal timing of blood pressure and cholesterol treatment for diabetes patients. The authors devoted a separate section to model validation, where data validation and comparison of model outputs to other validated models are discussed and a brief report on the validation procedures and outcomes are provided.

In summary, despite both well-recognized need for appropriate validation of OR models in the OR/MS literature and the relative abundance of health OR/MS models reported in the literature, only very few health non-simulation OR/MS publications could be identified that

not only *mention the fact* of performing one or more OR model validation activities as a part of the reported study, but also *systematically discuss both the process and the results* of the undertaken OR model validation activities.

3.4 A proposed generic framework for validation

As a result of literature search, we identified that there is a research gap in the reported knowledge about *practical aspects of how to validate an OR model excluding simulation models for investigation and improvement in the context of health systems and service operations*. To address the identified research gap and to contribute to OR/MS literature, we specified the research question as follows: What are the conceptual and application issues of conducting a comprehensive validation of an OR model for investigation and improvement in the context of health systems and service operations? To answer this research question we propose a generic validation framework which can be used to validate complex OR models for investigation and improvement.

We base our proposed framework on four categories of *data validity*, *conceptual model validity*, *computational verification,* and *operational validity*, as specified earlier in Section 3.2 of this chapter as the four generic aspects of model validation. For each category of model validation, we document the process of validation by addressing the applied validation task, motivation of each validation task (i.e. *Why*), the process of performing the validation task (i.e. *How*), and the conclusions/results achieved by the validation task. In this framework, we refer to following validation techniques for each aspect of model validation:

1. Validation tasks relevant to data validation: *representativeness* of the dataset, proper *documentation* of the data components, searching for *outliers*, and searching for *missing values*.
2. Validation tasks relevant to conceptual model validation: *degeneracy tests, data relationship correctness, tracing, mathematical and statistical validation methods*, and *structured walkthrough*.
3. Validation tasks relevant to computational verification: *debugging, walkthrough*, and *execution tracing*.
4. Validation tasks relevant to operational validation: *output analysis, robustness, comparison of the model outputs*, and *intended use of the model*.

Based on our suggested validation framework, each of the model components is validated by describing *why* to perform the validation task, *how* to perform the validation task, and mentioning all the conclusions and results due to the validation task. The process of data

validation, conceptual model validity, computerized verification, and operational validity has been summarized in Table 3-2 to Table 3-5.

Validation task	Why performing the validation task	How to perform the validation task	The conclusions/results of the validation task
Representativeness of the dataset	Based on: (Biau, et al., 2008; Ellenberg, 1994)		
	To ensure that demographics of different data obtained from multiple sources are similar.	By comparing demographics of data obtained from multiple sources.	The results of the study can potentially be generalized for a larger dataset with different demographics.
	To ensure that the data source used to estimate different parameters of the model is trustworthy.	By using the most updated data from valid sources.	Increased confidence in the accuracy of the estimations for different parameters of the model.
	To ensure that parameters used to build the model are obtained from a trustworthy data source.	By obtaining the model parameters from valid sources.	Increased accuracy of the parameters used in the model.
Proper documentation of the data components	Based on: (Balci, 1989; Gass, 1983; Sargent, 2013; Williams & Sikora, 1991)		
	To enable the study replicability.	Both the original and replicated data should be dated and stored on a password-protected computer.	Both original and replicated data can be retrieved when needed.
Searching for outliers	Based on: (Balci, 1989; Sargent, 2013)		

	The existence of the outliers in the dataset can affect the accuracy of the results.	Dataset should be searched for any outliers.	Reason for the existence of any outliers in dataset should be specified.
Searching for missing values	Based on: (Balci, 1989; Sargent, 2013)		
	Any data with missing values on parameters used to build the conceptual model cannot be included in the dataset.	Dataset should be searched for any missing values on parameters used to build the conceptual model. In case of finding missing values, they should be retrieved from the source documentation; otherwise data should be excluded from the study.	Under the assumption of missingness-at-random, we only included data without missing values on parameters used to build the conceptual model.

Table 3-2 Validation tests and techniques utilized for data validation of different components of OR models

Validation task	Why performing the validation task	How to perform the validation task	The conclusions/results of the validation task
Degeneracy test	Based on: (Gass, 1983; Sargent, 2013)		
	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	By obtaining required information from valid sources.	Increased credibility of the model.
Data relationship correctness	Based on: (Sargent, 2013)		
	To ensure that there is a logical relationship between different parameters of the model.	By comparing values of different parameters.	Increased credibility of the model formulations.
	To ensure that there is a logical relationship between different data components used to build the conceptual model.	By selecting large enough sample size to ensure that the precision of the developed conceptual model is no worse than the precision of the relationship between different parameters of the model.	This increased the overall precision of the estimates leading to the increased validity of the model.
Tracing	Based on: (Balci, 1994; Sargent, 2013)		
	To ensure that the logical behaviour of the model formulations is correct and the required accuracy obtained.	The process of building and selecting the equations to formulate the conceptual model was performed separately by three members of the model development team	The equations used to formulate the conceptual model were verified and the equations were corrected where necessary.

		and the results were compared for any inconsistency.	
Mathematical and statistical validation methods	Based on: (Balci, 1994; Gass, 1983; Schellenberger, 1974)		
	To ensure that the equations used to build the conceptual model are accurate enough and logically correct.	We verified the conceptual model and ensured that we derive the relevant analytical expressions with the best possible precision.	Verifying the relationships between different parameters of the model; thus increasing the credibility and accuracy of the conceptual model.
Structured walkthrough and face validity	Based on: (Balci, 1994; Hermann, 1967; Oral & Kettani, 1993; Sargent, 2013; Williams & Sikora, 1991)		
	To ensure that the conceptual model is accurate enough for its intended use.	The logic of the model structure, assumptions, and parameters were explained step by step to an expert who asked questions and challenged the choices, leading to significant iterative model changes.	The logic of the model follows the standard guidelines of the field.

Table 3-3 Validation tests and techniques utilized for conceptual model validation of different components of health OR models

Validation task	Why performing the validation task	How to perform the validation task	The conclusions/results of the validation task
Debugging	Based on: (Dunn, 1987; Whitner & Balci, 1989)		
	To confirm the correctness of the codes used to build the computational model.	The code script used to develop the model was screened to locate and correct the potential errors.	Typing and logic errors were identified and removed.
Walkthrough	Based on: (Adrion, et al., 1982; Deutsch, 1981; Myers, 1978; Yourdon, 1979)		
	To ensure that all the computations used to build the computational model are correct.	The analytical expert verified the correct storage and execution of the computations.	Storage and execution of relevant computations of the model were verified.
Execution tracing	Based on: (Whitner & Balci, 1989)		
	To confirm the correctness of the codes used to build the computational model.	Defects of the code script were located and corrected by line-by-line execution of the code by an analytical expert.	Typing and logic errors were identified and removed.

Table 3-4 Validation tests and techniques utilized for computational model verification of different components of OR models

Validation task	Why performing the validation task	How to perform the validation task	The conclusions/results of the validation task
Output analysis	Based on: (Balci, 1994; Gass, 1983; Sargent, 2001)		
	To identify any unusual behaviour of the model and pin-pointing errors that would not have been identified solely through summary statistics.	We created multiple graphical representations to validate the model outputs.	We found errors in the outputs as a result of either incorrect logic or implementation of the model which were subsequently corrected.
Robustness	Based on: (Balci, 1994; Boehm, et al., 1976; Gass, 1983; Myers, et al., 2011; Sargent, 2013; Whitner & Balci, 1989)		
	To check the model's behaviour while changing the parameters and inputs of the model.	By checking the robustness of the model.	Credibility of the outputs was increased by providing the users with estimates of uncertainty.
Comparison of the model outputs	Based on: (Sargent, 2013; Williams & Sikora, 1991)		
	To ensure that the model's outputs are accurate enough for the intended use of the model.	By comparing the outcomes of the model to the results of other valid models.	Credibility of the outputs was increased by providing the comparison to other relevant studies.
Intended use of the model	Based on: (Gass, 1983; Pidd, 2010)		
	To verify the decisions made based on the model outputs.	By discussing the limitations and boundaries of application of the model.	Users of the decision support model will understand the limitations and will not overgeneralize or use the model outside of its intended use.

Table 3-5 Validation tests and techniques utilized for operational validation of different components of OR models

The validation framework presented in Table 3-2 to Table 3-5 is generic and can be applied for validation of different types of models, even though not all validation techniques suggested in this framework are applicable to OR models with different nature and intended use and there is a wide variety of validation techniques which was not mentioned in this framework. In this thesis we use this framework specifically to validate three complex health OR models developed in Chapters 4 and 5 to demonstrate how comprehensive validation of OR models for investigation and improvement in the context of health systems and service operations can be performed.

3.5 Summary and conclusions

In this chapter, we first discussed the importance and needs of validating OR models, specifically for models with investigation and improvement intended use, in the context of health systems and service operations. We then reviewed the general approaches to model validation proposed in OR/MS literature by different authors. These were presented in the four distinct groups of *data validity*, *conceptual model validity*, *computational verification*, and *operational validity*.

In Section 3.3, we conducted a systematic literature review to investigate the extent of studies reported on comprehensive validation of the health OR models, where we concluded that even though the concept of validation has been widely addressed by different authors in literature, there is a lack of *reported knowledge about practical aspects of how to validate an OR model for investigation and improvement in the context of health systems and service operations*. We then used four broad validation categories described in Section 3.2 of this chapter (*data validation*, *conceptual model validation*, *computational model verification*, and *operational validation*) for classifying the identified studies according to the reported validation activities performed in that study. As a result, we found only seven articles out of 107 articles that simultaneously address some aspects of data, conceptual model, and operational validation.

In the last section, we proposed a generic validation framework which can be used to validate complex OR models with respect to four aspects of model validation. This is achieved by using validation tasks described by different authors in Section 3.2 of this chapter, to perform model validation. The process of model validation is then systematically documented in this framework to describe the intention of each validation task (i.e. Why), the process of performing the validation task (i.e. How), and the developed

conclusions/results. This framework addresses the third research question proposed in Chapter 1 of this thesis: *What are the conceptual and application issues of conducting* comprehensive *validation of an OR model for investigation and improvement in the context of health systems and service operations?*

In Chapters 4 and 5, we employ the generic validation framework proposed in this chapter to demonstrate how multiple aspects of data validity, conceptual model validity, computational model verification, and operational model validity can be systematically addressed when developing a complex OR model for investigation and improvement in the context of health systems and service operations. Even though in this thesis we use this framework for validation of OR models in the context of health systems and service operations, it is generic enough to be employed for validating OR models in non-health contexts.

Chapter 4: Population OR models for investigation and improvement of the long-term benefits of early access to hyperacute stroke treatment interventions

Introduction

In this chapter, we address the first and third research questions, namely: (1) '*How OR models can be designed, developed, and validated to provide an improved understanding of the earlier treatment benefits on patients' life-time outcomes for two different treatment interventions in hyperacute stroke care system?*' and (2)*'What are the conceptual and application issues of conducting* comprehensive *validation of an OR model for investigation and improvement in the context of health systems and service operations?'*

As discussed in Chapter 2, there are two effective treatment interventions for ischemic stroke patients: IV tPA and endovascular thrombectomy with both treatments being very time-sensitive. In this chapter, we design and validate two OR models used for better understanding of earlier treatment benefits for stroke patients for two treatment interventions in the hyperacute stroke care system. The first model is the '*IV tPA'* model used to investigate the long-term benefits of early access to IV tPA treatment for ischemic stroke patients. The model is then validated using the general validation framework proposed in Chapter 3. We then extend the 'IV tPA' model to develop the *'Endovascular Thrombectomy'* model used to investigate the long-term benefits of early access to endovascular thrombectomy therapy for ischemic stroke patients. The generic validation framework proposed in Chapter 3 is adopted to validate the 'Endovascular Thrombectomy' model. Both models developed in this chapter are used for quantifying the population benefits due to earlier treatment for ischemic stroke patients.

Two OR models developed in this chapter can be used for understanding the long-term effects of faster access to different treatment interventions on stroke patients' life-time outcomes in the hyperacute stroke care system. Discussion on validation is expected to provide further insights on the conceptual and application issues of conducting an comprehensive validation of an OR model for investigation and improvement in the context of health systems and service operations.

The content of this chapter is partially based on the following papers: (1)*"Stroke thrombolysis; save a minute, save a day"* published in the leading journal of the field, *Stroke* in 2014 (Meretoja, et al., 2014)*;* (2) *"Validation of a decision support model for*

investigation and improvement in stroke thrombolysis" published in the *European Journal of Operational Research* in 2016 (Keshtkaran, et al., 2016); and (3) "*Endovascular therapy for ischemic stroke; save a minute – save a week"* accepted for publication in *Neurology* at the time of submitting this thesis (Meretoja, et al., 2017).

4.1 Problem description and intended use of the 'IV tPA' model

Until 2014, intravenous thrombolysis (tPA) was the only medical therapy shown to improve patient outcomes in ischemic stroke patients (Jauch, et al., 2013). As evidenced by clinical trials, the earlier treatment for this intervention leads to higher chance of effective outcome in ischemic stroke patients (Emberson, et al., 2014; Lees, et al., 2010), while the upper time limit to receive this treatment is 270 minutes from stroke onset time. Despite the accepted health benefits of faster access to IV tPA treatment for stroke patients, prior to this research there was no method for quantifying the link between reductions in treatment delays for IV tPA treatment and patients' lifetime benefits. In this chapter, we present the 'IV tPA' model which designed and validated to provide better understanding of the benefits of earlier access to IV tPA treatment for ischemic stroke patients.

The 'IV tPA' model was constructed to investigate the effect of earlier tPA treatment on patient lifetime outcomes; thus, classified as a model for *investigation and improvement* with the aim of increasing the awareness of public policy decision makers, stroke campaigns, and stroke care system providers of the importance of benefits of faster thrombolysis treatment in an easier-to-understand manner.

The results of the 'IV tPA' model were originally published in the flagship journal; *Stroke*, titled *'Stroke thrombolysis; save a minute, save a day'* (Meretoja, et al., 2014) lead to a significant media exposure including sources like Bloomberg (Gale, 2014), The Times (Whipple, 2014), Reuters (Seaman, 2014), and Herald Sun (2014). American Heart and Stroke Association produced an infographics encapsulating the findings for the consumers (American Heart Association/American Stroke Association, 2014). The model's findings are also used by the Australian National Stroke Foundation and Victorian Stroke Telemedicine Initiative (State of Victoria, Australia) to advocate for wider use of stroke thrombolysis telemedicine in remote an rural areas (Bladin & Cadilhac, 2014; Stroke Foundation Australia, 2016). Overall, current levels of the actual model use are quite consistent with the original modelling expectations.

4.2 Overview of the 'IV tPA' model

The 'IV tPA' model is the first OR model used to explicitly quantify the link between reductions in treatment delays before IV tPA treatment and patients' lifetime benefits. This model extends the discussion provided in a journal article titled *'Stroke thrombolysis; save a minute , save a day'* originally published in *Stroke* in 2014 (Meretoja, et al., 2014). Inputs and parameters of the 'IV tPA' model are originating from a wide variety of data sources, empirical estimates and clinical literature. This includes observational real-life cohort data, pooled analysis of tPA effect over time, general population life expectancy data, and different parameters to derive the outcomes of the model. The main output of this model is expressed as number of disability-adjusted days saved per minute of earlier treatment for IV tPA treatment. Figure 4-1 presents an overview of the 'IV tPA' model with all the model inputs. Detailed description of these inputs is provided in next section.

Summary of different parameters used to conceptualize the 'IV tPA' model is presented in Table 4-1. These parameters are further described in details in Section 4.3 and 4.4 and are used in Section 4.4 to develop the model.

Parameter name	Definition
K (K=1 or 0)	age-weighting modulation factor
β (β=0.04)	age-weighting function
C (C =0.1658)	adjustment constant
r (r=0.03 or 0)	discounting rate
DWs	mRS specific disability weights
S	mRS specific annual risk of death
A	age of death
A_s	age of onset of disability
L	life expectancy of general population at the age of stroke
L_d	duration of disability at the age of stroke
t_0 *(maximum 270 min)*	observed onset-to-tPA treatment time
t (maximum 270 min)	OR model onset-to-tPA treatment time
$P_{mRS\ 0\text{-}1}(t_0)$	probability of mRS 0-1 at time t_0
$P_{mRS\ 6}(t_0)$	probability of mRS 6 at time t_0
$P_{mRS\ 0\text{-}1}(t)$	probability of mRS 0-1 at time *t*
$P_{mRS\ 6}(t)$	probability of mRS 6 at time *t*
odds ratio $_{mRS\ 0\text{-}1}(t)$	fitted value of odds ratios for mRS 0-1 at time *t*
odds ratio $_{mRS\ 6}(t)$	fitted value of odds ratios for mRS 6 at time *t*
odds ratio $_{mRS\ 0\text{-}1}(t_0)$	fitted value of odds ratios for mRS 0-1 at time t_0
odds ratio $_{mRS\ 6}(t_0)$	fitted value of odds ratios for mRS 6 at time t_0
YLL	years of life lost due to premature death
YLD	years of life lost due to disability
DALYs	disability-adjusted life years lost

Table 4-1 Summary of different parameters of the 'IV tPA' model

The 'IV tPA' model is a model for *investigation and improvement* according to Pidd (2010) classification, as it is used to provide better understanding of the long-term effects of earlier treatment on patients' outcomes with regard to IV tPA intervention. As discussed in Chapter 2, this type of model is used to "support investigations that are relatively unique, which may involve system design, system improvement or just an attempt to gain understanding of a very complex situation" (Pidd, 2010, p. 18).

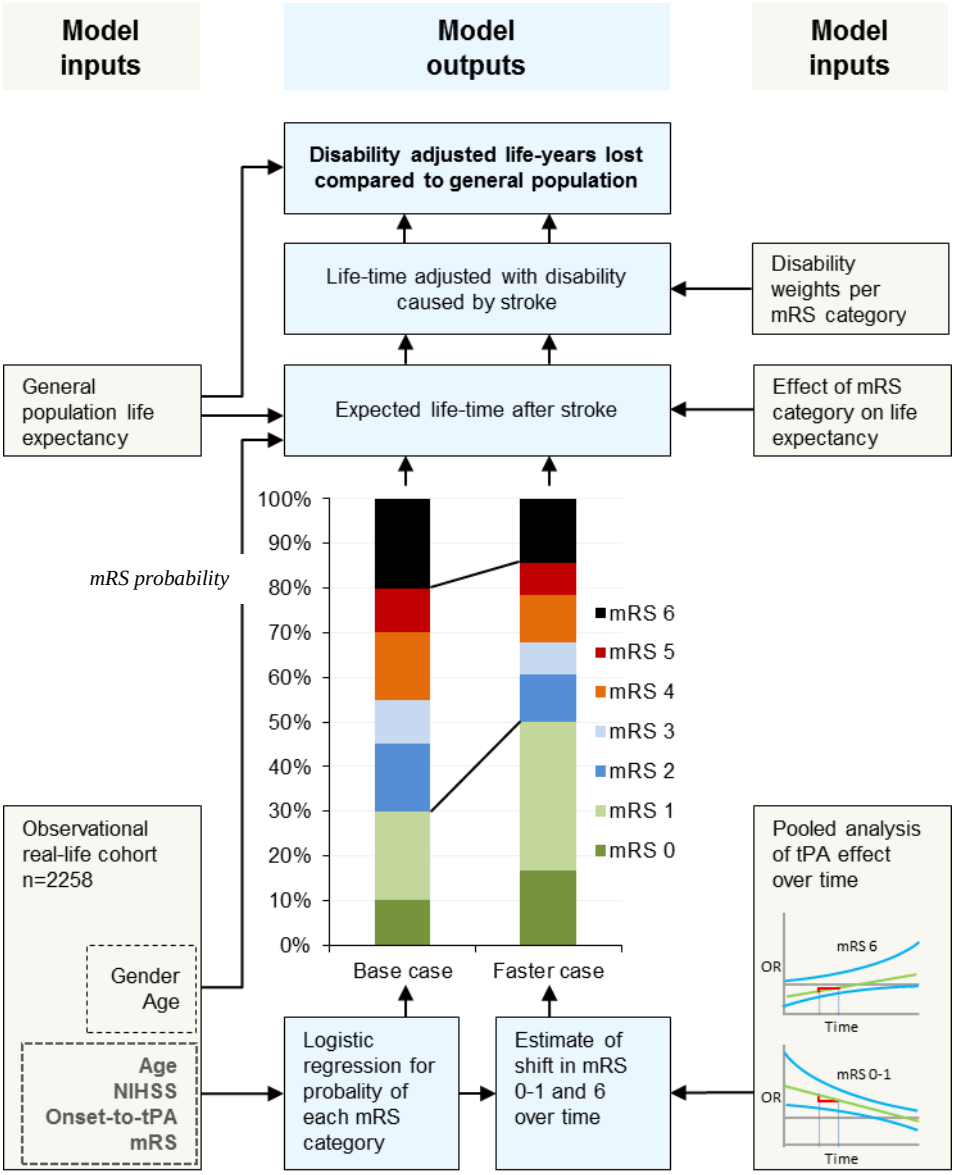

Figure 4-1 Overview of the 'IV tPA' model. mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; OR, odds ratio.

4.3 Overview of the 'IV tPA' model inputs

Following model inputs were used to construct the 'IV tPA' model:

1. **An observational cohort data of consecutive tPA patients**: This is based on a combined sample of 2258 patients retrieved from two databases: the Helsinki Stroke Thrombolysis Registry (Meretoja, et al., 2012), and the Safe Implementation of Treatments in Stroke (SITS-Australia) database (Simpson, et al., 2010). Helsinki Stroke Thrombolysis Registry contains the information about all cases of acute stroke thrombolysis given to patients at the Helsinki University Central Hospital.

The data used in this study was generated during the period between March 1998 and December 2011 and included relevant patient information for 1727 patients treated with tPA (Meretoja, et al., 2012). Similarly, SITS-Australia contains the information about the cases of acute stroke thrombolysis administered in various centres in Australia (Simpson, et al., 2010). The data from the SITS-Australia dataset used in this study was generated between December 2002 and December 2008 and included relevant patient information on 531 out of 704 patients from 14 treating centres.

We included 1727 patients from Helsinki registry dataset and 531 patients from SITS-Australia dataset to build a comparatively large sample size of 2258 patients, representing two potentially different demographic groups for the study. This cohort consisted of distribution data for age, sex, and stroke severity measured on the National Institutes of Health Stroke Scale (NIHSS)(Lyden, et al., 1994), onset-to-tPA treatment times; and post-stroke disability level at 3 months, measured by modified Rankin Scale (mRS) (Rankin, 1957). Table 4-2 shows distributions of age, gender, NIHSS, onset-to-tPA treatment time, and mRS for Helsinki and SITS-Australia databases.

Characteristics and Outcomes	**Total (n=2258)**	**Helsinki (n=1727)**	**SITS-Australia (n=531)**	***P* Value**
Age, y	70 (60-78) 68±13	70 (60-77) 67±13	73 (62-80) 70±13	<0.001 <0.001
Male sex	1247 (55%)	939 (54%)	308 (58%)	0.161
NIHSS at baseline	9 (6-15) 11±6	8 (5-14) 10±6	13 (8-19) 14±7	<0.001 <0.001
Onset-to-tPA treatment time, min	125 (92-162) 129±46	117 (86-160) 125±49	145 (123-167) 143±32	<0.001 <0.001
3-Month mRS score 0 to 1	850 (37.6%)	664 (38.4%)	183 (34.5%)	0.097
3-Month mRS score 0 to 2	1290 (57.1%)	1031 (59.7%)	259 (48.8%)	<0.001
3-Month mRS 6	252 (11.2%)	155 (9.0%)	97 (18.3%)	<0.001

Table 4-2 Characteristics of the observational cohort. Data are n (%), median (interquartile range), or mean±SD. Distributions of Helsinki and SITS-Australia data compared with Mann-Whitney U test x^2 test, or Student t test as appropriate, with 2-sided statistical significance set at P=0.05. mRS indicates modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; and SITS, Safe Implementation of Treatments in Stroke.

Since data from two different registries were used to build the 'IV tPA' model, in Figure 4-2 we provide a comparison between onset-to-tPA treatment distributions of these two cohorts. Even though is some cases the characteristics of the two samples are different, the combined cohort increases the generalizability of the results generated based on the 'IV tPA' model.

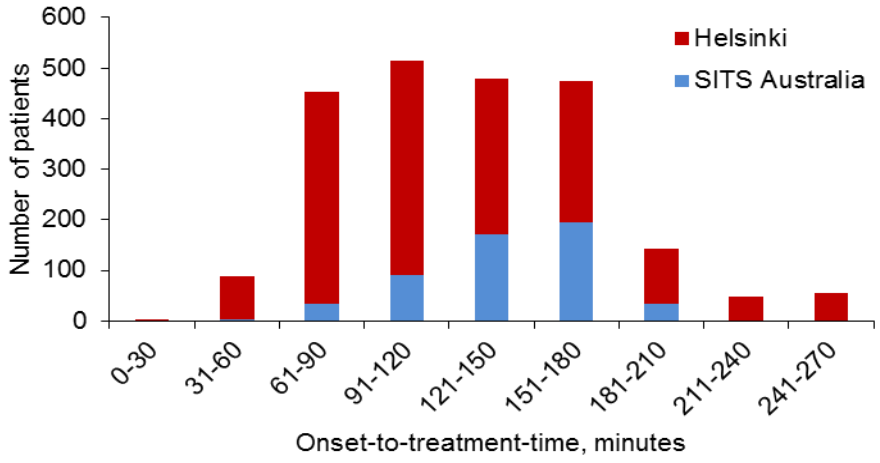

Figure 4-2 Histogram of onset-to-tPA treatment time distributions

The NIHSS scale is a validated tool used to assess the severity of stroke by clinicians in most stroke centres globally (Brott, et al., 1989). The mRS categorizes the functional disability into seven broad groups ordered from mRS 0 (No symptoms at all), to mRS 6 (Dead) as presented in Table 4-3 (Sulter, Steen, & De Keyser, 1999).

Level	**Description**
0	No symptoms
1	No significant disability, despite symptoms; able to perform all usual duties and activities
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requires constant nursing care and attention

Table 4-3 Descriptions of different levels of modified Rankin Scale (mRS) (Sulter, et al., 1999)

2. **Published pooled analysis of tPA effect over time** (Emberson, et al., 2014; Lees, et al., 2010): The effect is graphically summarized as odds ratios with corresponding confidence intervals for tPA treatment compared to placebo of obtaining favourable outcome (mRS 0-1) and for mortality (mRS 6) vs. onset-to-tPA treatment time as reported in a paper by Lees, et al. (2010). Updated results of these analyses were

published in a paper by Emberson, et al. (2014) where the authors only provided the odds ratio curve for the mRS 0-1 without providing any relevant analytical expression for the curves. As a result, we used the odds ratio lines for mRS 0-1 and mRS 6 provided in the paper by Lees, et al. (2010) to run the main analysis for the 'IV tPA' model and then replaced the odds ratio curve of mRS 0-1 in Lees, et al. (2010) paper with that of Emberson, et al. (2014) to validate the model outputs.

3. **General Australian population life expectancy age- and sex- specific data obtained from Australian Bureau of Statistics:** These included age and sex specific life-expectancies of the male and female residents in the State of Victoria, Australia for the period of 2011-2013. The life expectancy data contained the mortality rates for a group of 100,000 hypothetical newborn babies throughout their entire life, and all the necessary information to calculate the life expectancy for the mentioned group, such as the number of persons surviving to exact age of x, the proportion of persons dying between exact age x and exact age $x+1$ (mortality rate), the number of person years lived within the age interval x to $x+1$; and life expectancy at exact age x (Australian Bureau of Statistics, 2011-2013). The latest version of this data at the time of developing the 'IV tPA' model was used to model the long-term survival of patients at various mRS categories compared with the general population (Australian Bureau of Statistics, 2011-2013). We compared this data with its updated version (Australian Bureau of Statistics, 2013-2015) at the time of submitting this thesis and observed no significant difference between the databases.
4. **Parameters necessary to translate the 3-month mRS outcome data into a long-term metric of Disability-adjusted Life Years (DALYs) lost**: The parameters include age-weighting modulation factor (k), age-weighting function (β), adjustment constant (C), discounting rate (r), mRS specific disability weights (DWs), and mRS specific annual risk of death (s) (Murray, 1996; World Health Organization, 2014). The values of K, β, C, and r were originally determined by World Health Organization (WHO) as a result of Global Burden of Disease Project (GBDP) undertaken jointly by the World Bank, and Harvard School of Public Health in 1992 (Murray, 1996; World Health Organization, 2014). DWs were developed by WHO-GBDP for chronic post-stroke states for each of the seven mRS grades (0.000, 0.053, 0.228, 0.353, 0.691, and 0.998 for mRS categories 0-5, respectively). Lastly, the long-term annual risk of death after stroke is expressed as disability-linked mortality hazard ratios for premature annual mortality for mRS categories from 0 to 5 (1.53, 1.52, 2.17, 3.18, 4.55, and 6.55 times that of the general population for mRS categories 0-5, respectively)(Hong & Saver, 2010).

4.4 Overview of the model-building process

The 'IV tPA' model was constructed in four stages as shown in Figure 4-3. These stages have been discussed in details as follows:

Stage 1: **Generating patient-specific probabilities of achieving specific mRS categories at the cohort observed onset-to-tPA treatment time (t_0)** – We used a validated regression model with mRs categories as dependant variables and age, baseline NIHSS, and onset-to-tPA treatment time as independent variables to generate the patient-specific probability distributions for each mRS level. The choices of age and baseline stroke severity as input parameters reflect an evidence-based understanding of these variables being strong prognostic factors for the functional outcome after stroke (Jauch, et al., 2013). Using a simple normalization scaling procedure, we ensured that the sum of patient-specific probabilities for each mRS category is equal to one, and then we used the estimated probabilities to generate patient-specific probability distributions of achieving a given mRS category at the observed onset-to-tPA treatment times t_0.

Stage 2: Modelling the change in probabilities of achieving mRS 0-1 and mRS 6 over time - The pooled analysis of thrombolysis randomized controlled trials by Lees et al. (2010) provides an estimation of the effect of thrombolysis treatment delays compared to placebo. This has been reported by the authors in a mentioned paper in two separate graphs for mRS 0-1 and mRS 6 without providing any analytical expressions for the odds ratio curves. The graphical curves reported in that article demonstrate the change in the odds ratio of achieving mRS 0-1 and mRS 6 probabilities as a function of onset-to-tPA treatment for values between 60 and 360 minutes.

To build this model, since authors in Lees et al. (2010) paper have not provided any analytical equations for the odds ratio curves we derived relevant analytical expressions for odds ratios of mRS 0-1 and mRS 6 using the best fit (based on adjusted R^2 criterion) and used these equations to estimate the odds ratios for mRS 0-1 and mRS 6 as a function of onset-to-tPA treatment time for any value of onset-to-tPA treatment time between 0 and 270 (i.e. the currently accepted evidence-based upper time limit for tPA treatment) minutes (Jauch, et al., 2013; Lees, et al., 2010).

The odds ratio reported by Lees et al. (2010) presents the ratio of odds of achieving mRS 0-1 (or, respectively, mRS 6), by the patients treated with tPA at a time point t and the odds of achieving the same outcome by the patients not treated by tPA. To estimate the probabilities of mRS 0-1 and mRS 6 at any given time, we used formulae 4-1 and 4-2:

$$P_{mRS\ 0\text{-}1}(t)=1/\{1+(\text{odds ratio}_{mRS\ 0\text{-}1}(t_0)/\text{odds ratio}_{mRS\ 0\text{-}1}(t))*[(1-p_{mRS\ 0\text{-}1}(t_0))/p_{mRS\ 0\text{-}1}(t_0)]\} \quad (4\text{-}1)$$

$$P_{mRS\ 6}(t)=1/\{1+(\text{odds ratio}_{mRS\ 6}(t_0)/\text{odds ratio}_{mRS\ 6}(t))*[(1-p_{mRS\ 6}(t_0))/p_{mRS\ 6}(t_0)]\} \quad (4\text{-}2)$$

All the parameters used to develop these formulas are described earlier in Table 4-1.

Stage 3: Estimating probabilities of achieving a specific mRS at any time - Since the graphs presented in Lees et al. (2010) only report on the odds ratios for mRS 0-1 and mRS 6, we used the patient-specific probabilities of achieving mRS 0-1 and mRS 6 at any given time *t* obtained at Stage 2 to estimate the probability distributions for each individual mRS category. These probabilities were estimated assuming that the ratios of probabilities for achieving individual mRS categories remain identical to those obtained in Stage 1 from the logistic regression models based on the observed cohort data.

Stage 4: Estimating the expected Disability-adjusted Life Years (DALYs) lost - Disability adjusted life-years (DALYs) lost metric developed by the World Health Organization (WHO) was used to translate the 3-month mRS outcome data into a meaningful long-term metric. This metric expresses the total amount of optimal life-years lost due to both premature mortality and living with disability and consists of two components: years of life lost due to premature death (YLL) and years of life lost due to disability (YLD) (Rushby & Hanson, 2001).

YLL is calculated as the difference between general population life expectancy of a person at a given age and sex, that is, life expectancy of a person without stroke, and age-and sex-matched life expectancy of a stroke patient in a certain mRS category. The long-term annual risk of death after stroke was taken from published literature for mRS categories 0-5 times that of the general population for each mRS level (Hong & Saver, 2010).

Equation 4-3 was used to estimate YLL:

$$YLL[r,K]=KCe^{rA}/(r+\beta)^2\{e^{-(r+\beta)(L+A)}[-(r+\beta)(L+A)-1]-e^{-(r+\beta)A}[-(r+\beta)A-1]\}+[(1-K)/r](1-e^{-rL}) \quad (4\text{-}3)$$

whereas described earlier, K indicates age-weighting modulation factor ($K=1$ or 0); β is the parameter from age weighting function ($\beta = 0.04$); r is the discount rate ($r = 0.03$ or 0); C is a constant ($C= 0.1658$); A is the age of death, and L is the life expectancy of general population at the age of stroke.

YLD is calculated by multiplying the life expectancy of a stroke patient by a disability weight and, therefore, demonstrates how much the value of life has diminished in years lived after stroke (Hong & Saver, 2009). Equation 4-4 was used to estimate YLD:

$$YLD[r,K]=DKCe^{rA_s}/(r+\beta)^2\{e^{-(r+\beta)(Ld+As)}[-(r+\beta)(L_d+A_s)-1]-e^{-(r+\beta)A_s}[-(r+\beta)A_s-1]\}+[(1-K)/r](1-e^{-rLd}) \quad (4\text{-}4)$$

where K, β, r and C are the same parameters as in YLL formula; A_s is age of onset of disability; L_d is duration of disability; and DWs is disability weights.

Having estimated the values for YLL and YLD, DALYs are then derived by summing up the values of YLL and YLD as shown in equation 4-5. For the 'IV tPA' model, DALYs lost for each patient in the observational cohort at onset-to-tPA treatment time has been initially estimated, and then we have modeled the DALYs lost with regard to the treatment delays for each patient (Hong & Saver, 2010).

$$DALYs[r,K] = YLL[r,K] + YLD[r,K] \quad (4\text{-}5)$$

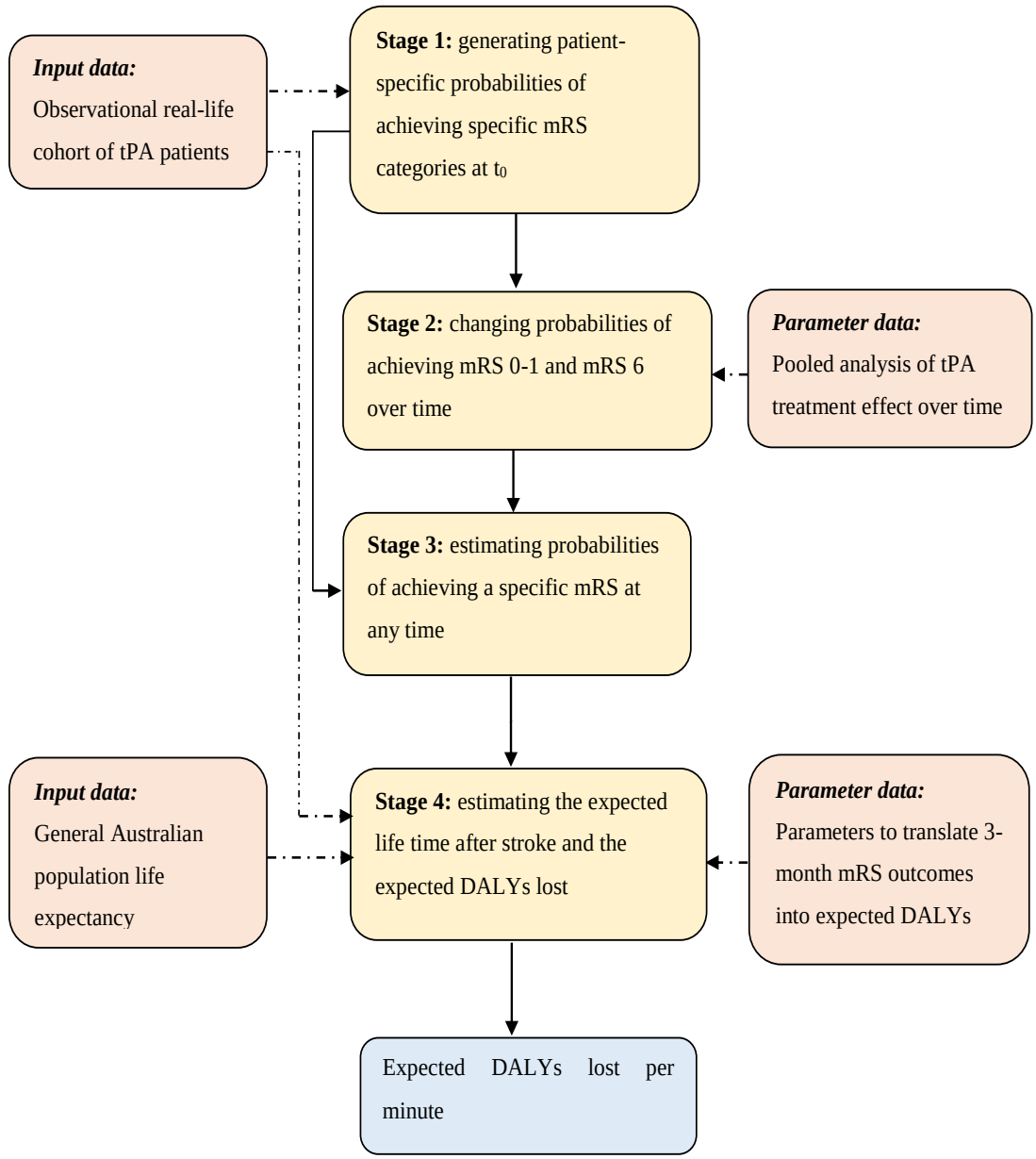

Figure 4-3 Overview of different stages of the model building process

4.5 Result of treating faster in the whole cohort and individual patients

In the whole cohort, we generated the results for one minute earlier of real-life onset-to-tPA treatment time according to the World Health Organization (WHO) policy updated in 2012 to report DALYs without age-weighting (*K = 0*) and discounting (*r = 0*) factors (Murray, et al., 2013). For these parameters (*K=0, r=0*), we estimated on average extra 1.8 days of DALYs saved per minute of earlier treatment (median 1.7, IQR, 1.1–2.3, standard deviation 0.8, range 0.1–4.6 days of DALY) for the full cohort.

It is evidenced by clinical trials that patients with various age and disease severity benefit differently from faster treatment. To evaluate these findings, we ran the 'IV tPA' model for five individual female patients, namely:

- a patient with median age (70 y.o.) and median stroke severity (NIHSS 9);
- two patients with old ages (90^{th} decile, 83 y.o.) and respectively low (10^{th} decile, NIHSS 4) and high stroke severities (90^{th} decile, NIHSS 20); and
- two patients with young ages (10^{th} decile, 50 y.o.) and respectively low (NIHSS 4) and high (NIHSS 20) stroke severities.

On average a 70 years old female patient with median stroke severity gained extra 2.1 days, a 50 y.o. patient with mild stroke and severe stroke gained extra 2.7 and 3.5 days respectively, and a 83 y.o. patient gained extra 0.9 and 0.6 days respectively for each minute saved (Meretoja, et al., 2014). As it is evidenced by the results of the 'IV tPA' model, the younger patients gain more benefit from faster treatment as a result of their longer lifetime.

Moreover, we generated disability adjusted days saved per minute of earlier treatment for female and male stroke patients for different age and severity groups. In two graphs presented in Figure 4-4, patients from cohort data has been categorized into five NIHSS severity groups (0-4, 5-9, 10-14, 15-19, 20+), and six age groups (<45, 45-54, 55-64, 65-74, 75-84, 84+), while the point estimates show the disability adjusted days saved per minute of earlier treatment for that group of patients. Even though in these figures we categorized the patients into different groups in a way that we have enough number of patients in each group, those groups with very young and high disease severity or very old and mild severity eventually had fewer patients compared to other groups; thus changing the linear trend of age group lines.

By comparing data between the female and male groups, it can be observed that female patients often benefit more from faster treatment over their longer life time. For patients

younger than 64, disability-adjusted days saved per faster treatment increases from NIHSS (0-4) to NIHSS (15-19). Lastly, by fixing the NIHSS group in any of the figures presented below, and moving from patients with younger ages towards those with older ages, the benefits of faster treatment decreases. Point estimates and 95% prediction intervals for each of these groups have been provided in Table 4-4.

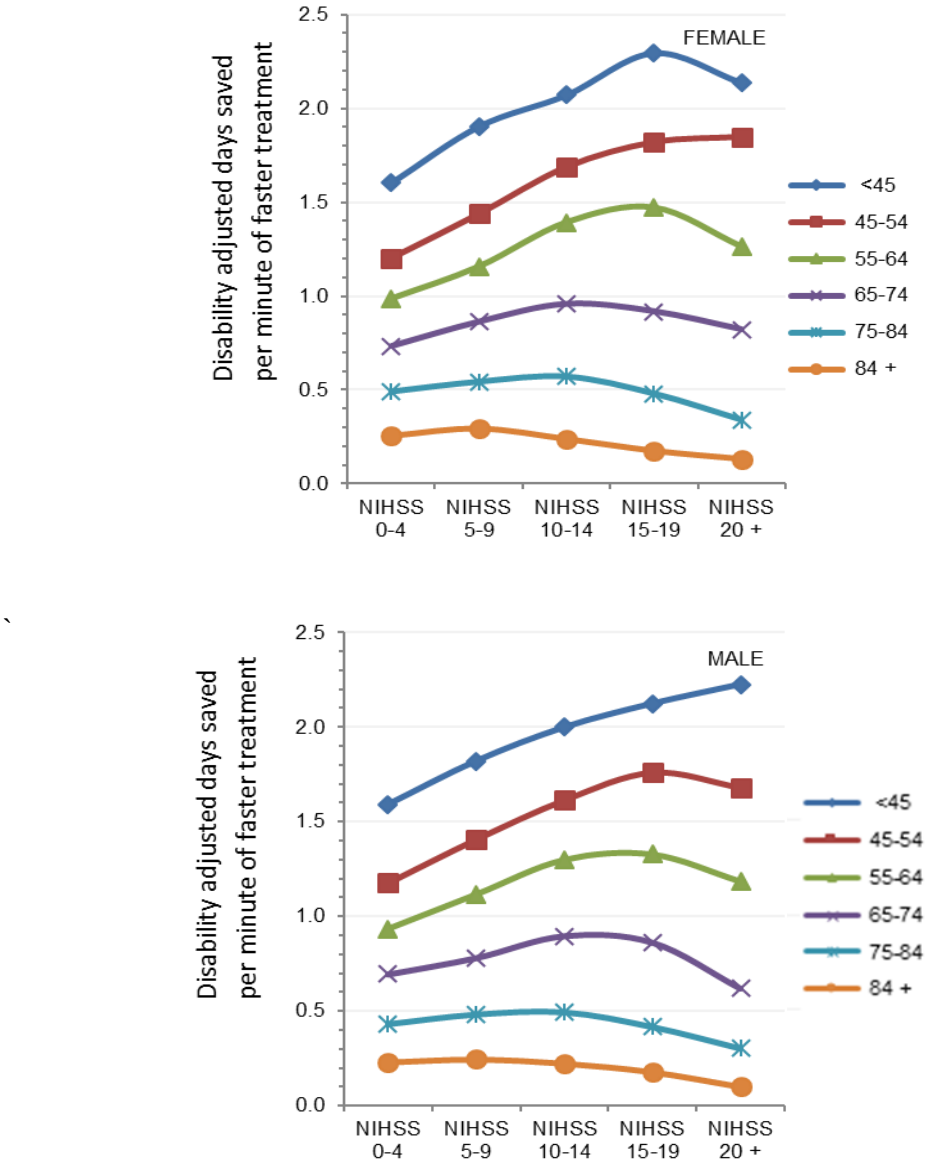

Figure 4-4 Relationship between disability-adjusted days gained per minute of faster treatment, age, and stroke severity. Baseline stroke severity measured with the National Institute of Health Stroke Scale (NIHSS) where higher scores indicate more severe stroke

Sex, Age	NIHSS 0-4	NIHSS 5-9	NIHSS 10-14	NIHSS 15-19	NIHSS 20 +
Male					
<45	3.01 (1.02-5.01)	3.40 (1.56-5.24)	3.67 (1.62-5.73)	3.75 (1.91-5.60)	3.83 (2.18-5.48)
45-54	2.30 (0.80-3.79)	2.70 (1.08-4.31)	3.02 (1.26-4.79)	3.17 (1.26-5.08)	2.86 (1.31-4.41)
55-64	1.87 (0.73-3.01)	2.20 (0.97-3.43)	2.49 (1.08-3.90)	2.45 (1.23-3.68)	2.11 (1.06-3.15)
65-74	1.45 (0.72-2.18)	1.61 (0.71-2.52)	1.81 (0.82-2.80)	1.69 (0.81-2.57)	1.19 (0.68-1.69)
75-84	0.97 (0.51-1.44)	1.08 (0.48-1.68)	1.09 (0.56-1.62)	0.91 (0.44-1.37)	0.65 (0.29-1.01)
85 +	0.59 (0.37-0.81)	0.63 (0.29-0.97)	0.57 (0.27-0.86)	0.45 (0.25-0.64)	0.26 (0.14-0.37)
Female					
<45	3.24 (1.80-4.67)	3.79 (1.90-5.67)	4.05 (1.74-6.36)	4.30 (2.57-6.04)	3.86 (2.16-5.55)
45-54	2.54 (1.03-4.05)	2.98 (1.25-4.71)	3.40 (1.33-5.47)	3.55 (1.80-5.29)	3.48 (0.47-6.50)
55-64	2.14 (0.98-3.31)	2.48 (1.17-3.79)	2.89 (1.49-4.29)	2.95 (1.44-4.45)	2.45 (1.05-3.84)
65-74	1.65 (0.78-2.52)	1.91 (0.91-2.91)	2.07 (0.97-3.18)	1.93 (0.96-2.90)	1.66 (0.74-2.58)
75-84	1.16 (0.58-1.75)	1.28 (0.62-1.94)	1.32 (0.70-1.94)	1.09 (0.54-1.64)	0.76 (0.37-1.15)
85 +	0.67 (0.37-0.98)	0.76 (0.46-1.06)	0.62 (0.35-0.89)	0.45 (0.27-0.63)	0.33 (0.15-0.51)

Table 4-4 Point estimates and 95% prediction intervals for disability adjusted days gained per minute saved in tPA delivery, per sex, age, and stroke severity (NIHSS)

Figure 4-5, is presenting the effect of treatment delay on Life Expectancy (LE) and Disability-adjusted Life Years (DALYs) for five individual female patients. While for the whole cohort DALYs was generated without age-weighting ($K = 0$) and discounting factor ($r = 0$) according to updated policy of the WHO in 2012 (Murray, et al., 2013), here DALYs estimations are provided with discounting to present values at 3% annually both with and without age-weighting as per standard methodology (Rushby & Hanson, 2001). In Figure 4-5, this has been presented by blue line for DALYs with age-weighting ($K=1$) and discounting rate ($r=0.03$), by green line for DALYs without age-weighting ($K=0$) and with discounting rate ($r=0.03$), and by red line for DALYs without age-weighting ($K=0$) and discounting factor ($r=0$). As it can be seen in these figures, as the onset-to-tPA treatment time increases from 0 to 270 minutes, the DALYs lost also increases in all cases. Thus, it can be concluded that patients with different age and severity benefit by earlier tPA treatment. On the other hand, the life expectancy of the patients after stroke decreases in all cases with more delays of onset-to-tPA treatment time. This has been presented in Figure 4-5 by purple lines. The 95% prediction intervals in all cases have been plotted by dashed lines. The methodology used to estimate these prediction intervals have been described in details in Section 4.6.

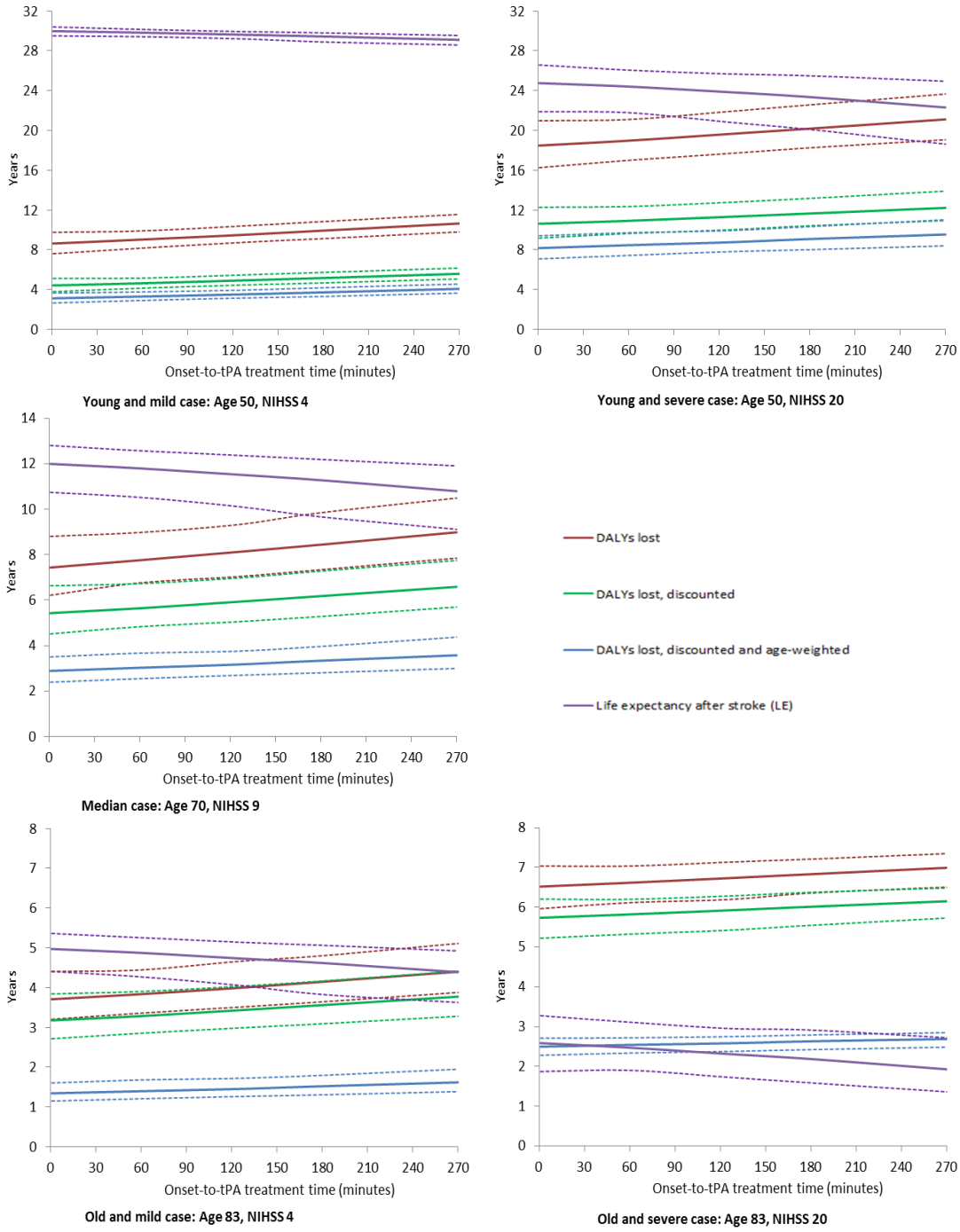

Figure 4-5 Effect of treatment delay with 95% prediction interval on Life Expectancy (LE) and Disability-adjusted Life Years (DALYs) in 5 individual female cases with median, top, and bottom decile age/National Institute of Health Stroke Scale (NIHSS). tPA indicates tissue plasminogen activator.

4.6 Robustness analysis

For the 'IV tPA' model, we first varied each model input to their upper and lower 95% CIs and evaluating the model robustness with regard to those uncertainties in the inputs. We refer to this method as one-way robustness analysis which was performed by substituting the upper and lower 95% CIs values for the regression coefficients for the age and NIHSS generated by the binary logistic regression models used to estimate different levels of mRS. To account for potential uncertainties of the pooled analysis by Lees et al. (2010), we modified the equations of *odds ratio(t)* for mRS 0-1 and mRS6 in the mRS probability distribution formula to sequentially reflect the upper and lower 95% confidence limits for these two mRS categories as reported by Lees et al. (2010).

In one-way analysis by varying the odds ratio of mRS 0-1 to the lower and upper 95% CIs respectively adopted from the paper by Lees at al (2010), a patient benefits on average extra 0.84 and 2.75 days for each minute saved. These values are changing between 1.41 and 2.08 days when varying the odds ratio of mRS 6 to the lower and upper 95% CIs as presented in a paper by Lees at al (2010). With respect to the effect of age and NIHSS on outcome, a patient benefits vary from 1.65 to 1.90 days for age, and 1.75 to 1.81 days for NIHSS with respectively changing the lower and upper 95% CIs (Table 4-5).

Inputs in the one-way analysis	**Disability-adjusted days saved per minute of faster treatment**	
	Lower value	Upper value
Odds of mRS 0-1[a]	0.84	2.75
Odds of mRS 6[a]	1.41	2.08
Effect of age on outcome[b]	1.65	1.90
Effect of NIHSS on outcome[b]	1.75	1.81

[a] *Upper and lower 95% CIs from the pooled analysis of Lees at al (2010)*
[b] *Upper and lower 95% CIs from the logistic regression model in the observational cohort.*

Table 4-5 Robustness of model when inputs changed one at a time. Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale. The point estimate is 1.78 days per minute in all cases.

The probabilistic analysis was performed by sampling according to an underlying Normal distribution from the feasible space of the mRS 0-1 and mRS 6 odds ratio curves bounded by the 95% confidence interval limits provided in a paper by Lees at al (2010) and reflecting various potential time effects based on the pooled analysis, through a set of 1000 independent runs. The resulting probability profiles for all mRS categories were then used to estimate DALYs gained or lost if either the whole cohort or an individual patient would have

been treated faster or slower. As a result, we estimated a 95% prediction interval from 0.9 to 2.7 days for each minute saved. Both one-way analysis and probabilistic analysis demonstrated that the results were robust overall, with the average point estimate of 1.78 days for each minute saved for the robustness analyses.

Appropriate validation of the 'IV tPA' model is particularly very challenging as the model relies on the wide variety of datasets and parameters used as model inputs, while it should address multiple aspects of conceptual model validity, computational verification, and operational validity. To achieve this, in the next section we adopt the validation framework developed in Chapter 3 to demonstrate how multiple aspects of data validity, conceptual model validity, computational model verification, and operational validity can be systematically addressed.

4.7 Comprehensive validation of the 'IV tPA' model

In this section, we provide comprehensive validation of the 'IV tPA' model using the validation framework presented earlier in Chapter 3. To achieve this, we validate the model with regard to the four categories of data validity, conceptual model validity, computational verification, and operational validity.

4.7.1 Data validity

Both input data (e.g. stroke thrombolysis cohort and general population life expectancy data) and previously published data in the form of various parameters estimators (e.g. pooled analysis of tPA, annual risk of death and disability weights) were used to build the 'IV tPA' model model. This data as shown in Figure 4-3 in orange boxes has been validated as follows:

4.7.1.1 Validation of input data

Observational cohort data: Both registries used to build the observational cohort are valid in terms of the representativeness as they represent consecutive patients with prospectively collected data on age, sex, stroke severity, onset-to-tPA treatment time of ischemic stroke patients for Finland and Australia. They were created and maintained in accordance to the best practice guidelines for clinical registries and were approved by the relevant institutional authorities.

Based on pre-specified inclusion criteria, in both datasets, the patients with onset-to-tPA treatment time greater than 4½ hours (n=150 in Helsinki database), and those with deviations

from standard treatment procedure (n=56 in Helsinki database) and missing value on onset-to-tPA treatment time, stroke severity or mRS outcome (n=65 in Helsinki database and n=173 in Safe Implementation of Treatment in Stroke database) were excluded. Each dataset was searched separately for any outliers before inclusion to the study. We also searched the combined dataset for any outliers generated as a result of combining two different datasets and no outliers were found. The original databases as well as all the subsequent datasets used to develop the model were stored and documented on a password protected computer.

Having validated the observational cohort in terms of the representativeness, outliers, missing values and documentation, we then used the individual patient data to generate the patient-specific probabilities of achieving specified mRS categories as described in Stage 1 of the model development.

General population life expectancy: As described at stage 4 of the model development, general population life expectancies data were used in the model to calculate DALYs. Being produced by the main government body in charge of the official statistics for the purposes of the analysis of life expectancy, this dataset was assumed to be valid. After ensuring that there are no outliers or missing values in the data, the full dataset along with its explanatory notes was documented in an Excel file for any retrieval purposes in the future.

4.7.1.2 Validation of parameters

Pooled analysis of tPA effect over time: As described at stage 3 of the model development, pooled analysis of tPA treatment effect over time by Lees et al. (2010) was used to derive how the effect of tPA treatment varies with delays for onset-to-treatment time. The parameters obtained from this meta-analysis are most representative of the current state of the knowledge in the area of stroke thrombolysis as the study includes eight major randomized placebo-controlled trials of intravenous recombinant tissue plasminogen activator for acute stroke (Lees, et al., 2010).

Parameters to calculate expected DALYs: As described at stage 4 of the model development different parameters were derived from previously validated and published literature to transfer the 3-month mRS outcome into a long-term metric. DWs were also developed by WHO-GBDP for chronic post-stroke states, using the person trade-off method where healthcare professionals judge health conditions from a broad public health point of view, ensuring equity across different health states (Murray, 1996; Nord, 1992). Hong and Saver (2009) then formed an international panel of 9 experts to use the trade-off procedure combined with a Delphi process to estimate DWs. Lastly, the long-term annual risk of death

after stroke was adopted from previously validated published literature (Hong & Saver, 2010), even though this publication did not provide the CIs around DWs and long-term annual risk of death after stroke that could be used for model validation purposes.

The summary of different validation methods and techniques used to obtain data validity for 'IV tPA' model has been provided in Table 4-6.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Representativeness of the dataset	Based on: (Biau, et al., 2008; Ellenberg, 1994)		
Observational cohort data	To ensure that demographics of the observed data have similar distributions to that of the published literature.	We obtained consecutive prospective data from two registries in Finland and Australia. We compared patient demographics to those in published literature.	The results of the study can potentially be generalized for a larger group of patients.
General population life expectancy	To ensure that the data source used to estimate the life expectancies is trustworthy.	At the time of developing the 'IV tPA' model, we used the latest official data for age and sex specific life-expectancies of the residents of Victoria, Australia, obtained from ABS (2011-2013). We compared these with similar life-expectancy data from Finland, observing minimal differences (the average life expectancy at birth for men is 79.2 years in Australia versus 76.8 years in Finland and for women 83.8 years versus 83.3 years).	Increased confidence in the accuracy of the estimations for the general population life expectancy.
Pooled analysis of tPA effect over time	To ensure that parameters used to model the effect of tPA treatment over time were obtained from a trustworthy data	The parameters used to model the effect of tPA treatment over time were obtained from the pooled analysis of individual patient data of tPA randomized controlled trials by Lees et al. This study includes eight major randomized placebo-controlled trials of tPA for acute stroke (86% of the total number of patients in all trials for	Increased accuracy of the parameters used to model the effect of tPA treatment changing with onset-to-tPA treatment times.

	source.	tPA treatment), which is the most representative of the current state of the knowledge in the field of stroke thrombolysis.	
Parameters to calculate DALYs lost	To ensure that the data source used to obtain parameters for estimating DALYs lost is trustworthy.	We used the parameters obtained from WHO-GBDP, which was undertaken jointly with the World Bank, and Harvard School of Public Health.	Increased accuracy of the parameters used to estimate the expected DALYs.
Proper documentation of the data components	Based on: (Balci, 1989; Gass, 1983; Sargent, 2013; Williams & Sikora, 1991)		
Observational cohort data	To enable the study replicability.	Both the original and replicated data were dated and stored on a password-protected computer.	Both original and replicated data can be retrieved when needed.
General population life expectancy	To enable the study replicability.	Both the original and replicated data were dated and stored on a password-protected computer.	Both original and replicated data can be retrieved when needed.
Searching for outliers	Based on: (Balci, 1989; Sargent, 2013)		
Observational cohort data	The existence of the outliers in the dataset can affect the	Each dataset from Finland and Australia as well as the combined dataset from these two registries were searched for any outliers.	Neither improbable nor impossible outliers were found in the observed dataset.

	accuracy of the results.		
General population life expectancy	The existence of the outliers in the dataset can affect the accuracy of the results.	The dataset was searched for any outliers.	Neither improbable nor impossible outliers were found in the observed dataset.
Searching for missing values	Based on: (Balci, 1989; Sargent, 2013)		
Observational cohort data	Any data with missing values on parameters used to build the conceptual model could not be included in the observational cohort.	Each dataset from Finland and Australia as well as the combined dataset were searched for any missing value on age, sex, stroke severity, and onset-to-tPA treatment time. We tried to retrieve data from the source documentation where missing, if not found it was excluded from study.	Under the assumption of missingness-at-random, we included those patients from the observational cohort without missing values on age, sex, stroke severity, and onset-to-tPA treatment time to build the logistic regression model.
General population life expectancy	Any data with missing values on parameters used to build the conceptual model could not be included in the general population life expectancy dataset.	The dataset was searched for any missing value on the parameters needed to estimate the life expectancy of the general population. No missing values were found in this dataset.	We could include patients of all ages to estimate the life expectancy of the general population as we had life-expectancies for everyone.

Table 4-6 Validation tests and techniques utilized for data validation of different components of the 'IV tPA' model

4.7.2 Conceptual model validity

The conceptual model of the effect of onset-to-tPA treatment time delays on mRS probabilities was mainly developed at Stage 2 and Stage 3 of the model development. As shown in Figure 4-3 in yellow boxes, conceptual model validation consists of validating the model's assumptions and its logical and mathematical structure. Different methods and validation tests used to validate the conceptual model were: degeneracy test, data relationship correctness test, mathematical and statistical methods, tracing and structured walkthrough. Each of these types of data has been validated as follows:

4.7.2.1 Validation of the model assumptions

All the four mentioned assumptions were validated by formally obtaining the opinion of the clinical expert- the approach presented in the validation literature as walkthrough validation technique (Sargent, 1996). The choice of 270 minutes as the upper time limit to receive tPA treatment is the evidence-based upper time limit adopted by majority of international stroke clinical guidelines (Jauch, et al., 2013). The appropriate selection of this parameter was validated using what is known as the degeneracy test.

4.7.2.2 Validation of model structure/formulation

The logical structure of the conceptual model was validated through checking the *mRS probability distributions*, *change over time formulation*, *numerical relationships in the model*, and *DALYs mathematical formulation*.

The mRS probability distributions: We first validated the standard assumptions underlying the use of logistic regression (such as independence of individual observations, appropriate distributional assumptions, collinearity, and model fit). We then randomly selected 80% of the combined observational cohort and created seven separate binary logistic regression models; one for each individual mRS category as the dependent variable and age, baseline NIHSS, and onset-to-tPA treatment time as independent variables. Then, the statistical validity of the mRS prediction model was evaluated in the remaining 20% of the observational cohort, with no significant difference between predicted and observed mRS categories being identified (χ^2 p-value=0.51). Using these regression models we then generated the patient-specific probability distributions for each mRS category, and ensured that the sum of the probabilities for each patient is equal to one; thus validating the normalization scaling procedure performed at Stage 1 of the model development.

Numerical relationships in the model: By selecting a large enough original cohort sample size we ensured that the relationship between age, NIHSS, and mRS at a given point of onset-to-tPA treatment time (based on the cohort data), is no worse than the precision of the relationship between mRS and time (based on meta-analysis data).

Changes over time formulation: As previously stated in stage 2 of the model development, to model how the onset-to-treatment time affects the probability of mRS 0-1 and mRS 6 for a specific patient, we derived relevant independent analytic expressions for mRS 0-1 and mRS 6 curves and validated the resulting equations using the best fit R^2 criterion. For both curves the corresponding values were R^2 =0.999.

DALYs mathematical formulation: As described at Stage 4 of the model development, DALY is a measure consisting of two components: years of life lost due to premature death (YLL) and years of life lost due to disability (YLD). Data relationship correctness technique was employed to validate different parts of DALYs' formulation. For instance, if we compare the values for DALYs between a female and a male patient with identical age and mRS category, the DALYs for a female patient is expected to be greater than that of the male patient.

Each of the three mentioned components of the conceptual model structure were validated by tracing the formulation separately by different members of the model development team and the results were compared to identify and resolve inconsistencies. Also, the structured walkthrough validation technique was employed to ensure that the logical behaviour of the conceptual model is aligned with the clinical practice by explaining the model assumptions, parameters and formulation to a clinician.

The summary of different validation methods and techniques used to obtain conceptual validity of the 'IV tPA' model has been provided in Table 4-7.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Degeneracy test	Based on: (Gass, 1983; Sargent, 2013)		
Limitation of upper treatment time to 270 minutes	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	Based on published international stroke clinical guidelines we observed that the vast majority of these studies implemented the 270 minutes time window, although a few still used the old 180 minutes, which was based on guidelines up to year 2008.	Increased credibility of the model as the vast majority of the users of the model outputs will consider the time window appropriate.
Data relationship correctness	Based on: (Sargent, 2013)		
DALYs mathematical formulation	To ensure that there is a logical relationship between DALYs' values of female and male patients.	The values for DALYs between a female and a male patient with similar characteristics were compared.	Increased credibility of DALYs formulation used for male and female patients.
Numerical relationships in the model	To ensure that there is a logical relationship between different data components used to build the conceptual model.	We selected a large enough original cohort sample size to ensure that the precision of the regression coefficient estimates describing the relationship between age, NIHSS, and mRS at a given point of onset-to-tPA treatment time (based on the cohort data) is no worse than the precision of the relationship between mRS and time (based on the meta-analysis data)	This increased the overall precision of the estimates leading to the increased validity of the model.
Tracing	Based on: (Balci, 1994; Sargent, 2013)		

Change over time formulation	To ensure that the logical behaviour of the formulation is correct and the required accuracy obtained.	The process of building and selecting the equations to formulate the effect of onset-to-tPA treatment times on probability distributions was performed separately by three members of the model development team and the results were compared for any inconsistency.	The equations used to formulate the effect of onset-to-tPA treatment times on probability distributions were verified and the equations were corrected where necessary.
mRS probability distributions	To ensure that the logical behaviour of the prediction model is correct and the required accuracy obtained.	The statistical process of constructing the prediction model was performed separately by three members of the model development team and the results were compared for any inconsistency.	We confirmed that there is no significant difference between predicted and observed mRS categories to be used for building the conceptual model.
DALYs mathematical formulation	To ensure that the logical behaviour of the DALYs formulation is correct and the required accuracy obtained.	The logical behaviour of the DALYs formulations was reviewed separately by three members of the model development team and the results were compared for any inconsistency.	DALYs formulations were verified and the equations were corrected where necessary.
Mathematical and statistical validation methods	Based on: (Balci, 1994; Gass, 1983; Schellenberger, 1974)		
Change over time formulation	To ensure that the equations used to build the conceptual model are accurate enough.	We derived the relevant analytical expressions for mRS 0-1 and mRS 6 curves by selecting 5 point estimates in the lines and selected the best fit among the resulting equations using the	Correct representation of the relationship between OR and time is achieved.

		R^2criterion (achieving R^2 of 0.999).	
	To ensure that the probability equations used to build the conceptual model are logically correct.	We ensured that the sum of probabilities for each patient generated in Stage 1 of the model is equal to one.	Increased credibility and accuracy of the probability equations.
mRS probability distributions	To ensure that the mRS probability distributions used to build the conceptual model are logically correct.	We randomly selected 80% of the combined observational cohort and constructed binary logistic regression models for each individual mRS category. The statistical validity of the mRS prediction model was evaluated in the remaining 20% of the observational cohort.	We ensured that the regression model constructed based on the 80% of the observational cohort was reflecting the nature of the relationships in the remaining 20%, therefore being valid for the full observational cohort.
Structured walkthrough and face validity	Based on: (Balci, 1994; Hermann, 1967; Oral & Kettani, 1993; Sargent, 2013; Williams & Sikora, 1991)		
Conceptual model building	To ensure that the conceptual model is accurate enough for its intended use.	The logic of the model structure, assumptions, and parameters were explained step by step to a clinician who asked questions and challenged the choices, leading to significant iterative model changes.	The logic of the model follows true clinical practice.

Table 4-7 Validation tests and techniques utilized for conceptual model validation of different components of the 'IV tPA' model

4.7.3 Computational verification

By computational model verification, the modeller ensures that the computer programs and codes to build the computer model of the conceptual model have been used and implemented correctly. For the present model, this consisted of two main stages: (1) computations verification in Excel; and (2) code scripts verification in Stata. Different techniques used for computational verification were debugging, walkthrough and execution tracing. All the model components shown in Figure 4-3 have been verified using different techniques of the computational verification.

4.7.3.1 Computations validation in Excel

The observational cohort data, mRS category-specific life expectancies, and DALYs lost for each combination of age and sex of stroke patients were all stored in Excel worksheets accessible to Stata software through a set of Stata codes. After running the model in Stata, the model outcomes were also exported and stored in a separate Excel worksheet for data processing purposes. The walkthrough verification technique was employed by the analytical expert to verify the correct storage and execution of the computations in the Excel worksheets.

4.7.3.2 Code scripts verification in Stata

The conceptual model implementation and outcome analysis were mainly executed in Stata, through a set of codes developed within the software to run the model as well as to link Stata to Excel worksheets. Debugging and execution tracing verification techniques (Whitner & Balci, 1989) were employed to verify the codes in Stata.

The summary of different verification methods and techniques used for computational verification of the ‘IV tPA’ model has been provided in Table 4-8.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Debugging	Based on: (Dunn, 1987; Whitner & Balci, 1989)		
Code scripts in Stata	To confirm the correctness of the codes used to build the computational model.	The code script in Stata was screened to locate and correct the potential errors.	Typing and logic errors were identified and removed.
Walkthrough	Based on: (Adrion, et al., 1982; Deutsch, 1981; Myers, 1978; Yourdon, 1979)		
Computations in Excel	To ensure that all the computations used to build the computational model are correct.	The analytical expert verified the correct storage and execution of the computations in the Excel worksheets.	Storage and execution of relevant computations of the model were verified and revised in Excel worksheets.
Execution tracing	Based on: (Whitner & Balci, 1989)		
Code scripts in Stata	To confirm the correctness of the codes used to build the computational model.	Defects of the code script in Stata were located and corrected by line-by-line execution of the code by an analytical expert.	Typing and logic errors were identified and removed.

Table 4-8 Validation tests and techniques utilized for computational model verification of different components of the 'IV tPA' model

4.7.4 Operational validity

To achieve operational validity, the outputs of the DS model as shown in Figure 4-3 in blue box, were verified to obtain the accuracy needed for the intended use of the model. Since the 'IV tPA' model presents the first OR model used to investigate the effect of faster access to thrombolysis treatment, there was no data available in a real-life system to be used for specifying a clear range of the values of the DALYs per unit of onset-to-treatment time. However, other studies in stroke literature have addressed the issues of a plausible range of expected DALYs in the absence vs the presence of treatment, thus providing an acceptable range for the model outputs over the full range of plausible onset-to-treatment time. In this scenario, different techniques used to validate the operational model are output analysis, robustness analysis, comparison to the results produced by other known models, and tests to validate an appropriate application of the model. The summary of different validation methods and techniques used to obtain operational validity of the 'IV tPA model' model has been provided in Table 4-9.

4.7.4.1 Validation of the model output

The accuracy of the expected DALYs (as the final output of the model) was validated by output analysis, robustness analysis, and comparison to the results produced by other models as described below:

Different graphs and summary statistical measures (i.e. mean, median, 95% CIs) were generated to validate the model outputs (Meretoja, et al., 2014). The updated results of the tPA randomized controlled trials published by Emberson, et al. (2014) were used to validate the model outputs. In that update, the authors only provided the odds ratio of the mRS 0-1 graphically which we used with that of the mRS 6 provided earlier in a paper by Lees, et al. (2010) to validate the initial outcomes of the 'IV tPA' model. As a result, for every minute of onset-to-tPA treatment time saved the patients gained on average extra 1.5 days of healthy-life; which was consistent with the results obtained earlier from the meta-analysis by Lees, et al. (2010).

Also, DALYs gained per tPA treated patient for this study were compared to the results of a long-term utility of tPA (DALY/QALY gains) from other studies (Meretoja, et al., 2014). Additionally, we ran both one-way analysis and probabilistic analysis to validate the model outputs with results from both analyses confirming the robustness of the model.

4.7.4.2 Validation of the model application

In order to ensure operational validity, the model developers and users should formulate their understanding of the intended application of the model and its boundaries before employing the model and its results as a decision support tool. For our model, these included the following considerations:

1. **Intended model use in different population demographics:** since the study dataset is based on two separate populations, the characteristics of the Helsinki and SITS-Australia cohort, as well as the mixed cohort were provided for comparison (Table 4-2). In addition, as presented in Figure 4-2, we developed a histogram of onset-to-treatment time distributions for each of the two cohorts separately to be considered before generalizing the results of the study (Meretoja, et al., 2014).
2. **Intended model use in different patient groups:** the findings of the study demonstrate that patients with different gender, age and NIHSS benefit differently in terms of disability-free life over their full life-time. These differences were presented earlier in Figure 4-4 and Table 4-4 (Meretoja, et al., 2014).Therefore, caution should be exercised if the model were to be used as a decision support tool to understand the long term effects of earlier tPA treatment for specific patient groups.
3. **Intended model use compared to other studies:** The results generated by this study seem to be consistent with other studies with regard to an increased benefit in patient's outcome when treated with tPA. Table 4-9 provides the summary of studies comparing the long-term utility of tPA vs. no tPA in acute ischemic stroke

Study	Population	Time horizon	Discount rate of future utilities	QALYs or DALYs gained per tPA treated patient
Fagan, et al. (1998)	USA	30 years	0%	0.75
Sinclair, et al. (2001)	Canada	30 years	3%	3.46
Sandercock, et al. (2004)	UK	Lifetime	6%	0.04
J. Mar, Begiristain, and Arrazola (2005)	Spain	Lifetime	3%	0.53 to 0.66
Ehlers, Andersen, Clausen, Bech, and Kjolby (2007)	Denmark	30 years	5%	0.43
Johnston (2010)	USA	30 years	0%	0.75
Tung, Win, and Lansberg (2011)	USA	Lifetime	3%	0.28
National Institute for Health and Clinical Excellence (NICE) (2012)	UK	Lifetime	3.5%	0.33
Present paper (Meretoja, et al., 2014)	Finland and Australia	Lifetime	0%	0.71*
			3%	0.52*

**Median onset-to-treatment of 125 minutes compared to not treating at all.*

Table 4-9 Studies comparing long-term utility of tPA vs. no tPA in acute ischemic stroke. DALYs, Disability-Adjusted Life Years; QALYs, Quality-Adjusted Life Years.

4. **Actual model use in terms of benefits for the stroke patients:** In practice, IV tPA treatment is successful only in half of the patients who are given this treatment (Lees, et al., 2010). Therefore, while half of the patients do not benefit from faster tPA treatment, the other half benefit twice as much as we stated here for the whole cohort, since these are often patients with younger ages and lower stroke severities. While in medical practice, there is no accurate method of distinguishing between these two groups of the patients, it is important to provide the fastest possible treatment for all the patients.
5. **Actual model use for increased public awareness:** The 'IV tPA' model was developed to provide better understanding of the effect of faster tPA treatment on patient lifetime outcomes. Ideally, this is supposed to directly lead to an increased

awareness of public policy decision makers, stroke campaigns, and stroke care system providers of the importance of faster treatment for stroke patients. The summary of different validation methods and techniques used to obtain operational validity of the 'IV tPA' model has been provided in Table 4-10.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Output analysis	Based on: (Balci, 1994; Gass, 1983; Sargent, 2001)		
Model output	To identify any unusual behaviour of the model and pin-pointing errors that would not have been identified solely through summary statistics.	We created multiple graphical representations of individual patients and time series to validate the model outputs.	We found errors in the outputs as a result of either incorrect logic or implementation of the model which were subsequently corrected.
Robustness	Based on: (Balci, 1994; Boehm, et al., 1976; Gass, 1983; Myers, et al., 2011; Sargent, 2013; Whitner & Balci, 1989)		
Model output	To check the model's behaviour while changing the parameters and inputs of the model.	Two approaches of the robustness were used: one-way analysis and probabilistic robustness analysis.	Credibility of the outputs was increased by providing the users with estimates of uncertainty.
Comparison of the model outputs	Based on: (Sargent, 2013; Williams & Sikora, 1991)		
Model output	To ensure that the model's outputs are accurate enough for the intended use of the model.	DALYs gained per tPA treated patient for this study was compared to the results of a long-term utility of tPA (DALY/QALY gains) from other studies (DALYs gained per tPA treated patient for the "Save a minute – save a day" model is 0.72 compared to 0.75 of QALYs gained for	Credibility of the outputs was increased by providing the comparison to other relevant studies.

		two other similar studies.)	
	To ensure that the model's outputs are accurate enough for the intended use of the model.	The updated results of tPA randomized controlled trials used to estimate the tPA effect treatment over time published by (Emberson, et al. (2014)) were used to generate the model outputs, and the results were compared to the previous results obtained by the model.	Increased credibility of the model's outputs.
Intended use of the model	Based on: (Gass, 1983; Pidd, 2010)		
Model application	To verify the decisions made based on the model outputs.	We discussed the limitations and boundaries of application of the model in the original article discussion section.	Users of the decision support model will understand the limitations and will not overgeneralize or use the model outside of its intended use.

Table 4-10 Validation tests and techniques utilized for operational validation of different components of the 'IV tPA' model.

To summarize, the 'IV tPA' model is a model for investigation and improvement as it was used to provide better understanding of the effects of early access to IV tPA treatment on patients' long-term benefits. The generic validation framework developed in Chapter 3 was adopted to validate the model in four aspects of data validity, conceptual model validity, computational verification, and operational validity. This increased the credibility of the outcomes generated by this model for its intended use.

4.8 Problem description and intended use of the 'Endovascular Thrombectomy' model

The results of a new generation of acute stroke trials from different parts of the world, all published in one of the prominent medical journals in the world called 'New England Journal of Medicine' has shown that the intra-arterial (IA) endovascular thrombectomy intervention is a new gold treatment for ischemic stroke patients (Berkhemer, et al., 2015; Campbell, et al., 2015; Goyal, et al., 2015; Jovin, et al., 2015; Saver, et al., 2015). According to these studies, this intervention can be successfully used to further improve the outcomes when given within 6 hours from stroke onset to eligible stroke patients who already have received tPA treatment. Despite the accepted health benefits of faster access to endovascular thrombectomy treatment for stroke patients, prior to this research there was no method for quantifying the link between reductions in treatment delays for endovascular thrombectomy and patients' lifetime benefits. In this thesis, we describe the *'Endovascular Thrombectomy'* OR model which is designed and validated to provide better understanding of the benefits of earlier access to endovascular thrombectomy therapy.

The 'Endovascular Thrombectomy' model is a model for *investigation and improvement* as it is used to provide better understanding of the long-term effects of earlier treatment on patients' outcomes with regard to endovascular thrombectomy intervention. As discussed in Chapter 2, this type of model is often used to "support investigations that are relatively unique, which may involve system design, system improvement or just an attempt to gain understanding of a very complex situation" (Pidd, 2010, p. 18).

At the time of the submission of this thesis, the results of the 'Endovascular Thrombectomy' model were accepted for publication in *'Neurology'* (Meretoja, et al., 2017). The findings of this model are expected to be used by service providers in the hyperacute stroke care system to advocate for equipping the stroke unit centres with expertise and facilities needed for endovascular thrombectomy intervention.

4.9 Overview of the 'Endovascular Thrombectomy' model

The 'Endovascular Thrombectomy' model is the first OR model used to explicitly quantify the link between reductions in treatment delays before endovascular thrombectomy treatment and patients' lifetime benefits. The 'Endovascular Thrombectomy' model was developed by extending the 'IV tPA' model presented in this chapter. Most inputs and parameters used to develop this model were adopted from the 'IV tPA' model; this includes pooled analysis of tPA effect over time, general population life expectancy data, and different parameters to estimate DALYs. Other model inputs used to develop this model are observational real-life cohort data of endovascular eligible patients and pooled analysis of endovascular thrombectomy effect over time.

Summary of new parameters used to conceptualize the 'Endovascular Thrombectomy' model is presented in Table 4-11. These parameters are used in Section 4.12 to develop the 'Endovascular Thrombectomy' model.

Parameter name	**Definition**
t (maximum 270 min)	onset-to-tPA treatment time
t_{IA} *(maximum 360 minutes)*	onset-to-IA treatment time
I	different levels of mRS
tPA cumulative odds mRS_i *(t)*	cumulative odds ratio of a specific mRS level at time *t* after delivery of the IV tPA intervention
IA effect odds ratio (t_{IA})	fitted value of the odds ratio for common mRS outcome at time *t*
IA cumulative odds mRS_i (t_{IA})	cumulative odds ratio of a common mRS at time t_{IA} after delivery of the endovascular thrombectomy intervention

Table 4-11 Summary of different parameters of the 'IV tPA' model

The main output of this model is expressed as number of disability-adjusted days saved per minute of earlier treatment for endovascular thrombectomy. Figure 4-6 presents an overview of the 'Endovascular Thrombectomy' model with all the model inputs. Detailed description of these inputs is provided in the next section.

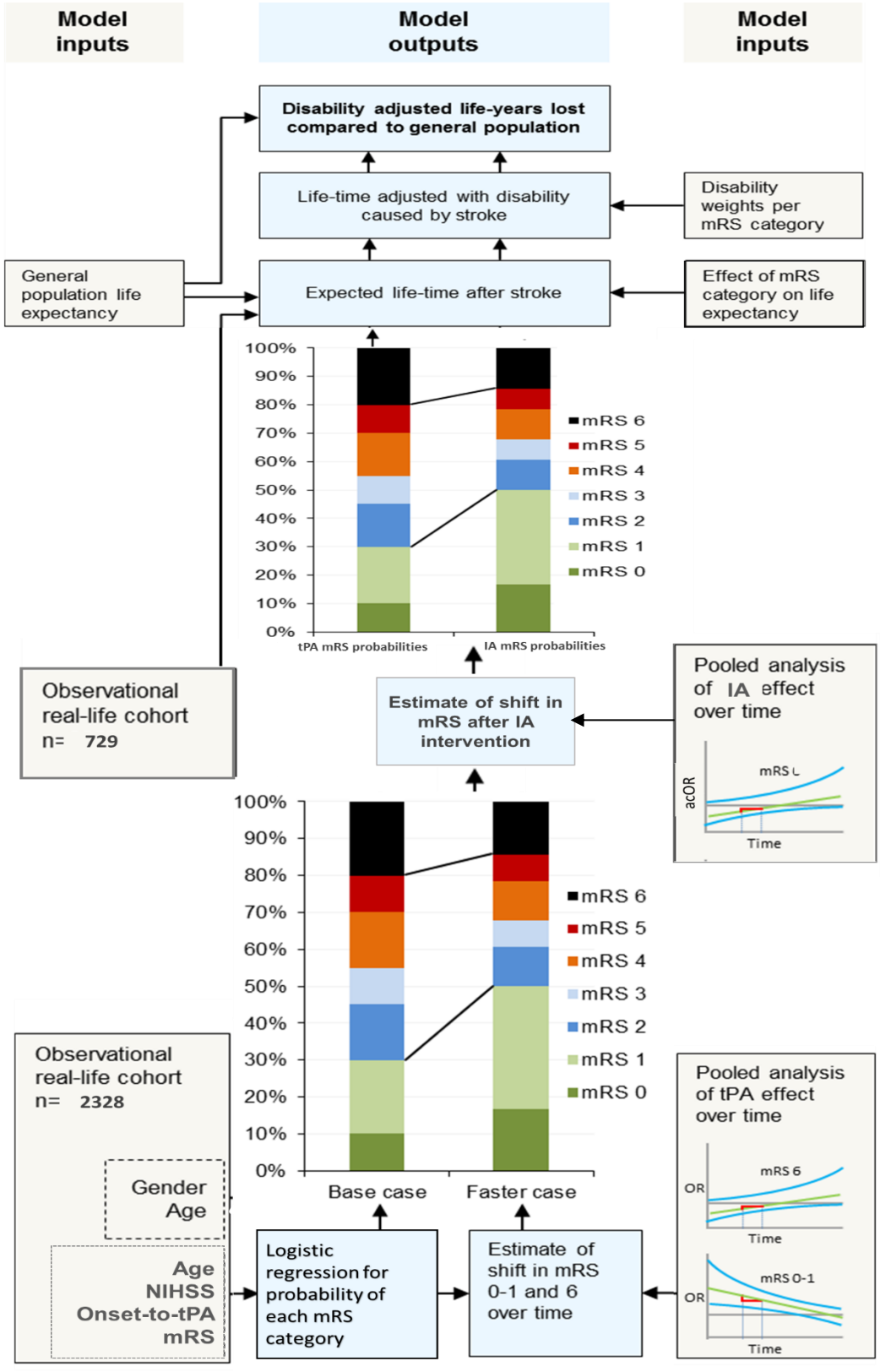

Figure 4-6 Overview of the 'Endovascular Thrombectomy' model. mRS indicates modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator; IA, intra-arterial clot removal therapy; OR, odds ratio of tPA effect of mRS 0-1 and mRS 6 over time; acOR, accumulative odds ratio of the IA effect of common mRS over time

4.10 Overview of the 'Endovascular Thrombectomy' model inputs

To build the 'Endovascular Thrombectomy' model, part of data was adopted from the 'IV tPA' model, which has been described in Section 4.2. In this section, we describe the new model inputs used to build the 'Endovascular Thrombectomy' model as follows:

1. **An observational cohort data of consecutive tPA patients**: While for the 'IV tPA' model we retrieved data from both Finnish and Australian databases, for the 'Endovascular Thrombectomy' model, we extracted the observational cohort only from an updated Helsinki Stroke Thrombolysis Registry database since only data in this registry included eligible patients to receive endovascular thrombectomy treatment. Data for this registry was generated during the period between June 1995 and September 2014 and included relevant patient information for 2799 patients treated with tPA. Of this population, we included data for 2474 patients with their distributions of age, sex, and stroke severity, onset-to-tPA treatment times; and mRS. Of these patients, 2328 did not receive endovascular thrombectomy therapy, and 729 would have been eligible to receive endovascular therapy (i.e. patients who already have received or would have been eligible to receive endovascular therapy). Table 4-12 shows distributions of age, gender, NIHSS, onset-to-tPA treatment time, and mRS for IV tPA only and endovascular suitable cohorts.

Characteristics and outcome	IV tPA only cohort (n=1745)	Endovascular suitable cohort (n=729)	*P* Value
Age, y	70 (60-77) 68±13	69 (61-76) 67±13	0.209 0.360
Male sex	1247 (55%)	939 (54%)	0.704
NIHSS at baseline	7 (4-11) 8±5	13 (7-18) 13±6	<0.001 <0.001
Onset-to-tPA treatment time, min	120 (88-163) 129±52	106 (79-150) 120±53	<0.001 <0.001
3-Month mRS score 0 to 1	801 (45.9%)	187 (25.7%)	<0.001
3-Month mRS score 0 to 2	1164 (66.7%)	333 (45.7%)	<0.001
3-Month mRS 6	112 (6.4%)	103 (14.1%)	<0.001

Table 4-12 Characteristics of the observational cohort. Data are n (%), median (interquartile range), or mean ± SD. Distributions of IV tPA only and endovascular suitable data compared with Mann-Whitney U test x^2 test, or Student t test as appropriate, with 2-sided statistical significance set at P=0.05. mRS indicates modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

2. **Published pooled analysis of IV tPA and endovascular thrombectomy effects over time**: We used the results of a published pooled analysis by Lees, et al. (2010) as described earlier in this chapter for the 'IV tPA' model to model the effect of tPA over time. Then, to model the effect of endovascular therapy in addition to tPA treatment compared with tPA alone over time, we used the common odds ratio for the improved outcome of the 6-level of mRSs with corresponding confidence intervals as summarized graphically in a paper by Saver, et al. (2016). This pooled analysis has been derived from the results of the five recent randomized trials, all published in the New England Journal of Medicine (Berkhemer, et al., 2015; Campbell, et al., 2015; Goyal, et al., 2015; Jovin, et al., 2015; Saver, et al., 2015).
3. **General Australian population life expectancy age- and sex- specific data obtained from Australian Bureau of Statistics:** An updated version of the life expectancy data used in the 'IV tPA' model (available at the time of developing this

model), were adopted here to model the long-term survival of patients at various mRS categories compared with the general population (Australian Bureau of Statistics, 2013-2015). The average life-expectancy of this updated database was compared to that of the 'IV tPA' model and no significant difference was observed. Similar to the 'IV tPA' model, this data was used to model the long-term survival of patients at various mRS categories compared with the general population.

4.11 Model assumptions

Five main assumptions were formulated to build this model. The first two assumptions are adopted from the 'IV tPA' model, while the other three assumptions have been specifically formulated to build the 'Endovascular Thrombectomy' model as follows:

1. The upper time limit to receive tPA treatment was set to 270 minutes.
2. To generate mRS probabilities after tPA intervention, we assumed that the relative ratios of probabilities of achieving mRS 0 and mRS 1 are identical to those at the baseline onset-to-tPA treatment time. Similarly, we assumed that the relative ratios of achieving mRS categories 2-5 at any time, are identical to those at the baseline onset-to-tPA treatment time.
3. To build this model, we assumed that endovascular eligible cohort patients first receive tPA treatment and then undergo endovascular thrombectomy therapy.
4. The upper time limit to receive thrombectomy treatment was set to 360 minutes.
5. We assumed 90 minutes delay between IV tPA and thrombectomy intervention to estimate the added value of endovascular therapy over and above tPA alone for stroke patients.

4.12 Overview of the model building process

The 'Endovascular Thrombectomy' model was constructed in six stages as shown in Figure 4-7. These stages have been discussed in details as follows:

To build this model, we first repeated Stages 1 to 3 of the 'IV tPA' model (i.e. described in Section 4.4 of this chapter), to model the effect of onset-to-tPA treatment time delays on the probability of achieving each mRS category for stroke patients. A difference to the 'IV tPA' model here is that, in this model we used data of the observed 3-month outcomes of the patients from cohort who did not receive endovascular thrombectomy therapy (n=2328) to construct the binary logistic regression model. We then used data of the endovascular eligible cohort patients (n=729) to build the rest of the model. These included patients who

already received or were eligible to receive endovascular thrombectomy therapy. We then built the rest of the model using Stages 4 to 6 as described below:

Stage 4: Generating patient-specific cumulative odds for each mRS outcome after tPA intervention- We used the probabilities of achieving a specific mRS level at any time generated earlier in Stage 3 of the model building process to generate the patient-specific cumulative odds for each mRS category after IV tPA treatment (*tPA cumulative odds* mRS_i *(t)*). The cumulative odds for each mRS category is estimated using the equation 4-6. This will be used in the next stage to generate the probabilities of achieving each mRS category after endovascular thrombectomy intervention.

$$\text{tPA cumulative odds } mRS_i(t) = \text{tPA cumulative } mRS_i(t)/(1 - \text{tPA cumulative } mRS_i(t)) \quad (4\text{-}6)$$

$i = 0, 1, 2, 3, 4, 5, 6$

Stage 5: Modelling the change in probabilities of achieving a specific mRS outcome after endovascular thrombectomy intervention at any time - We used the result of a recent pooled analysis trial recognized as HERMES (Saver, et al., 2016), where the authors provide a graphical estimation of the effect of endovascular therapy treatment delays in addition IV tPA treatment compared to tPA alone for ischemic stroke patients. This has been reported by the authors in a graphical format for improved outcome of the 6-level of mRSs without providing any analytical expressions for the odds ratio curve. The graphical curve reported in that article demonstrates the change in the odds ratio of achieving a common mRS outcome as a function of onset to expected-arterial-puncture time between 120 and 510 minutes (Saver, et al., 2016). In this thesis, we refer to this time as onset-to-IA treatment time (t_{IA}).

To build this model we derived relevant analytical expressions for common mRS odds ratio using the best fit (based on adjusted R^2 criterion) and used this equation to estimate the odds ratio for common mRS as a function of onset-to-IA time for any value of onset-to-IA time between 0 and 360 minutes (i.e. the currently accepted evidence-based upper time limit for tPA treatment) (Berkhemer, et al., 2015; Powers, et al., 2015).

The *IA effect odds ratio(*t_{IA}*)* reported by Saver, et al. (2016) presents the ratio of odds of achieving common mRS, by patients treated with endovascular thrombectomy in addition to IV tPA treatment at onset-to-IA treatment time *(*t_{IA}*)* and the odds of achieving the same outcome by the patients treated with tPA alone. As it will be stated explicitly in the model assumptions, in this model we assume that the patients receive endovascular therapy with

90-minutes delay after they receive tPA treatment. Then, using the patient-specific *tPA cumulative odds* mRS_i *(t)* estimated earlier in Stage 4, we calculate the cumulative odds for each mRS category after endovascular therapy using the equation 4-7:

$$IA\ cumulative\ odds\ mRS_i\ (t_{IA}) = IA\ effect\ odds\ ratio\ (t_{IA}) * tPA\ cumulative\ odds\ mRS_i\ (t) \quad (4\text{-}7)$$

$$i = 0, 1, 2, 3, 4, 5, 6$$

We stated earlier in Section 4.11 of this chapter, that to build this model we assumed 90 minutes delay between the IV tPA and endovascular thrombectomy intervention, thus:

$$t = t_0 + 90 \quad (4\text{-}8)$$

Having generated the *IA cumulative odds* for each mRS outcome (*IA cumulative odds* mRS_i (t_{IA})), we then estimated the probabilities of achieving a specific mRS after endovascular thrombectomy intervention at any time for individual patients.

Stage 6: Estimating the expected Disability-adjusted Life Years (DALY) lost - Using DALYs equation as described in Stage 4 of Section 4.4 of this chapter, we estimated DALYs lost for each patient in the observational cohort at onset-to-IA treatment time, and then we modelled the DALYs lost with regard to the treatment delays for each patient after endovascular thrombectomy treatment.

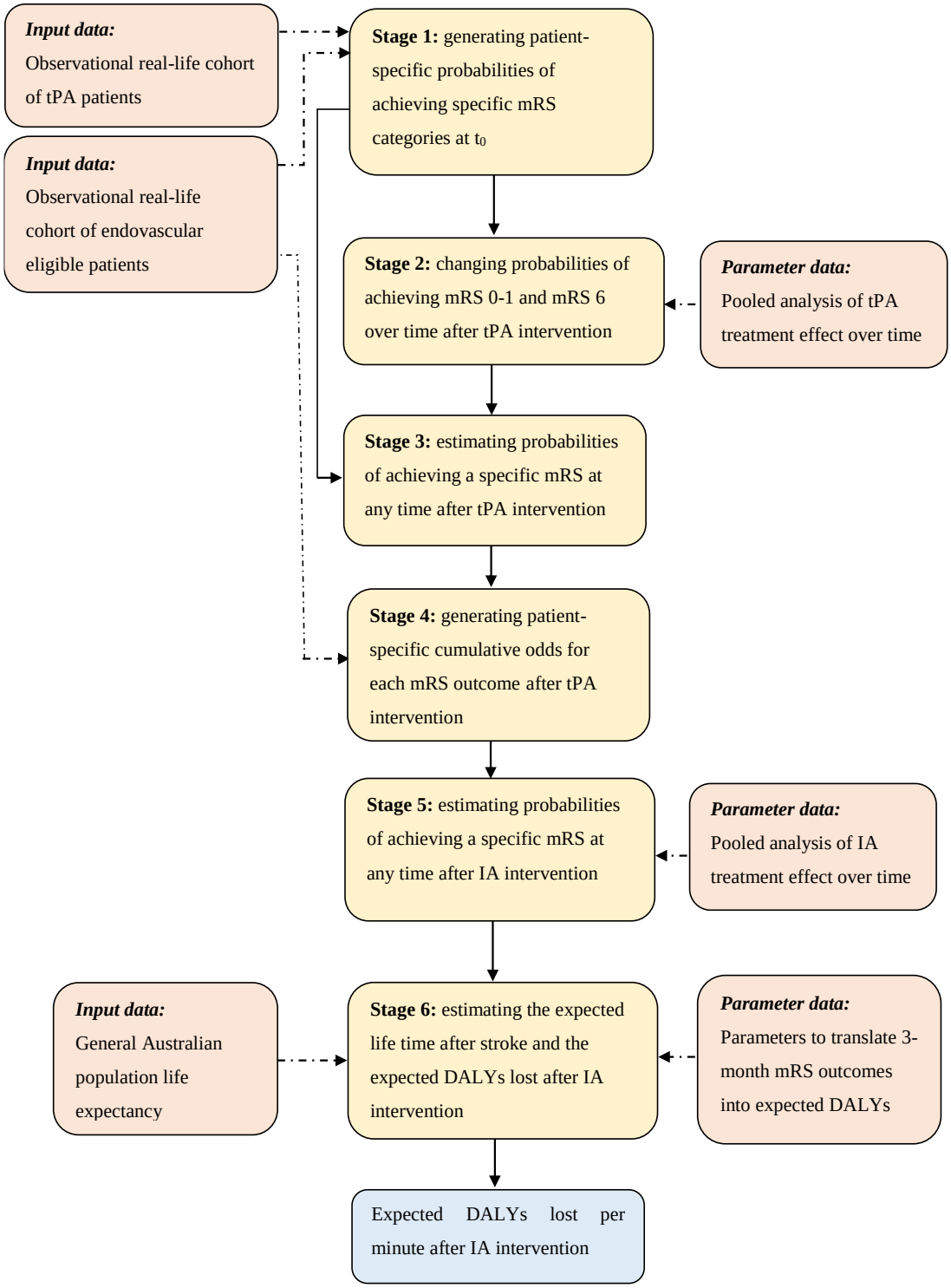

Figure 4-7 Overview of different stages of model building process

4.13 Result of treating faster in the whole cohort and individual patients

In the whole cohort, we generated the results for one minute earlier of onset-to-IA treatment time according to the World Health Organization (WHO) policy updated in 2012 to report DALYs without age-weighting ($K = 0$) and discounting ($r = 0$) factors (Murray, et al., 2013). For these parameters ($K=0, r=0$), we estimated on average extra 3.2 days of DALYs saved per minute of earlier treatment (median 3.0, IQR, 2.0-4.1, SD 1.5, range 0.2-9.6 days of DALY) for the full cohort.

It is evidenced by clinical trials that patients with various age and disease severity benefit differently from faster treatment. To evaluate these findings, we ran the 'Endovascular Thrombectomy' model for five individual female patients, namely:

- a patient with median age (69 y.o.) and median stroke severity (NIHSS 13);
- two patients with old ages (90th decile, 83 y.o.) and respectively low (10th decile, NIHSS 4) and high stroke severities (90th decile, NIHSS 21); and
- two patients with young ages (10th decile, 50 y.o.) and respectively low (NIHSS 4) and high (NIHSS 21) stroke severities.

On average a 69 years old female patient with median stroke severity gained extra 3.7 days, a 50 y.o. patient with mild stroke and severe stroke gained extra 2.9 and 6.9 days respectively, and a 83 y.o. patient gained extra 1.2 and 1.6 days respectively for each minute saved. As it is evidenced by the results of the model, the younger patients gain more benefit from faster treatment because of their longer lifetime.

Moreover, as it can be seen in Figure 4-8, we generated disability adjusted days saved per minute of earlier treatment for female and male stroke patients for different age and severity groups. In two graphs presented in Figure 4-8, patients from cohort data has been categorized into five NIHSS severity groups (0-4, 5-9, 10-14, 15-19, 20+), and five age groups (<55, 55-64, 65-74, 75-84, 84+), while the point estimates show the disability adjusted days saved per minute of earlier treatment for that group of patients. Due to small number of patients in few groups (those with very young and high disease severity or very old and mild severity), the linear trend of age group lines is changed for these cases. As shown in Figure 4-8, this non-linear trend can be observed especially for male patients above age 84, and female patients below age 55.

By comparing data between the female and male groups, it can be observed that female patients often benefit more from faster treatment over their longer life time. For patients with different age groups, disability-adjusted days saved per faster treatment often increases as NIHSS increases. Also, by fixing the NIHSS group in any of the figures presented below, and moving from patients with younger ages towards those with older ages, the benefits of faster treatment decreases. Point estimates and 95% prediction intervals for each of these groups have been provided in Table 4-10.

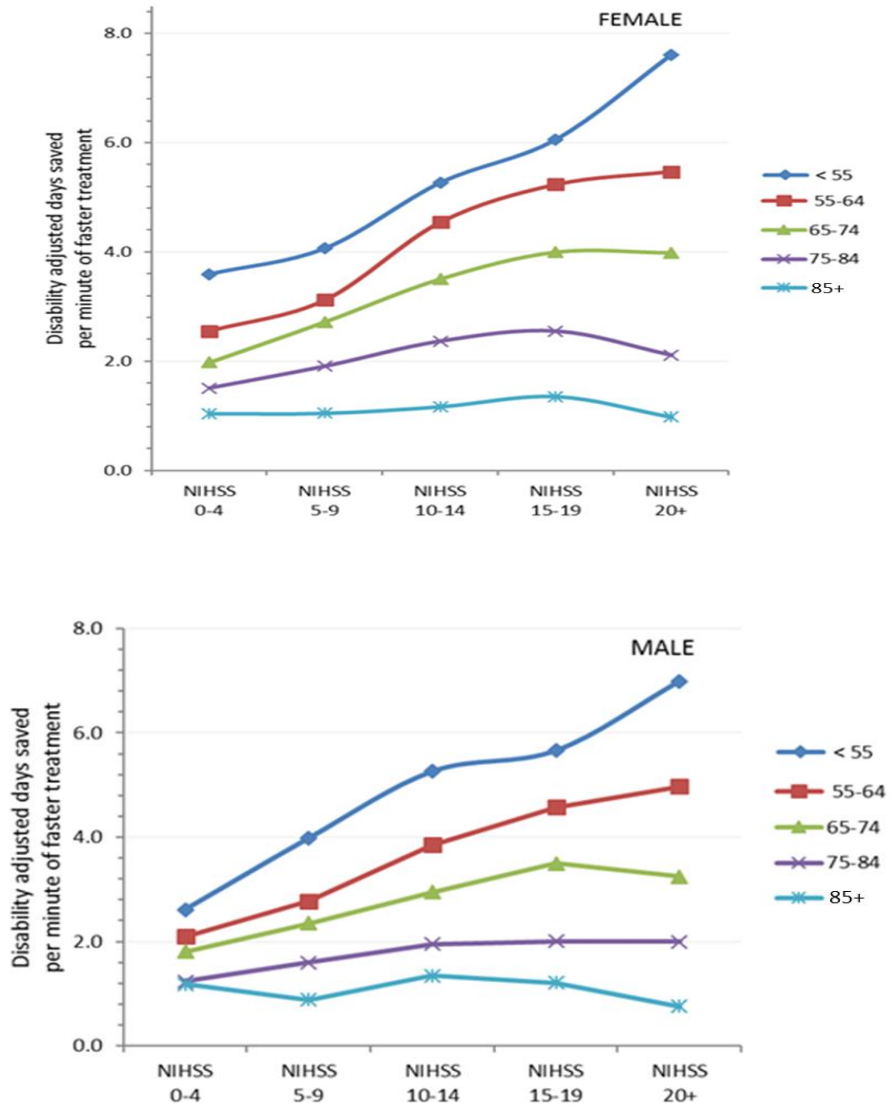

Figure 4-8 Relationship between disability-adjusted days gained per minute of faster treatment by age and stroke severity. Baseline stroke severity measured with the National Institute of Health Stroke Scale (NIHSS) where higher scores indicate more severe stroke

Sex, Age	NIHSS 0-4	NIHSS 5-9	NIHSS 10-14	NIHSS 15-19	NIHSS 20 +
Male					
<55	2.61 (0.63-3.45)	3.98 (1.12-5.00)	5.26 (1.37-6.61)	5.66 (1.28-7.31)	6.99 (1.88-8.25)
55-64	2.09 (0.54-2.72)	2.77 (0.70-3.61)	3.85 (1.02-4.88)	4.57 (1.11-5.70)	4.97 (1.36-5.93)
65-74	1.81 (0.53-2.27)	2.35 (0.72-2.88)	2.95 (0.76-3.76)	3.50 (0.95-4.25)	3.24 (0.84-3.94)
75-84	1.23 (0.37-1.53)	1.60 (0.48-1.99)	1.95 (0.60-2.35)	2.01 (0.50-2.54)	2.00 (0.55-2.43)
85 +	1.18 (0.30-1.44)	0.88 (0.24-1.41)	1.35 (0.40-1.73)	1.20 (0.23-1.77)	0.76 (0.22-0.93)
Female					
<55	3.59 (1.10-4.36)	4.06 (1.00-5.15)	5.27 (1.23-6.67)	6.06 (1.45.-7.54)	7.61 (1.82-9.04)
55-64	2.55 (0.71-3.15)	3.12 (0.84-3.87)	4.54 (1.33-5.39)	5.23 (1.31-6.38)	5.47 (1.26-6.63)
65-74	1.98 (0.61-2.41)	2.72 (0.81-3.27)	3.51 (0.96-4.24)	4.00 (1.23-4.59)	3.99 (0.92-4.87)
75-84	1.50 (0.47-1.82)	1.91 (0.55-2.33)	2.37 (0.74-2.77)	2.55 (0.75-3.01)	2.11 (0.61-2.49)
85 +	1.04 (0.33-1.23)	1.04 (0.36-1.18)	1.16 (0.34-1.54)	1.35 (0.42-1.70)	0.98 (0.29-1.26)

Figure 4-9 Point estimates and 95% prediction intervals for disability adjusted days gained per minute saved in tPA delivery, per sex, age, and stroke severity

Figure 4-10 presents the effect of treatment delay on Disability-adjusted Life Years (DALYs) for five individual female patients. For the 'IV tPA' model, this was presented using different age weighting and discounting factors without observing significant difference between the generated results associated with these parameters. Therefore, in this model we only report the results for DALYs without age-weighting ($K = 0$) and discounting factor ($r = 0$) with its 95% prediction intervals.

As it is shown in Figure 4-10, by increasing the onset-to-IA treatment time from 90 to 360 minutes, the DALYs lost increases for all the five individual patients. Thus, it can be concluded that all patients with various characteristics will benefit by earlier endovascular thrombectomy treatment. The choice of 90 minutes as the minimum onset-to-IA treatment is based on the assumption stated earlier for the 'Endovascular Thrombectomy' model that there is 90 minutes delay between the IV tPA and endovascular thrombectomy treatments for the patients receiving these interventions.

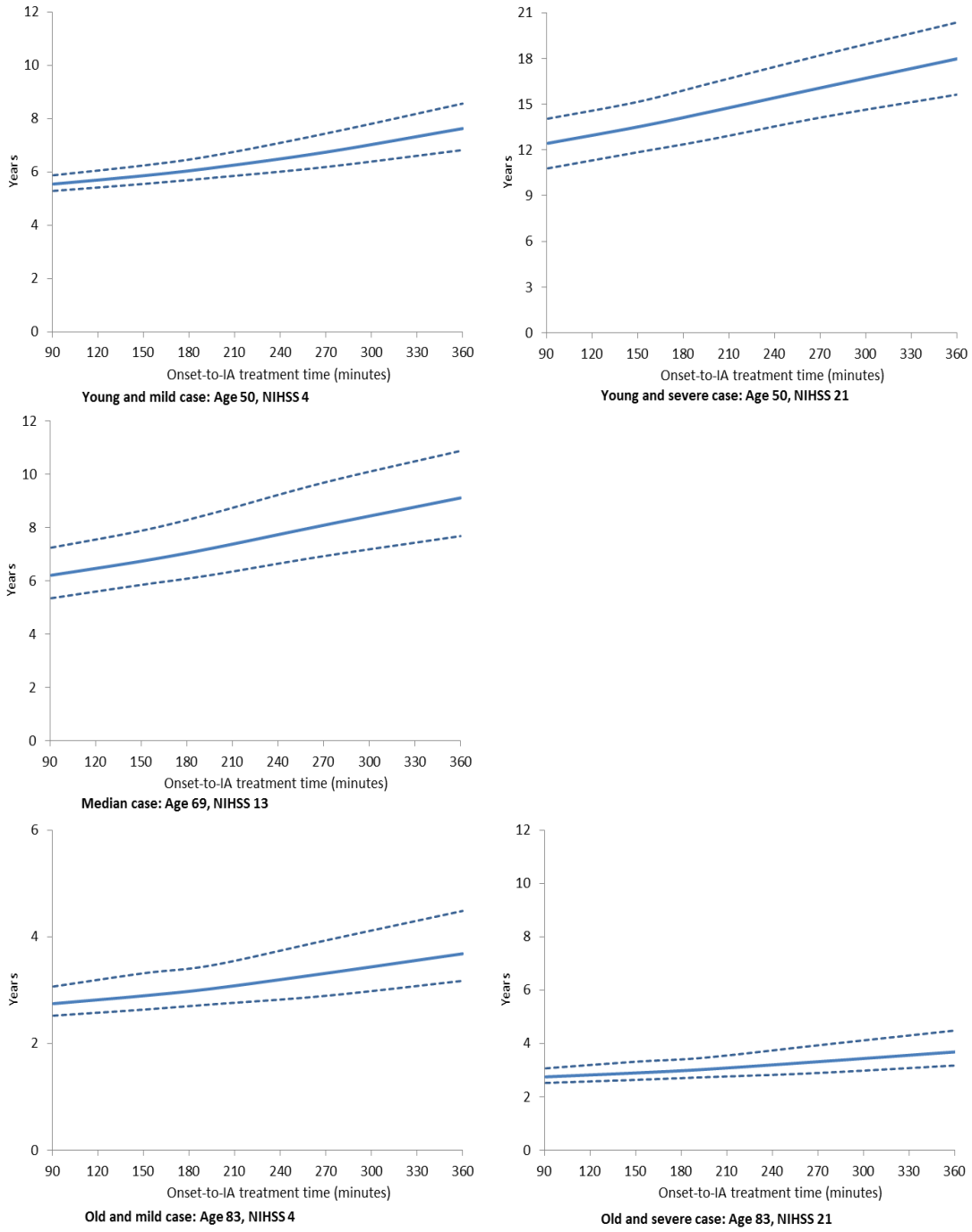

Figure 4-10 Effect of treatment delay with 95% prediction interval on Disability-adjusted Life Years (DALYs) in 5 individual female cases with median, top, and bottom decile age/National Institute of Health Stroke Scale (NIHSS). IA indicates Intra-arterial clot removal therapy.

4.14 Robustness analysis

Similar to the 'IV tPA' model, we ran both one-way analysis and probabilistic analysis to evaluate the model robustness. To account for potential uncertainties in the cohort data, we performed a series of one-way analyses by systematically and sequentially substituting the upper and lower 95% CIs values for the regression coefficients for the age and NIHSS generated by the binary logistic regression models used to estimate different levels of mRS. To account for potential uncertainties of the pooled analysis of tPA and endovascular therapy effects over time, we modified the equations of odds ratio for mRS 0-1 and mRS6 and common mRS odds ratio reported respectively in a paper by Lees et al. (2010) and Saver, et al. (2016) to sequentially reflect the upper and lower 95% confidence limits for these odds ratio curves.

In one-way analysis by varying the odds ratio of mRS 0-1 to the lower and upper 95% CIs respectively adopted from the paper by Lees at al (2010), a patient benefits on average extra 2.29 and 4.02 days for each minute saved. These values are changing between 2.34 and 3.38 days when varying the odds ratio of mRS 6 to the lower and upper 95% CIs as presented in a paper by Lees et al (2010). These values are changing between 2.85 and 3.32 days when varying the odds ratio of IA common mRS to the lower and upper 95% CIs as reported in a paper by Saver, et al. (2016).

Regarding the effect of age and NIHSS on outcome, a patient benefits vary from 2.83 to 3.51 days for age, and 3.08 to 3.23 days for each minute saved. For all of these robustness analyses a point estimate was 3.15 days for each minute saved (Table 4-13).

Inputs in the one-way analysis	Disability-adjusted days saved per minute of faster treatment	
	Lower value	Upper value
Odd of endovascular on mRS*	2.85	3.32
Odds of tPA on mRS 0-1†	2.29	4.02
Odds of tPA on mRS 6†	2.34	3.38
Effect of age on outcome ‡	2.83	3.51
Effect of NIHSS on outcome ‡	3.08	3.23

** Upper and lower 95% CIs from the pooled analysis of Saver, et al. (2016)*
† Upper and lower 95% CIs from the pooled analysis of Lees et al (2010)
‡ Upper and lower 95% CIs from the logistic regression model in the observational cohort.
The point estimate is 3.15 days per minute in all cases.

Table 4-13 Robustness of model when inputs changed one at a time. mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

The probabilistic analysis was performed by sampling according to an underlying Normal distribution from the feasible space of the mRS 0-1 and mRS 6 odds ratio curves of the tPA effect (Lees, et al., 2010) and the common mRS odds ratio of the endovascular thrombectomy effect (Saver, et al., 2016) over time bounded by the 95% confidence interval limits. Sampling from this area will reflect various potential time effects based on the pooled analysis, through a set of 1000 independent runs. The resulting probability profiles for all mRS categories were then used to estimate DALYs gained or lost if either the whole cohort or an individual patient would have been treated faster or slower. As a result, we estimated a 95% prediction interval from 2.24 to 4.05 days for each minute saved. Both one-way analysis and probabilistic analysis demonstrated that the results were robust overall, with the average point estimate of 3.15 days for each minute saved for the robustness analyses.

Lastly, we assumed different delay times between IV tPA and endovascular thrombectomy interventions adopted form individual trials included in the HERMES pooled analysis trial, and regenerated DALYs to test the robustness of the model when changing the delay time between the two interventions. As shown in Table 4-14, results of these analyses were consistent and did not change much compared with the original outcome of the model while assuming 90 minutes delay between the two interventions.

Name of the trial	Delay between tPA and endovascular interventions, min	Average disability-adjusted days saved per minute of faster treatment
MR CLEAN (Berkhemer, et al., 2015)	155	3.3
EXTEND IA (Campbell, et al., 2015)	74	3.1
ESCAPE (Goyal, et al., 2015)	51	3.0
SWIFT PRIME (Saver, et al., 2015)	110	3.2
REVASCAT (Jovin, et al., 2015)	150	3.3

Table 4-14 Average disability-adjusted days saved per minute of faster endovascular provision for the cohort patients

4.15 Comprehensive validation of the 'Endovascular Thrombectomy' model

In this section, we provide comprehensive validation of the 'Endovascular Thrombectomy' model using the validation framework presented earlier in Chapter 3. To achieve this, we validate the model with respect to four categories of data validity, conceptual model validity, computational verification, and operational validity. Since 'Endovascular Thrombectomy' model is an extension to the 'IV tPA' model, most parts of the model have been previously validated in Section 4.7 of this chapter; while in this section, we mainly focus on validating the new developed parts of the model.

4.15.1 Data validity

Both input data (e.g. observational cohort and general population life expectancy data) and previously published data in the form of various parameters estimators (e.g. pooled analysis of IV tPA and endovascular thrombectomy effects, annual risk of death, and disability weights) were used to build the 'Endovascular Thrombectomy' model. These data as shown in Figure 4-7 in orange boxes has been validated as follows:

4.15.1.1 Validation of input data

Observational cohort data: The Helsinki Stroke Thrombolysis Registry used to build this model was previously used and validated to build the 'IV tPA' model.

Based on pre-specified inclusion criteria, the patients with onset-to-tPA treatment time greater than 4½ hours (n = 192), and those with deviations from standard treatment procedure (n = 88) and missing value on onset-to-tPA treatment time, stroke severity or mRS outcome (n = 43) were excluded.

General population life expectancy: The updated version of life expectancy tables for the period of 2011-2013 (Australian Bureau of Statistics, 2011-2013) were adopted and validated to estimate DALYs, as described earlier in Section 4.7.1 of the 'IV tPA' model.

4.15.1.2 Validation of parameters

Both the validated *pooled analysis of tPA effect over time,* and *parameters to calculate expected DALYs* were adopted from 'IV tPA' model to build the 'Endovascular Thrombectomy' model. Moreover, the *pooled analysis of IA effect over time* by Saver, et al. (2016) were used to drive how the effect of IA treatment varies with delays for onset-to-IA treatment time. The parameters obtained from this meta-analysis are most representative of the current state of the knowledge in the area of stroke endovascular intervention as the study includes five major randomized placebo-controlled trails of endovascular intervention for acute stroke patients (Berkhemer, et al., 2015; Campbell, et al., 2015; Goyal, et al., 2015; Jovin, et al., 2015; Saver, et al., 2015).

The summary of different validation methods and techniques used to obtain data validity of the 'Endovascular Thrombectomy' model has been provided in Table 4-15.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Representativeness of the dataset	Based on: (Biau, et al., 2008; Ellenberg, 1994)		
Observational cohort data	To ensure that demographics of the observed data have similar distributions to that of the published literature.	We obtained consecutive prospective data from the Helsinki Stroke Thrombolysis registry, and compared patient demographics to those in published literature.	Increased credibility of the data used to construct the model.
	To ensure that we have used suitable data to model the effect of tPA alone.	We used the observed 3-month outcomes of the patients who did not receive endovascular therapy to estimate an outcome after IV tPA alone.	Increased confidence in data used to build the logistic regression model for investigating the effect of IV tPA alone.
	To ensure that we have used suitable data to model the effect of endovascular therapy.	We used data for patients who either received or were eligible to receive endovascular therapy to estimate an outcome after endovascular thrombectomy treatment.	Increased confidence in data used to model the effect of time in endovascular thrombectomy therapy.
General population life expectancy	To ensure that the data source used to estimate the life expectancies is trustworthy.	At the time of developing the 'Endovascular Thrombectomy' model, we used the latest official data for age and sex specific life-expectancies of the residents of Victoria, Australia, obtained from ABS (2013-2015). We compared these with dataset obtained from ABS for development of the 'IV tPA' model and we observed minimal	Increased confidence in the accuracy of the estimations for the general population life expectancy.

		differences. We also compared these with similar life-expectancy data from Finland which was the source country for our cohort. We observed minimal differences (the average life expectancy at birth for men is 80.1 years in Australia versus 78 years in Finland and for women 84.3 years versus 84.1 years).	
Pooled analysis of endovascular effect over time	To ensure that parameters used to model the effect of endovascular therapy over time were obtained from a trustworthy data source.	The parameters used to model the effect of endovascular thrombectomy treatment over time were obtained from the pooled analysis of individual patient data of endovascular thrombectomy randomize trials by Saver et al. This study includes five major randomized trials of the effect of endovascular thrombectomy for acute stroke, which is the most representative of the current state of the knowledge in the field of stroke endovascular thrombectomy therapy.	Increased accuracy of the parameters used to model the effect of endovascular thrombectomy treatment changing with onset-to-IA treatment times.

Table 4-15 Validation tests and techniques utilized for data validation of different components of the 'IV tPA' model

4.15.2 Conceptual model validity

The conceptual model of the effect of treatment delays on mRS probabilities was mainly developed at Stages 1 to 8 of the model development. As shown in Figure 4-7 in yellow boxes, its validation consisted of the validation of the model's assumptions and its logical and mathematical structure. Different methods and validation tests similar to the 'IV tPA' model were used to validate the conceptual model. These included: degeneracy test, data relationship correctness test, mathematical and statistical methods, tracing and structured walkthrough.

4.15.2.1 Validation of the model assumptions

All the five mentioned assumptions were validated by formally obtaining the opinion of the clinical expert. The choice of 270 minutes as the upper time limit to receive tPA treatment (Jauch, et al., 2013) and 360 minutes as the upper time limit to receive endovascular thrombectomy were adopted according to majority of international stroke clinical guidelines (Berkhemer, et al., 2015; Campbell, et al., 2015; Saver, et al., 2015). The choice of 90-minutes delay between tPA and IA intervention assumed earlier to build this model allows for treatment of a stroke patient with endovascular therapy when the patient receives the tPA treatment with maximum 270 minutes delay from stroke onset. Lastly, based on the recent trials (Saver, et al., 2016) all eligible patients first receive IV tPA and then undergo the process of receiving endovascular thrombectomy therapy.

Using the walkthrough validation technique, these five assumptions were validated by formally obtaining the opinion of the clinical expert (Sargent, 1996).

4.15.2.2 Validation of model structure/formulation

The logical structure of the conceptual model was validated through checking the mRS probability distributions, numerical relationships in the model, change over time formulation, and DALYs mathematical formulation separately after tPA and endovascular thrombectomy interventions.

To validate the *mRS probability distributions*, we applied the 80-20 validation method, as described earlier in 4.7.2, to IV tPA cohort patients, and as a result we observed no significant difference between predicted and observed mRS categories (χ^2 p-value equal to 0.53).

Having generated the probability distributions for individual mRS categories after tPA treatment, we ensured that the sum of the probabilities for each patient is equal to one. Then, we used these tPA mRS probabilities to generate the endovascular thrombectomy mRS probabilities which we ensured again that the sum of the probabilities for each patient is equal to one; thus validating the normalization scaling procedure performed at Stage 1 of the model development.

To validate the *numerical relationships in the model* similar to the 'IV tPA' model, we selected a large enough original cohort sample size to ensure that the relationship between age, NIHSS, and mRS at a given point of onset-to-treatment time for both tPA and endovascular interventions (based on the cohort data), is no worse than the precision of the relationship between mRS and time (based on the meta-analyses data).

Validating the *change over time formulation* was performed by deriving relevant independent analytic expressions for common mRS odds ratio curve for the effect of endovascular thrombectomy over time and validating the resulting equation using the best fit R^2 criterion. The corresponding value for this curve was $R^2 = 0.996$.

Last but not least, we validated the *DALYs mathematical formulation* using the same approach as described earlier in Section 4.7.2.

Each of the three mentioned components of the conceptual model structure were validated by tracing the formulation separately by different members of the model development team and the results were compared to identify and resolve inconsistencies. Also, the structured walkthrough validation technique was employed to ensure that the logical behaviour of the conceptual model is aligned with the clinical practice by explaining the model assumptions, parameters and formulation to a clinician. The summary of different validation methods and techniques used to obtain conceptual validity of the 'Endovascular Thrombectomy' model has been provided in Table 4-16.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Degeneracy test	Based on: (Gass, 1983; Sargent, 2013)		
Limitation of upper treatment time to 360 minutes for endovascular thrombectomy treatment	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	Based on published international stroke clinical guidelines we observed that the vast majority of these studies implemented the 360 minutes time window to receive the endovascular thrombectomy treatment.	Increased credibility of the model as the vast majority of the users of the model outputs will consider the time window appropriate.
Delay time between tPA and endovascular thrombectomy treatment	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	In this model, we assumed 90-minutes delay between tPA and IA interventions. This assumption allows for treatment of all patients within 6 hours of onset as adopted in current guidelines.	Increased credibility of the model as the vast majority of the users of the model outputs will consider the time delay appropriate.
Tracing	Based on: (Balci, 1994; Sargent, 2013)		
Change over time formulation	To ensure that the logical behaviour of the formulation is correct and the required accuracy obtained.	The process of building and selecting the equations to formulate the effect of onset-to-IA treatment time on probability distributions was performed separately by three members of the model development team and the results were compared for any inconsistency.	The equations used to formulate the effect of onset-to-IA treatment time on probability distributions were verified and the equations were corrected where necessary.

Mathematical and statistical validation methods	Based on: (Balci, 1994; Gass, 1983; Schellenberger, 1974)		
Change over time formulation	To ensure that the equations used to build the conceptual model are accurate enough.	We derived the relevant analytical expressions for mRS common odds ratio curve by selecting 5 point estimates in the line, and choosing the best fit among the resulting equations using the R^2 criterion (achieving R^2 of 0.996).	Correct representation of the relationship between odds ratio and time is achieved
	To ensure that the probability equations used to build the conceptual model are logically correct.	We ensured that the sum of probabilities for each patient generated after the endovascular thrombectomy effect in the model is equal to one.	Increased credibility and accuracy of the probability equations.

Table 4-16 Validation tests and techniques utilized for conceptual model validation of different components of the 'IV tPA' model

4.15.3 Computational verification

Similar to the 'IV tPA' model, this was performed by verifying the computations in Excel and code scripts in Stata as described earlier is Section 4.7.3, using debugging, walkthrough and execution tracing techniques. All the model components shown in Figure 4-7 have been verified using these techniques. The summary of different validation methods and techniques used to obtain computational model verification of the 'Endovascular Thrombectomy' model has been provided in Table 4-8.

4.15.4 Operational validity

To achieve operational validity, the outputs of the 'Endovascular Thrombectomy' model (i.e. shown in Figure 4-7 in blue box) were verified to obtain the accuracy needed for the intended use of the model. This model presents the first OR model used to investigate the effect of faster access to endovascular therapy, there was no data available in a real-life system to be used for specifying a clear range of the values of the DALYs per unit of onset-to-IA treatment time. However, since according to clinical trials giving the endovascular therapy in addition to tPA treatment has even more benefits for stroke patients compared to tPA alone, we expected that for the 'Endovascular Thrombectomy' model, that patients benefit even more compared to the results of the 'IV tPA' model for every minute that they receive the IA therapy earlier. In this scenario, different techniques were used to validate the operational model are output analysis, robustness analysis, and tests to validate an appropriate application of the model. The summary of different validation methods and techniques used to obtain operational validity of the 'Endovascular Thrombectomy' model has been provided in Table 4-17.

4.15.4.1 Validation of the model output

We validated the expected DALYs (as the final output of the model) using output analysis, robustness, and comparison to the results produced by other models as described below:

Different graphs and summary statistical measures (i.e. mean, median, 95% CIs) were generated to validate the model outputs. The 'Endovascular Thrombectomy' model was an extension to the 'IV tPA' model which was previously validated in this chapter. This eventually resulted in the increased credibility of the outputs for the 'Endovascular Thrombectomy' model. We compared DALYs gained per endovascular thrombectomy treated patient from this model with DALYs gained per tPA treated patient from the 'IV tPA' model. According to 'IV tPA' model, each minute of the onset-to-tPA treatment time

saved resulted in on average extra 1.8 days of healthy life, while for the 'Endovascular Thrombectomy' model the patients benefit on average extra 3.2 days of healthy life; thus confirming the results of the clinical trials regarding the increased benefits for the stroke patients when they receive endovascular thrombectomy therapy compared to tPA alone.

Also, we varied the delay time between tPA and endovascular therapy and compared the results for DALYs gained per endovascular thrombectomy treated patient. Lastly, we ran both one-way analysis and probabilistic analysis to validate the model outputs with results from both analyses confirming the robustness of the model.

Similar to the 'IV tPA' model, different techniques used to validate the operational model are output analysis, robustness analysis, comparison to the results produced by other known models, and tests to validate an appropriate application of the model.

4.15.4.2 Validation of the model application

The intended use of the model and its limitations were validated by the model developers to ensure the operational validity of the model as a decision support tool. For our model, these included the following considerations:

1. **Intended mode use in different population demographics:** Since the study dataset is based on two subgroups, the characteristics of the tPA only cohort and endovascular suitable cohort was provided for comparison in Table 4-12.
2. **Intended model use in different patient groups:** Similar to the 'IV tPA' model, findings of the 'Endovascular Thrombectomy' model demonstrate that patients with different gender, age and NIHSS benefit differently in terms of disability-free life over their full life-time. Therefore, the younger patients and women with longer overall life-expectancies, gain more over their life-time.
3. **Intended model use for true effect of the IV tPA and endovascular treatment interventions**: In practice, it is not clear for the clinicians how long it takes for the individual stroke patient to fully realizing the effect of IV tPA treatment. Thus, while the goal is to deliver both IV tPA and endovascular thrombectomy interventions to the eligible patients at the earliest possible time, it is not evident how different patients would benefit from each of these interventions separately, if we stretch or shorten the delay time between the two interventions. To build the 'Endovascular Thrombectomy' model, we consulted an expert team of neurologists and assumed 90-minutes delay between the interventions.

4. **Actual model use for increased public awareness**: The ‘Endovascular Thrombectomy’ model was developed to provide better understanding of the effect of faster endovascular thrombectomy therapy on patient lifetime outcomes. Compared to the results of the ‘IV tPA’ model, speed is even more essential in endovascular therapy, and the results of this model supposed to directly lead to an increased awareness of public policy decision makers, stroke campaigns, and stroke care system providers of the importance of faster treatment for stroke patients. As endovascular therapy is being set up around the world, time needs to be taken into account as a critical component of service design. We expect that the findings of this model promote the rational allocation of endovascular services and ambulance transfer patterns.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Output analysis	Based on: (Balci, 1994; Gass, 1983; Sargent, 2001)		
Model output	To ensure that the model's outputs are accurate enough for the intended use of the model.	We extended the 'IV tPA' model to build the 'Endovascular Thrombectomy' model. The 'IV tPA' model was previously validated by comparing the results of the model with that of a long-term utility of tPA (DALY/QALY gains) from other studies; thus ensuring the outputs are accurate enough for the intended use of the model.	Credibility of the outputs was increased by providing the comparison to other relevant studies.
Comparison of the model outputs	Based on: (Sargent, 2013; Williams & Sikora, 1991)		
	To ensure that the model's outputs are accurate enough for the intended use of the model.	DALYs gained per IA treated patient for this study was increased compared to DALYs gained per tPA treated patient from the 'IV tPA' model; thus confirming the results of clinical trials regarding the increased benefits for the patients when they receive IA therapy compared to tPA alone.	Increased credibility of the model's outputs.

Robustness	Based on: (Balci, 1994; Boehm, et al., 1976; Gass, 1983; Myers, et al., 2011; Sargent, 2013; Whitner & Balci, 1989)		
Model output	To check the model's behaviour while changing the parameters and inputs of the model.	We adopted different time delays between tPA and IA interventions from the five clinical trials included in the HERMES study and generated the model outputs accordingly. Results from different studies were compared for consistency.	Increased credibility of the model's outputs.

Table 4-17 Validation tests and techniques utilized for operational validation of different components of the 'IV tPA' model.

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To summarize, the 'Endovascular Thrombectomy' model is a model for investigation and improvement as it was used to provide better understanding of the effects of early access to endovascular thrombectomy treatment on patients' long-term benefits. The generic validation framework developed in Chapter 3 was adopted to validate the model in four aspects of data validity, conceptual model validity, computational verification, and operational validity. This increased the credibility of the outcomes generated by this model for its intended use.

4.16 Summary and conclusions

The chapter started with a brief description of the 'IV tPA' model followed by description of the model inputs, model-building process, and model results. As a result of this model, it was identified that each minute of onset-to-tPA treatment time saved result in on average extra 1.8 days of healthy life for stroke patients. A generic validation framework as described in Chapter 3 was then adopted to provide comprehensive validation of the model by demonstrating how multiple aspects of data validity, conceptual model validity, computational verification, and operational validity can be systematically addressed for a complex OR model.

The validated 'IV tPA' model was then extended to construct the 'Endovascular Thrombectomy' model adopting the similar model development stages for the base model followed by comprehensive validation of the model using the generic validation framework. For the 'Endovascular Thrombectomy' model, it was demonstrated that on average acute ischemic stroke patients who undergo endovascular therapy stand to gain 4.2 days of healthy life for every minute of reduction in treatment delays. Additionally, it was concluded that younger patients and women with longer overall life-expectancies gain more over their life-time.

As far as the modelling purpose is concerned, both 'IV tPA' and 'Endovascular Thrombectomy' models are fall into the category of models for *investigation and improvement*. In both models, there was very limited or no data on the model behaviour to be used for 'output-based' validation of the model, and therefore model validation was performed by critically testing all the model inputs, assumptions, parameters, and comparing the model outputs with the results of other similar studies. Insights obtained by validating these two models addressed the third research question of this thesis.

Two OR models developed in this chapter were used to measure the population benefits for stroke patients due to earlier treatment thus addressing the first research question of this thesis. Both models also provided important insights on the benefits of earlier treatment for the individual patients.

Chapter 5 relies on the results of the ‘IV tPA’ model and ‘Endovascular Thrombectomy’ models developed in this chapter to design and develop an effective OR model to assist with maximizing the individual patients’ life-time benefits over two pathways of the hyperacute stroke care system. We then adopt the validation framework described in Chapter 3 to validate the developed model.

Chapter 5: Individual patient OR model for investigation and improvement of long-term benefits of early access to hyperacute stroke treatment interventions

Introduction

In this chapter, we address the second research question of this thesis: *'How OR models can be designed, developed, and validated to assist with maximizing the individual patient's life-time benefits over two pathways of the hyperacute stroke care system?'*

As discussed in the previous chapter, existing stroke treatment interventions (i.e. IV tPA and endovascular thrombectomy) should be used for the speediest arterial recanalization of the eligible ischemic stroke patients, with time being even more important for endovascular thrombectomy compared to tPA alone. Two OR models developed and validated in the previous chapter, were used to measure the population benefits for stroke patients due to earlier treatment, while these models could also be applied to individual patient cases to provide insights on the gained benefits for the individual patients. In this chapter, we reflect even more on the individual patients' benefits associated with earlier treatment by developing a new OR model used for understanding the patient-specific benefits due to faster access to IV tPA and endovascular thrombectomy treatment interventions.

With emergence of new evidence about effectiveness of endovascular thrombectomy treatment in late 2014, new questions were raised in the clinical and health management domain in an attempt to design new protocols that support the new time sensitive treatment needs of the stroke patients. These questions mainly concern the issue of treatment pathway selection between two groups of hospitals with different facilities and expertise providing treatments for the stroke patients. In general, there are two types of treatment centres internationally:

(1) primary hospital which is the hospital that is only capable of providing IV tPA treatment, and

(2) comprehensive hospital which is the hospital that is capable of providing both IV tPA and endovascular thrombectomy treatment.

Questions associated with pathway selection were formulated in an *Editorial* article published in *Journal of the American Medical Association (JAMA)* as follows: "*Should primary stroke centres be bypassed to transport patients to comprehensive centres, even if it means delaying the start of IV tPA? How much delay in bypass is acceptable? How much of a delay to start IV tPA would eliminate the benefit of earlier thrombectomy*? (Warach & Johnston, 2016, p. 1266)"

To answer these questions, we used selected components of the 'IV tPA' and 'Endovascular Thrombectomy' models developed and validated in Chapter 4, to design the 'Individual Patient' model in this chapter. The model developed in this thesis is a model for *investigation and improvement*, since it is intended to support new investigations in the hyperacute stroke care system by comparing the long-term benefits for individual patients, associated with different pathways of the hyperacute stroke care system. However, in the future, with some extra refinements, this model can be adopted for *routine decision support* which are used to "assist, but not replace, people making routine, repeated decisions" (Pidd, 2010, p. 17).

The 'Individual Patient' model developed in this chapter compares the patient-specific benefits between the two pathways of *Drip and Ship* and *Mothership* as described later in next section of this chapter. The main objective of this model is to assist with maximizing the individual patients' life-time benefits in choosing different pathways of the hyperacute stroke care system. Similar to the OR models validated in Chapter 4, the generic validation framework provided earlier in Chapter 3 is adopted in this chapter to validate the 'Individual Patient' model.

By the end of this chapter, a validated OR model used to assist with maximizing the individual patient's life-time benefits associated with different pathways of the hyperacute stroke care system is developed. Discussion on validation is expected to provide further insights on the conceptual and application issues of conducting comprehensive validation of an OR model for investigation and improvement in the context of health systems and service operations.

5.1 Problem description and intended use of the 'Individual Patient' model

The results from a new generation of acute stroke trials became available in late 2014 and early 2015 (Berkhemer, et al., 2015; Campbell, et al., 2015; Goyal, et al., 2015; Jovin, et al., 2015; Saver, et al., 2015; Saver, et al., 2016). These trials demonstrated that endovascular thrombectomy intra-arterial clot removal can be successfully used to further improve the outcomes in patients with ischemic stroke who already have received tPA treatment. Now that the benefit of the intra-arterial (IA) therapy has been convincingly proven, stroke care systems worldwide face a serious challenge of incorporating the intra-arterial treatment into the existing care processes by providing and optimizing the necessary resources for such a change. One of the main issues here is that in reality, there are two types of medical centres with only one type being capable of delivering the necessary services for the endovascular thrombectomy treatment in the hyperacute stroke care system. In this scenario there are two options for a suspected stroke patient:

(1) *Drip and Ship* pathway: to take the patient to the closest *non-endovascular capable centres (non-ECC)* to receive the IV tPA treatment and then transfer the patient to the closest *endovascular capable centre (ECC)* to receive endovascular thrombectomy treatment if needed; or

(2) *Mothership* pathway to take the patient directly to the nearest ECC, where the patient first receives the IV tPA treatment and then, if eligible, in the same centre receives the endovascular thrombectomy treatment.

With the important effect of time delays on individual patient's life-time outcomes, it is crucial for the stroke care providers to compare the benefits associated with each treatment pathway for each individual patient. In this chapter, we present the 'Individual Patient' model which is designed and validated to provide insights on how to maximizing the individual patients' benefits over two pathways of the hyperacute stroke care system.

The 'Individual Patient' model is constructed to investigate the effect of earlier treatment interventions on individual patient's life-time benefits; thus, is as a model for *investigation and improvement.* The insights obtained from this model can be used in the clinical and health management domains to design more efficient and effective stroke care system pathways, thus maximizing the individual patient's benefits associated with choosing different pathways of the hyperacute stroke care system. This is achieved by comparing DALYs metric between the *Drip and Ship* pathway and the *Mothership* pathway for different scenarios of time delays associated with each of these pathways. The outcome of this model is reported in this chapter as the proportion that an individual patient will benefit more by the *Mothership* pathway over the *Drip and Ship* pathway, thus, assisting the health service providers in effective and improved provision of the services for the patients.

5.2 Overview of the 'Individual Patient' model

To build the 'Individual Patient' model described in this chapter, we used inputs and parameters of the 'IV tPA' and 'Endovascular Thrombectomy' models developed and validated in Chapter 4; this includes pooled analyses of tPA and endovascular thrombectomy effect over time, general population life expectancy data, and different parameters to estimate DALYs. The 'Individual Patient' model can be used to provide insights on how to maximizing the individual patients' life-time benefits over the two pathways of the hyperacute stroke care system (i.e. *Drip and Ship* pathway and *Mothership* pathway).

The summary of different parameters used to conceptualize the 'Individual Patient' model is provided in Table 5-1. These parameters are used to develop the 'Individual Patient' model in Section 5.5.

Parameter name	**Definition**
T_1	onset-to-tPA treatment delay for the *Drip and Ship* pathway
T_2	onset-to-tPA treatment delay for the *Mothership* pathway
T_3	transfer delay time between non-ECC and ECC for the *Drip and Ship* pathway
T_4	in-hospital delay time in the *ECC* to receive endovascular thrombectomy for both pathways
$t_{IA\text{-}drip\ and\ ship}$	onset-to-IA treatment delay for the *Drip and Ship* pathway
$t_{IA\text{-}mothership}$	onset-to-IA treatment delay for the *Mothership* pathway
p	probability of receiving endovascular thrombectomy for both pathways
$Exp\_DALY_{mothership\text{-}tPA}$	expected DALYs lost after tPA intervention in ECC for the *Mothership* pathway
$Exp\_DALY_{drip\ and\ ship\text{-}tPA}$	expected DALYs lost after tPA intervention in non-ECC for the *Drip and Ship* pathway
$Exp\_DALY_{mothership\text{-}IA}$	expected DALYs lost after endovascular thrombectomy intervention in ECC for the *Mothership* pathway
$Exp\_DALY_{drip\ and\ ship\text{-}IA}$	expected DALYs lost after endovascular thrombectomy intervention in ECC for the *Drip and Ship* pathway
$Exp\_DALY_{drip\ \mathrm{and}\ ship}$	expected DALYs lost for the *Drip and Ship* pathway
$Exp\_DALY_{mothership}$	expected DALYs lost for the *Mothership* pathway

Table 5-1 Summary of different parameters of the 'Individual Patient' model

Even though that based on the results of the OR models developed in Chapter 4, stroke patients benefit more when they receive endovascular thrombectomy intervention rather than tPA alone, not every patient is eligible to receive the endovascular treatment. As a result, it is crucial to know which treatment strategy is suitable for individual patients, thus maximizing the patient's life-time benefits

depending on time delays associated with the two pathways of the hyperacute stroke care system. Moreover, since these benefits often vary for individual stroke patients with different age, stroke severity, gender and treatment delay times, the results of the 'Individual Patient' model are generated for patients with different characteristics to provide insights on these varied gained benefits for different groups of patients.

Last but not least, based on the results of the OR models developed in Chapter 4 it was concluded that there is a link between treatment delay times and patients' long-term benefits, with every minute being counted when a stroke patient intervened with either IV tPA or endovascular thrombectomy interventions. As a result, for the 'Individual Patient' model the results are generated for different scenarios associated with *Drip and Ship* and *Mothership* pathways to investigate how the long-term benefits for the individual patients will be affected by changing delay time parameters for the two pathways of the hyperacute stroke care system. Figure 5-1, represents an overview of the 'Individual Patient' model, while detailed description of these inputs is provided in next section.

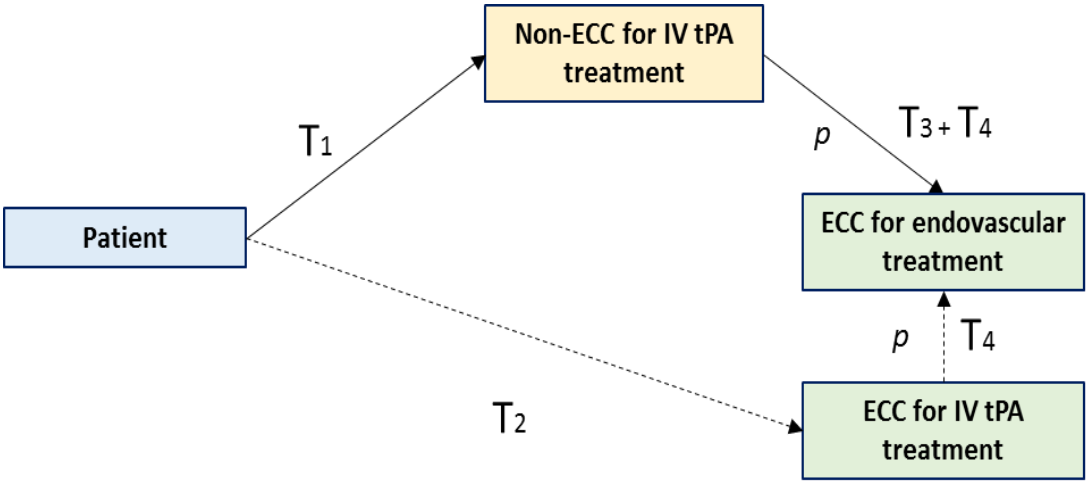

Figure 5-1 Overview of the hyperacute stroke care system. T_1 and T_3 respectively represent the onset-to-tPA treatment time and transfer time between non-ECC and ECC for the Drip and Ship pathway shown by the solid lines. T_2 represent the onset-to-tPA treatment time for the mothership pathway. T_4 is the in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways. p indicates the eligibility of the patients to receive endovascular thrombectomy.

5.3 Inputs of the 'Individual Patient' model

Parts of data used to build 'Individual Patient' model has been adopted from the previously developed and validated 'IV tPA' and the 'Endovascular Thrombectomy' models, for which we refer to the relevant sections in Chapter 4. These are as follows:

- Published pooled analysis of tPA randomized controlled trials to estimate the tPA treatment effect over time (refer to Section 4.3 of Chapter 4) (Emberson, et al., 2014; Lees, et al., 2010).
- Published pooled analysis of endovascular thrombectomy randomized controlled trials to estimate the endovascular thrombectomy treatment effect over time (refer to Section 4.10 of Chapter 4) (Saver, et al., 2016).
- An updated version of the general Australian population life expectancy age- and sex-specific data obtained from Australian Bureau of Statistics at the time of developing this model (refer to Section 4.3 of Chapter 4) (Australian Bureau of Statistics, 2013-2015)
- Parameters necessary to translate the 3-month mRS outcome data into a long-term metric of Disability-adjusted Life Years (DALYs) lost (refer to Section 4.3 of Chapter 4) (Hong & Saver, 2010; Murray & Lopez, 1996).

Since at the time of developing this model, there was no adequate prediction tool with enough accuracy to be used for estimating the patients' eligibility for thrombectomy treatment, we consulted an expert team of neurologists who work in several treating centres in Melbourne, Australia. These experts advised on using the NIHSS and *Large Vascular Occlusion (LVO)* as two main parameters to build a prediction model. While we used LVO and NIHSS as two key parameters to develop this prediction model, other studies globally are investigating development of more accurate prediction methods. In some of these studies, researchers and clinicians suggest to use Los Angeles Motor Scale (LAMS) as a key parameter for specifying the eligibility of the patients to receive endovascular thrombectomy (Holodinsky, et al., 2017).

We used a new observational cohort of stroke patients based on a combined sample of 391 patients retrieved from two medical centres in Melbourne, Australia: *Box Hill Hospital* and *Royal Melbourne Hospital*. The database contains information about stroke patients admitted in these two hospitals in 2016. Of 391 patients included in this study, 334 cases were obtained from the Royal Melbourne Hospital and 57 cases were obtained from the Box Hill Hospital. This cohort contained distributions data of stroke severity and Large Vascular Occlusion (LVO). To build the prediction model, we constructed a logistic regression model with LVO as a dependant variable, and stroke severity as an independent variable. The validation process of constructing this prediction model has been explained in more details in Section 5.7.2 of this chapter.

5.4 Model assumptions

Similar assumptions to that of the 'IV tPA' and 'Endovascular Thrombectomy' models discussed in Chapter 4 were used to build this model. All the assumptions listed here are validated later in this chapter in the validation section.

1. To build this model, the only criterion for specifying the eligibility of the patients to receive tPA treatment was onset-to-tPA treatment time, with the upper time limit to receive tPA treatment set to 270 minutes.
2. To generate mRS probabilities after tPA intervention, we assumed that the relative ratios of probabilities of achieving mRS 0 and mRS 1, as well as the relative ratios of achieving mRS categories 2-5 at any time, are identical to those at the baseline onset-to-tPA treatment time.
3. To build this model, we assumed that patients first receive tPA treatment and then undergo IA therapy.
4. The upper time limit to receive IA treatment was set to 360 minutes.
5. For specifying the eligibility of the patients to receive endovascular therapy, in addition to onset-to-IA treatment time eligibility criteria, we also used the LVO as a predictive parameter to estimate the clinical eligibility of the patients to receive endovascular thrombectomy.
6. Because of the time restrictions on the eligibility of the stroke patients to receive endovascular therapy, for any scenario combination of T_1, T_3, T_4 where sum of these parameters exceeds 360 minutes, we assume that the patient goes to the ECC.
7. For T_1 and T_2, we assumed 60 minutes as the minimum range, and 270 minutes as the maximum range, with 15-minutes interval between the values within these ranges. For T_3, we assumed 35 minutes as the minimum range, and 260 minutes as the maximum range, with 15-minutes interval between this range. For the in-hospital delay time (T_4), we assumed 40-minutes delay in all cases.

5.5 Model building process

To build the 'Individual Patient' model we repeated some stages of the model building process described in Sections 4.4 and 4.12 of Chapter 4, respectively for the 'IV tPA' and 'Endovascular Thrombectomy' models. To avoid repeating those stages, we have explained different stages of developing the 'Individual Patient' model through 11 Stages as shown in Table 5-2.

Stage 1: Create simulation delay times

For T_1 = 60, 75, …, 270

  For T_2 = 60, 75, …, 270

    For T_3 = 35, 50, …, 260

      For T_4 = 40

Stage 2: Create patient population

For Gender i = 0,1

  For Age j = 20, 30, 40, 50, 60, 70, 80, 90

    For NIHSS k = 2, 7, 12, 17, 22, 27, 32, 37

    Let

      patient (i, j, k) = $p_{i,j,k}$

      p = probability of the patient (i, j, k) to receive endovascular thrombectomy

Stage 3: Generating patient-specific probabilities of achieving specific mRS category at baseline onset-to-tPA treatment time

For baseline onset-to-tPA treatment time = 270

  Get the logistic regression equations from the 'Endovascular Thrombectomy' model

  Generate patient-specific mRS probabilities at baseline onset-to-tPA as per the 'IV tPA' model

Stage 4: Estimating the probabilities of achieving a specific mRS after IV tPA intervention for both pathways

For any feasible combination of (T_1, T_3, T_4) for *Drip and Ship* pathway

  For any feasible combination of (T_2, T_4) for *Mothership* pathway

    Get the analytical expression of tPA mRS odds ratios with 95% CIs from the 'IV tPA' model

      For counter number m = 1, 2, …, 1000

        For counter number n = 1, 2, …, 1000

          Get m^{th} to sample from an underlying distribution between the mRS 0-1 odds ratio

          Generate mRS probabilities after tPA intervention for *Drip and Ship* pathway at T_1

          Get n^{th} to sample from an underlying distribution between the mRS 6 odds ratio

          Generate mRS probabilities after tPA intervention for *Mothership* pathway at T_2

Stage 5: Estimating patient-specific expected DALYs lost after IV tPA intervention for both pathways

Get DALYs formula from the 'IV tPA' model

Generate DALYs after tPA intervention for *Drip and Ship* pathway ($Exp\_{}_{DALYdrip\ and\ ship\text{-}tPA}$)

Generate DALYs after tPA intervention for *Mothership* pathway ($Exp\_DALY_{mothership\text{-}tPA}$)

Stage 6: Estimating the probabilities of achieving a specific mRS after endovascular intervention for both pathways

Get the analytical expression for IA common mRS odds ratio with 95% CIs from the 'Endovascular Thrombectomy' model For counter $y = 1, 2, \ldots, 1000$ Get y^{th} to sample from an underlying distribution between the common mRS odds ratio Generate mRS probabilities after IA intervention for *Drip and Ship* pathway at $(T_1 + T_3 + T_4)$ Generate mRS probabilities after IA intervention for *Mothership* pathway at $(T_2 + T_4)$
Stage 7: Estimating patient-specific expected DALYs lost after endovascular thrombectomy for both pathways
Get DALYs formula from the 'IV tPA' model Generate DALYs after thrombectomy intervention for *Drip and Ship* pathway $(Exp\_DALY_{drip\ and\ ship\text{-}IA})$ Generate DALYs after thrombectomy intervention for *Mothership* pathway $(Exp\_DALY_{mothership\text{-}IA})$
Stage 8: Estimating the expected DALYs lost for both pathways
Let $Exp\_DALY_{drip\ and\ ship} = (1\text{-}p) * (Exp\_DALY_{drip\ and\ ship\text{-}tPA}) + p * (Exp\_DALY_{drip\ and\ ship\text{-}IA})$ Let $Exp\_DALY_{mothership} = (1\text{-}p) * (Exp\_DALY_{mothership\text{-}tPA}) + p * (Exp\_DALY_{mothership\text{-}IA})$
Stage 9: Specifying the outcome of the model for each individual patient out of 1000 runs for a given scenario of delay times
Let the patient (i, j, k) follow the mothership pathway, if $Exp\_DALY_{drip\ and\ ship} > Exp\_DALY_{mothership,}$ Estimate the proportion that a patient (i, j, k) benefit more by the *Mothership* pathway Increment m, n, y by one unit
Stage 10: Increment time delays
Next feasible combination of (T_1, T_3, T_4)*where the sum of time delays is less than 360 minutes* Next feasible combination of (T_2, T_4)*where the sum of time delays is less than 360 minutes*
Stage 11: Repeat Steps 1 to 10 for the next patient
Next patient $(i, j, k) = p_{i,j,k}$

Table 5-2 Simulation pseudocodes for the 'Individual Patient' model

To investigate the effect of time delays associated with different pathways of the hyperacute stroke care system on individual patient's life-time outcomes, in this model we run simulations for different combination of $T_1, T_2, T_3,$ and T_4. These parameters and values assigned to them were generated in Stage 1 of the simulation model as shown in Table 5-2. We sought the opinion of the clinical experts from several treating centres in Melbourne. As a result, we chose15 minutes granularity to cover the plausible range of delay times associated with different pathways of the hyperacute stroke care system.

The implemented simulation model allows generating the results of the 'Individual Patient' model for patients with different characteristics. This includes 64 male and 64 female patients, to whom we assigned different age (20, 30, 40, 50, 60, 70, 80, 90) and severity (2, 7, 12, 17, 22, 27, 32, and 37).

The baseline onset-to-tPA treatment time was set to 270 minutes for all the 128 patients. These parameters were generated in Stage 2 of the simulation model as shown in Table 5-2. Finally, To capture the variability of the model outputs when testing different interventions, each individual scenario was implemented through 1000 simulation runs. This was performed in Stages 4 and 6 of the simulation model as shown in Table 5-2. In the next section, we report on the results of the simulation model for patients with different characteristics, and for different scenarios of delay times.

5.6 Model results

Running the simulation experiments over 128 individual "model" patients, for the total of 3600 scenarios of delay times, each simulated 1000 times, result of this model is reported as proportion of the runs that an individual patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway for a given scenario. It is evidenced by clinical trials that patients with various age and disease severity benefit differently from faster treatment. Since it is not possible to fully report the results of this model given the large number of simulation runs, in this section, we illustrate the results of the 'Individual Patient' model for six individual patients. For the first patient, we provide three examples to demonstrate how individual patient's long-term benefits change depending on time delays associated with different pathways of the hyperacute stroke care system. Last example illustrated for the first patient is used for the rest of the patient examples provided in this section to discuss how different characteristics of individual patients affect their long-term outcomes.

1. ***Patient 1 (age 50, NIHSS 17, p 0.33)***: Three illustrative examples are described for this patient to investigate the effect of time delays associated with different pathways of the hyperacute stroke care system on patient's life-time outcomes.

   Example 1: The first example shows the results generated for different scenarios by fixing the values of T_2, T_3, T_4 and tabulating the values of T_1 as presented in Figure 5-2. As described below, the values assigned to T_2, and T_3 are selected from the mid-range values used to run the experimental design:

   1. Onset-to-tPA treatment delay for the *Drip and Ship* pathway (T_1) changing from 60 to 270 minutes;
   2. Onset-to-tPA treatment delay for the *Mothership* pathway (T_2) equals to 165 minutes;
   3. In-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways (T_4) equals to 40 minutes;
   4. Transfer delay time between non-ECC and ECC for the *Drip and Ship* pathway (T_3) changing from 125 to 170 minutes.

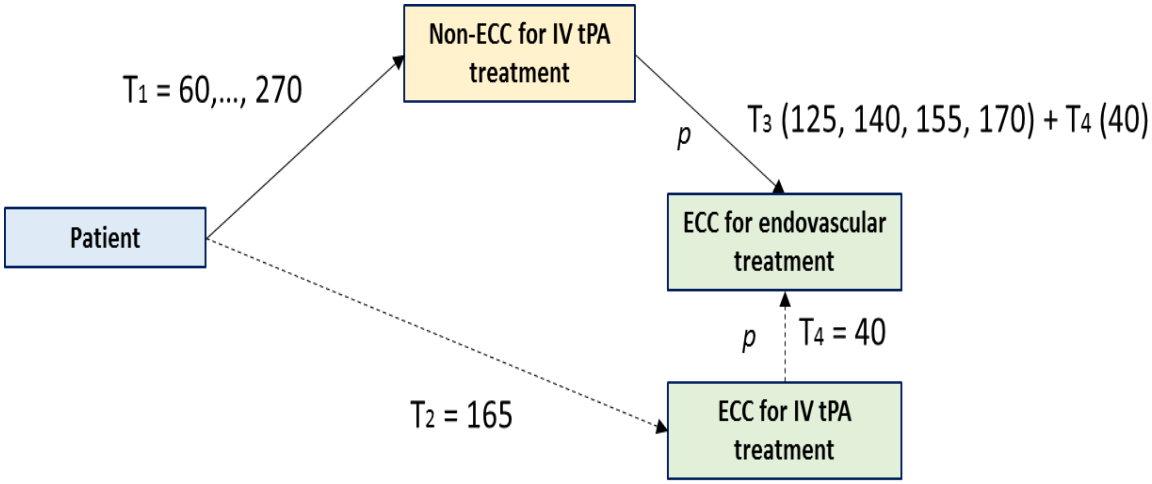

Figure 5-2 First example for different scenarios for a female patient with a 50 y.o, and severity of 17

Figure 5-2 illustrates the results for this patient for different scenarios. In Table 5-3 different rows and columns respectively reflect values of T_1 and T_2. In this table, cells shown in yellow denote the scenarios where in all cases this patient will benefit (losing less DALYs) the *Drip and Ship* pathway over the *mothership* pathway. Cells shown in dark green denote the scenarios where in all cases this patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway. Lastly, cells shown in light green, show the proportions (out of 1000 simulation runs) where the patient will benefit either the *Mothership* pathway or the *Drip and Ship* pathway.

In this table, for values of T_3 equal to 125, 140, 155, and 170 minutes, and for lower values of T_1 (less than 135 minutes) in majority of the scenarios the patient will benefit the *Drip and Ship* pathway over the *Mothership* pathway. As we increase the values of T_1 (more than 135 minutes) in majority of the scenarios the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway. As indicated by dark green shades in Table 5-3, for these scenarios the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway in all cases.

For this patient, for the scenarios where the sum of T_1, T_3 and T_4 (onset-to-IA treatment time) for the *Drip and Ship* pathway exceeds 360 minutes, we assume that the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway. For T_3 equals to 170 minutes for instance, and for values of T_1 more than 150 minutes the onset-to-IA treatment time exceeds 360 minutes, thus, in all cases the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway. For all the other scenarios, it can be observed in the Table 5-3, that there is a linear trend in results for fixed values of T_2, T_3, and T_4 when we change the values of T_1.

The granularity of delay times (15 minutes) used in this model to generate the results were selected by seeking the opinion of the experts and neurologists who work in several treating centres in

Melbourne, Australia. The values of T_3 (125, 140, 155, 170 minutes) and T_2 (165 minutes) in this example were selected from the mid-range values assigned to these parameters in the experimental design. For these scenarios, there was a linear trend in results generated by the model with an exception in results for a fixed value of T_3, where the model is very sensitive to small changes in the values of T_1. This can be observed in Table 5-3, for value of T_3 equals to 125 minutes, and in changing the values of T_1 from 120 to 135 minutes, where the results are changing from 9% to 72% for choosing the *Mothership* pathway over the *Drip and Ship* pathway.

T_1 \ T_3	125	140	155	170
60	0%	0%	0%	1%
75	0%	0%	1%	2%
90	0%	1%	2%	4%
105	2%	3%	7%	14%
120	9%	20%	35%	55%
135	72%	90%	97%	99%
150	100%	100%	100%	100%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-3 Proportions of going to the ECC, for a female patient with a 50 y.o, severity of 17, T_2 =165, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC *to receive endovascular thrombectomy for both pathways*

Example 2: The second example shows the results generated for different scenarios by fixing the values of T_1, T_2, T_4 and tabulating the values of T_3 as presented in Figure 5-3. As described below, the values assigned to T_1, and T_2 are selected from the mid-range values used to run the experimental design:

1. Onset-to-tPA treatment delay for the *Drip and Ship* pathway *(T_1)* changing from 135 to 180 minutes;
2. Onset-to-tPA treatment delay for the *Mothership* pathway (*T_2)* equals to 165 minutes;
3. In-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways *(T_4)* equals to 40 minutes;
4. Transfer delay time between non-ECC and ECC for the *Drip and Ship* pathway *(T_3)* changing from 35 to 260 minutes.

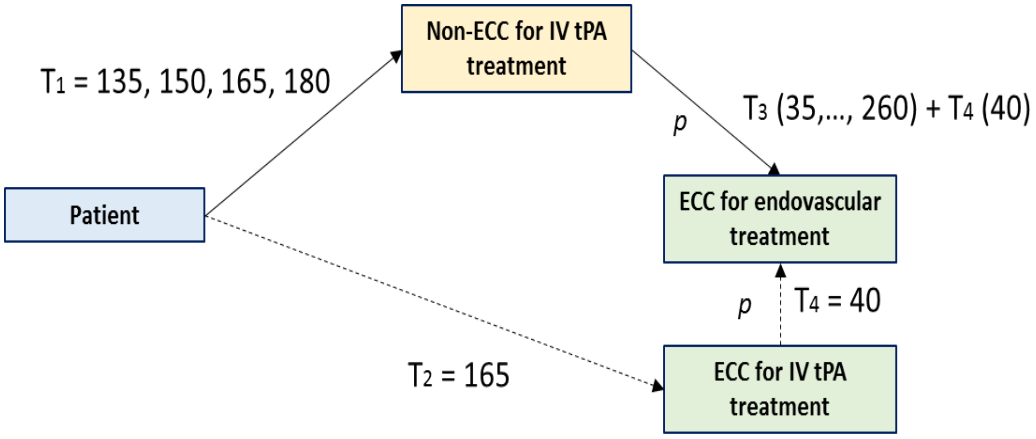

Figure 5-3 Second example for different scenarios, for a female patient with a 50 y.o, and severity of 17

Figure 5-3 illustrates the results for this patient for different scenarios. In Table 5-4 different rows and columns respectively reflect values of T_1 and T_2. In this table, for value of T_1 equals to 135 minutes; and for lower values of T_3 (less than 125 minutes) in majority of the cases the patient will benefit more the *Drip and Ship* pathway over the *Mothership* pathway, while as we increase the values of T_3 (more than 125 minutes) in majority of the cases the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway. As it can be observed in Table 5-4, with increased values of T_1, in majority of the cases the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway, thus maximizing her life-time benefits.

For this patient, similar to the first example for the scenarios where the sum of T_1, T_3 and T_4 (onset-to-IA treatment time) for the *Drip and Ship* pathway exceeds 360 minutes, we assume that the patient benefit by *Mothership* pathway over the *Drip and Ship* pathway. The values of T_1 (135, 150, 165, 180 minutes) and T_2 (165 minutes) in this example were selected from the mid-range values assigned to these parameters in the experimental design. For these scenarios, there was a linear trend in results generated by the model in most cases.

T_3 \ T_1	135	150	165	180
35	0%	1%	100%	100%
50	0%	21%	100%	100%
65	1%	76%	100%	100%
80	4%	98%	100%	100%
95	18%	100%	100%	100%
110	42%	100%	100%	99%
125	72%	100%	100%	100%
140	90%	100%	100%	100%
155	97%	100%	100%	100%
170	99%	100%	100%	100%
185	100%	100%	100%	100%
200	100%	100%	100%	100%
215	100%	100%	100%	100%
230	100%	100%	100%	100%
245	100%	100%	100%	100%
260	100%	100%	100%	100%

Table 5-4 Proportions of going to the ECC, for a female patient with a 50 y.o, severity of 17, T_2 =165, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the mothership pathway; T_3, transfer delay time between non-ECC and ECC for the drip and ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

Example 3: The third example shows the results generated for different scenarios by fixing the values of T_2, T_3, T_4 and tabulating the values of T_1 as presented in Figure 5-4. As described below, the values assigned to T_1, and T_3 are selected from the mid-range values used to run the experimental design:

1. Onset-to-tPA treatment delay for the *Drip and Ship* pathway *(T_1)* changing from 60 to 270 minutes;
2. Onset-to-tPA treatment delay for the *Mothership* pathway (T_2) changing from 135 to 180 minutes;
3. In-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways *(T_4)* equals to 40 minutes;
4. Transfer delay time between non-ECC and ECC for the *Drip and Ship* pathway *(T_3)* equals to 155minutes.

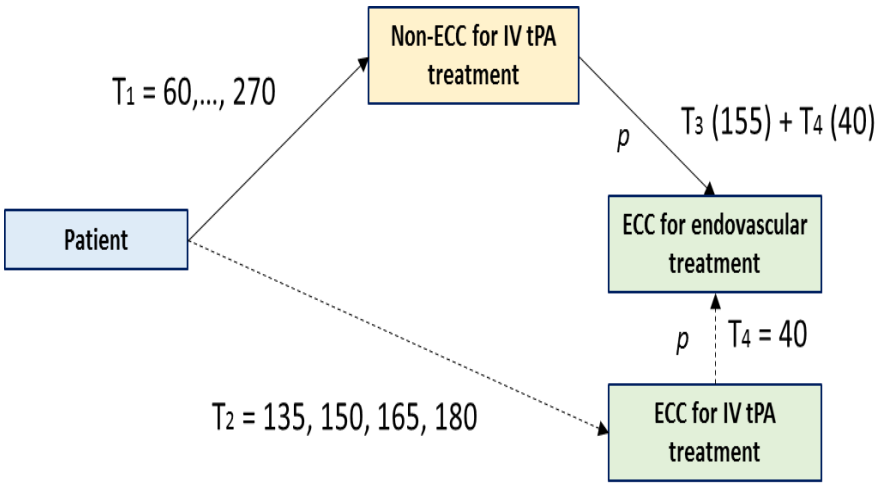

Figure 5-4 Third example for different scenarios, for a female patient with a 50 y.o, and severity of 17

Figure 5-4 illustrates the results for this patient for different scenarios. In Table 5-5 different rows and columns respectively reflect values of T_1 and T_2. In this table, for value of T_2 equals to 135 minutes and lower values of T_1 (less than 90 minutes) in majority of the cases the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway over the, while as we increase the values of T_2, the number of cases where the patient will benefit the *Drip and Ship* pathway over the *Mothership* pathway increases.

For this patient, similar to the first example for the scenarios delay times where the sum of T_1, T_3 and T_4 (onset-to-IA treatment time) for the *Drip and Ship* pathway exceeds 360 minutes, we assume that the patient benefit the *Mothership* pathway over the *Drip and Ship* pathway. The values of T_2 (135, 150, 165, 180 minutes) and T_3 (155 minutes) in this example were selected from the mid-range values assigned to these parameters in the experimental design. For these scenarios, there was a linear trend in results generated by the model in most cases. Where there is a less linear trend in the results, the model is sensitive to small changes in T_1.

T_1 \ T_2	135	150	165	180
60	4%	2%	0%	0%
75	11%	3%	1%	0%
90	33%	9%	2%	0%
105	90%	33%	7%	1%
120	100%	94%	35%	5%
135	100%	100%	97%	39%
150	100%	100%	100%	98%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-5 Proportions of going to the ECC, for a female patient with a 50 y.o, severity of 17, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

Three examples described in this section, demonstrated how the results of the 'Individual Patient' model change by fixing two of T_1, T_2, and T_3 parameters and tabulating the remaining parameter. To show how the results of this model changes for patients with different characteristics, below we provide example three provided for the first patient by fixing the values of T_2, T_3, and T_4 and tabulating the values of T_1.

2. ***Patient 2 (age 50, NIHSS 17, p 0.33)***: Table 5-6 demonstrates the results for this patient for different scenarios where different rows and columns respectively reflect values of T_1 and T_2. By comparing the results obtained for this patient with that of the female patient in Table 5-6 it can be concluded that there is no significant difference between the results for a female and male patient with other similar characteristics.

T_1 \ T_2	135	150	165	180
60	5%	2%	1%	0%
75	12%	4%	1%	0%
90	35%	10%	3%	1%
105	88%	35%	9%	1%
120	100%	92%	37%	8%
135	100%	100%	93%	40%
150	100%	100%	100%	94%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-6 Proportions of going to the ECC, for a male patient with a 50 y.o, severity of 17, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

3. ***Patient 3 (age 30, NIHSS 17, p 0.33)***: Table 5-7 demonstrates the results for this patient for different scenarios where different rows and columns respectively reflect values of T_1 and T_2. By comparing the results obtained for this patient, with that of the female patient in Table 5-6 it can be concluded that for majority of the simulation runs there is a slight decrease in the proportion of choosing the *mothership pathway* for this patient due to her younger age.

T_1 \ T_2	135	150	165	180
60	6%	3%	1%	0%
75	10%	5%	2%	0%
90	29%	9%	3%	1%
105	80%	29%	8%	2%
120	100%	84%	31%	7%
135	100%	100%	87%	32%
150	100%	100%	100%	90%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-7 Proportions of going to the ECC, for a female patient with a 30 y.o, severity of 17, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

4. ***Patient 4 (age 80, NIHSS 17, p 0.33)***: Table 5-8 demonstrates the results for this patient for different scenarios where different rows and columns respectively reflect values of T_1 and T_2. For this patient, the result of the model is more sensitive to changes in delay times potentially due to old age of the patient.

T_1 \ T_2	135	150	165	180
60	4%	1%	0%	0%
75	10%	2%	0%	0%
90	44%	8%	1%	0%
105	99%	45%	6%	0%
120	100%	100%	47%	4%
135	100%	100%	100%	51%
150	100%	100%	100%	100%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-8 Proportions of going to the ECC, for a female patient with a 80 y.o, severity of 17, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

5. ***Patient 5 (age 50, NIHSS 7, p 0.09)***: Table 5-9 demonstrates the results for this patient for different scenarios where different rows and columns respectively reflect values of T_1 and T_2. Compared to other patients, this patient benefit more by receiving IV tPA treatment earlier in the non-ECC by choosing the *Drip and Ship* pathway over the *Mothership* pathway for values of T_1 less than 120 minutes due to her younger age and lower severity.

T_1 \ T_2	135	150	165	180
60	1%	0%	0%	0%
75	1%	0%	0%	0%
90	1%	1%	0%	0%
105	8%	6%	0%	0%
120	43%	23%	13%	0%
135	100%	68%	54%	8%
150	100%	100%	73%	61%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-9 Proportions of going to the ECC, for a female patient with a 50 y.o, severity of 7, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

6. ***Patient 6 (Age 50, NIHSS 27, p 0.70)***: Table 5-10 demonstrates the results for this patient for different scenarios where different rows and columns respectively reflect values of T_1 and T_2. Even though this patient has the same age as the previous patient, due to higher severity of this patient, in majority of the simulation runs the patient will benefit the *Mothership* pathway over the *Drip and Ship* pathway, for values of T_1 less than 120 minutes.

T_1 \ T_2	135	150	165	180
60	72%	30%	8%	1%
75	99%	77%	29%	6%
90	100%	99%	81%	29%
105	100%	100%	99%	84%
120	100%	100%	100%	99%
135	100%	100%	100%	100%
150	100%	100%	100%	100%
165	100%	100%	100%	100%
180	100%	100%	100%	100%
195	100%	100%	100%	100%
210	100%	100%	100%	100%
225	100%	100%	100%	100%
240	100%	100%	100%	100%
255	100%	100%	100%	100%
270	100%	100%	100%	100%

Table 5-10 Proportions of going to the ECC, for a female patient with a 50 y.o, severity of 27, T_3 =155, T_4 = 40. T_1, onset-to-tPA treatment delay for the Drip and Ship pathway; T_2, onset-to-tPA treatment delay for the Mothership pathway; T_3, transfer delay time between non-ECC and ECC for the Drip and Ship pathway; T_4, in-hospital delay time in the ECC to receive endovascular thrombectomy for both pathways

As demonstrated in results section, patients with different characteristics benefit differently by choosing different pathways of the hyperacute stroke care system. The results of the 'Individual Patient' model presented in this chapter can provide important insights on the gained benefits for the patients, thus, providing assistance in choosing appropriate pathway of the hyperacute stroke care system, so patients can maximize their life-time benefits.

5.7 Comprehensive validation of the 'Individual Patient' model

In this section, we are validating the 'Individual Patient' model using the generic validation framework discussed earlier in Chapter 3. Since this model was developed based on the 'IV tPA' and 'Endovascular Thrombectomy' models, both validated in Chapter 4 of this thesis; in this section, we focus on validating the new developed parts of the model.

5.7.1 Data validity

Both input data and parameters data were used to build the 'Individual Patient' model were validated as follows:

An observational cohort of stroke patients: We obtained relevant stroke patients data from Box Hill Hospital and Royal Melbourne Hospital and included all dataset to generate the patient-specific probabilities of LVO used as predictive parameter to estimate the eligibility of the patients to receive endovascular thrombectomy. The dataset was maintained in accordance to the best practice guidelines. It was also stored and documented on a password protected computer during the process of model development.

General population life expectancy: An updated version of life expectancy tables (at the time of developing this model) for the period of 2013-2015 (Australian Bureau of Statistics) were adopted and validated (as described earlier in Section 4.7.1 of Chapter 4 for the 'IV tPA' model) to estimate DALYs.

The *pooled analysis of tPA effect* and *IA effect over time,* and *parameters to calculate expected DALYs* used to build the 'Individual Patient' model were adopted from the validated 'Endovascular Thrombectomy' model.

The summary of different validation methods and techniques used to obtain data validity of the 'Individual Patient' model has been provided in Table 5-11.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Representativeness of the dataset	Based on: (Biau, et al., 2008; Ellenberg, 1994)		
General population life expectancy	To ensure that the data source used to estimate the life expectancies is trustworthy.	We used the latest official data for age and sex specific life-expectancies of the residents of Victoria, Australia at the time of developing the model, obtained from ABS. We compared these with similar life-expectancy data from Finland which was the source country of the cohort used in this model to develop the logistic regression model. We observed minimal differences (the average life expectancy at birth for men is 80.3 years in Australia versus 78.3 years in Finland and for women 84.3 years versus 84.1 years).	Increased confidence in the accuracy of the estimations for the general population life expectancy.
Observational cohort data	To ensure that the data source used to estimate the probability of the stroke patients to receive endovascular thrombectomy is trustworthy.	We obtained data from the Royal Melbourne Hospital and Box Hill Hospital.	Increased accuracy of the parameters used to estimate the probability of the patients to receive endovascular thrombectomy.

Table 5-11 Validation tests and techniques utilized for data validation of different components of the 'Individual Patient' model

5.7.2 Conceptual model validity

The conceptual framework of the 'Individual Patient' model was described in 11 Stages as shown in Table 5-2. The validation of these parts involves validating the model assumptions and its logical and mathematical structure. Different methods and validation tests similar to the 'IV tPA' and 'Endovascular Thrombectomy' models were used to validate the conceptual model. These included: degeneracy test, data relationship correctness test, mathematical and statistical methods, tracing and structured walkthrough. With exception to parts of the model previously validated in the 'IV tPA' and the 'Endovascular Thrombectomy' models, the process of validating the conceptual framework of the 'Individual Patient' model is described below:

5.7.2.1 Validation of the model assumptions

All the six mentioned assumptions were validated by formally obtaining the opinion of team of clinical experts and neurologists. The choice of 270 minutes as the upper time limit to receive tPA treatment, and 360 minutes as the upper time limit to receive endovascular thrombectomy were adopted according to majority of international stroke clinical guidelines (Berkhemer, et al., 2015; Campbell, et al., 2015; Jauch, et al., 2013; Saver, et al., 2015). Also, based on the recent stroke trials (Saver, et al., 2016) all eligible patients first receive IV tPA and then undergo the process of receiving endovascular thrombectomy therapy, which was the basis assumption in conceptualizing the 'Individual Patient' model.

The values assigned to delay time parameters (including the selection of minimum and maximum values) were verified by running face validity and obtaining the opinion of clinical experts. The choice of incrementing delay time parameters by 15-minutes was also validated by clinicians, given the fact that running the model with lower granularity of delay times was not mathematically possible for this model.

5.7.2.2 Validation of model structure/formulation

The logical structure of the conceptual model was validated through checking the mRS probability distributions, numerical relationships in the model, change over time formulation, endovascular thrombectomy eligibility formulation, and DALYs mathematical formulation after both tPA and endovascular thrombectomy interventions. While some of these have been previously validated in Chapter 4, here we discuss the validation process of the new developed parts of the model while referring to different stages of the model building process as described in Table 5-2. These stages can be categorized into two groups: first

group includes Stages 3-8 where we describe the process of formulating the problem, and second group includes Stages 1-2 and 9-11 where we use simulation to generate the outputs of the model for different scenarios, and for different patient groups. While later in this chapter, in the operational validity section we further discuss the validation of the simulation part, here we focus on validating the model formulation developed in Stages 3-8.

mRS probability distributions: This includes generating the patient-specific probabilities of achieving mRS category at baseline onset-to-tPA treatment time (Stage 3), estimating the probabilities of achieving a specific mRS after IV tPA intervention (Stage 4), and estimating the probabilities of achieving a specific mRS after endovascular intervention (Stage 6). As described in Table 5-2, in Stages 4 and 6 we adopted the validated analytical expressions of the odds ratio lines respectively from the 'IV tPA' model and the 'Endovascular Thrombectomy' model. In Stage 3, we adopted the validated logistic regression model from the 'Endovascular Thrombectomy' model.

Change over time formulation: This includes Stages 4 and 6, which were developed by adopting elements of the 'IV tPA' and the 'Endovascular Thrombectomy' models previously validated in Chapter 4. Additionally, we used three set of 1000 normally distributed random numbers to sample according to an underlying Normal distribution from the feasible space of the odds ratio lines bounded by 95% confidence interval limits. As a result, we avoided underestimating or overestimating the effect of time delays on treatment benefits regarding both interventions.

Endovascular thrombectomy eligibility formulation: For estimating the eligibility of the patients to receive endovascular thrombectomy, we used LVO and stroke severity as two key parameters to build a prediction model. As mentioned earlier, this choice of parameters was based on the opinion of a neurologist team, since there was no adequate prediction tool with enough accuracy to be used for this purpose. To build this model, we used the combined dataset obtained from Royal Melbourne Hospital and Box Hill Hospital, and randomly selected 80% of data to construct a binary logistic regression model to estimate the patient-specific probabilities of LVO as a dependant variable and baseline NIHSS as an independent variable. Once we generated these probabilities, we used the Receiver Operating Characteristics (ROC) analysis to identify the cut-point value of the LVO (area under ROC curve at cut-point = 0.78), used as a diagnostic tool to estimate the eligibility of the patients to receive endovascular thrombectomy. We then applied the LVO prediction model in the remaining 20 percent of the dataset by using the cut-off point generated earlier to split the probabilities into two groups. Lastly, we compared the predicted probabilities of the new

developed model with that of the observed probabilities in 20 percent of data, using the ROC analysis threshold (with 0.85 under the ROC area). The probability estimated by this model was used in Stage 8 of the model building process described in Table 5-2, for specifying the eligibility of the patients to receive endovascular thrombectomy.

While we used LVO and NIHSS as two key parameters to develop this prediction model, other studies globally are investigating development of more accurate prediction methods. In some of these studies, researchers and clinicians suggest to use Los Angeles Motor Scale (LAMS) as a key parameter for specifying the eligibility of the patients to receive endovascular thrombectomy (Holodinsky, et al., 2017). For validation purposes, we compared the results of our prediction model with that of the model developed based on using the LAMS parameter.

DALYs mathematical formulation: Different parameters used to estimate DALYs were adopted from the validated 'IV tPA' model, described earlier in Stages 5 and 7 of Table 5-2.

Lastly in the same table, Stages 1, 2, 10, and 11 describe the process of designing the conceptual framework to run the model simulation. The validity of the experimental design related to this is discussed in details in Operational validity section of this chapter.

The summary of these validation methods and techniques used to obtain the conceptual model validity of the 'Individual Patient' model has been provided in Table 5-12.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Degeneracy test	Based on: (Gass, 1983; Sargent, 2013)		
Delay time assumptions	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	We assumed 40-minutes in-hospital delay time to receive endovascular thrombectomy in the ECC. This value was selected based on the opinion of a neurologist team.	Increased credibility of the model as the vast majority of the stroke care units will consider the time delay appropriate.
	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual model.	For T_1 and T_2, we assumed 60 and 270 minutes respectively as the minimum and maximum delays. The lower ranges for these parameters were selected based on the opinion of a neurologist team. The upper time limits for these parameters are the evidence-based values adopted by majority of international stroke guidelines. The upper and lower range for T_3 were also selected based on the opinion of the neurologist team.	Increased credibility of the model as most clinicians will consider these values appropriate.
	An appropriate selection of the internal parameters directly affects the accuracy of the logical behaviour of the conceptual	We incremented the values for T_1, T_2, and T_3 by 15-minutes. We obtained the opinion of a mathematician expert and	While running the model with less granularity of delay time parameters was not feasible for this model, the logical behaviour of the model

	model.	clinicians to check the validity of the values assigned to these parameters.	was reasonable.
Baseline onset-to-tPA treatment time assumption	To ensure that the assigned baseline onset-to-tPA delay time is allowing the model to encapsulate the effect of earlier treatment with respect to IV tPA intervention.	The baseline onset-to-tPA treatment time was set to 270 minutes for the individual patients' data.	Increased credibility of the model in formulating the effect of earlier treatment with respect to tPA intervention.
Data relationship correctness			
Endovascular thrombectomy eligibility probability	To ensure that there is a logical relationship between the parameters used in the prediction model and the probability of receiving endovascular thrombectomy.	LVO and NIHSS were as key parameters to build a predictive parameter, used for estimating the eligibility of the patients to receive endovascular thrombectomy. This parameter choice was validated based on the opinion of clinicians. Also, we compared the results of our prediction model with that of the model developed based on using the LAMS parameter.	This increased the overall precision of the estimates used to generate the probabilities of the patients to receive endovascular thrombectomy therapy, thus increasing the validity of the model.
Tracing	Based on: (Balci, 1994; Sargent, 2013)		

Endovascular thrombectomy eligibility probability	To ensure that the logical behaviour of the prediction model is correct and the required accuracy obtained.	The statistical process of constructing the prediction model was performed separately by different members of the model development team and results were compared for any inconsistency.	Prediction model used to estimate the probability of the individual patients to receive endovascular thrombectomy was verified.
Mathematical and statistical validation methods	Based on: (Balci, 1994; Gass, 1983; Schellenberger, 1974)		
Change over time formulation	To ensure that the equations used to build the conceptual model are accurate enough.	We adopted relevant modelling components of the OR models developed in Chapter 4, to formulate the change over time formulation for the 'Individual Patient' model. Additionally, we used three set of 1000 normally distributed random numbers to sample according to an underlying Normal distribution from the feasible space of the odds ratio lines bounded by 95% confidence interval limits.	Avoiding underestimating or overestimating the effect of time delays on treatment benefits regarding each of the treatment interventions, thus providing correct representation of the relationship between odds ratio and treatment time.
Endovascular thrombectomy eligibility probability	To ensure that the probability equation used as predictive parameter to estimate the eligibility of the patients to receive endovascular therapy is logically correct.	We randomly selected 80% of the combined observational cohort and constructed a logistic regression model to estimate the probability of LVO as a	We ensured that the prediction model constructed based on 80 percent of the cohort was reflecting the nature of the relationships in the remaining 20 percent, therefore being

		predictive parameter to estimate the eligibility of the patients to receive endovascular therapy. The statistical validity of the regression model was evaluated in the remaining 20% of the observational cohort.	valid for the full cohort.

Table 5-12 Validation tests and techniques utilized for conceptual model validation of different components of the 'Individual Patient' model

5.7.3 Computational verification

Similar to the 'IV tPA' and 'Endovascular Thrombectomy' models, this was performed by verifying the computations in Excel and code scripts in Stata as described earlier is Section 4.7.3 of Chapter 4, using debugging, walkthrough and execution tracing techniques.

5.7.4 Operational validity

To achieve operational validity, the outputs of the 'Individual Patient' model were verified to obtain the accuracy needed for the intended use of the model. Additionally, using modelling elements of the validated 'IV tPA' and the 'Endovascular Thrombectomy' models, there was an increased credibility in the outputs generated by this model. Since this model was the first OR model used to provide insights regarding the life-time benefits for the individual patients over two pathways of the hyperacute stroke care system, there was no data available in real-life system to be used for validating the simulation results. Below, we discuss different techniques used to validate the operational model of the 'Individual Patient' model, while the summary of these methods have been provided in Table 5-13.

5.7.4.1 Validation of the model output

The expected DALYs generated for two pathways of the 'Individual Patient' model were compared between different simulation scenarios of the model, for patients with different characteristics to validate the outcomes.

To build the 'Individual Patient' model, we used selected modelling elements of the 'IV tPA' and 'Endovascular Thrombectomy' models which both have been validated previously in Chapter 4. This eventually increased the credibility of the outputs for the 'Individual Patient' model. Additionally, as described previously, for each individual patient with a given scenario, we ran 1000 simulations to increase the credibility of the outputs generated by this model.

5.7.4.2 Validation of the model application

The intended use of the model and its limitations were validated by the model developers to ensure the operational validity of the model as a decision support tool. For our model, these included the following considerations:

1. **Intended model use for patients with different characteristics:** As shown by results of the 'IV tPA' and 'Endovascular Thrombectomy' models developed in

Chapter 4, the benefit of earlier treatment is different for patients with different characteristics. Similarly, for the 'Individual Patient' model it is important to generate the outcomes for different group of patients, thus understanding how patients with specific characteristics can maximize their life-time benefits over two pathways of the hyperacute stroke care system. To achieve this, we ran simulations for 64 males and 64 females, to whom we assigned different age and severities and compared the results for different patients. Even though these characteristics were selected on a basis that they represent wide range of patients, caution should be exercised in using the outcomes of the model for patients with characteristics other than those used in this model.

2. **Intended model use for different scenarios:** For T_1 and T_2, we assumed 60 minutes as the minimum range, and 270 minutes as the maximum range, with 15-minutes interval between values within this range. For T_3, we assumed 35 minutes as the minimum range, and 260 minutes as the maximum range, with 15-minutes interval between the values within this range. For the in-hospital delay time (T_4), we assumed 40-minutes delay for all delay time scenarios. While it was not feasible to generate the results with the higher granularity of delay times, the current results generated by the model for different scenarios were consistent and had a monotonic trend. An exception to this was results of the model generated for very low values of transfer time between ECC and non-ECC, where we noticed sudden changes in the proportion of going to ECC by increasing the values of onset-to-tPA treatment time to the non-ECC, suggesting less credibility of the outcomes generated in that part of the model.

   Additionally, we fix the value of T_4 (i.e. the in-hospital delay time to receive endovascular thrombectomy in the ECC) to 40 minutes for all scenarios. In reality, different stroke care units have different in-hospital delays; thus, caution should be exercised in generalizing the outcomes of this model.

3. **Intended model use for true effect of the IV tPA and endovascular treatment interventions**: In practice, it is not clear for the clinicians how long it takes for the individual stroke patient to fully realizing the effect of IV tPA treatment. Thus, while the goal is to deliver both IV tPA and endovascular thrombectomy interventions to the eligible patients at the earliest possible time, it is not evident how different patients would benefit from each of these interventions separately, if we stretch or shorten the delay time between the two interventions.

4. **Increased credibility of the outputs generated by the model using simulation**: We used 1000 simulation runs to generate the outputs of the model for each patient, and then estimating the proportion that a patient will benefit more by the *Mothership*

pathway over *Drip and Ship* pathway. Using simulations evidently increased the credibility of the outputs generated by this model.

5. **Actual model use to provide insights for the benefits of individual patients**: The 'Individual Patient' model was developed to provide better understanding of the benefits of the individual patients over two pathways of the hyperacute stroke care system. The results of this model can be potentially used by stroke care system, and ambulance service providers to ensure that individual stroke patients gain their utmost benefit by choosing the right stroke care system pathway. We expect that the findings of this model promote design and implementation of policies for more effective and efficient management of the individual stroke patients in the hyperacute stroke care system.

Validation task	Why we performed the validation task	How we performed the validation task	The conclusions/results of the validation task
Output analysis	Based on: (Balci, 1994; Gass, 1983; Sargent, 2001)		
Model output	To identify any unusual behaviour of the model and pin-pointing errors.	We compared the results for different scenarios and for patients with different characteristics to validate the model outputs.	We found errors in the outputs as a result of either incorrect logic or implementation of the model which were subsequently corrected.
Intended use of the model	Based on: (Sargent, 2013)		
Model output	To ensure that the model's outputs are accurate enough for the intended use of the model.	We used selected modelling components of the 'IV tPA' and 'Endovascular Thrombectomy' models to build the 'Individual Patient' model.	All the modelling components of the 'IV tPA' and 'Endovascular Thrombectomy' models used to develop the 'Endovascular Thrombectomy' model were previously validated in Chapter 4. This increased the credibility of the outputs generated by the 'Endovascular Thrombectomy' model.
Model application	To verify the decisions made based on the model outputs.	We discussed the limitations and boundaries of application of the model in Section 5.7.4.2 of this chapter.	Users of the DS model will understand the limitations and will not overgeneralize or use the model outside of its intended use.
Robustness	Based on: (Balci, 1994; Boehm, et al., 1976; Gass, 1983; Myers, et al., 2011; Sargent, 2013; Whitner & Balci, 1989)		
Model output	To check the model's behaviour while changing the parameters and inputs of the	For each individual patient and a given scenario, we ran 1000 simulations to	Increased credibility of the model's outputs.

	model.	generate the model outputs. Out of these runs, we then specified the proportion that the patient will benefit the *Mothership* pathway over *Drip and Ship* pathway.	

Table 5-13 Validation tests and techniques utilized for operational model validation of different components of the 'Individual Patient' model

5.8 Summary and conclusions

In this chapter, we discussed different stages of developing a new OR model used to address the following research question: '*How OR models can be designed, developed, and validated to assist with maximizing the individual patients' life-time benefits over two pathways of the hyperacute stroke care system?*' This was achieved by using selected modelling elements of the previously validated 'IV tPA' and 'Endovascular Thrombectomy' models to build the 'Individual Patient' model in this chapter. Regarding the intended use of the model, this model is categorized as a model for *'investigation and improvement'* as it is used to understand the link between the long-term benefits for the individual stroke patients and a selected stroke treatment pathway, thus providing assistance in maximizing the life-time benefits for stroke patients over two pathways of the hyperacute stroke care system.

While OR models developed in previous chapter were used to reflect on the population benefits regarding two different treatment interventions for stroke patients, the 'Individual Patient' model developed in this chapter was used to better understand the long-term benefits associated with two different treatment pathways for the individual stroke patients. As the result, we found that the long-term gained benefits due to earlier treatment are different for patients with various characteristics. These include patients' age, gender, stroke severity, and treatment delay times before IV tPA and endovascular thrombectomy interventions. It is expected that the findings of this model provide important insights for the clinicians and emergency services providers as they are facing the challenges of redesigning the hyperacute stroke care system since the emergence of new evidence about the effectiveness of the endovascular thrombectomy treatment in late 2014 and early 2015.

The generic validation framework described earlier in Chapter 3 was employed in this chapter to systematically perform data validation, conceptual model validation, computational model verification, and operational validation of the model. Having very limited data on the model behaviour to be used for validating the model outputs, the validation of the model was performed based on critically testing all the model inputs, assumptions, parameters used to develop the model as well as running simulation to increase the credibility of the outcomes generated by the model.

Results obtained from this model can provide assistance in designing an efficient and effective hyperacute stroke care system capable of addressing new treatment needs for the patients.

Chapter 6: Discussion and conclusion

Introduction

In this chapter, we summarize findings, contributions, limitations of the research presented earlier, and outline future directions identified by addressing the research questions. Sections of this chapter are organized based on the three research questions formulated in Chapter 1.

6.1 Research question 1

How OR models can be designed, developed, and validated to provide an improved understanding of the earlier treatment benefits on patients' life-time outcome for two different treatment interventions in hyperacute stroke care system?

To address this research question, we first conducted a literature review in Chapter 2 of this thesis using different search methodologies to find OR stroke related studies reported in OR/MS and clinical literature. We then adopted a conceptual framework proposed by Churilov and Donnan (2012) to classify the papers identified as a result of this literature review in relation to both the specific parts of the stroke care system (problem area) being addressed and the nature and purpose of the OR intervention.

Even though OR models have been applied successfully by researchers to address different problems in the stroke care system, prior to the research reported in this thesis, there was no OR model used to measure the population benefits due to earlier provision of IV tPA and endovascular thrombectomy treatments for the stroke patients. In Chapter 4 of this thesis, we designed and developed two OR models, namely the 'IV tPA' and the 'Endovascular Thrombectomy' models, used to investigate the gained population benefits associated with existing treatment interventions for the stroke patients.

6.1.1 Findings

As a result of literature review classification conducted in Chapter 2, we concluded that OR interventions such as *stroke care process design and performance*, *stroke team scheduling and workforce planning*, and *stroke service planning* were addressed more frequently than other interventions, while there was a lack of research attention in using *stroke units*, *imaging and surgical equipment evaluation* and *selection models* OR interventions to address different problems in the stroke care system. With regard to different problem areas, *stroke prevention*, *pre-hospital*, *stroke unit care*, *rehabilitation* and *social and community*

care fields were among the most addressed areas; while *information and support for stroke patients*, *appropriate management of TIAs*, *appropriate stroke care expertise*, and *financial viability* were among the least addressed areas in the literature.

As a result of the 'IV tPA' and the 'Endovascular Thrombectomy' models developed in Chapter 4, we found that few minutes of earlier treatment in delivering IV tPA and endovascular thrombectomy can be translated into days, weeks, and even months of healthy-life for stroke patients. Following is the list of findings for these OR models:

- Both models are categorized as models for *investigation and improvement* according to Pidd (2010) taxonomy as they are used to provide insights on the effect of time delays associated with IV tPA and endovascular thrombectomy treatment interventions on patients' life time outcomes
- One minute earlier of IV tPA treatment time provides on average extra 1.8 days of healthy life for the stroke patients; while one minute earlier of endovascular thrombectomy provides on average extra 3.2 days of healthy life for the stroke patients. Thus, it was concluded that faster treatment is even more important in the endovascular therapy.
- For both IV tPA and endovascular thrombectomy treatment interventions, female and young patients benefit more by earlier treatment due to their longer lifetime.

6.1.2 Contributions and implications

The literature review conducted in Chapter 2 demonstrated the extent of stroke related OR studies reported in OR/MS literature by different authors and how these studies have used OR interventions to address specific problem areas in the hyperacute stroke care system. The result of this literature review was partially published in a conference paper "*Stroke care systems: can simulation modelling catch up with the recent advances in stroke treatment?"*, in 2015 in the *Proceedings of Winter Simulation Conference* (Keshtkaran, et al., 2015).

The 'IV tPA' model developed in this research, was the first OR model used for investigating the benefits of faster access to IV tPA treatment on patients' life-time outcomes. Findings of this model had significant impacts on increasing the awareness of the public policy decision makers on the importance of faster delivery of the IV tPA treatment to stroke patients. The non-technical overview of this model was presented for a clinical audience in 2014 in the leading journal of the field, *Stroke*, titled *"Stroke thrombolysis; save a minute, save a day"(Meretoja, et al., 2014).* Since its publication, this article has been cited more than 60 times according to Scopus database, at the time of submitting this thesis. This

publication led to a significant media exposure including sources like Bloomberg (Gale, 2014), the Times (Whipple, 2014), Reuters (Seaman, 2014), Herald Sun (2014), and ABC national television news in Australia (ABC News 24, 2014). Moreover, American Heart and Stroke associations produced an infographics encapsulating the findings for the consumers (American Heart Association/American Stroke Association, 2014). The model's findings are also used by the Australian National Stroke Foundation and Victorian Stroke Telemedicine Initiative (State of Victoria, Australia) to advocate for wider use of stroke thrombolysis telemedicine in remote and rural areas (Bladin & Cadilhac, 2014).

Similarly, the 'Endovascular Thrombectomy' model developed in this research, was the first OR model used for investigating the benefits of earlier access to endovascular thrombectomy therapy on patients' life-time outcomes, thus, advocating for the importance of equipping the clinical centres with necessary expertise and facilities for faster delivery of this intervention to stroke patients. The non-technical overview of the 'Endovascular Thrombectomy' model has been accepted for publication in *Neurology* journal (Meretoja, et al., 2017) and authors expect to receive considerable interest by researchers and clinicians by its publication. Both 'IV tPA' and 'Endovascular Thrombectomy' models were validated using the generic validation framework developed in Chapter 3; thus, providing an improved confidence for decision makers to use the recommendation proposed by these models. Discussion on validation of these OR models is provided in Section 6.3 of this chapter in addressing the third research question of this thesis.

6.1.3 Limitations of the research and future directions

Since data used to develop the 'IV tPA' and the 'Endovascular Thrombectomy' models were obtained from different clinical centres and potentially different countries, caution should be exercised before generalizing the results for different populations of stroke patients. To build the 'Endovascular Thrombectomy' treatment, we assumed an average 90 minutes delay between the IV tPA and thrombectomy treatments. In Chapter 4, we validated the outputs of the model to ensure the validity of this delay time parameter used to build the model, however it should be noted that in practice this delay time can be shorter or longer for different clinical centres.

Given the significant effect of small treatment time reductions on patients' lifetime outcomes, further research is needed to investigate how different OR interventions can be employed to further reduce treatment delay times in the hyperacute stroke care system. This can be achieved by using a system approach and continuous improvement practices to shorten both the pre-hospital and in-hospital delays (Fonarow, et al., 2011; Köhrmann, et al.,

2011; Meretoja & Kaste, 2012; Meretoja, et al., 2012; Tilley, et al., 1997). Furthermore, few studies have reported on the effectiveness of using the portable *Computed Tomography (CT)* vehicles and point-of-care laboratories in reducing treatment delay times upon the availability of these services for the hyperacute stroke care system (Walter, et al., 2012; Weber, et al., 2013). Since application of such services implies significant capital investment and personnel training for the system, it is necessary to conduct the cost-effectiveness analysis before promoting the practice change by use of these services. Results obtained by the 'IV tPA' and 'Endovascular Thrombectomy' models developed in this thesis can be used as model inputs to evaluate the feasibility of these services.

6.2 Research question 2

How OR models can be designed, developed, and validated to assist with maximizing the individual patients' life-time benefits over two pathways of the hyperacute stroke care system?

To provide background information to the second research question we conducted a literature review in Chapter 2 of this thesis as discussed in Section 6.1. Then, to address the identified research gap regarding lack of OR models used to investigate the individual patient's benefits associated with different pathways of the hyperacute stroke care system, in Chapter 5 of this thesis we designed and developed the 'Individual Patient' OR model. This model used to address very recent and important questions raised by the clinicians and stroke care providers with the emergence of new evidence about the effectiveness of the endovascular thrombectomy treatment in late 2014 and early 2015, such as "*Should primary stroke centres be bypassed to transport patients to comprehensive centres, even if it means delaying the start of IV tPA? How much delay in bypass is acceptable? How much of a delay to start IV tPA would eliminate the benefit of earlier thrombectomy* (Warach & Johnston, 2016, p. 1266)"?

6.2.1 Findings

Following is the list of findings for the 'Individual Patient' model:

- The 'Individual Patient' model is categorized as a model for *investigation and improvement* according to Pidd (2010) taxonomy as it is used to provide insights on the individual patient's benefits associated with different pathways of the hyperacute stroke care system.

- The long-term gained benefits due to earlier treatment are different for patients with various characteristics. This includes patients' age, gender, stroke severity, and treatment delay times before IV tPA and endovascular thrombectomy interventions.
- Both stroke severity and eligibility of the patients to receive endovascular thrombectomy are functions of the presence of Large Vascular Occlusion (LVO).
- We ran simulations for the total of 3600 scenarios of time delays over 128 individual patients, each simulated 1000 times. Results of this model were reported as proportion of runs when a patient benefits more (loosing less DALYs) by *Mothership* pathway over the *Drip and Ship* pathway.

6.2.2 Contributions and implications

The 'Individual Patient' model developed in this thesis was used to compare the stroke patients' long term treatment benefits associated with different pre-hospital and in-hospital delay times of the *Drip and Ship* and *Mothership* pathways in the hyperacute stroke care system. Results obtained from this model provide insights on how individual patients with different characteristics can maximize their long-term benefits over two pathways of the hyperacute stroke care system.

The 'Individual Patient' model was validated using the generic validation framework developed in Chapter 3; thus, providing an improved confidence for decision makers to use the recommendation proposed by this model. Discussion on validation of this OR model is provided in Section 6.3 of this chapter to address the third research question of this thesis.

6.2.3 Limitations of the research and future directions

The main assumptions and limitations of the experimental results to build the 'Individual Patient' model were as follows:

- We assumed an average 40 minutes in-hospital delay for receiving the endovascular thrombectomy in the endovascular capable centre (ECC). In practice, different clinical centres may have shorter/longer delay times.
- Since it was not feasible to generate the results of this model with higher granularity of delay times, we incremented delay time parameters used to build this model by 15 minutes.
- Lastly, at the time of developing this model, no adequate prediction tool was available to estimate the patients' eligibility for thrombectomy treatment with enough accuracy. Hence, we consulted an expert team of neurologists who advised

on using stroke severity and Large Vascular Occlusion (LVO) as the two main parameters to build a prediction model. Using new prediction methods and eligibility scales (Kamal, et al., 2014; Nazliel, et al., 2008) can potentially increase the accuracy of the outcomes generated by this model.

Other factors at the patients' level, process level, and system level can be conceptualized to improve the precision of the outcomes generated by the model. Regarding the patients' level, an example is comorbidities; regarding the process level, examples are the capacity of the stroke care units in the hospitals, the number of non-endovascular (nECC) and endovascular capable (ECC) centres, and operating days and hours of both nECC and ECC centres; and regarding the system level examples are the financial impacts of different strategies (such as using mobile stroke unit, ambulances with computed tomographic scanners) within the hyperacute stroke care system. To conceptualize all these factors multiscale simulation models (Borshchev, 2013) can be applied to develop more efficient and effective hyperacute stroke care systems.

6.3 Research question 3

What are the conceptual and application issues of conducting comprehensive *validation of an OR model for investigation and improvement in the context of health systems and service operations?* To address this research question, in Chapter 3 of this thesis we provided a discussion on different conceptual and application issues of conducting comprehensive validation of OR models used for investigation and improvement in the context of health systems and service operations. In the same chapter, we also proposed a validation framework that can be used to validate OR models in both health and non-health contexts. We adopted his validation framework in Chapter 4 and 5 of this thesis to validate the three OR models developed in this research.

OR models used to address different decision problems emerging in health systems have often a complex nature, as model developers use a wide variety of data sources and empirical estimates to develop these models. Interactions between different components of these models often lead to complexity on health OR models. Moreover, such models are usually developed to support unique and new investigations, which often lead to designing a new system, improving a system or just providing an understanding of a very complex situation (Pidd, 2010), with the aim of improving the efficiency and effectiveness of the entire system. Even though different authors in OR/MS literature emphasize the importance of validating OR models, as demonstrated by the results of a literature review conducted in Chapter 3,

there is a lack of reported knowledge about practical aspects of how to validate OR models in the context of health systems and service operations.

6.3.1 Findings

We proposed a generic validation framework by reviewing a wide variety of methodological published articles reported by different authors in OR/MS literature over the last three decades. This framework can be used to systematically address the generic aspects of model validity (i.e. *data validity*, *conceptual model validity*, *computational verification*, and *operational validity*) using relevant validation tasks and techniques. The validation process based on this framework consists of addressing the applied validation task, describing the purpose of performing each validation task (i.e. *Why*), the process of validation (i.e. *How*), and the results and conclusions obtained. This validation framework was used to validate three OR models developed in Chapters 4 and 5 in the context of the hyperacute stroke care system.

We found that some of the validation tasks are more generic (e.g. data relationship correctness, tracing, walkthrough, or historical data validation) and can be applied to different types of models (e.g. simulation, optimization, and analytical/statistical modelling), while other validation tasks might be only applicable to a specific type of model. Moreover, we concluded that the importance of a particular validation task is tightly coupled with the intended use of the model; therefore, for models used for *investigation and improvement*, there is often more emphasis on the application of validation techniques used to critically testing all the model inputs, assumptions, and parameters; since often there is lack of empirical data to conduct the 'output-based' validation of such models.

The three OR models developed in this research are categorized as models for *investigation and improvement* according to Pidd (2010) as they were used to explicitly provide insights on the effect of time delays associated with IV tPA and endovascular thrombectomy treatment interventions on patients' life time outcomes. The process of developing these OR models involved using different data bases and parameters obtained from relevant literature with no empirical data available on model behaviour to validate the outputs of the model. Thus, the validation process of these models consisted of critically testing all the model inputs, assumptions, parameters to have a better understanding of the model boundaries and its application.

6.3.2 Contributions and implications

Having validated these complex health OR models, we demonstrated how different aspects of data validity, conceptual model validity, computerized verification, and operational validity can be systematically validated given the complex nature of such models designed for investigation and improvement purposes. This is a novel contribution to OR/MS literature, since as discussed in Chapter 3, even though different authors in OR/MS literature generally agree on the importance of validating OR models, examples from the literature where authors provide a systematic and comprehensive validation of such models is scarce. Since the validation framework proposed in this thesis was developed based on the generic validation techniques and aspects of model validity reported in OR/MS literature, it is not specific to health OR models and can be utilized to validate all different types of models in the field of OR/MS.

Discussion on validation of the 'IV tPA' presented in Chapter 4 of this thesis was published in the *European Journal of Operational Research* in 2016, titled *"Validation of a decision support model for investigation and improvement in stroke thrombolysis"* (Keshtkaran, et al., 2016).

6.3.3 Limitations of the research and future directions

As demonstrated by results of the literature review conducted in Chapter 3, there is a lack of reported knowledge about the practical aspects of how to validate an OR model in the context of health systems and service operations. We believe the validation framework proposed and used in this thesis to validate OR models with investigation and improvement purposes can be used with some refinements for the validation of OR models with other purposes as classified by Pidd (2010). Moreover, it seems plausible that this validation framework can be used to validate models in the context of simulation, optimization, and analytical/statistical modelling – we suggest these hypotheses as potential directions for future research. Also, the question of the additional validation techniques that can be used for each modelling methodology in this framework is an important subject that can be further investigated. Lastly, since this framework was developed based on the generic validation techniques reported in OR/MS literature, it may have a wider applicability beyond the health systems OR - it is likely that various validation aspects may require different amount of attention depending on the specific application area, which could also be the topic of future research.

6.4 Summary

This research investigated the issue of design, development and validation of OR models used for investigation and improvement of the hyperacute stroke care systems. Two of the OR models developed in this research used for the first time to quantify the effect of faster treatment on patient life time outcomes. Insights obtained from these models are supposed to directly lead to an increased awareness of public policy decision makers, stroke campaigns, and stroke care system providers of the importance of faster treatment for stroke patients. The third OR model developed in this research addresses some of the most burning questions raised by clinicians in the field to support more effective and efficient provision of the services to hyperacute stroke patients. To conclude, all three OR models developed and validated in this thesis are novel and contribute to both OR/MS and clinical literature.

List of abbreviations

ABS: Agent Based Simulation

AF: Arterial Fibrillation

AHA: American Heart Association

CI: Confidence intervals

CSS: Canadian Stroke Strategy

DALYs: Disability-adjusted Life years

DEA: Data Envelopment Analysis

DES: Discrete Event Simulation

DS: Decision Support

DWs: Disability Weights

ECC: Endovascular Capable Centre

EEAST: East of England Ambulance Service Trust

GBDP: Global Burden of Disease Project

IA: Intra Arterial

IQR: Interquartile Range

IHD: Stroke and Ischemic Heart Diseases

IV tPA: Intravenous Tissue Plasminogen Activator

JAMA: Journal of the American Medical Association

LAMS: Los Angeles Motor Scale

LE: Life Expectancy

LVO: Large Vascular Occlusion

MCS: Monte Carlo Simulation

mRS: modified Rankin Scale

MSUs: Mobile Stroke Units

MRI: Magnetic Resonance Imaging

NIHSS: National Institute of Health Stroke Scale

Non-ECC: non-Endovascular Capable Centre

NINDS: National Institute of Neurological Disorders and Stroke

OR: Operations Research

OR/MS: Operations Research/Management Science

QALYs: Quality-adjusted Life years

ROC: Receiver Operating Characteristics

SD: System Dynamics

SITS: Safe Implementation of Treatment in Stroke

TIA: Transient Ischaemic Attack

YLL: Years of Life Lost due to pre-mature death

YLD: Years of Life Lost due to Disability

WHO: World Health Organization

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