MASTER THESIS

Early Health Technology Assessment of the Ultrasound Photoacoustic Needle for guiding a ventricular catheter

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Preface

Beste lezer,

Afgelopen jaar heb ik mijn Industrial Engineering & Management Master thesis uitgevoerd bij onderzoeksgroep Health Technology and Services Research aan de Universiteit Twente. Voor mijn opdracht heb ik, onder begeleiding van van Erik Koffijberg en Derya Demirtas, een early health technology assessment uitgevoerd voor de ultrasound photoacoustic needle (USPAN). Het device wat ik heb helpen ontwikkelen gedurende mijn master Biomedical Engineering.

First of all, I would like to thank the members of the exam committee for reading and reviewing my thesis. Moreover, I would like to thank Erik and Derya for their supervision during this assignment the last years. Erik, who was involved from the start of this project, and Derya, later on. It was hard to combine finishing this thesis and starting up a PhD. But I'm glad for your patience and time! Daarnaast wil ik Kuan Kho, neurochirurg bij het MST, bedanken voor de mogelijkheid om mee te kijken bij de operaties en zijn klinische input. Ook wil ik een aantal vrienden, bedanken die met zorg delen van mijn thesis doorgelezen hebben.

Met deze thesis rond ik niet alleen mijn afstudeeropdracht, maar nu ook echt mijn studententijd in Enschede af. Ik heb met veel plezier gestudeerd aan de UT, ook stage mogen lopen in Zweden. Daarnaast heb ik veel nieuwe vrienden gemaakt en contacten opgedaan, bij verschillende samenwerkingen, het doen van commissiewerk, tijdens mijn bestuursjaar en in mijn tijd bij mijn dispuut. Ik wil jullie graag allemaal bedanken voor het onvergetelijk maken van deze tijd!

Rianne

Real-time image guidance of a ventricular catheter to optimize the placement in the ventricles may increase correct ventricular catheter placement in hydrocephalus patients. To achieve this, a forward-looking Ultrasound Photoacoustic Needle (USPAN) was proposed. This USPAN is also expected to lower the number of insertions required to place the ventricle catheter inside the ventricle. However, no assessment has been performed on this device's suitability for the current market. Therefore, an early health technology assessment (HTA) could help to inform the developers about the current fit of the USPAN for the market. The early HTA starts with an analysis of the clinical conditions, after which the headroom is determined.

The goal of this research was to determine the headroom of the USPAN in the Netherlands, resulting in the main research question: What is the headroom of the USPAN for hydrocephalus patients who undergo a shunting procedure in the Netherlands?

To answer this question, first, the clinical conditions of hydrocephalus patients undergoing a shunting procedure were determined with a literature study. The hydrocephalus population is mainly classified into two age groups: paediatric patients and adults. The paediatric patient population is approximately 1.3x smaller than the elderly population. However, the number of revisions, and thus the total number of surgeries, is higher in paediatric patients than in adults. Considering that the USPAN impacts the surgical procedure, we expect the USPAN to have the highest impact in the paediatric patient group, as the highest impact factor is the total number of surgeries required. The USPAN can potentially reduce the number of insertion attempts required for placing the ventricle catheter. However, the effects of this are inconclusive in the literature. Literature was also inconclusive about post-operative complications due to shunting surgery.

Expert elicitation was performed based on a questionnaire to quantify the complications due to shunting surgery or complications induced by the number of catheter insertion attempts. The questionnaire showed that post-operative complications are less than 20%. No conclusive results were found about the complications caused by the number of catheter insertion attempts.

A semi-Markov model was developed to obtain the costs and QALYs related to both surgical strategies: current care (free-hand technique) and with use of the USPAN. The model structure was based on the care pathway of hydrocephalus patients, which was derived from interviews with neurosurgeons. Moreover, the model structure was verified by a neurosurgeon. Subsequently, model parameters were derived from literature and expert elicitation. Model simulations were performed to obtain the QALYs and costs for both strategies over a time horizon of 5, 10 and 20 years. The simulation outcomes determined the $\Delta costs$ and Δ quality adjusted life years (QALYs) between both strategies to calculate the headroom. The headroom for the maximum reimbursable price (MRP) with a WTP threshold of €50,000 for a time horizon of €9,420, €14,219, and €20,905. Taking into account the prevalence of paediatric hydrocephalus in the Netherlands, the headroom is €4.5 million, €6.8 million and €10.0 million, respectively. If the manufacturing costs are considered, the headroom lowers compared to the MRP. The most probable manufacturing costs are €1200, resulting in a headroom of €7602. When the probability of optimal placement is considered with the same manufacturing costs, the headroom is positive for all optimal catheter tip placement probabilities above 0.71.

Altogether, this research shows that the USPAN might have benefits in the clinic based on the headroom calculations. However, the headroom is an iterative process, so the model parameters need to be updated and more accurately determined to get a more accurate outcome for the headroom.

Contents

1 Introduction

Hydrocephalus is a condition where the cerebral ventricles are enlarged, which causes an increase of intracranial pressure [1]. It is most often caused by an overproduction of cerebrospinal fluid (CSF), which can occur either congenital or acquired. The most frequent symptoms that children presenting hydrocephalus have are headaches, double vision, poor balance, urinary incontinence, personality changes, and/or mental impairment [2]. In infants, a rapid enlargement of the head is a typical symptom [3]. The most dominant patient groups are pediatrics ($\leq$ 18 years) and elderly ($\geq$ 65 years), with a global prevalence of, respectively, 88 out of 100,000 pediatrics and 175 out of 100,000 elderly [4]. In adults (18 - 64 years) the prevalence is much lower, with only 11 out of 100,000 adults.

The standard treatment of hydrocephalus is the insertion of a valved ventricular shunt by freehand placement [2], shown in Figure 1.1. A shunt is a permanent and life long implant, which contains a ventricular and distal connected by a valve. The ventricular catheter is placed into the cerebral ventricle, and is connected via the valve to the distal catheter, where the excess of CSF is drained into the abdomen or chest.

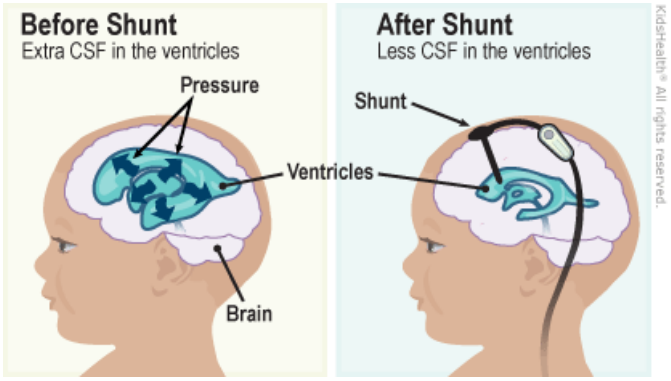

Figure 1.1: Brain ventricles before and after shunting [5]

Suboptimal final placement of the ventricular catheter is ranging 12.3 - 40 % of the shunt placements [6, 7]. This results in a higher risk of shunt failure, which is 4.9 (95% CI = 1.3 - 18.9) times higher for incorrectly placed shunts than for correctly placed shunts [8]. If shunt failure occurs, the shunt needs to be revised which has a high impact on the quality of life of the patient and extra surgery costs are involved [9]. Additionally, the average number of attempts needed for successful shunt placement is respectively 2.4 (SE = 0.7) and 1.4 (SE = 0.5) in junior and senior neurosurgeons[1] [10].

Techniques to improve the placement of the ventricle catheter are: The Ghajar Guide, neuronavigation, and ultrasound guidance [11, 12, 13, 14]. The Ghajar Guide is a device that allows a fixed-angle path towards the ventricle, where the choice of the angle is based on the skull surface. It is highly portable, however, the trajectory is determined without prior knowledge about the location of the ventricle, which is patient specific. Neuronavigation is a technique which uses a preoperative CT or MR image to guide the ventricular catheter during insertion. It gives more visibility during the otherwise 'blind' freehand procedure, and a dynamic choice of the trajectory is possible. The drawbacks of this technique are the relative long setup time and the fact that image guidance relies on a static preoperative image rather than real-time imaging. Furthermore, ultrasound guidance needs a relative large hole in the skull compared to the catheter insertion point. The ultrasound probe is placed on the cortex to guide the ventricle catheter

[1] Little is known of the morbidity associated with the number of attempts.

real-time to the ventricle. The major drawbacks are additional setup time and the relative large hole, which gives a higher probability of infection.

An ideal technique for guiding the ventricular catheter would provide real-time feedback of the location of the ventricle and allow different insertion angles of the ventricular catheter. Moreover, the technique would fit closely into the current practice, have a relative short setup time, and have low purchase and usage costs.

One design design that fits all criteria is the design of the ultrasound photoacoustic needle (USPAN) which is proposed within the Imaging Needle project (coordinator S. Manohar, [15]), a project within the Multi-Modality Medical Imaging Group (M3i) at the University of Twente (UT). The USPAN is a miniature forward-looking ultrasound probe, which fits within the ventricular catheter and provides real-time feedback of the location of the ventricle using ultrasound. The project is funded by Department of Biotechnology (DBT), Government of India and the Netherlands Organisation for Scientific Research (NWO) / the Netherlands Organisation for Health Research and Development (ZonMw). The technologies developed are intended for resource-strapped world regions, and are expected to be inexpensive while being effective.

The focus of this research lies on a) the development, fabrication and testing of the first prototype of the USPAN, to provide information about the working principle of the USPAN, and b) performing an early health technology assessment to provide information about the potential value of this innovation in the early stage of product development.

This thesis starts with an explanation of the clinical context regarding hydrocephalus. Next, the development, fabrication and testing of the first prototype of the USPAN is addressed in *Part I: Biomedical Engineering*. Thereafter, the early Health Technology Assessment will be addressed in *Part II: Industrial Engineering & Management*. Finally, an overall conclusion and discussion is drawn.

2 | Clinical context

In this chapter background information of the anatomy of the human brain, hydrocephalus, the current treatments and the possible ventricular catheter positions is given, which is relevant to define the requirements of the USPAN and acoustic brain phantom, and understand the clinical problem for the early Health Technology Assessment. In section 2.1 the anatomy of the human brain is explained. Next, hydrocephalus and its causes are explained in section 2.2. Followed by possible treatments in section 2.3.

2.1 | Anatomy of the human brain

The brain is an organ which functions as the centre of the nervous system, together with the spinal cord it makes up the central nervous system (CNS). The brain controls most of the activities in the human body. It is located in the head, close to the sensory organs, such as vision. The brain consists primarily of three parts: the cerebrum, the brain stem and the cerebellum. The cerebrum is formed by two cerebral hemispheres, which are separated by a groove. [1]

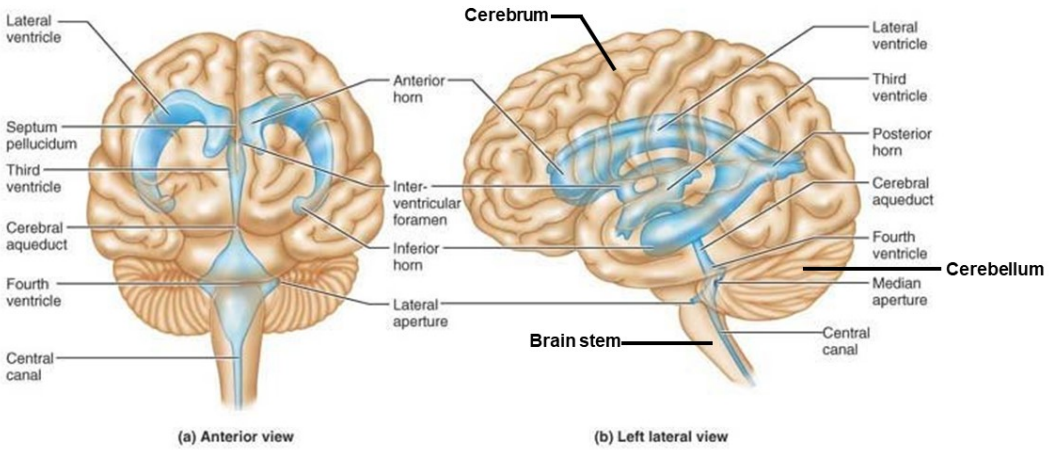

Figure 2.1: The anatomy of the human brain with the primarily parts and the ventricular system, adapted from Marieb et al. [1]

Within the cerebrum the ventricular system of the brain is located. It consists of four freely communicating cavities: The two lateral ventricles, the third ventricle, and the fourth ventricle. The two lateral ventricles are located deep within the left and right cerebral hemisphere, and separated by the septum pellucidum. Both lateral ventricles are connected with the third ventricle, which turns into the fourth ventricle, which is located between the brain stem and the cerebrum, and connected with the subarachnoid space, which forms a protective layer around the brain and spinal cord. [1, 16] Figure 2.1 shows the primarily parts and ventricular system of the human brain. The ventricles are filled with

cerebrospinal fluid (CSF), which transports body fluids found outside the cells [1]. In Figure 2.2 all layers covering the human brain are shown. The CNS is covered with a protection membrane, called meninges. The meninges are formed out of three different layers: dura mater, arachnoid mater, and pia mater, which are the outer, middle, and inner layer, respectively [1, 17].

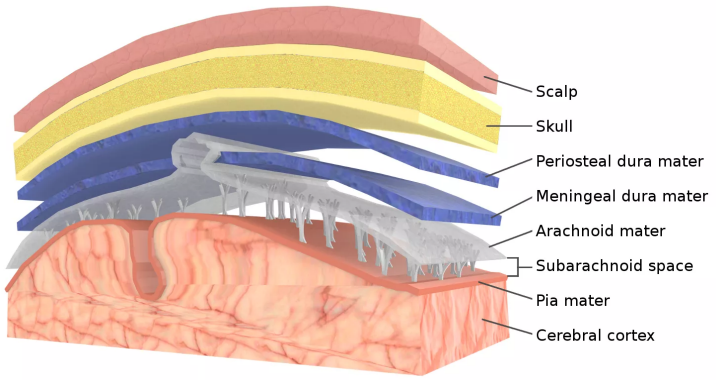

Figure 2.2: Cross-section of the layers of the brain from scalp up to cerebral cortex [17]

2.2 | Hydrocephalus

Hydrocephalus is a condition where an excess of CSF causes an increase in intracranial pressure (ICP) in the ventricles and/or subarachnoid space of the brain, which results in enlargement of the ventricles or subarachnoid space. [3] In Figure 2.3, an MR image of a hydrocephalus patient is shown, where in the left image the lateral and fourth ventricle are enlarged. In the right image the patient is shown after shunting, which leads to decompression of the ventricular system.

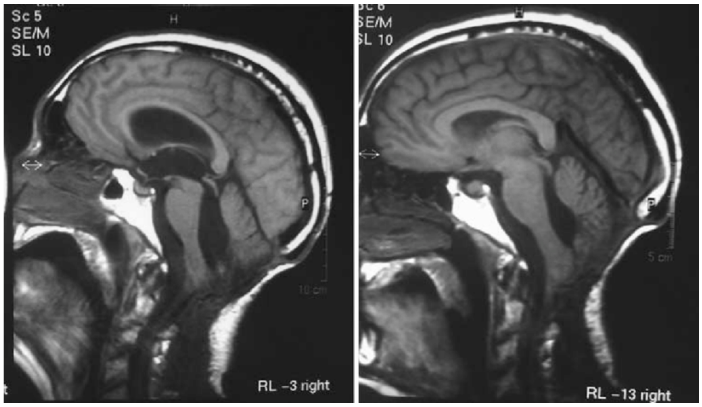

Figure 2.3: MR image of the brain. Left: communicating hydrocephalus showing an enlarged lateral ventricle and fourth ventricle. Right: decompression of the ventricular system after ventriculoperitoneal shunting [18]

Hydrocephalus can be caused by a blockage of CSF flow in the ventricular system or by inadequate re-absorption of CSF fluid, respectively obstructive/non-communicating hydrocephalus or non-obstructive/communicating hydrocephalus. Moreover, it can be caused by congenital or acquired disease [3, 19]. In Table 2.1 an overview of the diseases classified by pathology and etiology is given.

Table 2.1: Hydrocephalus classification based on: obstructive, communicating, congenital, and acquired [2, 4, 20, 3]

	Obstructive	**Communicating**
Congenital	Aqueductal stenosis Dandy Walker cysts Arachnoid cysts Vascular malformation Genetic/metabolic	Chiari malformation Encephalocele Venous congestion: craniosynostosis, achondroplasia Genetic/metabolic
Acquired	Tumour Septae after bleeding/infection	Infection Subarachnoid haemorrhage Venous hypertension Meningitis carcinomatosis Over production

Normal pressure hydrocephalus (NPH), a different class of hydrocephalus, cannot be classified as obstructive or communication hydrocephalus. The ventricles are enlarged, and there is an increase of ICP. However, this increase is not as significant as in the other hydrocephalus types, which is why it is called 'normal'. NPH has often no clear cause, and is mostly diagnosed in elderly. [3]

2.3 | Hydrocephalus treatments

Treatment of hydrocephalus depend on a several factors, namely: etiology, severity, age of patient, and response to previous treatments. The two most performed treatments are, implantation of a shunt and endoscopic third ventriculostromy (ETV).

Shunt surgery Patients with communicating hydrocephalus, including NPH, or hydrocephalus patients who undergone previous surgery, such as ETV, but still suffer from an increase in ICP are treated with shunt surgery. A shunt consist out of three parts: a ventricular/proximal catheter, a valve, and a distal catheter. First, a point of insertion is determined, at this position a burr hole is made into the skull and an opening is cut into the meninges. Next, the distal drain is placed underneath the skin from the burr hole towards the peritoneal cavity (ventriculoperitoneal shunt (VP shunt)) or right atrium (ventriculoatrial shunt (VA shunt)). With a stylet, shown in 2.4 the ventricular catheter is placed by freehand from the cortex, through the cerebral hemisphere into the lateral ventricle. The valve, which is placed under the skin against the skull, connects both catheters and controls CSF drainage. If the ventricular catheter is inserted and incorrect placed, it is not possible to change the track. To obtain a better placement, the catheter should be reinserted.

In Figure 2.4 six insertion points are shown. Kocher's point is the most popular insertion point, in which a penetration depth of approximately 5 cm from the cortex until the frontal horn of the lateral ventricle is reached. In general, the ventricular catheter is placed in the right cerebral hemisphere which corresponds usually to the nondominant hemisphere. Moreover, this region has a reduced amount of vascularization, according to the knowledge of Dr. Kho, neurosurgeon at the MST hospital, and no major blood vessels. The accuracy of cannulation is relative low, with inaccurate placement up to 40 %. [21, 6] Keen's point is followed, and still increasing in popularity, especially in elective shunt placement. The penetration depth from the cortex to the trigone of the lateral ventricle (right in front of the posterior horn) is approximately 4 to 5 cm. Even though successful cannulation is reported, no clinical evidence is found on the accuracy of insertion. [21]

Techniques to improve the placement of the ventricle catheter are: The Ghajar Guide, neuronavigation, and ultrasound guidance [11, 12, 13, 14]. In the introduction (Chapter **??**) the advantages and disadvantages of these techniques are explained.

Endoscopic third ventriculostomy Endoscopic third ventriculostomy (ETV) is mostly performed in patients with obstructive hydrocephalus. Via a burr hole a tube is free hand placed into the lateral ventricle. A neuroendoscope enters the ventricle via the tube, and visualize the anatomy of the ventricle

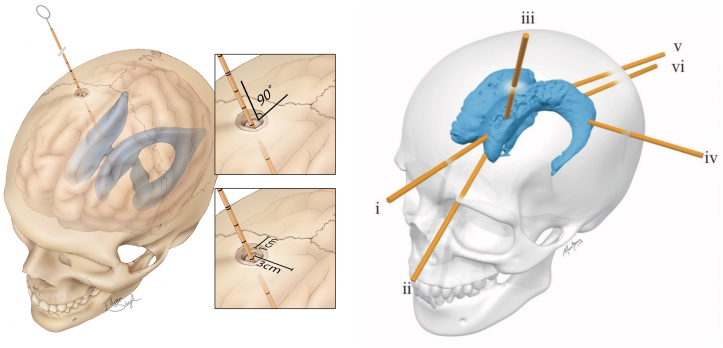

Figure 2.4: Schematic overview of shunt insertion points: i Kaufman, ii Tubbs, iii Kocher, iv Keen, v Frazier, vi Dandy [22]

and floor of the third ventricle. A hole is punctured into the floor of the third ventricle to make a new passage to drain CSF. [3]

Part I

Industrial Engineering & Management

3 | Introduction

In the general introduction of this thesis (Chapter 1), the ultrasound photoacoustic needle (USPAN) is introduced. The ultimate goal for the USPAN is to 1) lower the number of insertion attempts of the ventricular catheter and 2) increase the accuracy of the ventricular catheter's tip location inside the brain's ventricle compared to the free-hand technique (described in Chapter 2). Recently developed miniature ultrasound transducers try to obtain this goal by providing real-time imaging of the ventricles. However, these transducers do not fit within the burr hole. Therefore, a larger burr hole must be drilled in the skull, resulting in a higher risk of infection [23, 24, 25].

The USPAN uses state-of-the-art technical principles to transmit and receive ultrasound waves. A laser-induced ultrasound (LIUS) transmitter allows for simpler electronic circuits to be used compared to current ultrasound devices. The transmitter can easily be fabricated on a miniaturised scale and can image up to the ventricle depth. A double-ring sensor is a highly forward looking-probe which receives only the on-axis ultrasound waves. The expectation is that the combination of the LIUS transmitter with a double-ring sensor would result in a miniaturised, highly forward-looking probe that can detect the brain's ventricle in real-time. The developers aim to replace the stylet used in the free-hand technique with the USPAN. Figure 3.1 shows a schematic drawing of the USPAN. A detailed description of the technical principles and specifications of the USPAN can be found in Part **??** of this thesis.

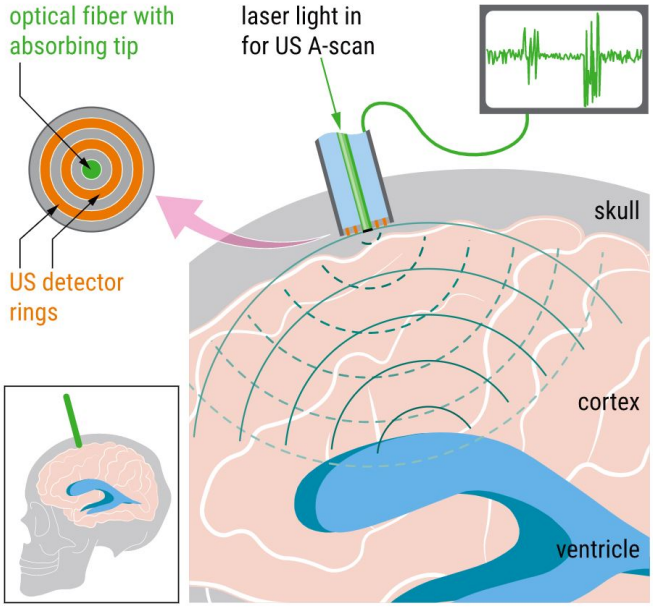

Figure 3.1: Schematic overview of the USPAN positioned at the cortex. *Top left*: a frontal view of the USPAN is shown. *Bottom left*: USPAN insertion from Kochers' point is shown. *Right*: LIUS transmission and detection by the double ring sensor read out by an A-scan.

3.1 | Problem description

The USPAN is a medical device under development on which the first proof of principle has been performed (See Part I). However, no assessment has been performed on this device's suitability for

the current market. Therefore, an early health technology assessment (HTA) could help to inform the developers about the current fit of the USPAN for the market. Additionally, an early HTA could help the developers decide on specific features or minimal clinical performance to compete with existing products [26].

An early HTA is an iterative evaluation process performed during technology development before the standard (regular) HTA is performed [26, 27]. An overview of an early HTA framework introduced by Cosh et al. *et al.* and adapted by Markiewicz *et al.* is shown in Figure 3.2 [28, 29]. The framework starts with an analysis of the clinical conditions, such as prevalence, incidence, long-term health benefits, and competitor treatment. The analysis will help to structure the product features and potential but does not quantify the decision alternatives or include the decision uncertainty.

The second step is to determine the 'headroom', which is the maximum reimbursable price (MRP) of a product by using the current willingness-to-pay threshold combined with the maximum theoretical health benefits provided by the technology [30, 29]. The headroom analysis forces developers to think about the added value of their medical product from a business perspective, as well as the expected added value of their product for society [29]. A major advantage of the headroom analysis, compared to full economic modelling, is that only limited data are needed to derive preliminary results. These data can be derived from literature and/or expert elicitation [31]. Moreover, the headroom method could inform the developers to identify the parameters that drive their device's future value and analyse the parameters' uncertainty by performing a sensitivity analysis [32]. Furthermore, the headroom calculation can be updated with more accurate estimates of parameters or additional parameters at the early stages of development, thus iteratively and efficiently decreasing the overall decision uncertainty [29].

The headroom analysis starts with calculating the effectiveness gap between the current procedure and the procedure with the new medical device. Effectiveness is mainly expressed in Quality-Adjusted Life Years (QALYs), a measure of preference or value that an individual or society places upon a particular health state. QALY takes the quantity of life in years, in terms of survival or remaining life expectancy, and the health-related quality of life measured by health utilities [26]. The range in which the QALY is reported is between 1, perfect health, and 0, death. The next step is to estimate a maximum reimbursable price (MRP) for a medical device that can be justified by the willingness-to-pay (WTP) threshold. This threshold represents the societal WTP per QALY, and is country dependent. In the Netherlands, the WTP ranges from €20,000 to €80,000, depending on the burden of disease [33]. In hydrocephalus patients, the WTP threshold is €50,000. Subsequently, the expectations of the health service cost compared to the current golden standard in clinical practice should be calculated. With the estimation of the intended impact of the new device on the health service costs and QALYs, a standard incremental cost-effectiveness ratio (ICER) equation can identify the MRP. The calculation of the headroom (h) will be as follows:

$$h = \lambda \times \Delta QALY - \Delta costs \tag{3.1}$$

where λ is the WTP, $\Delta QALY$ is the difference in QALYs due to the use of the new device compared to the current golden standard, and $\Delta costs$ are the difference in expected health service cost of the new device compared to the current golden standard.

Based on the results of the headroom calculation, the developers could proceed with developing the new device if the expected production and operation costs are lower than the anticipated headroom. When the headroom is insufficient, this may justify a recommendation to revisit the development of the new medical device or to stop further development and invest in other devices more likely to produce societal value [34]. Finally, the return on investment can be estimated using the headroom, likely device production costs and expected sales volume, discounted over the time horizon of the device use [28]. At the moment, little information about the clinical conditions related to the current procedure and USPAN procedure is available by the developers. The imaging needles project proposal was technology-driven, with sparse clinical information. A brief clinical context of the USPAN can be found in the project proposal [15]. Therefore, the starting point of the early HTA will be to determine the clinical conditions of hydrocephalus patients undergoing a shunting procedure. Next, the costs and QALYs with the current procedure and with use of the USPAN will be determined, after which the headroom will be calculated.

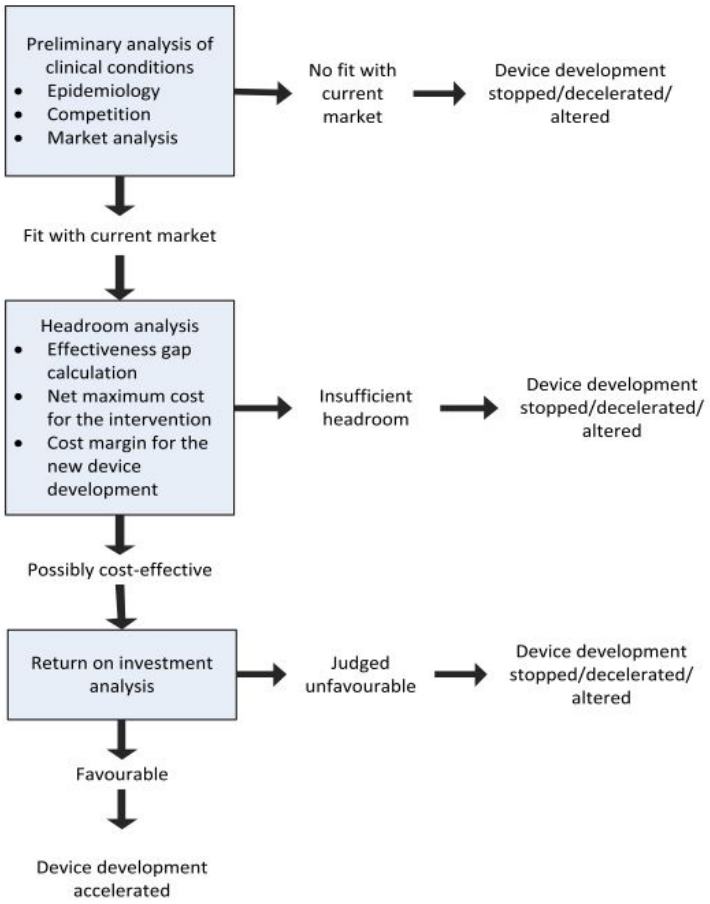

Figure 3.2: Flowchart for product development decisions of new medical technologies [29]

3.2 | Motivation and research questions

The imaging needle proposal describes that in India (the country of origin of one of the project partners) and other low- and middle-income countries surgical care is inadequate and remains inaccessible to the majority [15]. In such countries, minimally invasive surgery will be beneficial because these procedures often result in lower amount of infections and an earlier return to work. These countries, however, have no access to advanced imaging devices, such as neuronavigation. The imaging needle consortium, therefore, aims to develop surgically guidance technology, such as the USPAN, which has the potential to enhance minimally invasive surgery in resource-limited settings.

Data on the costs and QALYs of the current care of hydrocephalus patients in low- and middle-income countries is needed to calculate the headroom of the USPAN. However, data from these countries is hard to access since it is poorly reported. Also, data from India for this research was unavailable, making it impossible to calculate the headroom. However, after interviews with two neurosurgeons from the Netherlands, the USPAN can also be advantageous in surgery in the Netherlands, because of the presumable ease of use, short set-up time, and low costs compared to neuronavigation. In contrast to the free-hand technique, the USPAN gives added information because of the real-time feedback. Therefore, the core problem we address during this research is to inform the developers about the clinical and commercial potential value of the USPAN only in the Netherlands. The developers aim to use the device for hydrocephalus patients. Therefore, it is decided to focus this research on this disease, which will be explained in detail later on. Consequently, this results in the following main research question:

What is the headroom of the USPAN for hydrocephalus patients who undergo a shunting procedure in the Netherlands?

Before the main research question can be answered, multiple steps need to be taken. The main research question can be divided into multiple sub-questions, which each help to answer the main research question. Each chapter answers a specific sub-questions:

Clinical conditions - Chapter 4

I - What could be the impact of the USPAN on both the current surgical procedure and care pathway of the hydrocephalus patient group who might benefit the most from the USPAN?

(a) *What clinical conditions can impact the quality of life of hydrocephalus patients?*

(b) *What is the impact of the accuracy of the ventricular catheter's tip location and the number of insertion attempts of the ventricular catheter on the quality of life of hydrocephalus patients?*

(c) *Which hydrocephalus patient group might benefit most from the USPAN?*

(d) *What is the current care pathway of hydrocephalus patients who undergo a shunting procedure?*

Expert elicitation - Chapter 5

II - Which information about the clinical conditions of hydrocephalus patients who received a shunt could not be derived from the literature?

(a) *How can this missing information from literature be determined?*

Model design - Chapter 6

III - What are the requirements of a model which reflects the care pathway of hydrocephalus patients to determine the effectiveness gap and health services costs difference between the current procedure and the procedure with the USPAN?

(a) *Which type of model can be used?*

(b) *What assumptions are needed to obtain a simplistic and realistic model?*

Model parameters - Chapter 7

IV - What model parameter values are used for the model to determine the effectiveness gap and health services costs differences between the current procedure and the procedure with the USPAN?

(a) *What model parameter values are used with the current care?*

(b) *What model parameter values are used with the procedure with the USPAN?*

(c) *What is the uncertainty of the model parameter values?*

Headroom analysis - Chapter 8

V - What are the results of the headroom analysis of the USPAN?

(a) *What are the results of the headroom analysis of the USPAN compared to the current procedure?*

(b) *What are the results of the headroom analysis of the USPAN in various scenarios?*

(c) *What is the impact of the uncertainty range of the model parameter values on the headroom results?*

3.3 | Thesis overview

This research is structured by providing answers to each sub-research question in the assigned chapters. After answering the sub-research questions, the results are discussed in Chapter 9, and the main question is answered in Chapter 10.

4 | Clinical conditions

In this chapter, the first sub-question is answered: *What could be the impact of the USPAN on the current surgical procedure and care pathway of the hydrocephalus patient group that might benefit the most from the USPAN?* This chapter is divided into three sections contributing to answering this question. First, the characteristics of the hydrocephalus population are described in section 4.1. Next, section 4.2 describes the current care pathway of hydrocephalus. Subsequently, a literature review to determine the complication in current hydrocephalus patients to obtain the expected long-term health benefits of using the USPAN is provided. Finally, this chapter is closed by section 4.4, which answers the first sub-question.

4.1 | Population

Hydrocephalus occurs among all age categories but is mainly classified into paediatric patients and adults. Paediatric patients are all patients younger than 18 years old, including infants, children, adolescents and young adults. Adults incorporate the group adults (18 to 64 years) old and elderly (>65 years old). However, some articles prefer to focus only on elderly. The prevalence and etiology of hydrocephalus among all age categories are described below.

4.1.1 | Prevalence

The prevalence of hydrocephalus in paediatrics has been estimated to range from 0.8 to 81 per 10,000 live births [35, 36, 4, 37, 38, 39]. This wide range is mainly due to the variety in the definition of etiology being used in hydrocephalus patients. Additionally, the in- and exclusion criteria differ between studies, and the prevalence is country-specific. Only one systematic review article categorises the prevalence in the country's income or age. Isaacs et al. distinguished between low- and middle, and high-income countries worldwide, where the prevalence is 10.5 out of 10,000 and 7.7 out of 10,000 congenital hydrocephalus patients, respectively [4]. However, no distinction was made between age categories and etiology. Additionally, they reported the prevalence for each age category, which is 7.7 out of 10,000 paediatric patients, 1.1 out of 10,000 adults, and 17.5 out of 10,000 elderly. However, no distinction was made between country income and etiology. The Dutch guidelines database assumes that congenital hydrocephalus occurs in 3 out of 1,000 live births in the Netherlands [33]. However, no prevalence was found in adults and elderly.

4.1.2 | Etiology

Multiple studies show that the etiology of hydrocephalus is diverse [35, 36, 6, 40]. Chapter 2 gives an overview of the etiologies in hydrocephalus. Most studies which report the etiology are single-centre studies or do not include descriptions about the etiologies they included [cite garne, iscaacs, thomale]. Only two European studies show the distribution of etiology per age category. Both are based on a national registry in the country of origin [35, 36]. A multiple-centre study from Great Brittain by Pickard et al. shows a difference in the distribution of the etiologies among the two main age categories, paediatric patients and adults. An overview is given in Figure 4.1 [35]. In paediatric patients, congenital communicating hydrocephalus, such as malformation, is often the reason for hydrocephalus, followed by haemorrhage and brain tumours. While in adults, and especially in elderly, the primary etiologies are brain tumours, followed by haemorrhage and normal pressure hydrocephalus (NHP). In contrast, a Dutch study by Holwerd et al. shows that haemorrhage is the primary etiology in paediatric patients in the Netherlands, followed by congenital hydrocephalus [36]. However, the Dutch database is younger

(from 2012) than Great Britain's (from 1998), and the Dutch population is 3.5x smaller. Therefore in total 17x more patients were included in the Great Britain's database compared to the Dutch one. A final limitation of the Dutch database is that some gaps were in the database due to software revisions. All these arguments make the results for pediatric patients of the Great Britain's database more reliable than the Dutch database. No studies show the incidence of hydrocephalus per etiology in adults in the Netherlands.

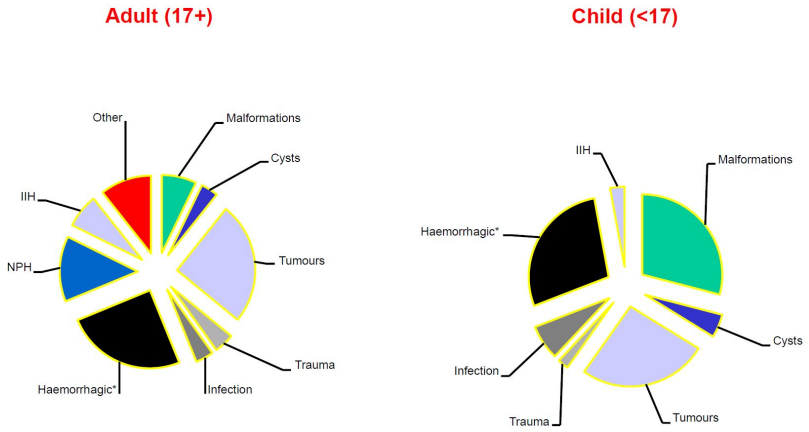

Figure 4.1: distribution of hydrocephalus causes among pediatrics and adults [35]. IHH: idiopathic intracranial hypertension (slit ventricles).

4.2 | Care pathway

The current care pathway of hydrocephalus patients in the Netherlands needs to be understood before the impact of the USPAN on this pathway can be determined. Therefore, interviews with clinical experts are performed to obtain the current care pathway of these patients. Two neurosurgeons from different hospitals are interviewed. One neurosurgeon performs shunt surgery only in adults, and the other neurosurgeon has expertise in paediatric shunt surgery. The interviews with both neurosurgeons can be found in Appendix 11. Based on the results of those interviews, the current care pathway is defined.

4.2.1 | Results

The two hospitals show many similarities in the care pathway of hydrocephalus patients. An overview of the care pathway is shown in Figure 4.2. In both hospitals, patients with symptoms such as headaches, double vision, poor balance, urinary incontinence, personality changes, and/or mental impairment are visiting the Neurosurgery department. After the consultation, the patient will get imaging. Most patients will receive a computed tomography (CT) scan. Only paediatric patients below two years old receive an ultrasound because they cannot receive radiation and have fontanels that allow ultrasound use. A couple of days after diagnosis, shunting surgery will be performed. Routinely the shunting surgery is performed with the free-hand technique (for details, see Chapter 2). Neuronavigation is only performed in high-risk or complex cases since this technique is time-consuming. Imaging is performed two to three days after surgery to determine if the ventricle system is shrunken. Additionally, the neurosurgeon checks if the ventricle catheter's tip is located within the ventricular system. Paediatric patients get a yearly consult with the neurosurgeon during their follow-up. Adults get only a consult if symptoms arise. If complications at the shunt or hydrocephalus symptoms arise, imaging will be performed again. Based on the results of the scan, a revision of the shunting system can be achieved. The revision is mostly a shunt replacement. After that, again imaging will be performed after 2 or 3 days. The USPAN will be introduced during surgery, where it replaces the stylet used in the free-hand technique. Differences compared to the current care pathway can be expected in the surgery duration due to setup time. Therefore, the impact is mainly on the surgical procedure, which impacts the proceedings of the neurosurgeon. The patient would not experience differences in surgery with the USPAN compared to the stylet used in the free-hand technique. Additionally, the impact of the USPAN can be expected in the follow-up. With the use of the USPAN an increase in the accuracy of the ventricle catheter's tip location

and a decrease in the number of insertion attempts of the ventricle catheter are expected, resulting in fewer complications and, thus fewer revisions of the shunt.

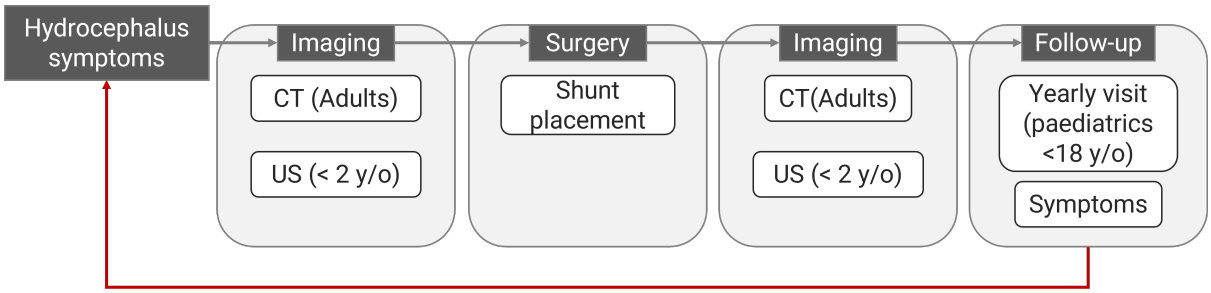

Figure 4.2: Care pathway of hydrocephalus patients in the Netherlands

4.3 | Complications

Complications and mortality in hydrocephalus patients who received a shunt with the free-hand technique should be mapped before the long-term health benefits of using the USPAN can be determined. A literature review is performed to obtain the current complications in hydrocephalus patients. In this section, the review method is described and followed by the results of this literature study.

4.3.1 | Method

Clinical information about the complications in hydrocephalus patients was obtained through a systematic review. A simplified form of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed [41]. Two databases (Scopus and Pubmed) were searched using keywords extracted from interviews with two neurosurgeons. The following keywords are incorporated in the search string:

1. TITLE(accuracy, position, placement, attempts, punctures, survival, complications, dysfunction, adverse event, revision, or mortality)
2. AND TITLE(ventricul* catheter, ventriculoperitoneal shunt, hydrocephalus, cerebral shunt, VP shunt, VA shunt)
3. AND NOT(tumor, biopsy, ETV, endosco*, vein*, laparo*, hemorrhage, infect*, flow, lumbar, case report, meningitis, rare, unusual)
4. Period: 2000 - 2020
5. Language: English

All publications in the period between 2000 - 2020 should contain in the title at least one keyword from (1) and (2). This time period is chosen, because hydrocephalus treatments are strongly improved in the last two decades. Resulting especially in less infections, and deaths. Titles with keywords from (3) are excluded. Only studies with hydrocephalus as primary disease and not coexisting with other diseases are incorporated in this research. This decision is made to incorporate only studies in which the cause of complications or shunt failure is not related to co-morbidities, such as spina bifida or a brain tumor. Additionally, only ventricular shunting surgery for treatment of hydrocephalus is included. All duplicates are removed and the abstract and titles are screened. Publications are excluded if they involve: animal studies, new developed procedure to place the ventricular catheter, focus other than on the human brain ventricles, a rare disease, or case studies. Thereafter full-text articles are assessed for eligibility, based on the study population, procedure and measures. From the included articles, the following information is extracted: shunt failure, post-operative complications, and mortality. Shunt failure is divided into insertion attempts of the ventricular catheter, accuracy of the ventricle catheter's tip location, and other reasons for shunt failure. As previously mentioned, it is expected that the USPAN will have an impact on the first two categories. Post-operative complications can be directly related to how the shunting surgery was performed. Mortality of hydrocephalus will have an effect on the long-term usability of the USPAN.

For example, suppose the mortality of the hydrocephalus population is high, and the life expectancy of these patients is low. In that case, the USPAN has a low impact because of the low usability compared to a population in which the mortality is low.

4.3.2 | Results

A schematic overview of the steps followed of the PRISMA guideline is shown in Figure 4.3. A total of 501 articles were retrieved from Scopus and Pubmed, in which 178 duplicates were found. 261 studies were excluded after screening the title and abstract based on the criteria mentioned in the previous section. In total thirty studies were included after full-text assessing for eligibility.

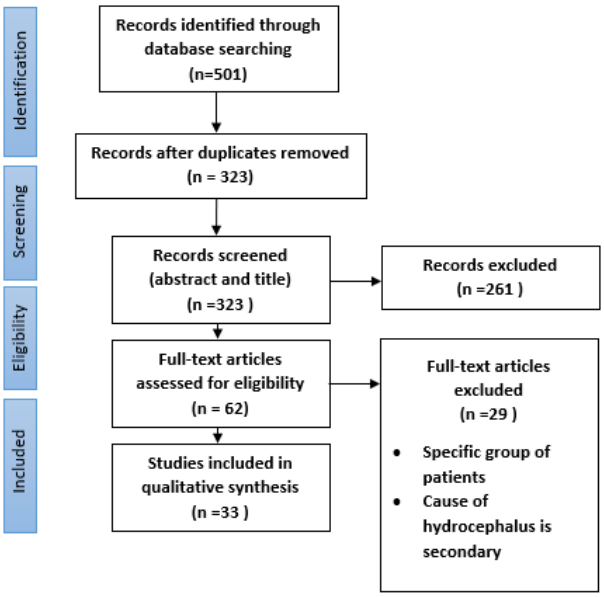

Figure 4.3: PRISMA flowchart of a systematic review of the outcomes after a non optimal ventricular catheter procedure of hydrocephalus patients

The results are discussed per category, starting with the possible reasons for shunt failure. This category is split into insertion attempts of the ventricular catheter, accuracy of the ventricle catheter's tip location, and other reasons for shunt failure. Next, post-operative complications. Finally, the mortality of hydrocephalus patients per age category is described.

Shunt failure

Eight publications were found about the causes of shunt failure [REF v onderstaande]. Most shunts fail within the first months after shunt surgery due to preventable causes [42]. Preventable causes are shunt failure due to infection, malposition of the ventricular or abdominal catheter, or an improperly assembled or inadequately secured shunt that resulted in post-operative disconnection, migration, kinking, or obstruction. Wherefrom the chance of infection might increase by the number of insertion attempts of the ventricular catheter. The most common preventable cause of failure is the malposition of the ventricle's catheter, which occur in 16% of all shunt failures [42, 43]. Followed by infection (14%) and inaccurate placement of the abdominal catheter (2%) [42]. Other complications which evolve later in time are valve dysfunction, shunt migration or occlusion of the ventricular or abdominal catheter [42, 44]. The USPAN only influences the number of insertion attempts of the ventricular catheter and the accuracy of the ventricle catheter's tip location. Therefore these two causes for shunt failure are discussed separately from the other shunt failures.

Insertion attempts of the ventricular catheter

Three publications discussed the number of insertion attempts for placing the ventricular catheter during surgery. O'Neill et al. [10] surveyed 934 neurosurgeons to determine the number of puncture attempts per practising neurosurgeon. On average, 2.4 attempts for successful catheter placement are needed for Junior neurosurgeons and 1.4 for senior neurosurgeons. Thomale et al. showed that the average number

of puncture attempts for practising neurosurgeons is 1.13 (9 different neurosurgical centres participated, number of neurosurgeons was not announced) [6]. Huyett et al. [7] showed an even higher number with 2.17 attempts on average (1164 reports of CT scans were studied). In all three studies, the authors expect that multiple insertion attempts result in a higher chance of complication, such as haemorrhage, neurological injury, and infection. Moreover, Huyette et al. [7] mention that CT or MRI often show the effect of trauma from catheter passes. Additionally, they state that even when no clinically detectable effect is found, more subtle neuropsychiatric effects may be present. However, no conclusions were drawn regarding the relationship between the number of puncture attempts and clinical outcomes.

Accuracy of the ventricle catheter's tip location

Four publications are found where the accuracy of the ventricle catheter's tip location is discussed. From these articles, we would like to extract the incidence of inaccurate placement and the incidence of related shunt failure per age category. However, all four articles use a different classification matrix for grading the accuracy of the catheter's tip location. Most studies use a three- to four-point grading scale, combining different aspects of the ventricle catheter's location, such as the post-operative location of the catheter's tip location for each location of the ventricle system, for the distance of the ventricle wall, for the distance compared to the monro foramen, for the skewness entering the ventricle system, but also the number of ventricle catheter perforation surrounded by the CSF [6, 7, 44, 45, 46]. Due to the use of different definitions, it is impossible to directly compare the results of these studies. Thomale et al. Introduced the most thorough classification system, in which possible factors which might be influenced by using the USPAN are discussed. These factors are: (1) the catheter tip position being in contact with paraventricular tissue, (2) the anatomical catheter tip position, (3) the position of the perforations of the ventricular catheter being inside the ventricle, (4) and the number of puncture attempts. In Figure 4.4 an overview of this classification system is shown, in which an optimal and incorrect catheter position is indicated in the green, and red box, respectively. Intermediate catheter position is defined as one attempt, grade II, and ipsilateral position. An optimal, intermediate and incorrect catheter position after surgery with the free-hand technique is obtained in 56.5%, 11.6%, and 31.9% of the procedures, respectively. It should be taken into account that this study was performed in adults with an average age of 62.5 $\pm$17.9 years old. Other results show an incorrect catheter position in 19.5 - 29.5% of the cases [7, 45, 46], which is lower than found in Thomale et al.[6]. However, an incorrect catheter position in these articles is defined most often in a 2D scan, which gives less information compared to a 3D scan, or more strict requirements are used compared to Thomale et al.. This results in a lower probability of having an incorrect catheter position. The relation of the accuracy of the ventricle's catheter tip location to shunt survival is only studied by Jeremiah et al. [8]. Over a period of four years, they did a follow-up in patients with an equal distribution of age categories. The authors found a strong correlation between poor shunt placement and shorter shunt survival. However, it should be considered that the follow-up period is short, which might result in missing shunt failures occurring later in time. Beuriat et al. support the findings of Jeremiah et al. by stating: "the position of the ventricular catheter is significantly associated with better shunt survival when the catheter is correctly placed" [43]. However, they provide no quantitative results.

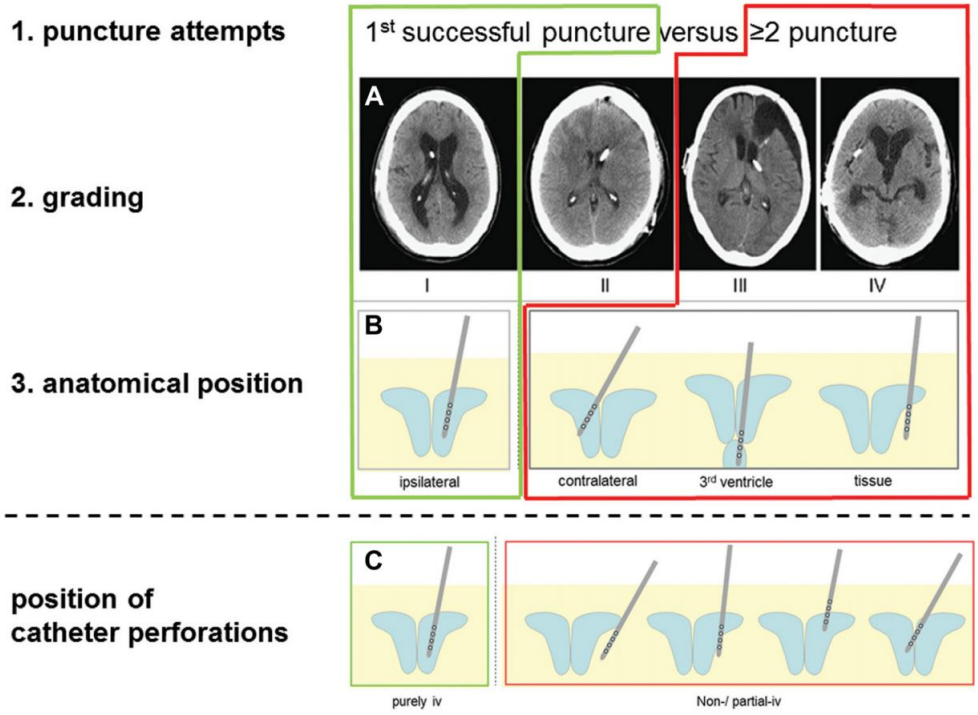

Figure 4.4: Overview of the quality of the ventricular catheter position evaluated [6]

Other reasons

Five articles did not specify the reason for shunt failure. However, they described shunt failure in terms of shunt survival. Shunt survival describes how long a shunt survives after surgery or revision. Shunt survival of the initial shunt in paediatric patients is lower compared to adults [47, 35, 20]. Initial shunt survival in adults becomes constant after 2 years with a 90% chance of survival, while in children the survival decreases till they reach the age of 18 years old, with a survival of 75% of the initially placed shunts [47, 40]. Initial shunt survival after 40 years of shunts placed in paediatric patients is only 4% [48]. However, a limitation of their study is that patients who died during the follow-up were not excluded from the studied population, which lowered the shunt survival rate. Pickard et al. and Shah et al. described shunt survival after revision in paediatric patients. Both found that the shunt survival after revision is shorter than shunt survival after initial shunt placement [20, 35]. In adults, shunt survival after revision was longer compared to paediatric patients. The first reason is that paediatric patients, especially babies, have a smaller ventricle system, which is harder to catheterise. The second reason is that paediatric patients grow a lot during this period of life, which can lead to shunt disconnection.

Post-operative complications

Six articles were found describing a direct relationship between complications and shunting surgery. Post-operative complications are mainly subdural haematoma, bleeding due to puncturing blood vessels in the brain. A subdural haematoma can be directly observed with medical imaging after surgery. However, symptoms are not always easy to predict, because patients can be asymptomatic and bleeding is only revealed on CT, to mass lesions with hemiparesis and coma [49]. Hultegard et al. describe that subdural haematoma occurs in around 10% of their patient population, of whom 18% need a revision or evacuation of the ventricular catheter. In the other patients, no action is performed [50]. Three other publications confirm this founding. However, the age categories are different from incorporating all patients who received a shunt to only elderly [49, 51, 52]. Infection and obstruction are also described as post-operative complications. These complications occur later, and, therefore, hard to relate if it is related to shunting surgery or other internal processes in the human brain.

Mortality

Four articles were found discussing the mortality rate within hydrocephalus patients. The mortality rate of patients receiving their initial shunt under fourteen years old is high. Twenty years after initial shunt placement, the mortality is 20-30%, and after fourty years, this rate increases over 50% [40, 48, 53]. Most deaths are in the first two years after initial shunt placement, ±20% of patients who received a shunt. In total, 10% of all deaths in this patient group are shunt related. Still, most deaths are of underlying diseases, which is often the case in hydrocephalus patients [40, 48, 54, 53]. In adults and elderly no long-term follow-up studies are found.

4.4 | Conclusion

In this section the first sub-research question is answered, which is formulated as follows:
What could the impact be of the USPAN on the current surgical procedure and care pathway of the hydrocephalus patient group who might benefit the most from the USPAN?

In this chapter, literature studies were performed in order to answer the sub-research question. First, the hydrocephalus population is described, which is mainly classified in literature into two age groups: paediatric patients and adults. Age appears to bear the most distinguishing features. Some studies prefer to split the total group of adults into adults (18 – 64 years old) and elderly (> 65 years old). In the subsequent sections, this classification by age was used to describe the prevalence, etiology, care pathway and possible complications. The surgical procedure in paediatrics and adults is similar, which results in the same impact of the USPAN in both procedures. Moreover, the care pathway of both age groups is similar in the current care. The expected major etiology in paediatrics is congenital hydrocephalus, while for adults this is brain cancer. Congenital hydrocephalus is a primary disease in which no other comorbidities influence the clinical outcome of a patient. For adults, with brain cancer as a primary disease, hydrocephalus is a comorbidity. As such, this has a high influence on the clinical outcome and health state of the adult patient. Often other complications take place earlier than complications occur due to an inaccurate location of the ventricle catheter's tip or multiple catheter insertions.

The paediatric patient population is approximately 1.3x smaller than the elderly population. However, the number of revisions, and thus the total amount of surgeries, is higher in paediatric patients compared to adults. Considering that the USPAN has an impact on the surgical procedure, we expect the USPAN to have the highest impact in this patient group, as the highest impact factor is the total amount of surgeries required. There are several factors that influence the amount of surgeries required. These factors relate to either the accuracy of shunt placement, the number of attempted surgeries, or other age-specific complications. As for the accuracy of the placement of the shunt, we note that a less accurate placement results in a shorter shunt survival, which in turn leads to more revisions. Shunts placed after revision have a shorter survival than a shunt placed after initial admission of the patient. As such, the importance of an accurate placement cannot be understated for a successful procedure.

The USPAN can potentially reduce the number of attempts required for successful surgery. However, the effects of this are inconclusive in literature. Finally, we note several age-specific complications. In pedriatic patients, shunt survival is lower than in the adult population affected. This increases the number of surgeries required, which in turn increases the probability of inaccurate placement. Finally, we note that the expected lifespan of paedriatics is implicitely higher than that of adults, which increases the probability of surgeries during the total lifespan of the patient.

Any other complications are not age-specific. Considering that literature mainly distinguishes between either paedriatics or adults, and taking the factors above into account, we conclude that paedriatic patients are the group of patients that might benefit the most from the USPAN in practice, as the USPAN reduces the amount of surgeries that a patient requires for successful shunt placement.

5 | Expert elicitation

In the previous chapter a literature study was performed to describe the impact of the USPAN on the hydrocephalus care pathway of the chosen patient group. However, inconsistency within publications and lack of evidence was found with regard to accurate shunt placement, the number of puncture attempts, and the relation with postoperative complications or shunt survival.

Expert judgements, also referred to as belief or expert elicitation, respectively, is a frequently used method in early HTA to obtain the missing evidence [55, 56, 34]. Moreover, elicited information can represent how uncertain experts are about the current state of knowledge regarding the topic of interest. In early health technology assessment, specifically health economic models, estimates of the missing parameters and a first indication of the uncertainty of these parameters is used [57, 27, 58]. Different methods are described in literature to perform expert elicitation, but no standardised methodology to perform the elicitation exists [55].

One method to obtain this information is to perform an online questionnaire. This method can reach many different neurosurgeons across the Netherlands within a short period of time, this is important due to time constraints of this research. Moreover, this method is within the COVID-19 restrictions of the Dutch government.

In this research the missing information and uncertainty of parameters of interest will be gathered. This will lead to the following research question, which will be answered within this chapter: *Which information about the clinical conditions of hydrocephalus patients who received a shunt could not be derived from the literature?* .

Next, the likelyhood of using the USPAN will be asked. This give insights for the developers in the requirements and wishes, and helps to sharpen the design criteria.

First, the method for expert elicitation will be explained in section 5.1, followed by the results in section 5.2. Finally, the results are discussed and conclusions are drawn in section **??** and 5.3, respectively.

5.1 | Methods

An online questionnaire (Online platform, Qualtrics) was designed to perform the expert elicitation. The questionnaire was divided in four main sections: Characteristics of the neurosurgeons, surgical experience with the freehand technique, surgical experience with image-guided techniques, experienced complications after shunt placement, judgement of the USPAN. In the second and third section, neurosurgeons were asked to give the probability of an event, the proportion of patients who will have an outcome, the relative risk of an outcome, and the weight for an dependent variable. The response options were probability estimates or predefined probability ranges. In the last section priority and desires regarding the USPAN were asked to inform take the experts opinion into account in the development process of the USPAN. The complete questionnaire is shown in Appendix 12.

Ethical approval for the study was granted by the BMS Ethics Committee of the University of Twente (project reference: 200900). The questionnaire was distributed within the Nederlandse Vereniging voor Neurochirugie (NVvN). The NVvN have around 130 members, containing neurosurgeons and neurosurgeon residents.

The outcome measures are the mean value or probability, respectively, per parameter. Calculations and visualisations of the obtained data was performed in the software package from Qualtrics.

5.2 | Results

In total 54 (100%) neurosurgeons started the questionnaire, of which 25 (46%) finished it. Due to incomplete responses, the weighted averages were determined based on the number of responders per question.

From the 54 neurosurgeons who started the questionnaire, in total 40 (74%) are staff lid and 14 (26%) are residents. In Figure 5.1 information of the experiences of the neurosurgeons is shown. All neurosurgeons (54, 100 %) perform ventricular catheter placement within adults of whom 18 neurosurgeons (33%) perform also catheter placement in children. In total 36.1 % (584) of the catheter placements are in children and 63.9 % (1069) are in adults. In children less catheters are placed with freehand (392, 67.1%) compared to adults (772, 72.3%).

	Children		Adults	
	n	%	*n*	%
Number of ventricular catheter placements (total)	**584**		**1069**	
2018	300	51.4	531	49.7
2019	284	48.6	538	50.3
Number of ventricular catheter placements (FH)				
2018	209	69.6	384	72.4
2019	183	64.6	388	72.2
Number of catheter attempts per surgery on average indicated per neurosurgeon (FH)	**18**		**54**	
1 attempt	14	78	34	63
2 attempts	4	22	20	37

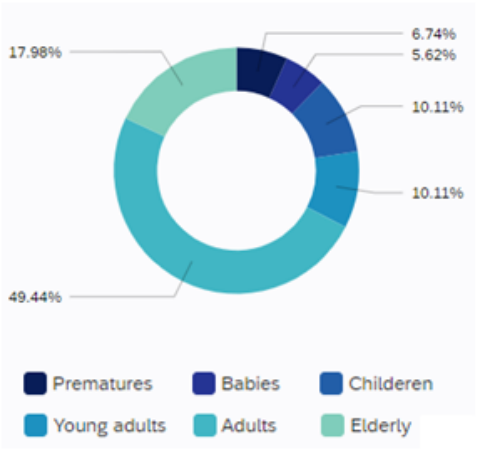

Figure 5.1: **Table** Statistics about the experience with ventricular catheter placement of the neurosurgeons who answered the questionnaire. **Figure** Distribution of patient groups within the neurosurgeons who answered the questionnaire

5.2.1 | Complications

In the section complication 32 neurosurgeons responded. Neurosurgeons who need commonly 2 attempts to place the ventricular catheter experience more complications, than neurosurgeons who commonly use 1 attempt. Moreover, complications related to the ventricle catheter placement have a higher probability within 30 days compared to 30-90 days after surgery. Moreover, neurosurgeons who perform catheter placement in children indicate that they experience less complications (less than 20 % in all cases) compared to adults. However, in children imaging techniques are used more often than in adults.

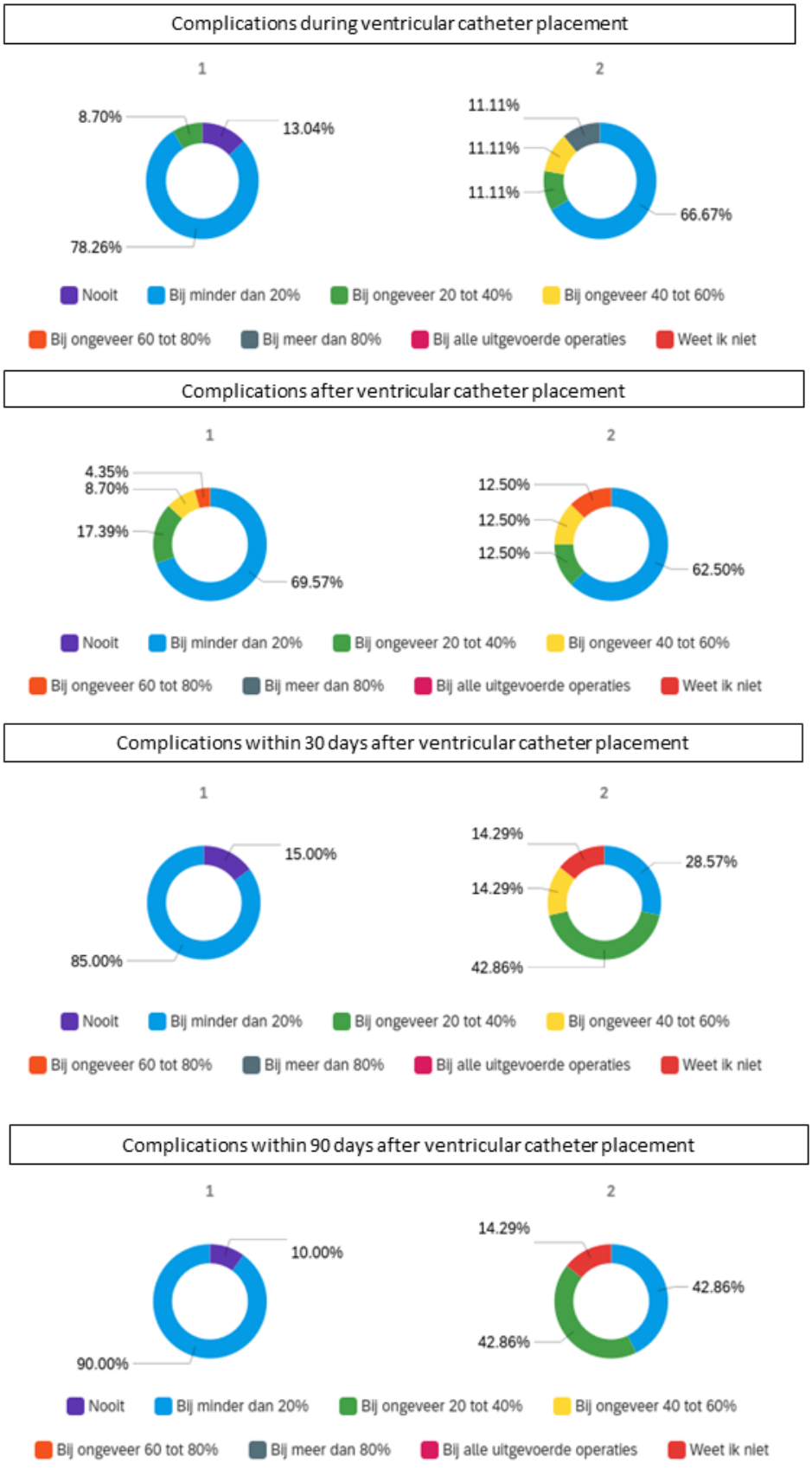

Figure 5.2: Number of complications after surgery according to the questionnaire results

5.2.2 | USPAN

In total 25 neurosurgeons answered the question in the section about the new technology. They ranked the parameters which they find the most important. Starting from most to less important, (1) probability of optimal placement of the ventricular catheter, (2) accuracy of the device, (3) usability for neurosurgeon, (4) time investment during surgery, (5) purchase costs, (6) usage costs, (7) quality of life of the patient, (8) burder for patient, (9) time investment to implement new device.

In Figure 5.3 the expected usage of the USPAN is indicated. It can be seen that the neurosurgeons expect a higher use of the USPAN when the ventricle is detectable from the cortex compared to when the ventricle is detectable when the USPAN is 1 to 2 cm inserted in the cerebrum.

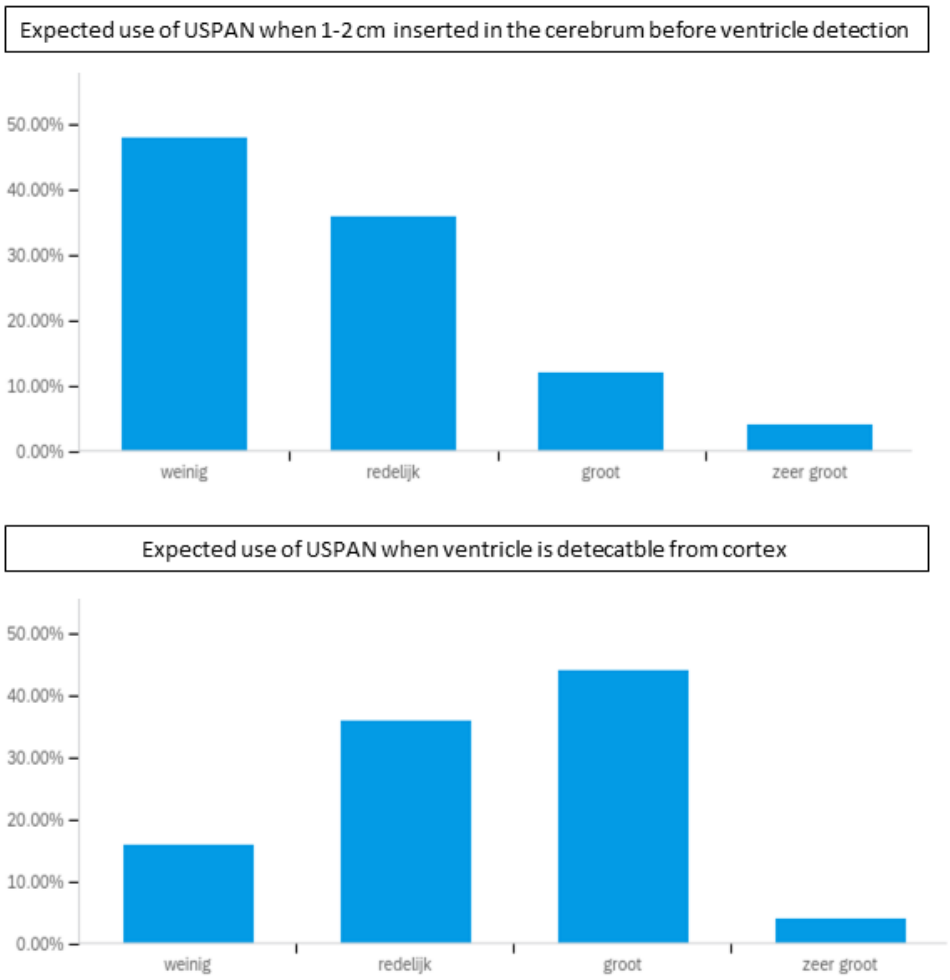

Figure 5.3: Expected use of USPAN in two scenarios according to the questionnaire results

5.3 | Conclusion

In this chapter the second research question is answered: *Which information about the clinical conditions of hydrocephalus patients who received a shunt could not be derived from the literature?* Missing information is questioned among neurosurgeons in the Netherlands by a questionnaire. Neurosurgeons indicated that less complications are expected when they use commonly 1 attempt to place the ventricle catheter. Moreover, complications related to the ventricle catheter placement have a higher probability within 30 days compared to 30-90 days after surgery. Next, neurosurgeons indicated that a new device is more favourable if the ventricle can be detected from the cortex, compared to the ventricle can be detected after 1 to 2 cm insertion. Moreover, the top 3 most important requirements to implement the device are (1) probability of optimal placement of the ventricular catheter, (2) accuracy of the device, (3) usability

for neurosurgeon. These requirements can be taken into account in the development process of the USPAN.

6 | Model design

In this chapter, the third research question is answered: *What are the requirements of a model which reflects the care pathway of hydrocephalus patients to determine the effectiveness gap and health services costs difference between the current procedure and the procedure with the USPAN?* This chapter is divided in three sections to answer this question. First, the model method and outline are discussed in section 6.1. Next, the model design and assumptions are discussed in section 6.2. Finally, the research question is answered in section 6.3.

6.1 | Markov model outline

In cost-effectiveness analysis for early health economic simulation, different types of analytical decision models can be applied to estimate patients' costs and benefits during their lifetime [59, 27]. These models consider possible future health states of patients with a specific condition that receive a chosen treatment based on probability values. Different types of models can be used depending on the nature of the problem, the patient's disease (acute or chronic), and the type of technology under assessment.

In this research, the care pathway of hydrocephalus patients with a permanent shunt is under assessment. As explained in the previous chapters, it is expected that the USPAN will affect the long-term health outcomes of hydrocephalus patients. Therefore, a Markov model can be applied, which is widely used for long-term and chronic diseases [60, 59].

A Markov model is structured around health states and movements between them. Therefore, the patient care pathway is essential in designing the model [59]. Within the model, the patient's care pathway is split into a finite number of disease statuses or *health states*, which must be mutually exclusive and cover all the patients in the model. Each health state is assigned with a *cost*, which represents the total costs of the healthcare consumed, and *effect*, in terms of QALYs. Patients can only be in one state at a time and stay in that state for a fixed period, called *cycle time*. After that, the patient can remain in the same health state or move to another.

The patients in a Markov model move in cohorts. The whole cohort begins the model at time 0 in the initial disease state. After that, the cohort can be distributed between all health states.

The movements between health states occur with a given probability p, known as *transition probabilities*. The transition probabilities are based on literature results and input from clinical experts during the early development stages. As described in Chapter 4, the shunt survival decreases and the mortality rate increases over time. This results in different consecutive transition probabilities and cannot be represented by a constant possibility, as within a classic Markov model. However, a semi-Markov model can be used to implement time dependency, [61]. A semi-Markov model contains a three-dimensional matrix of transition probabilities, which includes the current state, future state and an additional third dimension time. This third-time dimension is added compared to a classic Markov model. A schematic representation of the 3-dimensional transition matrix is shown in Figure 6.1. Due to this time dimension, the transition from one state to another can be with a probability assigned to the time spent in the state. This method is described in Hawkins et al. [61]. The patient cohort entering the state will leave the state based on the probability, which will be changed by further time development

The model is evaluated for a certain amount of time, known as *time horizon*, usually corresponding to the life time of the cohort of patients [27]. Costs and effects are summed up over the time horizon of the Markov model. In decision making current costs and effects get a greater weight than future costs and effects, and therefore need to be discounted.

$$P_t = P = \begin{bmatrix} p_{[1,1]} & p_{[1,2]} & \cdots & p_{[1,n_s]} \\ p_{[2,1]} & p_{[2,2]} & \cdots & p_{[2,n_s]} \\ \vdots & \vdots & \ddots & \vdots \\ p_{[n_s,1]} & p_{[n_s,2]} & \cdots & p_{[n_s,n_s]} \end{bmatrix} \text{ for } t = 0, \ldots, n_t,$$

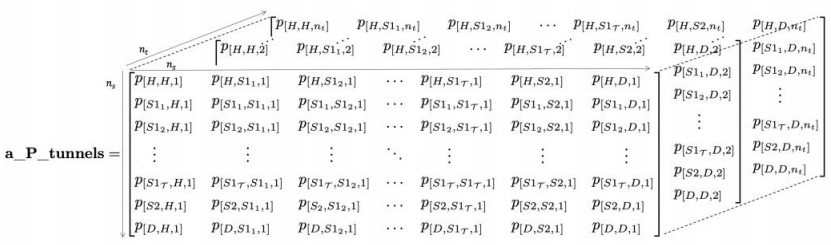

Figure 6.1: A schematic representation of a transition probability matrix. a) 2-dimensional transition probability matrix P with probabilities $p[n_s,n_a]$ from the current state, n_s, to future state, n_a. b) 3-dimensional transition probability matrix with the additional dimension time, n_t. [62]

6.2 | Model design and assumptions

The results from the literature review (Chapter 4) and expert elicitation (Chapter 5), together with the patient care pathway (Chapter 4) form the basis of the Markov model for hydrocephalus patients. Moreover, this model is varified with a neurosurgeon. This Markov model aims to compare the USPAN and current care (free-hand technique). The care pathway in both situations is the same, except for the surgical procedure. The difference in surgical procedure only impacts the model parameters, not the model structure. Therefore the same model structure is used for the free-hand technique and with the use of the USPAN. The assumptions and simplifications to obtain the structure of the model are based on the previous described Chapters. The assumptions are defined as follows:

1. All patients incorporated in the model are diagnosed with hydrocephalus.
2. All patients in the model are pediatric patients.
3. All patients receive pre- and post-operative imaging, which means before and after initial shunt placement and revision.
4. All patients receive an initial shunting procedure.
5. All patients remain one week in the hospital after shunting.
6. All patients stay dependent on a shunt.
7. The ventricular catheter can be placed in one or multiple attempts during surgery.
8. The tip of the ventricular catheter can be placed in an optimal, intermediate or incorrect position during surgery, based on the classification of Thomale et al. [6].
9. The patient outcome after surgery can be with or without post-operative complications.
10. If the patient has post-operative complications, the patient can get healthy or receive a revision.
11. A patient stays healthy until shunt failure occurs.
12. If a shunt fails, the patient gets a revision (multiple revisions are possible).
13. Health outcomes after initial shunt placement and revision are the same.
14. A patient can die in every health state.

With (4) and (10), the distinction between a first shunting procedure and revision is made. This distinction is necessary because the probability of shunt failure after revision is higher than after initial shunt placement, based on the literature review results (Chapter 4).

An overview of the Markov model for hydrocephalus patients is represented in figure 6.2. The Markov model is displayed by a state transition diagram, in which health states are represented by nodes and transition probabilities by arrows. The definitions of all health states in the Markov model and the events during the health states are shown in Table 6.3.

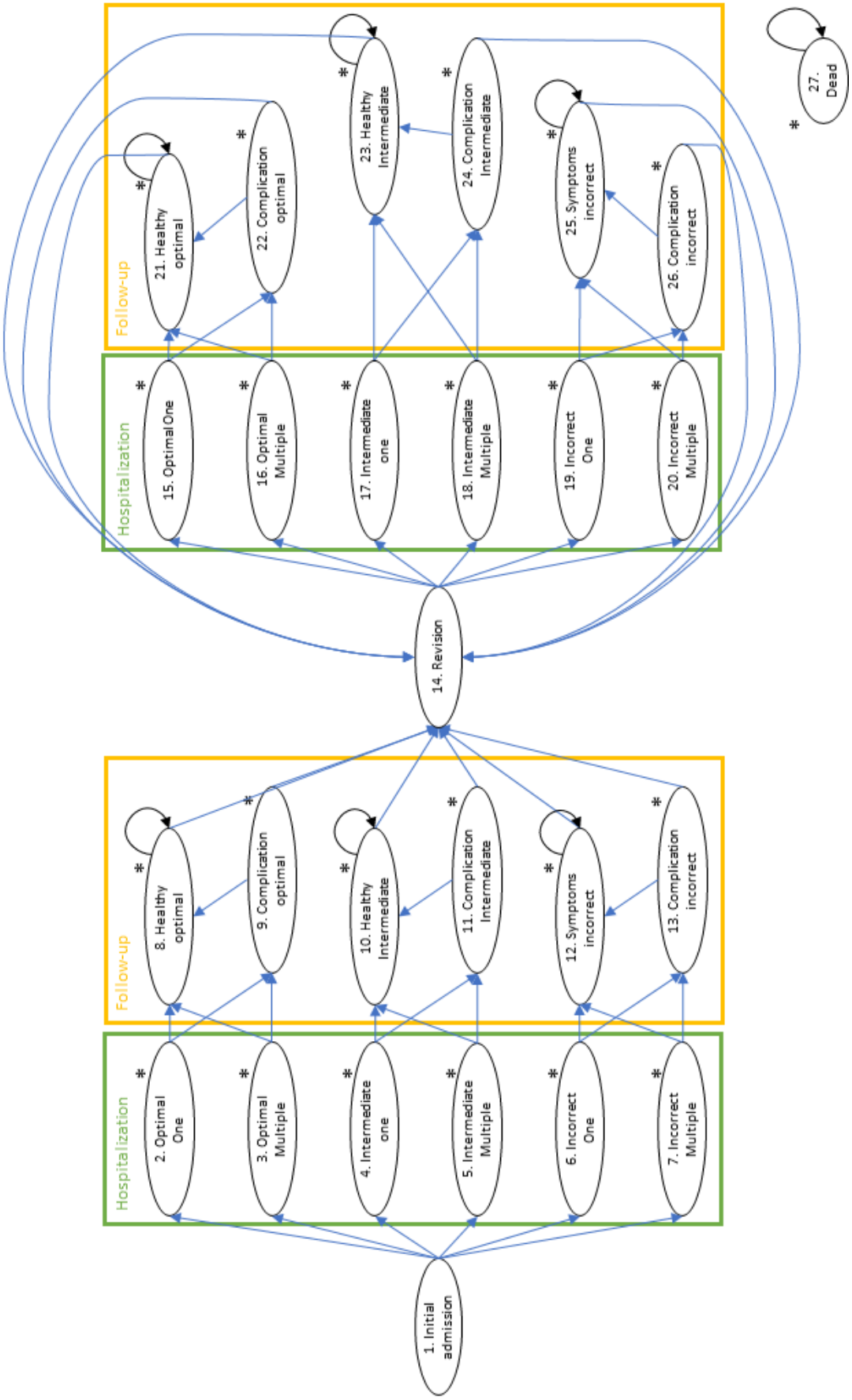

Figure 6.2: State transition diagram of the Markov model for hydrocephalus patiens who receive a shunt.

Figure 6.3: Definitions of the health states and disease related events during the health states.

State	Definition	Events
1.	Initial admission	- Consult with a Neurosurgeon - Pre-operative imaging - Hospital stay
2./15.	Optimal catheter tip position within one insertion	- Surgery - Post-operative imaging - Consult with a Neurosurgeon - Hospital stay
3./16.	Optimal catheter tip position within multiple insertions	
4./17.	Intermediate catheter tip position within one insertion	
5./18	Intermediate catheter tip position within multiple insertions	
6./19.	Incorrect catheter tip position within one insertion	
7./20.	Incorrect catheter tip position within multiple insertions	
8./21.	Healthy with optimal catheter tip position	- Yearly consult with Neurosurgeon
10./23.	Healthy with intermediate catheter tip position	
12./25.	Healthy with incorrect catheter tip position	
9./22.	Post-operative complication with optimal catheter position	- Consult with a Neurosurgeon - Intervention imaging - Hospital stay
11./24.	Post-operative complication with intermediate catheter position	
13./26.	Post-operative complication with incorrect catheter position	
14.	Revision	- Consult with a Neurosurgeon - Pre-operative imaging - Hospital stay
27.	Dead	

6.3 Conclusion

In this chapter the third research question is answered: *What are the requirements of a model which reflects the care pathway of hydrocephalus patients to determine the effectiveness gap and health services costs difference between the current procedure and the procedure with the USPAN?*

A semi-Markov model is able to determine the costs and effectiveness of the care pathway of hydrocephalus patients. Additionally, this model type can determine long-term health outcomes. This is necessary because hydrocephalus is a chronic disease. Moreover, with this model, the costs and QALYs of the free-hand technique and use of the USPAN can be determined and compared.

7 | Model parameters

In this chapter, the fourth research question is answered: *What model parameter values are used for the model to determine the effectiveness gap and health services costs differences between the current procedure and the procedure with the USPAN?* This chapter is divided into four sections. First, the model parameters for the current care, in which the free-hand technique is used are described in section 7.1. In section 7.2, the model parameters with the use of the USPAN are described. Next, the uncertainty of the model parameters is described in section 7.3. In the final section, the research question is answered.

7.1 | Model parameters in current care

In the Markov model shown in Figure 6.2 of section 6, costs and utilities are assigned to each state, and transition probabilities are set to move between health states. This section explains the method to define the input parameters, and the results are discussed in detail.

7.1.1 | Transition probabilities

The Markov model incorporates two types of transition probabilities: 1) time-dependent and 2) time-independent transition probabilities. The time-dependent transition probabilities in this model are based on survival curves, whereas the time-independent probabilities are constant values. In this section, first, the method of obtaining the time-dependent transition probabilities will be explained. Next, the method of obtaining the time-independent transition probabilities. Finally, the results will be shown.

Time-dependent transition probabilities

Methods
All time-dependent probabilities are based on survival curves found in the literature. However, the raw data of the curve is mainly unavailable, and only the figures in the selected articles provide information. A method to incorporate the survival curves is developed by Guyot et al. [63], which can reconstruct the Kaplan-Meier survival curves. Additions to the algorithm are made to be able to fit a survival curve after reconstruction and determine the corresponding 95% confidence interval (CI). The adapted algorithm can be found in Appendix 13. All survival curves are fitted by the generalised gamma distribution, which can be used as a good fit for survival data [64]. The fitted curve on the survival data is used as an input parameter for the transition probability in the Markov model.

Results
Four survival curves are used as input in the Markov model. Two types of survival curves are incorporated in the model shunt survival curves and survival curves. Shunt survival curves indicates the probability of shunt failure. Survival curves, indicates the mortality of hydrocephalus patients after shunting surgery. For both curves, the reconstructed Kaplan-Meier curve with corresponded 95%-CI, and the fitted generalised gamma distribution with corresponding 95%-CI is shown in Figure 7.1. Additionally, the exact fitted parameters of the generalised gamma distribution with the estimate, lower and upper 95 %-CI, and standard error for all survival curves are shown in Table 13.1 (Appendix 12). As described in Chapter 4, the shunt survival in children after initial placement is higher than after revision (see Figure 7.1a for initial admission, and c, and d for primary and secondary). Moreover, it can be seen that the shunt survival after the first revision is higher than after the second revision. However, to lower the computational costs and simplify the Markov model, the average between the fitted shunt survival curve after the first and second revision is used as a model parameter. Both shunt survival curves, after

initial admission and revision, are used if a patient has a good outcome ("healthy") after surgery, and has an optimal or intermediate position of the ventricular catheter's tip (transition probabilities: $p_{8,14}$, $p_{10,14}$, $p_{21,14}$, and $p_{23,14}$). One study described shunt survival after poor shunt placement [8]. The shunt survival after poor placement is based on a small population (n=13) in which no distinction is made between children and adults, and patients after revision are not included. However, the shunt survival after initial shunt placement with no indication of poor placement in this study corresponds well with the results of Shah et al. [20]. Since no other data in literature is available, the fit on this survival curve (see Figure 7.1b) is used as transition probability for patients with a good outcome after surgery and an incorrect ventricular catheter position (transition probabilities: $p_{12,14}$ and $p_{25,14}$). As described in Chapter 6, all patients have a chance to die during each cycle. The survival of hydrocephalus patients after initial shunt placement is based on a large (n=67) long-term (follow-up of 30 years) retrospective single-centre study [53]. The survival curve is used for all patients after surgical outcome (transition probabilities: $p_{8\text{-}13,27}$, and $p_{21\text{-}26,27}$)

Time-independent transition probabilities

Methods

The time-independent transition probabilities are all constant values based on literature results or expert elicitation. Most complications and disease progression values are often expressed in relative risks, odds ratio, or probabilities among a selective cohort. Those values must be converted into suitable transition probabilities for the Markov model. First, the rate should be transformed into a probability. This is expressed in the following equation:

$$p = 1 - exp(-rt), \tag{7.1}$$

where p is probability, r is rate, and t is time. The probability from the time frame used in the published article needs to be converted to the Markov cycle time of the model. The conversion in model time can be transformed by:

$$p = 1 - (1 - p)^{1/n}, \tag{7.2}$$

where $1/n$ is the new cycle length.

The transition probabilities explained in the results section are not converted to the model time of the Markov model. The cycle time in the model is short (months), which results in large confusing numbers. The transition probabilities finally used in the simulation (section **??**) are converted to the cycle time in the model.

Results

As described in Chapter 6, the position of the ventricular catheter is categorised as optimal, intermediate, or incorrect, based on the classification of Thomale et al. [6]. This results in a transition probability for an optimal, intermediate, or incorrect catheter tip position of 0.56, 0.11, and 0.31, respectively. The same probabilities are used for initial and revision surgery because both procedures are similar. The probability of placement in one catheter insertion attempt (0.2) is reported in the study of Huyette et al. [7]. Additionally, O'Neill et al. [10] describe that one or multiple insertions occur. However, they did not assess the probability.

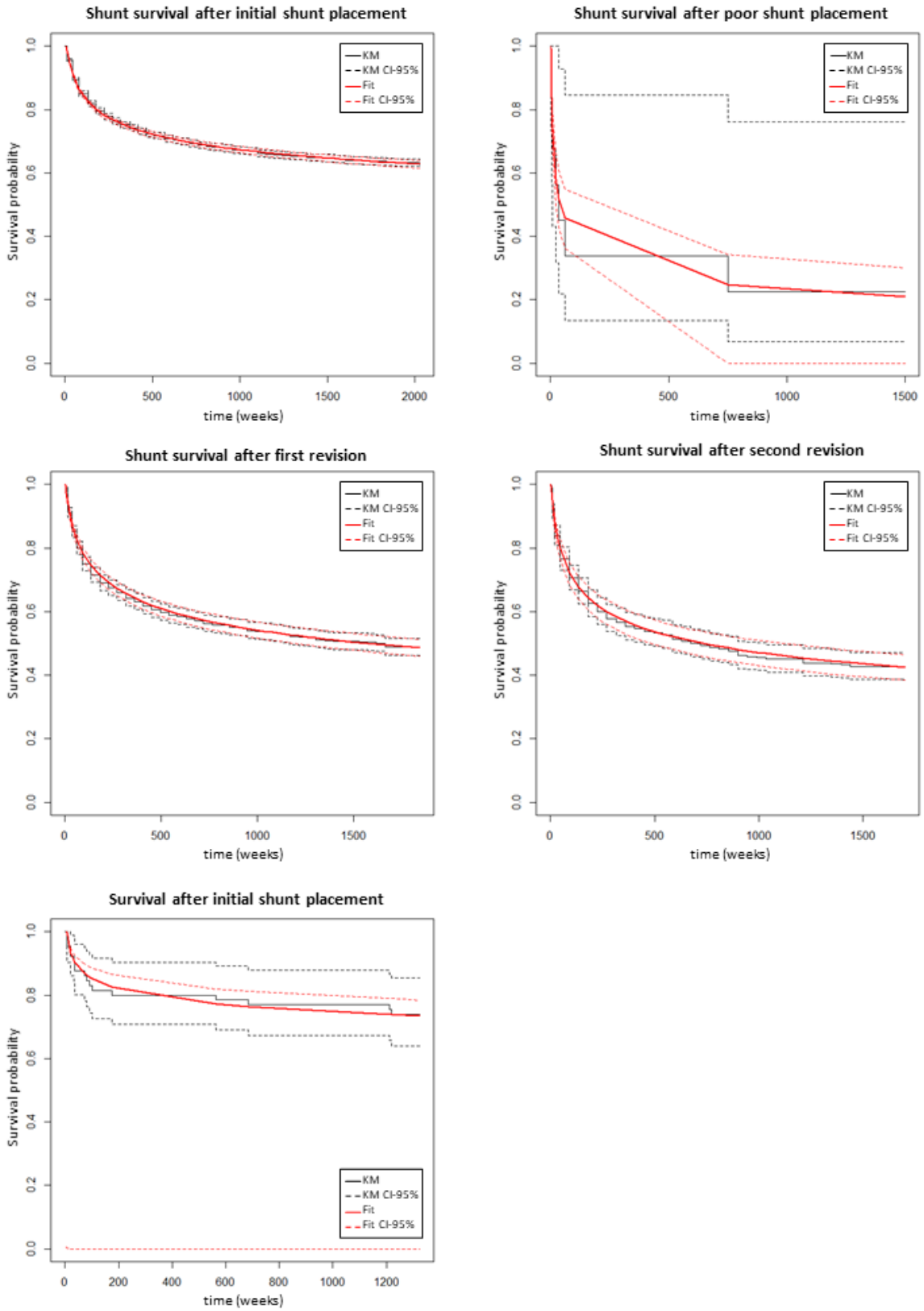

Figure 7.1: Survival curves for a) shunt survival after initial shunt placement [20] b) shunt survival after incorrect shunt placement [8] c) shunt survival after first revision [20] d) shunt survival after first revision [20] e) survival after initial shunt placement [53]

The final transition probabilities which can be used as input in the model are calculated by: The probability of the degree of accurate placement multiplied by the probability of the number of attempts, which results in 12 combinations in which no difference is made between the transition probabilities after initial admission or after revision (transition probabilities: $p_{2,8\text{-}9}$, $p_{3,8\text{-}9}$, $p_{4,10\text{-}11}$, $p_{5,10\text{-}11}$, $p_{6,12\text{-}13}$, $p_{7,12\text{-}13}$, and $p_{15,21\text{-}22}$, $p_{16,21\text{-}22}$, $p_{17,23\text{-}24}$, $p_{18,23\text{-}24}$, $p_{19,25\text{-}26}$, $p_{20,25\text{-}26}$).

The chance of having a complication after surgery is derived from the questionnaire. In Figure 5.1 of Chapter 5 the probabilities are shown to complications (adverse events) after ventricular catheter placement. Since the range of probabilities is broad, the centre value is chosen as the corresponding value (For example 20 to 40% the centre value is 30%). The mode is used as model parameter from the distribution with centre values. In post-operative complications, this results in a probability of 0.10 (transition probabilities: similar to the previously mentioned). This probability is affirmed by Sundstrom et al. [49], who studied only the prevalence of subdural hematoma (SDH), also known as stroke, in shunted idiopathic normal pressure hydrocephalus (iNPH) after surgery. This is the most serious adverse event in hydrocephalus patients, according to the neurosurgeons who filled in the questionnaire. Sundstrom et al. [49] also studied the prevalence of patients who need to be treated surgically after an SDH. This results in a probability of 0.34 (transition probabilities: $p_{9,14}$, $p_{11,14}$, $p_{13,14}$, $p_{22,14}$, $p_{24,14}$, $p_{26,14}$). In the questionnaire, no definitive conclusions could be drawn since a lot of variety was shown.

The last transition probability incorporated in the Markov model is the probability of surgery related mortality in paediatric patients after a shunting procedure which is 0.08 (transition probabilities: $p_{2\text{-}7,28}$, and $p_{15\text{-}20,28}$), derived from literature [65].

An overview of all transition probabilities given as input in the Markov model is shown in Table 7.3.

7.1.2 | Costs

The costs are assigned per state in the Markov model. In total, six categories can be made, which will be assigned to a specific state. The costs categories are:

1. Initial admission (state *1*): Costs from first hospital visit till surgery, which are consults with the neurosurgeon, imaging at the radiology department, and hospital stay till surgery at the neurosurgery department.
2. Hospital stay after initial admission (state *2-7*): Costs from surgery, imaging after surgery, and hospital stay at the neurosurgery department. All radiology within one month after surgery is incorporated in the costs since the model time is one month.
3. Follow-up after surgery (state *8, 10, 12, 21, 23, 25*): Costs for yearly consult with the neurosurgeon.
4. Adverse event after surgery (state *9, 11, 13, 22, 24, 26*): Costs from consulting with the neurosurgeon, imaging at the radiology department, and hospital stay at the neurosurgery department.
5. Revision (state *14*): Costs arise of hydrocephalus symptoms till surgery, which are: consulting with the neurosurgeon, imaging at the radiology department, and hospital stay till surgery at the neurosurgery department.
6. Hospital stay after revision (state *15-20*): Costs for a yearly consult with the neurosurgeon.

Methods

All costs are based on direct cost measures from the MST hospital for patients treated with a ventricular shunt. The patient-specific cost data of the neurosurgery department were received from the financial department of the MST and anonymised. Together with a neurosurgeon from the MST hospital, the patient-specific characteristics of the electronic health record (EHR) are connected to patient-specific costs. The patient-specific costs are then transformed into the costs from 2020 to determine the costs of current clinical practice. Next, the average costs based on the most common clinical pathway of the selected patients is used as model parameter for the costs per state.

A database from a neurosurgical department for paediatric patients in the Netherlands was preferred. However, it was impossible to visit this department due to COVID-19 constraints.

Results

In total 139 patients underwent a surgical procedure related to liquor drainage at the neurosurgery department of the MST hospital between 1/2013 and 11/2020. Of those patient, 49 patients received a liquor drainage (placement of an external drain or VP shunt). Only the costs of patients who received a VP shunt are determined. The patient characteristics are of those patients are shown in Table .

Table 7.1: Patient characteristics of patients who received a VP shunt between 1/2013 and 11/2020 at the MST hospital

Characteristics	**No. of patients (%)**
Cause of hydrocephalus	
Primary	7 (39%)
NPH	4 (58%)
Congenital childhood	1 (14%)
Congenital adult	1 (14%)
Slit ventricle	1 (14%)
Secondary (haemorrhage or tumour)	11 (61%)

The total costs per category based on the surgical procedure of the MST hospital are shown in Table 7.2. The costs of the surgical procedure are based on all 18 patients, who underwent a shunting procedure, in which distinction is made between initial admission and revision. In total 11 patient developed hydrocephalus as secondary disease. Those patients mostly require extra hospitalisation, consults and radiology for their primary disease. However, since the correlation of the clinical procedures to hydrocephalus was hard to make, those patients are excluded in the analysis for hospital stay, consults, and imaging. In total costs for revision are based on three patients who have hydrocephalus as primary disease and received a revision. For all patients the average number and range is assigned.

Table 7.2: Costs per category based on the patient specific cost from the neurosurgery department at the MST hospital

Parameter	Average	Range	Costs per attribute (€)
Initial admission			
Total (Monthly)			**2,799.44 (1,976.37 - 3,622.51)**
Hospital stay (no. of days)	3	2 - 4	823.07
Consult (no. of visits)	1	-	215.76
Radiology (no. of CT scans)	1	-	114.47
Hospital stay after initial admission			
Total (Monthly)			**8,098.86 (5,629.65 - 10,568.07)**
Surgery (no. of surgeries)	1	-	2,677.68
Hospital stay (no. of days)	6	3 - 9	823.07
Consult (no. of visits)	1	-	196.39
Radiology (no. of CT scans)	1	-	286.37
Follow-up after surgery			
Total (Yearly)			**196.39**
Consult (no. of visits)	1	-	196.39
Adverse event after surgery			
Total (Monthly)			***5,386.85***
Hospital stay (no. of days)	6	-	823.07
Consult (no. of visits)	1	-	260.75
Radiology (no. of CT scans)	1	-	187.68
Revision			
Total (Monthly)			**3,622.51 (1,976.37 - 5,268.65)**
Hospital stay (no. of days)	4	2 - 6	823.07
Consult (no. of visits)	1	-	215.76
Radiology (no. of CT scans)	1	-	114.47
Hospital stay after revision			
Total (Monthly)			**4,884.48 (3,238.34 - 8,176.76)**
Surgery (no. of surgeries)	1	-	1,932.51
Hospital stay (no. of days)	3	1 - 7	823.07
Consult (no. of visits)	1	-	196.39
Radiology (no. of CT scans)	1	-	286.37

7.1.3 | Utility

The health-related quality of life (HRQoL) can be used to calculate the QALY by:

$$QALY = HRQoL \times years \tag{7.3}$$

HRQoL values are assigned to all states in the Markov model. The QALYs can be determined by the time spent in the specific state. In total, seven health states could be derived based on the design of the Markov model:

1. Initial admission (state *1*): Patients diagnosed with hydrocephalus suffer from symptoms.
2. Hospital stay after initial admission (state *2-7*): Patients who suffer from hydrocephalus symptoms undergo surgery and thereafter need to recover.
3. Patients with a functional shunt (state *8, 10, 21, 23*): Patients who have a functional shunt.
4. Adverse event after surgery (state *9, 11, 13, 22, 24, 26*): Patients who have post-operative complications.
5. Adverse event after surgery and incorrect catheter position (state *9, 11, 13, 22, 24, 26*): Patients who have complications (adverse event) after surgery and in which hydrocephalus symptoms arise due to incorrect catheter placement.
6. Patients with an incorrect catheter position (state *12, 25*): Patients in which hydrocephalus symptoms arise due to incorrect catheter placement.

7. Revision (state *14*): Patients in which hydrocephalus symptoms have arisen and need a revision.
8. Hospital stay after revision (state *15-20*): Patients who suffer from hydrocephalus symptoms undergo surgery and thereafter need to recover.

Methods All HRQoL parameters are conducted from literature. The utility in paediatric hydrocephalus patients is mostly determined by the hydrocephalus outcome questionnaire (HOQ) developed by Kulkarni et al. [66]. The parents of the hydrocephalus patient can fill in the questionnaire since paediatrics are mostly below 1 year if they get their first shunting procedure and cannot fill in the standard questionnaires. The HOQ-score can be transformed to the utility by:

$$HRQoL = 0.98 * HOQ + 0.1 \tag{7.4}$$

The HRQoL is used as input in the Markov model.

Results
The utility values are based on five studies [66, 67, 68, 69, 70]. Only two of them are performed in paediatrics patients which did not have all the utility information for all states [66, 67]. Therefore, to obtain the utility values for the other states the description and difference is used to derive the other parameters [68, 69, 70]. The following assumptions for each utility category are made:

1. Initial admission: No information is found according to the utility value in paediatric patients suffering from hydrocephalus symptoms. Therefore, the same decrease in utility is assumed as in adults [70]. This results in a utility value of 0.63.
2. Hospital stay after initial admission: Similar to the previous category, since these patients suffer from hydrocephalus symptoms and need to recover.
3. Follow-up after surgery: Utility value (0.77) is based on a study in paediatric patients [66, 67].
4. Adverse event after surgery: Due to an adverse event, the utility value decreases with 0.11 of the utility value in the follow-up after surgery, which results in a utility value of 0.66 [67].
5. Patients with an incorrect catheter position: Hydrocephalus symptoms arise, which results in a utility similar to initial admission (0.63).
6. Adverse event after surgery and incorrect catheter position: Due to an adverse event, the utility value decreases with 0.11, and hydrocephalus symptoms arise due to incorrect placement (similar to the previous category), which results in a utility value of 0.52.
7. Revision: Paediatric patients in which hydrocephalus symptoms arise need an urgent revision. This results in a decrease of 0.18 compared to patients with a functional shunt, resulting in a utility value of 0.59 [66, 67].
8. Hospital stay after revision: Similar to hospital stay after initial admission.

In Table 7.3 the input parameters for the utility in paediatrics are shown.

7.2 | Model parameters with USPAN

To determine the maximum headroom for the USPAN, the assumption is made that the device works perfectly. In the model this is incorporated by always assigning an optimal ventricular catheter placement in one attempt to all patients. The transition probability of optimal, incorrect and intermediate ventricle catheter's tip location is therefore 1, 0, 0 with the use of the USPAN.

7.3 | Uncertainty model parameters

The model parameters are derived from literature or expert elicitation. However, in many cases limited data was available. Therefore, these model parameter values are uncertain. This uncertainty differs per model parameter. However, due to the limited amount of data, the uncertainty of the model parameter is unknown. To incorporate the uncertainty of the parameter values in the model, an estimate of the upper and lower bound per parameter is done. All transition probabilities are assigned with a lower and upper bound of ±20%, except from the probability of a complication after one or multiple catheter insertion attempts. An upper and lower bound of ±50% of the original parameter value is determined

for this parameter value. Lowering the number of insertion attempts is one of the main features of the USPAN. Moreover, this parameter is highly uncertain because no conclusive values were found in the literature, and expert elicitation shows much variation. The uncertainty of the cost values assigned in the model is described in the costs section. The upper and lower bound of the HRQoL is ±5%. The range cannot be more extensive because the HRQoL cannot be lower in a healthy state compared to a health state with complications. An overview of the upper and lower bound per parameter is shown in Table 7.3.

7.4 | Conclusion

In this section, the fourth research question is answered: *What model parameter values are used for the model to determine the effectiveness gap and health services costs differences between the current procedure and the procedure with the USPAN?* In this chapter, the model parameters for the transition probabilities, HRQoL, and costs with the free-hand technique and with use of the USPAN are shown. Next, the uncertainty of all model parameter values is determined. An overview of all model parameter values is shown in Table 7.3.

Table 7.3: Overview of the model parameters with use of the free-hand technique and use of the USPAN.

Parameter	Base-case values	UB - LB	Reference
Costs (in euros)			
Initial admission	€2,799.44	€1,976.37 - 3,622.51	
Hospitalization (initial admission)	€8,098.86	€5,629.65 - 10,568.07	
Follow-up (healthy)	€196.39	€158.05 - 237.07	
Post-operative complications	€5,386.85	€4,309.48 - 6464.22	
Revision	€3,622.51	€1,976.37 - 5,268.65	
Hospitalization (revision)	€4,884.48	€3,238.34 - 8,176.76	
HRQoL			
Initial admission	0.63	0.599 - 0.660	same decrease as adults
Healthy with functional shunt	0.77	0.732 - 0.809	[66, 67, 68, 69]
Post-operative complication	0.66	0.627 - 0.693	[66, 67]
Healthy due to incorrect position	0.63	0.599 - 0.660	same as initial admission
Symptomps due to incorrect position and post-operative complication	0.52	0.494 - 0.546	hydrocephalus - adverse event
Revision of ventricular catheter	0.59	0.560 - 0.620	[66, 67]
Dead	0		
Transition probabilities			
Post-operative complication	0.10	0 - 0.176	[10, 49]
Revision after post-operative complication	0.34	0.272 - 0.408	[49]
Shunt survival after initial shunt placement with optimal/intermediate position	Survival curve	95% CI	[20]
Shunt survival after initial shunt placement/revision with incorrect position	Survival curve	95% CI	[8]
Shunt survival after revision with optimal/intermediate position	Survival curve	95% CI	[20]
Mortality after initial shunt placement	Survival curve	95% CI	[53]
Surgery related mortality	0.08	0.0064 - 0.0096	[65]
Free-hand			
Shunt optimal placed	0.56	0.452 - 0.678	[6, 7]
Shunt intermediate placed	0.11	0.088 - 0.132	[6, 7]
Shunt incorrect placed	0.31	0.248 - 0.372	[6, 7]
Shunt placed in one insertion	0.20	0.160 - 0.240	[10, 7]
Shunt placed multiple insertions	0.80	0.640 - 0.960	[10, 7]
USPAN			
Shunt optimal placed	1		
Shunt intermediate placed	0		
Shunt incorrect placed	0		
Shunt placed in one insertion	1		
Shunt placed multiple insertions	0		
Discounting (the Netherlands)			
Cost discount per year	4%		[71]
Effect discount per year	1.5%		[71]

8 | Headroom analysis

In this chapter, the last research sub-question is answered: *What are the results of the headroom analysis of the USPAN?* To answer this question, this chapter is divided into four sections. First, the model simulation and results are discussed and verified in section 8.1. Then, in the next section 8.2, the headroom is calculated using the model results. At first, the headroom is calculated for different willingness-to-pay (WTP) thresholds. Subsequently, the headroom is calculated with varying production costs. Finally, the probability of optimal placement and production costs are both varied to calculate the headroom in different scenarios. In section 8.3 the parameter's uncertainty is analysed by performing a deterministic sensitivity analysis (DSA). The method of the deterministic sensitivity analysis is described and the results are shown. Finally, section 8.4 answers the research sub-question.

8.1 | Model analysis

In this section first the Markov model simulation method is explained, after which the results are described.

8.1.1 | Simulation method

The Markov model is simulated in Heemod, an R-statistics package for Markov model simulations for health economic evaluations [72]. The Heemod package is an extensive toolbox. For this research, a Heemod simulation is performed to simulate the semi-Markov model described in Chapter 6. An overview of the architecture can be found in Appendix 14. The input structures for this simulation are: *Strategies, model parameters, transition probability matrix, horizon time, cycle time and cohort size*
Strategies are the proposed treatment options. In our research, the strategies are shunt surgery using the free-hand technique or using the USPAN. The model parameters and transition probability matrix are strategy dependent and must be assigned in both strategies.
Model parameters are the transition probabilities, state values, and discount values. The model parameters and values used as input of this simulation are described in Chapter 7, where an overview of these parameters can be found in section 7.4. Each transition probability can be defined as time-independent or time-independent. Time-independent are fixed values. Time-dependent model parameters can depend on model time, time spent in the model, or state time, time spent in a given state. In our model, the mortality due to ageing depends on the model time. All other time-dependent model parameters depend on the state time. The State values are assigned for each health state and can be split into costs and HRQoL. The costs and HRQoL will be discounted during the model time.
The *Transition probability matrix* is based on the transition diagram described in Chapter 6. For each position in the matrix, a transition probability is assigned. The transition probabilities per row should always be 1.
The model can then be run for the chosen *time horizon, cycle time and cohort size*. Unfortunately, it is not possible with this simulation package to select a *time horizon* till all patients reach the death state. This resulted from limiting computer power needed to run the simulation, and the long running time. However, the approach of the simulation can be used in future research. Therefore, a model time of 5 years was used for most calculations in this research. A model time of 10 and 20 years was only used to calculate the maximum headroom, with a running time of 12 and 21 hours.
The *cycle time* in this simulation is in months. The ideal cycle time in this research would be in weeks because the initial admission, hospitalisation, and revision states are up to four weeks. However, this will increase the computational time, or a shorter model time should be chosen. The cohort size is 1000 paediatric patients, all suffering from hydrocephalus and will receive shunting surgery.

The *cohort size* is chosen large enough to determine the distribution of patients among all health states. The output of this simulation is the total costs and QALYs per strategy. The code can be found at Github [73].

8.1.2 | Model results

The simulation output is the number of patients assigned to a specific health state per cycle and the related costs and HRQoL per cycle. The results are separately shown for both surgical procedures and compared in this section. First, the distribution of patients is described for both strategies, whereafter the total costs and QALYs per strategy are defined.

Patient distribution

All 1000 patients are assigned with hydrocephalus and therefore start in the *initial admission* state. Next, they are all hospitalised, after which they are distributed to the health states for follow-up. The distribution of patients over the states in the follow-up for 90 days, one year and five years after hospitalisation is shown in Table 8.1. Additionally, the number of patients per health state per cycle is shown in Figure 14.3 (Appendix 14).
After 90 days, 58% of the patients in the follow-up and operated on using the free-hand technique have an optimal, 12% an intermediate, and 29% an incorrect ventricle catheter's tip location. This distribution of patients corresponds comparably with the transition probabilities for optimal, intermediate and incorrect placement of the catheter tip, which are 56.5%, 11.6% and 31,9%. This slight deviation between the in and output values is due to patients undergoing a revision (9.7%) or died (2.3%).
When the USPAN is used for surgery, all patients receive an optimal placement of the catheter tip. Therefore, fewer patients are undergoing a revision (6.1%). The USPAN does not influence mortality, which results in the same mortality as using the free-hand technique.
After one year, the model predicts that 83% of the patients with an optimal catheter tip location (without post-operative complications) and 84% of the patients with an intermediate location has still an operating initial shunt. Only 52% of patients with an incorrect catheter tip position still have an operating initial shunt. These three percentage corresponds relatively with the implemented transition probability for shunt survival with an optimal catheter tip location (Figure 7.1a). In the situation where the USPAN is used, the decrease of patients with an optimal catheter tip location is 83%, similar to the free-hand technique.
In total, 254 patients have at least one revision, of which 53% have an optimal catheter tip location, 0.5% have an intermediate, and 11% have an incorrect location. The other patients are hospitalised for revision. The distribution of patients in the follow-up after revision cannot be directly compared to the assigned transition probabilities. This is because patients in the follow-up after revision can have one, two or even more revisions, and are mixed up in these health states.
After five years, it can be noticed that the percentage of patients (63%) who have at least one revision, an optimal catheter tip location and no complication is increasing. This increase can be explained by the probability of getting an optimal catheter tip location being higher than getting an intermediate or incorrect catheter location and the possibility that the patient can have multiple revisions. Thus, Patients will have a higher chance of having an optimal catheter tip location every time they undergo a revision than an intermediate or incorrect catheter location.
The mortality after five years is 15%. This percentage corresponds well with the implemented mortality (see Figure 7.1e).

Costs

Figure 8.1 shows the costs per patient per cycle. In the first two cycles, the costs of using the free-hand technique or USPAN is the same because all patients receive the same treatment. In the subsequent cycles, the costs of using the free-hand technique are higher than using the USPAN. This is because more patients receive a revision when using the free-hand technique (55%) compared to the USPAN (44%), which entails higher costs. The total costs per patient after five years is €19,005 with the use of the free-hand technique, compared to €15,470 with the use of the USPAN (Table 8.2. This results in a cost difference of €3,535 in favour of using the USPAN.

Table 8.1: Distribution of hydrocephalus patients over the health states in the Markov model 90 days, 1 year and 5 years after initial shunting surgery. R/H contains the health states revision and hospitalization after revision. Compl are all patients who suffer from a post-operative complication.

	Follow-up initial admission				**Follow-up revision**					
	Opt	Interm	incorr	compl	Opt	Interm	incorr	compl	R/H	death
Time after surgery										
Free-hand										
90 days	517	106	257	0	0	0	0	0	97	23
1 year	431	89	144	0	134	1	28	2	89	82
5 years	316	65	66	0	263	54	57	1	19	159
USPAN										
90 days	916	0	0	0	0	0	0	0	61	23
1 year	764	0	0	0	128	0	0	1	26	82
5 years	560	0	0	0	269	0	0	1	12	159

QALY

All hydrocephalus patients undergoing a shunting procedure with use of the USPAN have an optimal placement of the shunt. In contrast, with use of the free-hand technique, patients can also have an intermediate or incorrect position. These patients have a higher chance of receiving a revision, which results in a lower HRQoL. Therefore, on average, the HRQoL is lower with use of the free-hand technique compared to the use of the USPAN, which causes lower QALYs with the free-hand technique compared to the USPAN (see Figure 8.1). The QALYs per patient after five years is 3.163 with the free-hand technique, compared to 3.281 with the use of the USPAN (see Table). This results in a QALY difference of 0.118 in favour of using the USPAN.

8.1.3 | Longer time horizon

The total costs and QALYs are also determined with a time horizon of 10 and 20 years. The results are shown in Table 8.2. The difference in costs and QALYs of both surgical procedures is increasing in favour of the USPAN (ΔQALY is 0.19 after 10 years and 0.31 after 20 years). This can be explained by the lower number of revisions on yearly basis using the USPAN compared to the free-hand technique.

Table 8.2: Total costs and QALYs with the free-hand technique and with use of the USPAN over a time horizon of 5, 10 and 20 years.

	Time horizon (years)		
	5	**10**	**20**
Free-hand			
Total costs (p.p.)	€ 19,005	€ 22,630	€ 26,461
QALY (p.p.)	3.163	5.884	10.405
USPAN			
Total costs (p.p.)	€ 15,470	€ 18,048	€ 20,935
QALY (p.p.)	3.281	6.076	10.713

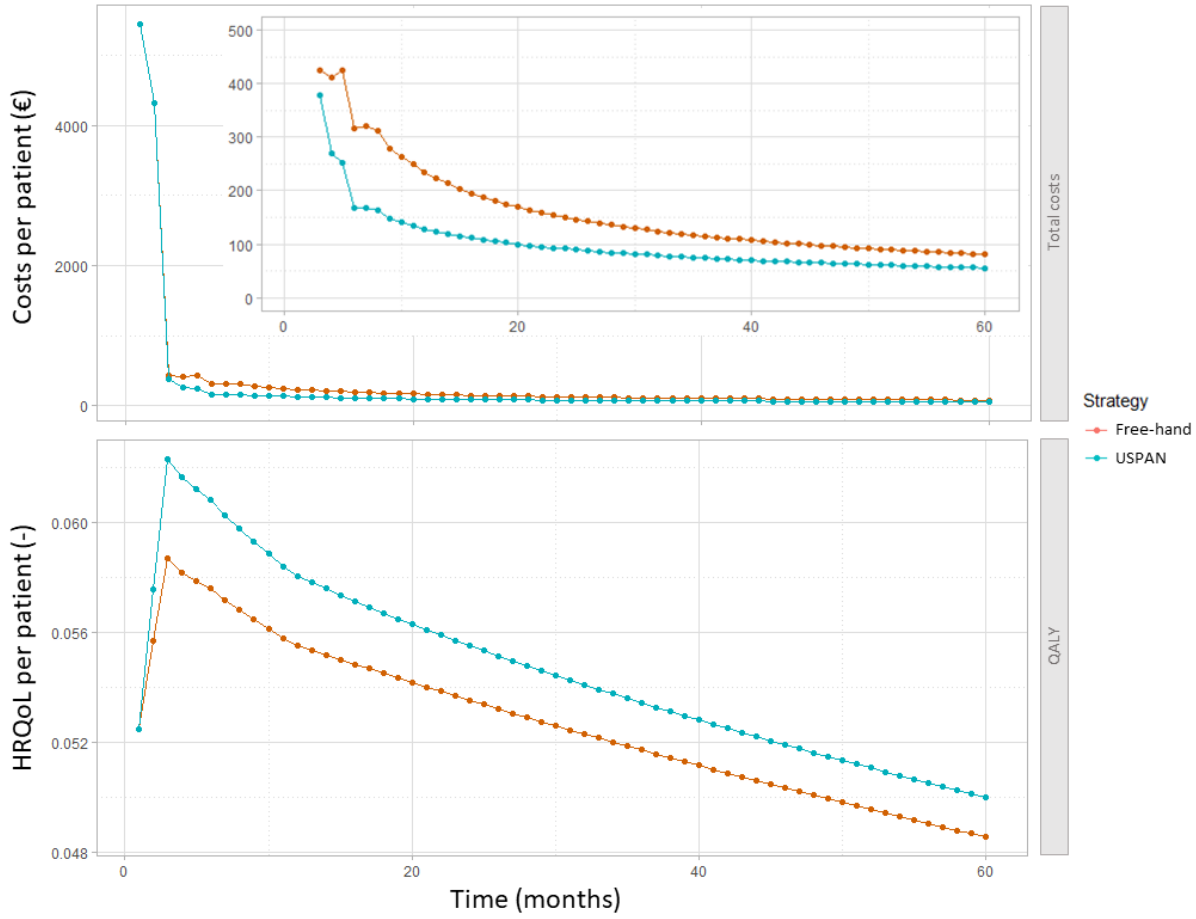

Figure 8.1: The output of the model simulation for the free-hand technique and with use of the USPAN, in which the cycle time in the model is in months with a time horizon of 5 years. a) Costs per patients per month, a.1) is a zoom in of a) in which the costs are shown over a smaller costs range (€0-500). b) HRQoL per patient per month.

8.2 | Headroom analysis

As introduced in the introduction (Chapter 3), the headroom can be calculated with the following equation:

$$h = \lambda \times \Delta QALY - \Delta costs \tag{8.1}$$

where λ is the willingness-to-pay (WTP) threshold, $\Delta QALY$ is the difference in QALYs due to the use of the new device compared to the current golden standard, and $\Delta costs$ is the difference in the expected health service cost of the new device compared to the current golden standard.

In the Netherlands, three WTP thresholds are used based on the burden of disease, €20,000, €50,000 and €80,000 [33]. The *Zorginstituut Nederland* describes in their report that the burden of disease is not easy unambiguously to establish. Moreover, they describe different methods in which age or urgency can be the driving factor. In this research, we use the proportional shortfall method, mainly applied by the *Zorginstituut Nederland*. The proportional shortfall method can be calculated by:

$$Burden\ of\ disease = \frac{(remaining\ QALYs\ without\ disease\ ) - (\ remaining\ QALY\ with\ disease)}{(remaining\ QALYs\ without\ disease)} \tag{8.2}$$

In hydrocephalus patients, this results in a burden of disease of 0.41 (remaining QALYS without disease is 85, remaining QALYS with the disease is 50.1), corresponding to a WTP threshold of €50,000. In this research €50,000 will be mainly used in the subsequent calculations. However, due to the unambiguous burden of disease and discussions on whether the proportional shotfall method is still conforming to the current zeitgeist, the headroom for the maximum reimbursable price is also calculated for the other WTP thresholds.

The simulation outcomes on the total costs and QALYs for both strategies (with the free-hand technique and using the USPAN) are described in the previous section. The $\Delta QALY$ and $\Delta costs$ (see Table 8.2) can be determined from these outcomes and are used to calculate the headroom.

In this section, the headroom is calculated for three different conditions. First, the headroom is calculated to determine the maximum reimbursable price (MRP) [REF chapman]. Next, the headroom is calculated by taking into account the manufacturing costs. Finally, the manufacturing and the probability of optimal ventricular catheter tip placement are considered to calculate the headroom.

8.2.1 | Headroom

The headroom is calculated for the MRP, which is the price without considering costs such as production or research costs. This headroom is calculated for three time horizons, 5, 10 and 20 years. Table 8.2 shows the input values for this calculation.

The total headroom for the prevalence of hydrocephalus can be calculated with the prevalence in the Netherlands. Every year, 3 out of 1000 paediatric patients in the Netherlands develop hydrocephalus (see Chapter 4). In addition, 160,000 babies are born in the Netherlands each year, resulting in 480 cases of hydrocephalus in paediatrics.

Results

The incremental cost-effectiveness plane for a time horizon of 5 years is shown in Figure 8.2. The blue dot displays the increase in costs and QALYs of the USPAN compared to the free-hand technique. The vertical dotted line shows the headroom for three WTP thresholds €20,000 (red), €50,000 (yellow), and €80,000 (blue), with a headroom of respectively, €5,899, €9,420, €12,951. The headroom for all three WTP thresholds is positive, which could allow proceeding with the development of the USPAN.

Next, the headroom is calculated for a 10 and 20 years time horizon considering the three WTP thresholds. The results are shown in Table 8.3. The headroom for a WTP threshold of €50,000 from

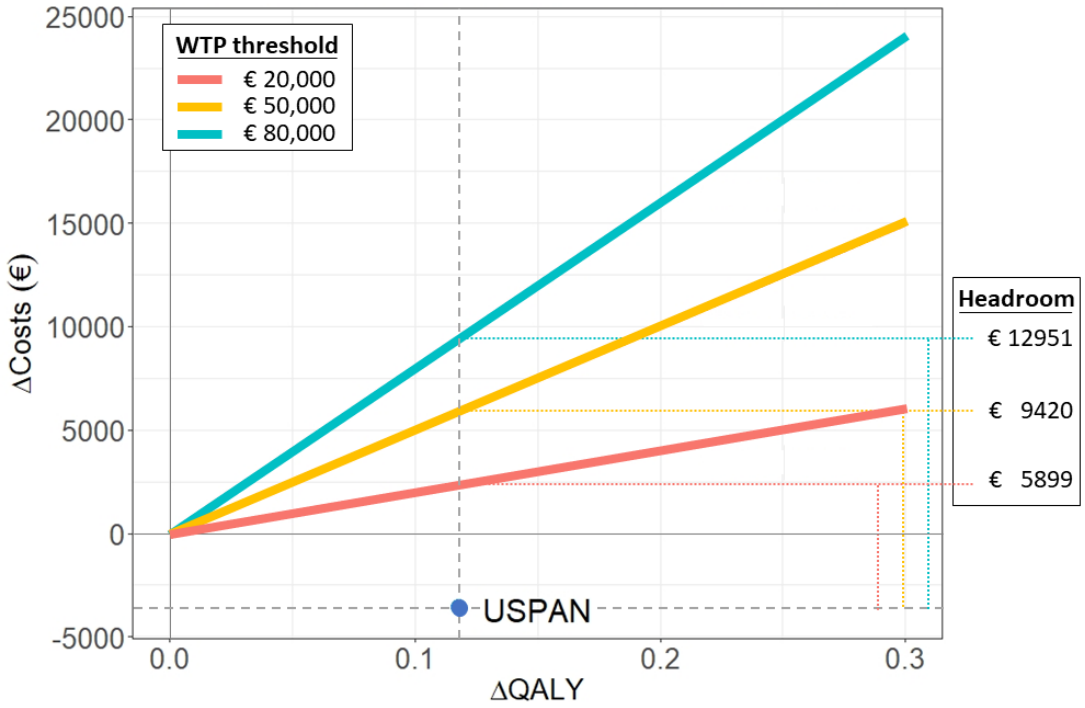

Figure 8.2: Incremental costs effectiveness plane showing the headroom for three different WTP thresholds. The time horizon was 5 years.

5 to 20 years time horizon increases with €11,485. This increase can be explained by the number of revisions, which is higher with the free-hand technique than with the use of the USPAN. Revisions are assigned with lower HRQoL and higher costs, which results in a lower QALY and higher total costs per person. Next, the rise in headroom over the time horizon decreases. From 5 to 10 years time horizon, the headroom increases with €4799. From 10 to 20 years time horizon, the headroom increases with €6686 while the difference in horizon time is doubled. This can be explained by more patients receiving an optimal catheter tip location, which results in a lower chance of shunt revision compared to lower accuracy of the tip location. The distribution of patients for both strategies is, therefore over time, getting closer to each other, which results in a decreasing rise of the headroom.

Finally, each year 480 paediatrics develop hydrocephalus in the Netherlands. The total headroom after a time horizon of 5 years and a WTP of €50,000 is €4.5 million. For a time horizon of 10 and 20 years, the total headroom is €6.8 million and €10,0 million, respectively.

Table 8.3: The headroom shown for three different WTP thresholds and three different time horizons

	Time horizon (years)		
	5	**10**	**20**
WTP (€)			
20,000	€ 5,889	€ 8,436	€ 11,678
50,000	€ 9,420	€ 14,219	€ 20,905
80,000	€ 12,951	€ 20,001	€ 30,133

8.2.2 | Headroom - manufacturing costs

Manufacturing costs are direct cotsts, which includes the raw materials and labor. This should not be confused with production costs, in which also indirect costs are involved, such as overhead expenses. The estimated manufacturing costs for the USPAN are €1200. This is based on the costs of the photoacoustic

needle (PAN), developed by the Imaging Needle consortium, which also includes the USPAN [15]. The costs of the PAN are €1500. However, the USPAN is less complex, which results in an expected lowering of €300. The costs are uncertain. Therefore the manufacturing costs used in the simulation range between 0 and 2000.
The developers propose to make the USPAN disposable since sterilisation of the device might be challenging. Therefore the manufacturing costs of the USPAN are added to the surgery costs in the USPAN simulation strategy.
The headroom is calculated for three WTP thresholds over a time horizon of 5 years.

Results

Figure 8.3 shows the headroom per manufacturing costs of the USPAN for three WTP thresholds. It can be seen that with manufacturing costs of €1200, the headroom is €7602 by a WTP threshold of €50,000. Moreover, the headroom is positive with maximum expected manufacturing costs of €2000 for all three WTP thresholds.
Taking the prevalence of hydrocephalus into account, the headroom for a time horizon of 5 years is €3.6 million for a WTP of 50,000. The headroom is 0.9 million lower than the headroom without considering the manufacturing costs.

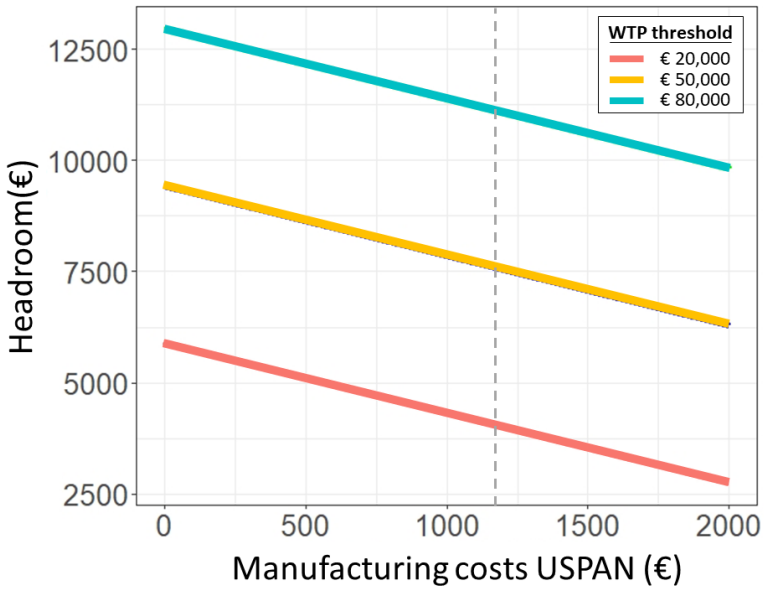

Figure 8.3: The headroom for different manufacturing costs with a time horizon of 5 years. Three different WTP thresholds are shown.

8.2.3 | Headroom - scenarios

In the previous calculation of the headroom, the manufacturing costs are taken into account. However, the probability of optimal ventricular catheter tip placement with use of the USPAN is 1. This means that in all shunting surgeries, the position of the catheter tip is optimal. However, this is not realistic. To determine the USPAN in a more realistic situation, the probability of optimal placement is lowered. The optimal catheter tip placement probability will range from 0.57 to 1, since the USPAN should always have a better performance than the free-hand technique to make the device functional. The manufacturing costs are again ranging from €0 to 2000. The costs are increasing to €2000 in 6 steps and the probability from 0.56 to 1 in six steps. More steps were impossible due to the lack of computer memory (32Gb RAM). The time horizon during the simulation was five years.

Results

Figure 8.4 shows the headroom after five years time horizon for each scenario with a WTP threshold of 50,000. It can be seen that the headroom is positive for all scenarios where the probability of optimal

catheter tip location is higher than 0.78. Moreover, with a probability of optimal placement of 0.71 and manufacturing costs lower than €2000 the headroom is positive. For a probability of optimal placement of 0.63 the headroom is only positive if the manufacturing costs are lower than €1200. This chance is low, since the expected manufacturing costs are €1200. When the probability of optimal placement of the USPAN is equal to the free-hand technique, the headroom is negative for all manufacturing costs. Due to a slight rounding factor in the probability of optimal placement of the USPAN, the headroom of the USPAN is negative for 0 manufacturing costs instead of 0.

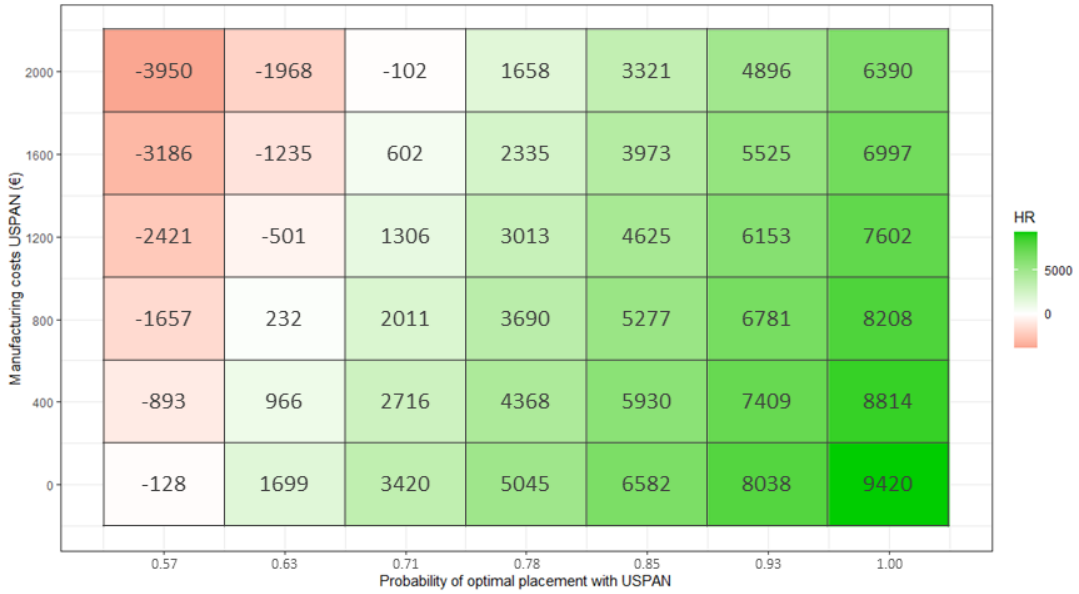

Figure 8.4: The headroom after 5 years time horizon for varying manufacturing costs and probability of optimal placement with the USPAN.

8.3 | Deterministic sensitivity analysis

Uncertainty is incorporated in all model parameters in our simulation. Therefore, the effect of this uncertainty can be assessed by varying the parameter values and determining the model results for this range of values. A method to assess the uncertainty is a sensitivity analysis. In this research, only each parameter's upper and lower bounds are known. Therefore a suitable method is the deterministic sensitivity analysis (DSA) [74]. Each parameter value in a DSA is changed one-by-one for the upper and lower bounds.

8.3.1 | Methods

In the Heemod package, a built-in module is available to calculate the total costs and QALYs per parameter's upper and lower bound. The input parameters are shown in section 7.4 of the previous Chapter. Based on the simulation outputs per parameter, the headroom can be calculated.

The DSA is highly computational expensive, resulting in a long running time. Therefore again, a horizon time of 5 years is used. The WTP threshold is €50,000.

8.3.2 | Results

Figure 8.5 shows a tornado diagram with the results of the DSA. For each parameter, the upper and lower bound values are displayed by the bar numbers. In addition, the headroom for each parameter's upper and lower bound is shown on the x-axis. The size of the bar describes the degree of variation in headroom. The parameters are ordered by the size of variation in headroom. The tornado diagrams for the $\Delta costs$ and $\Delta QALY$ are shown in Appendix 14.

It can be seen that the headroom is positive for all parameters upper and lower bound in the shown tornado diagram (see Figure 8.5). The three parameters with the most varying headroom will be described.
First, the probability of optimal placement in the free-hand technique shows the highest variation. The lower bound of this parameter (0.452) results in a headroom of €12,456, and the upper bound (0.678) results in a headroom of €6661. This parameter is the main deviating parameter of the free-hand strategy compared to the USPAN, in which this parameter is 1. This might be the reason that varying this parameter might have the most significant impact on the headroom. Additionally, for the $\Delta costs$ and $\Delta QALYs$ this is the parameter with the most variation in headroom. The highest influence is caused by the $\Delta QALY$.

Second, the HRQoL of healthy patients has a variation in headroom between €7814 (lower bound of 0.732) and €11026 (upper bound of 0.809). The states correlated to this parameter are the healthy states with an optimal or intermediate position of the catheter's tip. Most patients will enter and stay the majority of the cycles in these healthy states, which causes a high impact on variation in the headroom.

Finally, the HRQoL of patients with an incorrect catheter position has a variation in headroom between €10,624 (lower bound of 0.599) and €8,274 (upper bound of 0.660). Patients assigned to a health state with an incorrect catheter position have a lower HRQoL than those in the healthy states. However, these patients will not directly receive a revision. In this simulation, approximately 30% of the patients will enter this health state after initial admission, and around 50% of the patients stay there for at least 7 cycles. This might explain the high impact on the variation in the headroom.

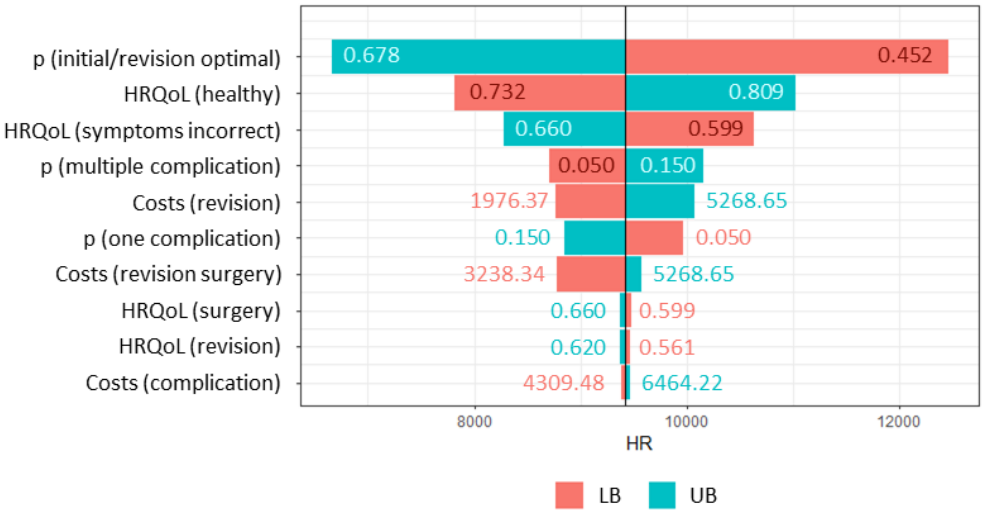

Figure 8.5: Tornado plot of the deterministic sensitivity analysis. LB = lower bound and UB is upperbound. The values in the diagram are the lower and upperbound of each parameter.

8.4 | Conclusion

In this section, the last sub-research question is answered: *What are the results of the headroom analysis of the USPAN?*
In this chapter, the headroom is first calculated for the MRP, after which the manufacturing costs and the probability of optimal placement of the catheter's tip. The headroom for the MRP with a WTP threshold of €50,000 is calculated for a time horizon of 5, 10 and 20 years, which results in a headroom of €9,420, €14,219, and €20,905, respectively. Taking into account the prevalence of paediatric hydrocephalus in the Netherlands, the headroom is €4.5 million, €6.8 million and €10.0 million, respectively. A decreasing rise in the headroom can be noticed from these three horizon times. If the manufacturing costs are considered, the headroom lowers compared to the MRP. The most probable manufacturing costs are €1200, resulting in a headroom of €7602. When the probability of optimal placement is considered with the same manufacturing costs, the headroom is positive for all optimal catheter tip placement probabilities above 0.71. Finally, based on the DSA the parameters with the most significant impact on the headroom are determined. These parameters are all derived from the free-hand technique strategy in

the simulation. The parameters in the order of the most significant impact are the probability of optimal placement, the HRQoL in healthy patients, and the HRQoL in patients with an incorrect catheter position.

9 | Discussion

This research consists of multiple steps to answer the final research question: *What is the headroom of the USPAN for hydrocephalus patients who undergo a shunting procedure in the Netherlands?* This chapter discusses the steps towards this final research question. The discussion is divided into six sections, corresponding to the chapters of this thesis.

9.1 | Clinical conditions

The literature study revealed that hydrocephalus has a complex origin. For example, the prevalence is wide (0.8 to 81 per 10,000 live births). Even in the Netherlands, where most diseases are well reported, the prevalence of hydrocephalus is hard to determine. This is due to the wide range of etiologies and definitions used for hydrocephalus. Moreover, the distribution of hydrocephalus patients among the etiologies is inconsistent in the literature. Due to inconsistency or incompleteness, only a limited number of studies could be used during this research. Moreover, the type and incidence of complications were doubtful or not addressed in the literature. Altogether, choosing a specific patient group among the hydrocephalus patients for this research was challenging based on this limited amount of data.

9.2 | Expert elicitation

This study was mainly performed during the COVID-19 pandemic, which was a period with a high workload for all physicians. Therefore, most neurosurgeons were not available for an interview, and travelling towards the experts was not allowed. For this reason, it was chosen to develop an online questionnaire to still acquire the needed information from neurosurgeons, which was not available in the literature. The questionnaire had a significant response (50 out of 150 neurosurgeons in the Netherlands), but not all experts finished the questionnaire since it was too time-consuming. Another limitation was that asked percentages were categorised in large bins. When these percentages were used as model parameter values, it was challenging to choose a reasonable probability. The last limitation was the limited possibility of explaining the USPAN. The USPAN is a new technique which might need more explanation to make it understandable. Moreover, verification, if the experts understand it correctly, is necessary. This is a major drawback of using a questionnaire instead of performing interviews. Therefore in this early stage of development, a device interview would be more helpful. A Delphi study, in which consensus between all experts is asked in several rounds, would result in more validated outcomes.

9.3 | Model design

A semi-Markov model was developed to determine the effectiveness gap and the difference in health service cost between the free-hand technique and the use of the USPAN. This model was based on the care pathway of hydrocephalus patients and verified with a neurosurgeon. The model is complete, but a limitation is that this model structure is large for a simulation. This could also be a reason for the high computational costs. Another reason to simplify this model is that some model parameters were similar, while this was not expected before. An example is the shunt survival for optimal and intermediate placement. Because both survival curves were identical, the related health states could be merged. An advantage of this structure is that this model could be used in future research. The headroom method is an iterative process, and currently, limited data is available. Therefore in future research, it could be possible that the parameters of optimal and intermediate placement are different, and both health states

are necessary.
Moreover, in this research, a cohort model was chosen over an individual patient. A cohort model is suitable because this early stage of technology development does not need to obtain individual patient results or vary patient characteristics within the cohort. However, the limitation is that it was not possible with this type of model to determine the number of revisions patients receive or how much time they spend in a specific health state. An individual patient model should be chosen above a cohort model to obtain this information, which would be helpful in a later stage of product development.

9.4 | Model parameters

The model parameters consist of three main categories: transition probabilities, HRQoL, and costs. The model parameters were mainly based on the literature study performed. Unfortunately, a lot of variation exists in the literature regarding hydrocephalus patients. This made it hard to find relevant data to implement in the model. However, since the data was best available, it was still chosen to use this data as parameter values. Due to the limited amount of data, a lot of uncertainty was incorporated into the model. A sensitivity analysis was performed to verify the amount of uncertainty. However, updating the model if better data is available is advisable.
Another limitation is the quality of the survival data found in literature. Most studies were retrospective single centre studies with a relatively small patient population, heterogeneous etiologies of hydrocephalus, and a wide variety in patient characteristics. Moreover, comparison was hardly possible since the studies have minor differences in the use of imaging during treatment, are performed in different decades (which can have a significant influence on the treatment outcome), and many patients were lost in the follow-up. However, since limited data was available this was the best to use.
The HRQoL assigned to patients who received an incorrect ventricle catheter's tip location is an important parameter, according to the DSA outcomes. Contradictaries are available about these patients in the literature. Some studies argue that these patients have a more extended period of shunt complications compared to patients with an optimal catheter position. Therefore an additional health state could be added in between incorrect position and revision to assign a lower HRQoL to these patients for a shorter period but longer than for patients with optimal catheter position. This will result in less impact on the headroom due to an incorrect catheter position and probably a more realistic situation. However, in this research, this was not incorporated to lower the computational costs.
Lastly, the costs were based on a database of the MST. However, in the MST hospital, no paediatric patients were treated. Therefore, the costs are not entirely accurate for the chosen patient group. But since the treatment in adults and paediatrics is the same, it was still chosen the use this database. The reason for not going to another hospital was the COVID-19 pandemic, in which less travelling was recommended. The MST hospital was willing to participate and was in the neighbourhood, which made it easier to still go to the hospital and acquire a database. Also, this was the best information available in this case, but if possible, a hospital with a paediatric care database would be favourable.

9.5 | Headroom analysis

To determine the costs and QALYs per strategy, a semi-markov model was simulated in the heemod package. This model uses time as a third dimension of the transition matrix. This resulted in an exponential increase of computational time. Therefore a limited time horizon was chosen. To overcome this problem, a different type of simulation should be used.
Next, the headroom calculations for the MRP were performed based on the Markov model outcome. The headroom was determined for three WTP thresholds (€20,000, 50,000, and 80,000) over a time horizon of 5, 10 and 20 years. In all situations, the USPAN was favourable in terms of costs and effectiveness, which resulted in positive headroom. However, currently medical devices have a short life span in the clinic. If we assume a horizon time of 20 years the USPAN is used for 5 years in the clinic, the headroom is €50.2 million. The developers should think if this is enough to subsidise the production costs and further research.
To get an idea of the uncertainty of the model parameter values, a DSA was performed. In most research a probabilistic sensitivity analysis (PSA) is used. However, no knowledge was available of the distribution fitted around the parameters.

9.6 General

One remarkable outcome of the questionnaire was in which situations the neurosurgeons wanted to use the USPAN. A majority of neurosurgeons only want to use the USPAN if the ventricle can be detected from the cortext. In addition, neurosurgeons are not willing to use the device if it is already inserted partly in the brain.
Another outcome during discussions with neurosurgeons was that the USPAN should fit in the current catheter, where the impact on the current procedure is minimal. If the USPAN fits inside the catheter, there is a higher chance of adapting this device in the clinic. Moreover, if current catheters do not work, higher costs will be involved in shunting surgery due to, for example, different types of catheters needed. The developers should take the dection length and the size of the USPAN into account for further development.

10 | Conclusion & outlook

10.1 | Conclusion

This research was performed to answer the main research question: What is the headroom of the USPAN for hydrocephalus patients who undergo a shunting procedure in the Netherlands? To answer this question, a literature study was performed to obtain knowledge about the impact of inaccurate placement of the ventricular catheter and the number of attempts needed to place the catheter during the current performed surgical procedure for hydrocephalus patients. After this, the patient group who might benefit from the USPAN and the related current care pathway are determined. Next, missing information from the literature was determined by expert elicitation. Thereafter, a Markov model to reflect the care pathway of hydrocephalus patients was developed. The input parameters for the model were mainly derived from literature and completed with inputs from experts. Finally, the headroom was calculated to obtain the MRP. The headroom was also calculated for incorporating manufacturing costs, and the lower probability of optimal catheter tip placement with the use of the USPAN was also assessed. The headroom for the MRP with a WTP threshold of €50,000 is calculated for a time horizon of 20,000, 50,000 and 80,000, which results in headroom of €9,420, €14,219, and €20,905, respectively. Taking into account the prevalence of paediatric hydrocephalus in the Netherlands, the headroom is €4.5 million, €6.8 million and €10.0. If the manufacturing costs are considered, the headroom lowers compared to the MRP. The most probable manufacturing costs of the USPAN are €1200, resulting in headroom of €7602. When the probability of optimal placement is considered with the same manufacturing costs, the headroom is positive for all optimal catheter tip placement probabilities above 0.71. Finally, based on the DSA the parameters with the most significant impact on the headroom are determined. The parameters in the order of the most significant impact are the probability of optimal placement, the HRQoL in healthy patients, and the HRQoL in patients with an incorrect catheter position. Altogether, this research shows that the USPAN might have benefits in the clinic based on the headroom calculations. However, the headroom is an iterative process, so the model parameters need to be updated and more accurately determined to get a more accurate outcome for the headroom.

10.2 | Outlook

In this section, three major suggestions for future work are given. First, the model parameters in hydrocephalus patients incorporate high uncertainty. However, based on the DSA, three parameters which induce the most uncertainty in headroom outcome are determined. The probability of optimal placement, the HRQoL in healthy patients, and the HRQoL in patients with an incorrect catheter position. The first parameter can be determined by assessing CT scans of hydrocephalus patients in Dutch hospitals. The HRQoL can be determined based on the Questionnaire of Kulkarni et al. [9]. For all parameters, the prevalence and etiology of these patients can be established to create better model input parameters related to the patient cohort. Moreover, the headroom is determined based on manufacturing costs predicted by the developers. These costs are based on a disposable device. However, the developers should consider if a disposable is necessary and compare it with sterilisation of the device because this might significantly impact the headroom. Additionally, the probability of optimal ventricular catheter tip placement should be researched well. This probability has a high impact on the headroom outcomes.

Secondly, this research determined the headroom for paediatric patients with hydrocephalus. However, due to an ageing population, especially in the Netherlands, hydrocephalus might have a major prevalence in the elderly. Unfortunately, this was not feasible for this research since no data on prevalence was available. However, the elderly population might be interesting for future research. Additionally, paediatric patients in low- and middle income countries were the original target group of the USPAN. This population might also be an interesting population for future research.

Lastly, suppose more evidence is incorporated into the model due to less uncertain model parameter values. In that case, the return on investment can be calculated as the next step of the early health technology assessment.

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11 | Appendix

[Confidential]

12 | Appendix

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Beste deelnemer,

Deze vragenlijst maakt deel uit van onderzoek uitgevoerd aan de Universiteit Twente (UT). Het doel van deze vragenlijst is om meer inzicht te krijgen in de procedure van het plaatsen van een ventriculaire katheter. Daarnaast worden vragen gesteld rondom de gewenste klinische impact, behoefte en bruikbaarheid van een nieuwe technologie, om de ventriculaire katheter nauwkeuriger te plaatsen.

De vragen op de hierna volgende pagina's zijn verdeeld in **3 onderwerpen**; 1) informatie over uw ervaring, 2) de huidige techniek, en 3) uw visie op een nieuwe technologie voor het plaatsen van een ventriculair katheter. Hierbij kunt u de normale omstandigheden in acht nemen, welke mogelijk afwijken van de huidige situatie door het COVID-19 virus. De vragenlijst zal **ongeveer 15 minuten** in beslag nemen.

Alvast hartelijk bedankt voor het invullen van deze vragenlijst. We zullen u te zijner tijd informeren over de uitkomsten.

Kuan Kho, *Neurochirurg MST*
Erik Koffijberg, *Associate Professor UT*
Srirang Manohar, *Full Professor UT*
Erik Kruit, *PhD student UT*
Rianne Bulthuis, *Master student Biomedical Engineering en Industrial Engineering & Management UT*

Uw deelname aan dit onderzoek is volledig vrijwillig en u kunt zich elk moment terugtrekken door te stoppen met deze enquête. De data zullen geanonimiseerd worden en we zullen er alles aan doen om de data zo veilig mogelijk op te slaan. Uw informatie kan gebruikt worden voor wetenschappelijke onderzoek en publicaties aan de Universiteit Twente.

☐ Ik ga akkoord met de bovenstaande privacy verklaring

Wat is uw geslacht?

Wat is uw leeftijd?

20 tot 30 jaar ○ 30 tot 40 jaar ○ 40 tot 50 jaar ○ 50 tot 60 jaar ○ 60 jaar of ouder ○

Wat is uw huidige functie?

- ◯ Neurochirurg - Staflid
- ◯ Neurochirurg - Fellow
- ◯ AIOS jaar 1
- ◯ AIOS jaar 2
- ◯ AIOS jaar 3
- ◯ AIOS jaar 4
- ◯ AIOS jaar 5
- ◯ AIOS jaar 6

Hoe lang bent u reeds werkzaam in uw huidige functie?

0 - 5 jaar	5 - 10 jaar	10 - 15 jaar	15 - 20 jaar	20 - 25 jaar	25 - 30 jaar	30 jaar of meer
◯	◯	◯	◯	◯	◯	◯

Waar bent u werkzaam?

- ◯ Nederland
- ◯ België
- ◯ Anders, namelijk: _____

In welk type ziekenhuis bent u werkzaam?

- ◯ Academisch ziekenhuis
- ◯ Topklinisch ziekenhuis
- ◯ Anders, namelijk: _____

Hoeveel ventriculaire katheters heeft u in de afgelopen twee jaar exact of naar schatting geplaatst?

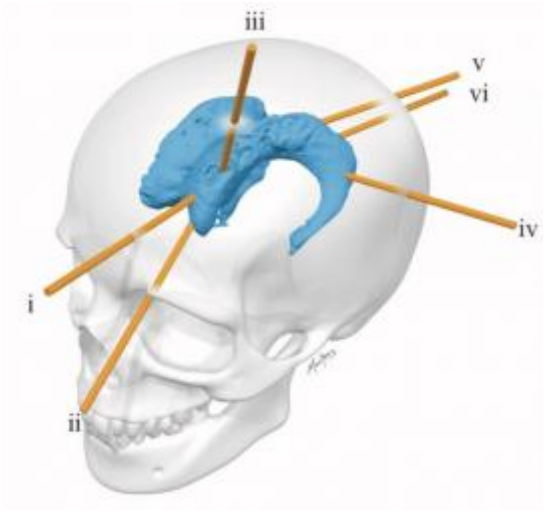
	Aantal ventriculaire katheters per jaar	Exact	Schatting
2019		◯	◯
2018		◯	◯

Bent u bereid vragen te beantwoorden met betrekking tot de nieuwe technologie?

- ◯ Ja

- ○ Nee

Via welke insertie punt(en) plaatst u de ventriculaire katheter voornamelijk? Maak een keuze uit een of meerdere van deze punten en gebruik hierbij onderstaande afbeelding.



Insertie punten: i) Kaufman, ii) Tubbs, iii) Kocher, iv) Keen, v) Frazier, vi) Dandy

- ☐ Kaufman
- ☐ Tubbs
- ☐ Kocher
- ☐ Keen
- ☐ Frazier
- ☐ Dandy

Wat is/zijn uw grootste doelgroep(en) voor het plaatsen van een ventriculaire katheter?

- ☐ Prematuren
- ☐ Baby's
- ☐ Kinderen
- ☐ Jong volwassenen
- ☐ Volwassenen
- ☐ Ouderen
- ☐ Anders, namelijk:

Welk type procedure voert u het meest uit?

- ◯ Spoed
- ◯ Electief
- ◯ Beide evenveel

Freehand-techniek

Onderstaande vragen gaan over het toepassen van de zogenoemde "freehand-techniek" bij het plaatsen van een ventriculaire drain. Bij de "freehand-techniek" word uitgegaan van het gebruik van de anatomische kenmerken voor het plaatsen van de ventriculaire katheter via een boorgat. Hierbij wordt géén gebruik gemaakt van technologie, zoals neuronavigatie of endoscopie.

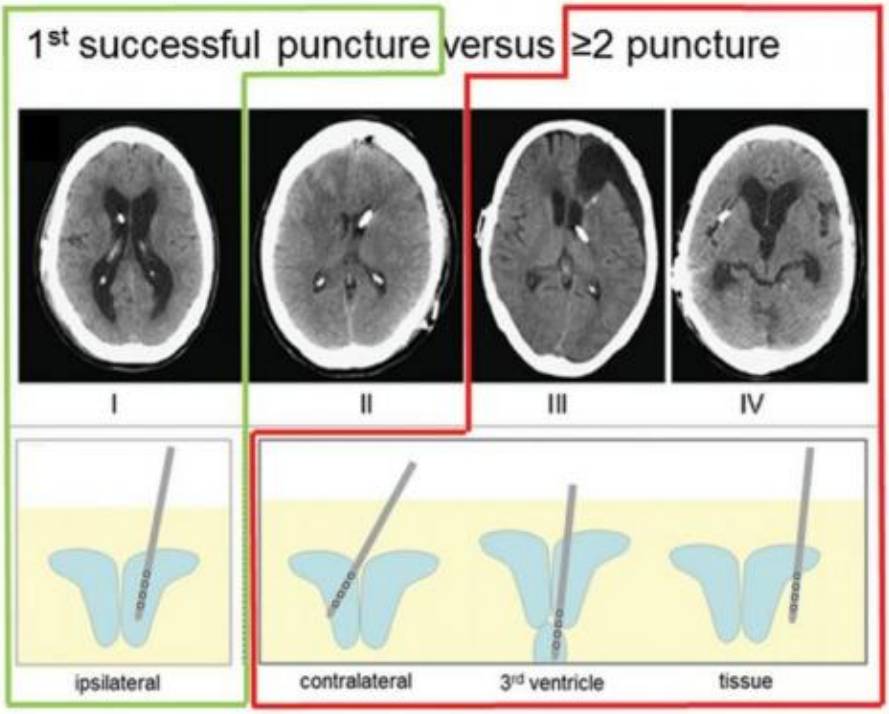
Welk deel van de ventriculaire katheters die u de afgelopen twee jaar geplaatst heeft, heeft u geplaatst met de freehand-techniek?

	Aantal ventriculaire katheters per jaar (%)
2019	
2018	

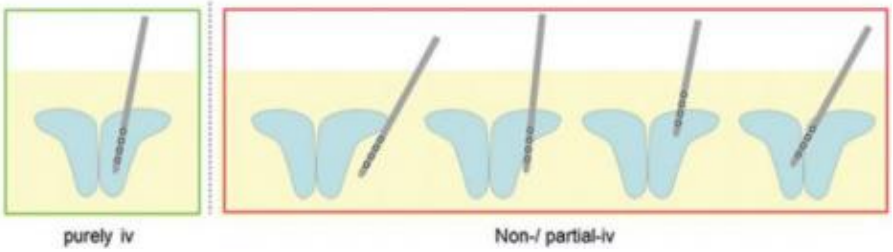
Onderstaande figuur (Thomale et al., 2018) illustreert een evaluatieschema voor de kwaliteit van de ventriculaire katheter positie. De evaluatie wordt gedaan aan de hand van 1) het aantal inserties tijdens de operatie, 2) de mate waarin de ventriculaire katheter omringd is met CSF, 3) de anatomische positie van de katheter punt 4) de positie van de katheter perforaties. Hierbij geeft de groene omkadering de ideale combinatie aan van deze 3 factoren en de rode omkadering de suboptimale combinatie.

De volgende vragen gaan over onderstaande figuur.

1. **Insertie pogingen**
2. **Gradatie**
3. **Anatomische positie**

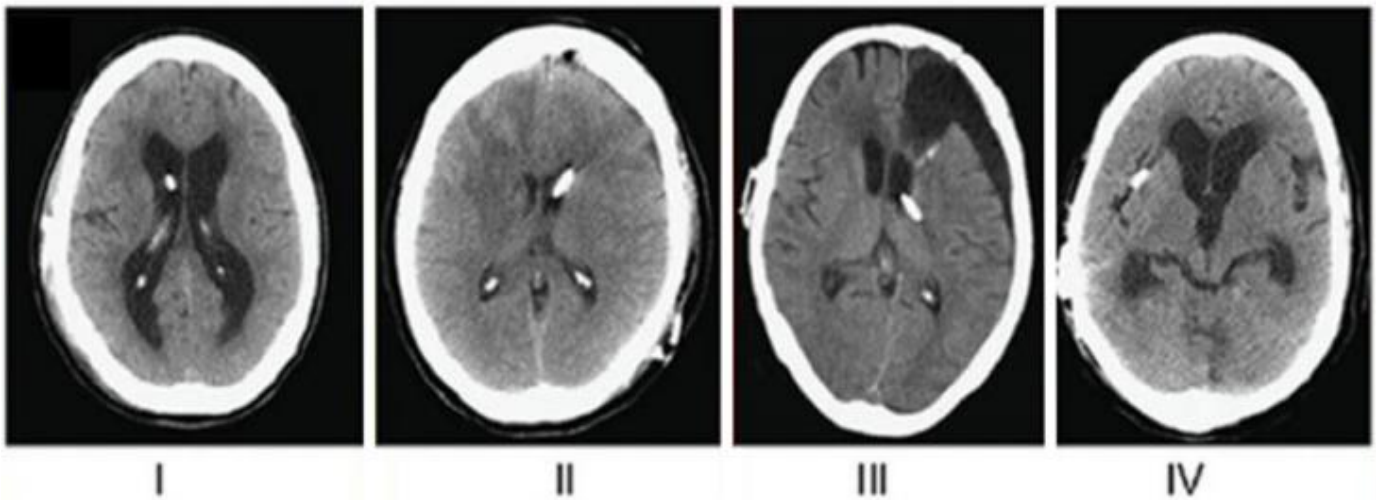


4. **Positie van de katheter perforaties**



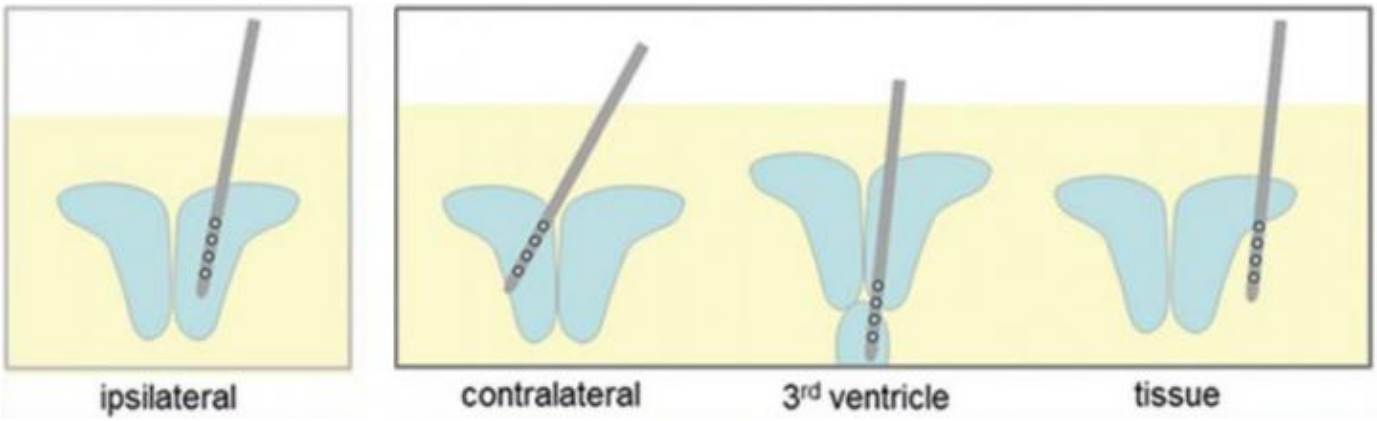
Hoe veel inserties heeft u gemiddeld nodig om de ventriculaire katheter te plaatsen tijdens een operatie?

1	2	3	4	Meer dan 4
○	○	○	○	○



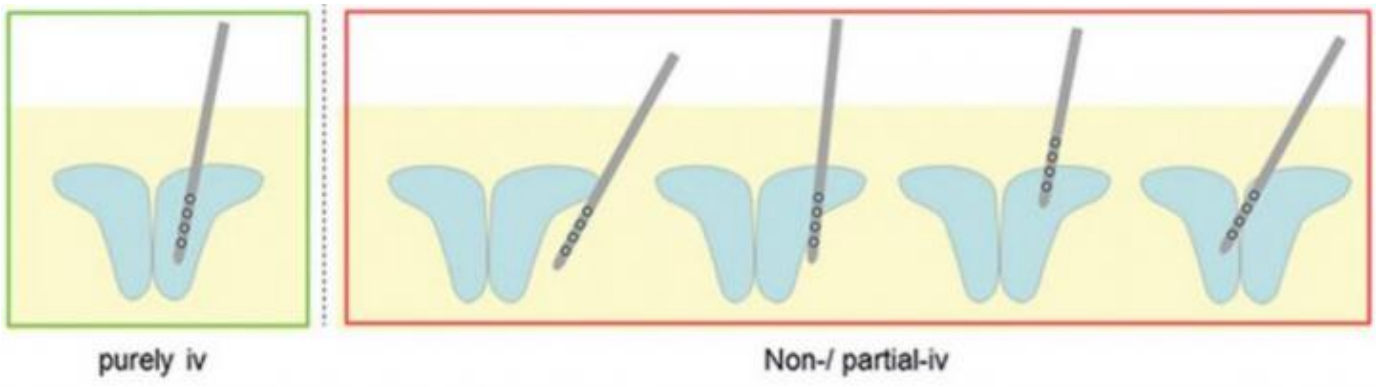
Als u naar de postoperatieve scans kijkt, hoe vaak heeft u de ventriculaire katheter naar schatting volgens de aangegeven gradatie geplaatst? Geef de kans dat u uit bent gekomen op de genoemde gradatie I-IV.

Grading I	0
Grading II	0
Grading III	0
Grading IV	0
Weet ik niet	0
Total	0



Als u naar de anatomische posities (figuur 3. anatomical positions) kijkt, hoe vaak heeft u de ventriculaire katheter naar schatting volgens de aangegeven posities geplaatst? Geef de kans dat u uit bent gekomen op de genoemde anatomische positie.

Ipsilateral	0
Contralateral	0
3rd ventricle	0
tissue	0
Weet ik niet	0
Total	0



Als u naar de positie van de katheter perforaties (figuur 4. position of catheter perforations) kijkt, hoe vaak heeft u de perforaties naar schatting volledig/gedeeltelijk of niet in de ventrikel geplaatst? Geef de kans dat u uit bent gekomen op de genoemde positie van de katheter perforaties.

volledig	0
gedeeltelijk	0
niet	0
Weet ik niet	0
Total	0

Als u naar de groene omkadering in het figuur bovenaan de pagina kijkt, hoe vaak heeft u de ventriculaire katheter optimaal geplaatst?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Als u naar de rode omkadering in het figuur bovenaan de pagina kijkt, hoe vaak heeft u de ventriculaire katheter suboptimaal geplaatst?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Beeldgestuurde technologie

Om een operatie te ondersteunen kan gebruik gemaakt worden van beeldgestuurde technologie. Hierbij kan gedacht worden aan neuronavigatie of robot gestuurde technieken op basis van een pre-operatieve MRI of CT, endoscopie, echografie etc.

Maakt u gebruik van beeldgestuurde technologie?

- ◯ Ja
- ◯ Nee

Welk deel van de ventriculaire katheters die u de afgelopen twee jaar geplaatst heeft, heeft u geplaatst met behulp van beeldgestuurde technologie? U hebt aangegeven dat u gebruikt maakt van de freehand-techniek in 2019 en in 2018 in ${q://QID64%231/ChoiceTextEntryValue/1/1}% en ${q://QID64%231/ChoiceTextEntryValue/2/1}% van de gevallen.

	Aantal ventriculaire katheters per jaar (%)
2019	
2018	

Welke beeldgestuurde technologie gebruikt u tijdens het plaatsen van een ventriculaire katheter en in hoeveel procent van de beeldgestuurde operaties gebruikt u deze?

Neuronavigatie op basis van een pre-operatieve scan	0
Robot gestuurd op basis van een pre-operatieve scan	0
Endoscopie	0
	0
	0
	0
Total	0

Complicaties

Onder complicaties verstaan we:
"een onbedoelde en ongewenste uitkomst tijdens of volgend op het handelen van een zorgverlener, die voor de gezondheid van de cliënt zodanig nadelig is dat aanpassing van het (be)handelen noodzakelijk is dan wel sprake is van onherstelbare schade."

Enkele voorbeelden van complicaties bij het plaatsen van een ventriculaire katheter zijn:

- Suboptimaal of incorrect plaatsen van de ventriculaire katheter
- Meerdere inserties tot het uiteindelijk plaatsen van de ventriculaire katheter
- Optreden van een bloeding
- Optreden van een infectie

Hoe vaak treden er complicaties op tijdens het plaatsen van de ventriculaire katheter?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Welke complicaties tijdens het plaatsen van een ventriculaire katheter heeft u meegemaakt en in hoeveel procent van deze complicaties komt dit voor?

Bloeding	0
Meerdere inserties	0
Incorrect plaatsen	0
	0
	0
	0
	0

Total	0

Hoe vaak treden er complicaties op na het plaatsen van de ventriculaire katheter?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Welke complicaties na het plaatsen van een ventriculaire katheter heeft u meegemaakt en in hoeveel procent van deze complicaties komt dit voor?

Obstructie van de katheter	0
Infectie	0
Bloeding	0
	0
	0
	0
	0
Total	0

Mocht u complicaties ervaren aan de ventriculaire katheter in hoeveel procent van de gevallen besluit u geen revisie te doen?

Welk deel van deze complicaties is te relateren aan het niet optimaal plaatsen van de ventriculaire katheter? Ga hierbij per complicatie uit van 0 (de complicatie is niet te relateren aan het niet optimaal plaatsen van de ventriculaire katheter) en 100 (de complicatie is volledig te relateren aan het niet optimaal plaatsen van de ventriculaire katheter)

Obstructie	0
Infectie	0
Bloeding	0
${q://QID37/ChoiceTextEntryValue/4}	0
${q://QID37/ChoiceTextEntryValue/5}	0
${q://QID37/ChoiceTextEntryValue/6}	0
${q://QID37/ChoiceTextEntryValue/7}	0
Total	0

Hoeveel patiënten hebben bij u een nieuwe chirurgische ingreep nodig voor het herplaatsen van de ventriculaire katheter binnen 30 dagen na het plaatsen van de shunt?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Hoeveel patiënten hebben een nieuwe chirurgische ingreep nodig voor het herplaatsen van de ventriculaire katheter binnen 90 dagen na het plaatsen van de shunt?

- ◯ Nooit
- ◯ Bij minder dan 20%
- ◯ Bij ongeveer 20 tot 40%
- ◯ Bij ongeveer 40 tot 60%
- ◯ Bij ongeveer 60 tot 80%
- ◯ Bij meer dan 80%
- ◯ Bij alle uitgevoerde operaties
- ◯ Weet ik niet

Nieuwe technologie

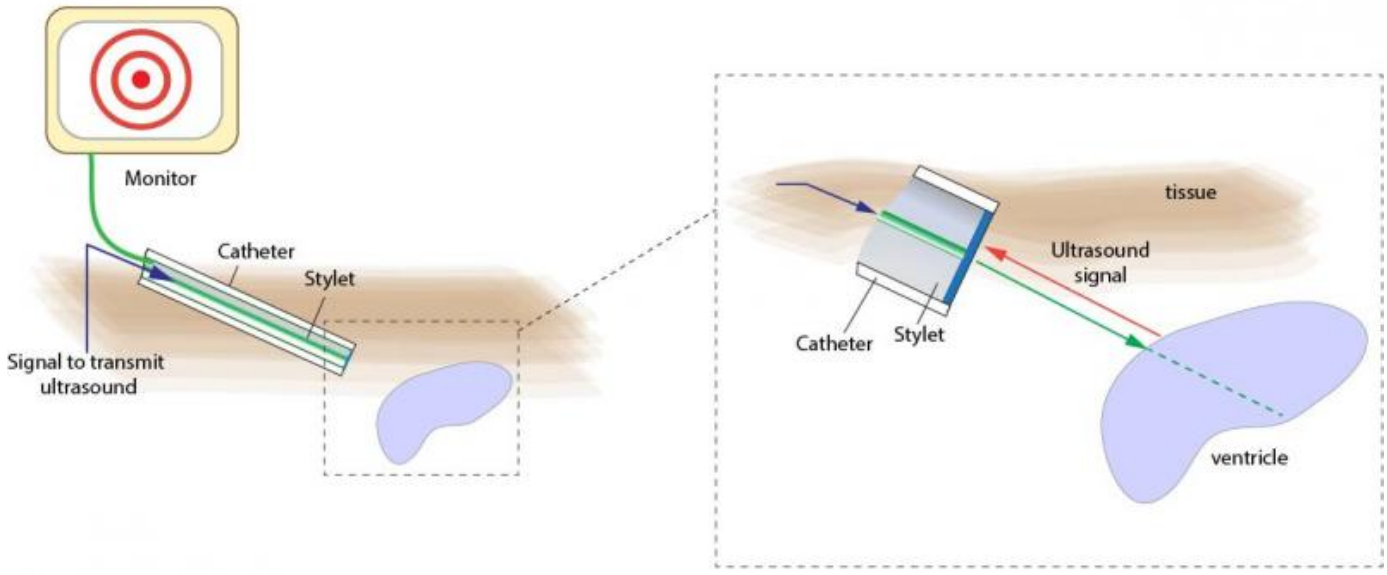
Het aanprikken van de ventrikel is een doorgaans blinde procedure. Huidige technieken die hierbij ondersteunen, zoals neuronavigatie en robot gestuurde methoden, kosten veel voorbereidingstijd.

Om de ventrikel tijdens de operatie real-time in beeld te brengen, zonder het gebruik van een pre-operatieve scan, is er momenteel een nieuw apparaat in ontwikkeling aan de Universiteit Twente. Het doel van deze innovatieve ultrasound techniek is om met hoge nauwkeurigheid het traject van de ventriculaire katheter uit te stippelen. Dit biedt de mogelijkheid om met grotere precisie, t.o.v. de freehand-techniek, de locatie van de ventrikel, de afstand tot de ventrikel, en de lengte van de ventriculaire katheter tijdens de operatie te bepalen.

In het onderstaande figuur is een illustratie van het nieuwe apparaat weergegeven. De procedure is vergelijkbaar met de freehand-techniek, waarbij het nieuwe apparaat de stylet vervangt. Op de tip bevindt zich een ultrasound transducer. Dit zorgt ervoor dat de ventrikel direct in beeld te brengen is vanaf de cortex en de insertie hoek bepaald kan worden. Het nieuwe apparaat kan door zijn kleine field of view aangeven of de ventrikel zich in het verlengde van de naald bevindt of niet. Met behulp van de monitor kan de neurochirurg real-time de hoek en de afstand bepalen tot de ventrikel.

We verwachten dat er met het nieuwe apparaat een grotere zekerheid en precisie kan worden verkregen bij het plaatsen van de katheter, met minimale aanpassingen en een lagere tijdsbelasting. Voor de chirurg is de verwachting dat het weinig verschil in handelingen met zich mee brengt. Het gebruik zal meer zicht geven op de locatie van de ventrikel, wat tot minder complicaties leidt, dan bij deze anders blinde procedure.

De volgende vragen gaan over bovenstaande informatie.



Welke kenmerken zijn volgens u belangrijk voor een goed en veelvuldig gebruik van het nieuwe apparaat? Rangschik (door te slepen) de kenmerken van hoogste (1) naar laagste prioriteit (9).

Kosten aanschaf

Kosten gebruik

Gebruiksvriendelijkheid voor neurochirurg

Tijdsinvestering implementatie nieuw apparaat

Tijdsinvestering tijdens de operatie

Nauwkeurigheid van het apparaat

Belasting voor de patient

Kwaliteit van leven van de patiënt

Kans op optimale positionering van de ventriculaire katheter

Gegeven de huidige mogelijkheden van het plaatsen van een ventriculaire katheter, namelijk: 1) freehand techniek 2) m.b.v. neuronavigatie op basis van preoperatieve CT of MRI scan 3) robot gestuurd op basis van een preoperatieve CT of MRI en 4) endoscopie. In hoeverre lijkt u de ontwikkeling van het nieuwe apparaat, een stylet met detector die in real-time, maar toch “freehand” kan worden geplaatst wenselijk.

In termen van kosten en tijd ten opzichte van de volgende technieken:

	Kosten		Tijd	
	Wenselijk	Niet wenselijk	Wenselijk	Niet wenselijk
Freehand-techniek	○	○	○	○
Neuronavigatie	○	○	○	○
Robot gestuurd	○	○	○	○
Endoscopie	○	○	○	○

Stel het nieuwe apparaat komt qua nauwkeurigheid overeen met neuronavigatie, wanneer zou u dan nog neuronavigatie gebruiken voor het plaatsen van een ventriculaire katheter?

- [ ] Nooit
- [ ] Als de vorm van de ventrikel van belang is
- [ ] Als de grootte van de ventrikel van belang is
- [ ] Anders, namelijk:

Stel het nieuwe apparaat komt qua nauwkeurigheid overeen met endoscopie, wanneer zou u dan nog endoscopie gebruiken voor het plaatsen van een ventriculaire katheter?

- [ ] Nooit
- [ ] Als de vorm van de ventrikel van belang is
- [ ] Als de grootte van de ventrikel van belang is
- [ ] Anders, namelijk:

In hoeverre denkt u dat er in de praktijk behoefte is aan het nieuwe apparaat om de ventriculaire katheter in te brengen, wanneer deze de ventrikel kan detecteren vanaf de cortex?
Geef een schatting van hoe groot de behoefte op de werkvloer zal zijn.

weinig	redelijk	groot	zeer groot
○	○	○	○

In hoeverre denkt u dat er in de praktijk behoefte is aan het nieuwe apparaat om de ventriculaire katheter in te brengen, wanneer het nieuwe apparaat de ventrikel kan detecteren als deze 1 à 2 centimeter vanaf de cortex is ingebracht?
Geef een schatting van hoe groot de behoefte op de werkvloer zal zijn.

weinig	redelijk	groot	zeer groot
○	○	○	○

Wat zal voor u de voornaamste reden zijn om het nieuwe apparaat te gebruiken?

Wat zal voor u de voornaamste reden zijn om het nieuwe apparaat niet te gebruiken?

Als u aanpassingen of aanvullingen kunt doen op het nieuwe apparaat, wat zal dit dan zijn?

Het nieuwe apparaat wordt gebruikt voor het plaatsen van een ventriculaire katheter. Zou dit nieuwe apparaat ook voor een andere ingreep gebruikt kunnen worden? Zo ja, welke en waarom?

Heeft u nog suggesties of opmerkingen?

Heel erg bedankt voor het invullen van de vragenlijst!

Bent u benieuwd naar deze technologie of nieuwe technologieën op het gebied van ultrasound of photoacoustics. Dan neem ik graag contact met u op.

naam:

e-mail adres:

telefoonnummer:

13 | Appendix

13.1 | Results

The generalised gamma density distribution used the parameterisation originating from Prentice et al. [75]. The parameters are: μ"location", σ"scale", and Q shape parameter, respectively. In table 13.1 the parameters with there estimate, upper and lower 95% confidence interval (CI), and standard error are shown.

Table 13.1: Results of fitting model for survival curves. Est = estimate, L 95%-CI = lower 95% confidence interval, U 95%-CI = upper 95% confidence interval, Se = standard error. Corresponding survival curves on which the data is fitted: Shunt survival - Initial placement[20], Shunt survival - First revision [20], Shunt survival - Second revision [20], Shunt survival - Poor placement [8], Survival - Initial placement [53].

	Est	L 95%-CI	U 95%-CI	Se
Shunt survival - Initial placement				
μ	4.473994	4.152722	4.795265	0.1639170
σ	2.645679	2.432479	2.877565	0.1134110
Q	-3.762486	-4.233141	-3.291831	0.2401345
Shunt survival – First revision				
μ	5.301067	4.870593	5.731541	0.2196337
σ	3.158501	2.965284	3.364308	0.1017261
Q	-1.601225	-1.920494	-1.281957	0.1628951
Shunt survival – Second revision				
μ	4.515555	3.891119	5.139991	0.3185958
σ	2.805718	2.504854	3.142719	0.1623753
Q	-1.767490	-2.271776	-1.263205	0.2572931
Shunt survival – Poor placement				
μ	0.9105627	0.8013934	1.0197320	0.05569965
σ	0.1893837	0.1478188	0.2426362	0.02394279
Q	-21.7709054	-22.1160592	-21.4257516	0.17610212
Survival – Initial placement				
μ	1.8898033	1.76421499	2.015392	0.06407686
σ	0.3846493	0.03130023	4.726964	0.49234178
Q	-45.3813784	- 57.24847047	66.485714	57.07609574

14 | Appendix

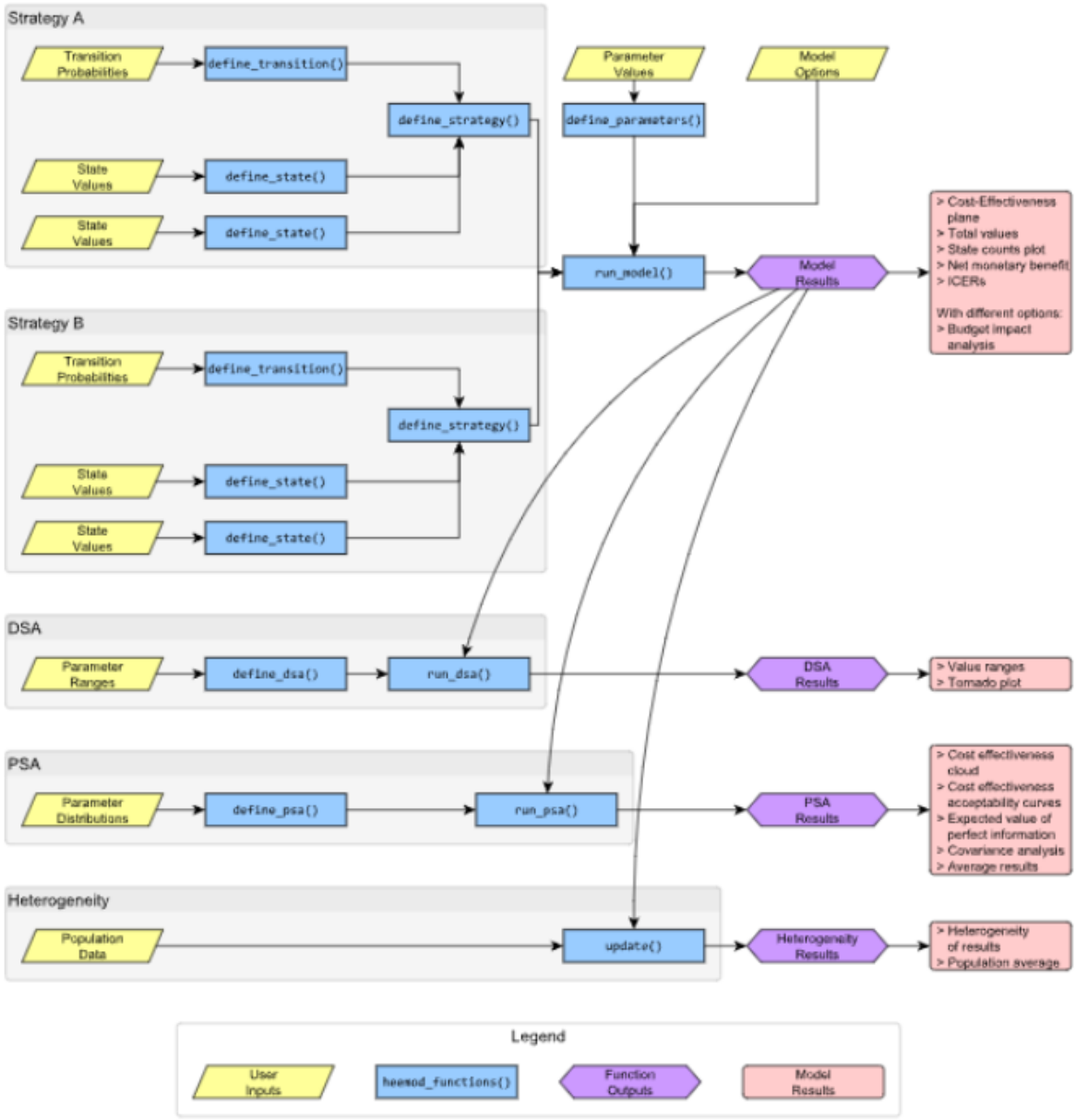


Figure 14.1: Overview of the Heemod package workflow [72]

14.1 | Intermediate model results

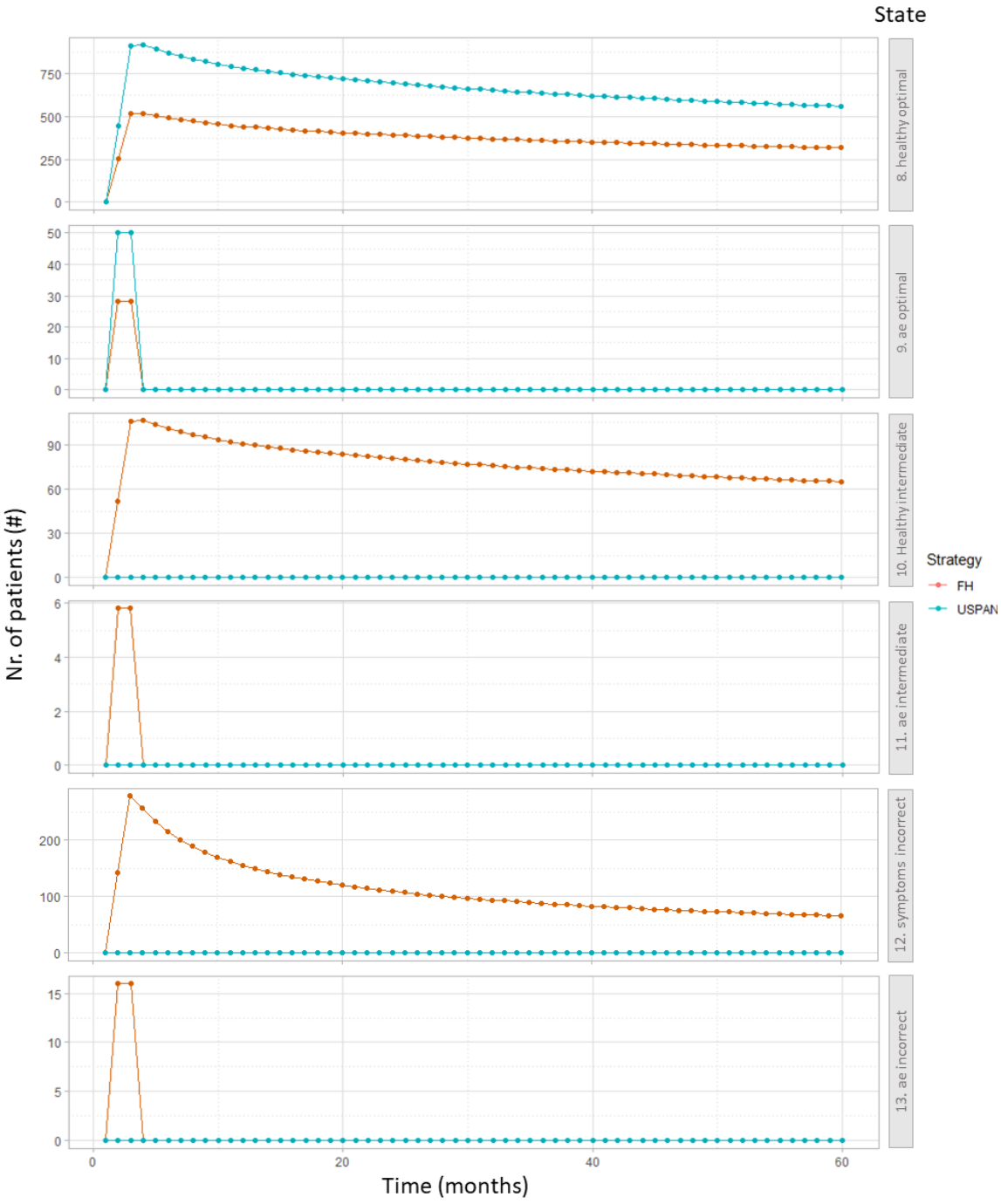


Figure 14.2: Intermediate results per state after initial admission.

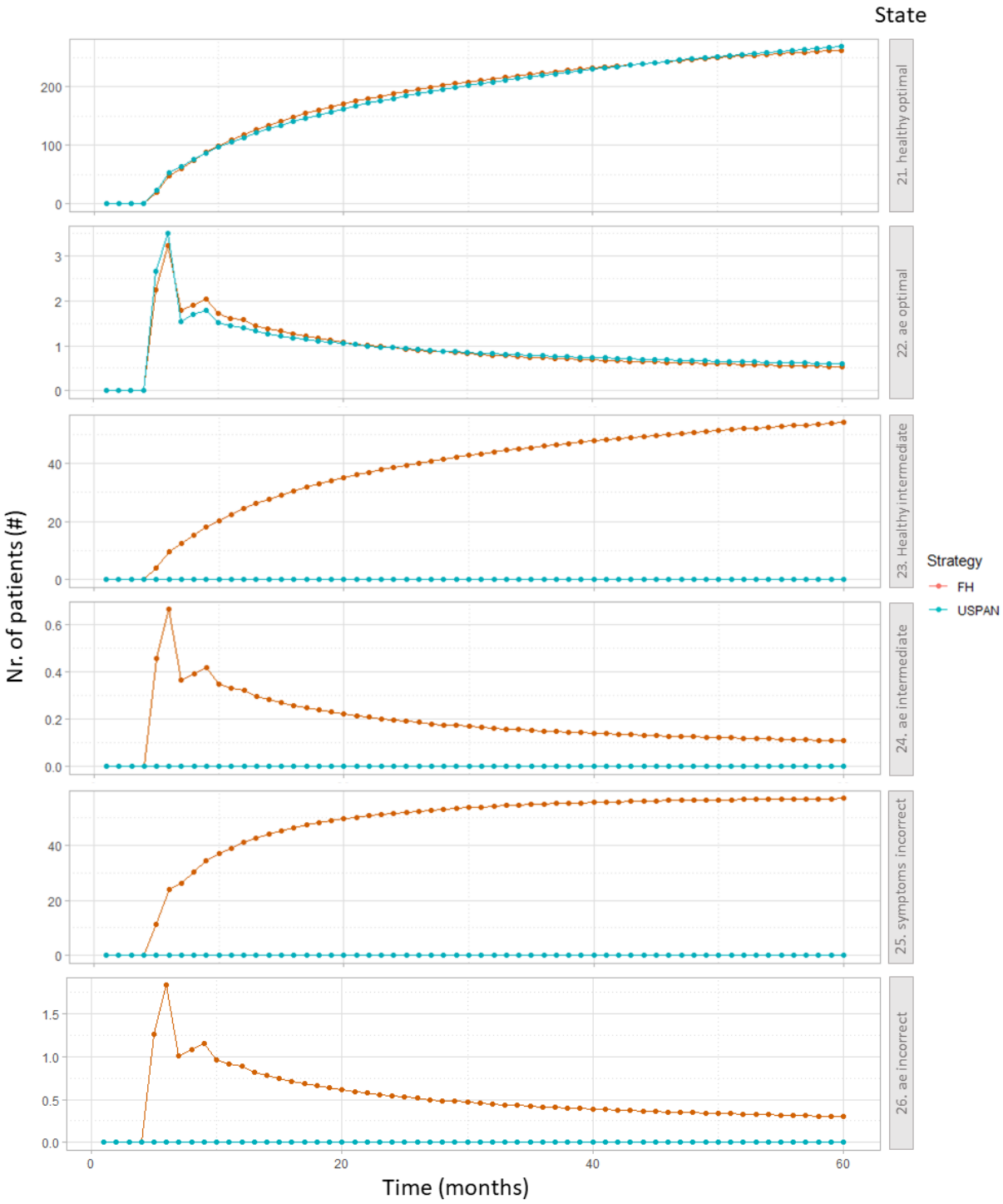


Figure 14.3: Intermediate results per state after revision.

14.2 | Deterministic sensitivity analysis results

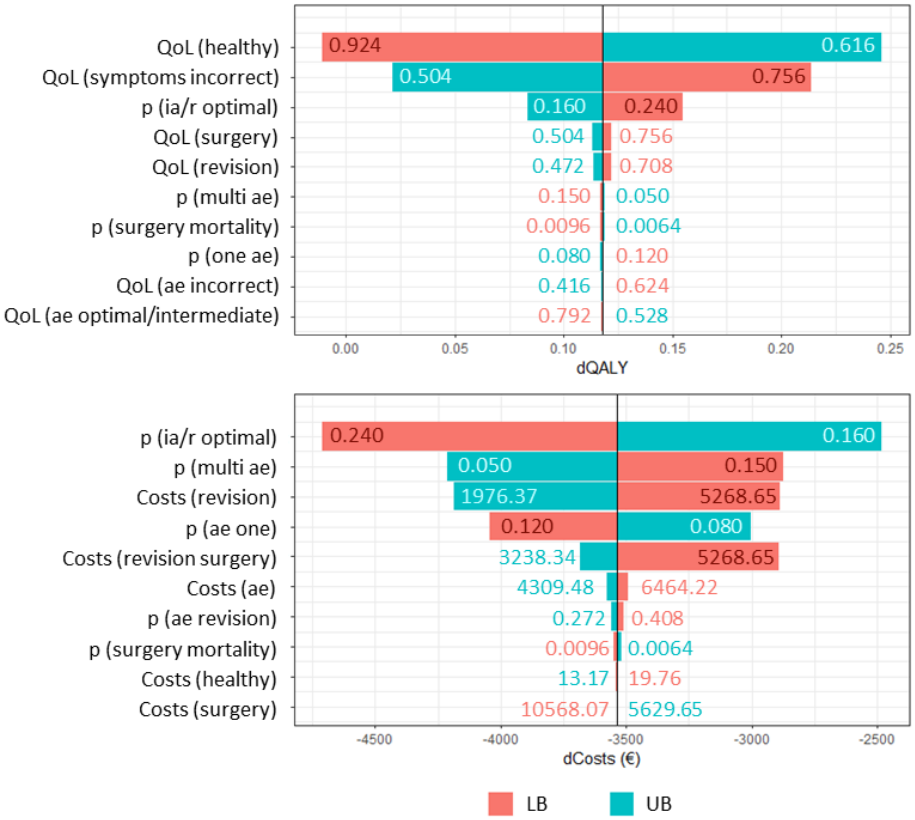


Figure 14.4: Deterministic sensitivity analysis results for delta Costs and delta QALY