Evaluation of the conditional reimbursement of Voretigene Neparvovec (Luxturna) for inherited retinal dystrophies caused by RPE65 gene mutations in Norway: A value of information analysis.

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European Master's in Health Economics and Management

Economic Evaluation in Healthcare

University of Oslo
June 2022

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This work is published digitally on DUO – Digitale Utgivelser ved UiO

https://www.duo.no/

Printed at: Reprosentralen, Universitetet i Oslo

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Abstract

Background: Novartis submitted their health technology assessment in 2019 to the Norwegian Medicine Agency (NOMA), however, in 2020, NOMA discarded the submission by Novartis as they deemed Voretigene Neparvovec (Luxturna) to not be cost-effective. However, in 2021, NOMA conditionally reimbursed Voretigene Neparvovec and approved it into clinical practice in Norway. The condition was that all eligible patients over a four-year period that was treated was to be included in a quality registry. When the four years will pass a new decision on the reimbursement would be made.

Objective: To assess whether NOMA's conditional reimbursement can be justified based on a value of information analysis. The value of information analysis can help us infer whether the additional information acquired over the four-year period can be regarded sufficient, what information is important and whether collecting this additional information is resource efficient.

Method: A replication of the cost-utility analysis submitted to NOMA by Novartis was performed. For purposes to maximize the uncertainty a willingness to pay threshold of 2,200,000 Norwegian Kroner was chosen. By running a Monte Carlo simulation to propagate uncertainty within the model the probabilistic sensitivity analysis could be stored. This output was collected and imported into RStudio to run a value of information analysis to collect EVPI, EVPPI, EVSI and ENBS results.

Results: By setting the willingness to pay threshold at 2,200,000 Norwegian Kroner we estimated that Voretigene Neparvovec compared to best supportive care would result in an incremental cost-effectiveness ratio of 2,200,934 Norwegian Kroner per quality-adjusted life year gained. We aggregated the population EVPI to be 9,941,417 Norwegian Kroner. Parameters shown to cause a lot of variation within the model from EVPPI results were categorized as parameters concerning clinical efficacy and the natural history disease progression. EVSI results for clinical efficacy was estimated for a sample size range between 10 and 500 patients, ENBS was negative for the complete interval and further research was therefore considered too potentially not be worthwhile.

Conclusion: Based on the results acquired by value of information analysis, the conditional reimbursement of Voretigene Neparvovec cannot be deemed justified. However, as Voretigene Neparvovec seek to treat individuals diagnosed with gene mutated RPE65 associated inherited retinal dystrophies, which is considered an orphan disease different criterion could be considered when assessing whether Voretigene Neparvovec should be included in Norwegian clinical practice. Further research is required to reduce decision uncertainty to get accurate estimates from the economic evaluation. As there are few eligible patients in Norway, cross-border co-operation could be considered.

Acknowledgement

I want to express my sincerest gratitude to my supervisor Natalia Kunst, PhD, for her encouragement, guidance, and invaluable feedback throughout the entire project. Her efforts have made this project an enjoyable experience where I have experienced a steep learning curve.

Furthermore, I want to acknowledge a most genuine thanks to Hannah Douglass Hylin at Novartis Norway for making connections and showing interest, Beth Hancock from Source Health Economics London, for guidance on converting the transitional rates from the natural history study and David Epstein, PhD, University of Granada, for helping me reviewing the Jones et al. (2017) procedure.

I wish also to express my appreciation to all fellow students and professors at the Joint Master's degree program; European Master's in Health Economics and Management especially within the specialization track, Economic Evaluation in Healthcare, your knowledge, cooperation, and cultural differences have added so much fun, color and made my studying enjoyable. I highly appreciate that I have witnessed the value of international connections while studying during the Covid-19 pandemic.

A final and utmost personal thanks to my family and friends for their continuous and unconditional encouragement and support during my studies. Studying during the Covid-19 pandemic has been rough; however, their moral boost has given me the endurance required to keep pushing on.

Christoffer Nedberg
Oslo, Norway, June 30th, 2022.

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List of abbreviations

AIC: Akaike's Information Criterion
BIC: Bayesian Information Criterion
BSC: Best supportive care
CEAC: Cost-effectiveness acceptability curve
CEAF: Cost-effectiveness acceptability frontier
CBA: Cost-benefit analysis
CEA: Cost-effectiveness analysis
CUA: Cost-utility analysis
CMA: Cost-minimization analysis
ConVOI: Collaborative Network for Value of Information group
DSA: Deterministic sensitivity analysis
EVPI: Expected value of perfect information
EVPPI: Expected value of partial perfect information
EVSI: Expected value of sample information
ENBS: Expected net benefit of sampling
EMA: European Medicine Agency
FDA: Food and Drug Administration
HTA: Health technology assessments
HRQoL: Health related quality of life
HS: Health state
HOD: Ministry of Health and Care Services
ICER: Incremental cost-effectiveness ratio
INMB: Incremental net monetary benefit
ICER: Institute of Clinical and Economic Review
IRD: Inherited retinal dystrophies
KM: Kaplan-Meier
LCA: Leber congenital amaurosis
MLMT: Multi-luminance mobility test
MSM: Multi-state model
NOMA: The Norwegian Medicine Agency
NMB: Net monetary benefit
NIPH: National Institute of Public Health
NICE: National Institute of Clinical Excellence
NOK: Norwegian Kroner
NHx: Natural History
PSA: Probabilistic sensitivity analysis
PICO: Patients, intervention, comparator, and outcome
QoL: Quality of Life
QALY: Quality adjusted life years
RRR: Relative risk reduction
RCT: Randomized controlled trial
SE: Standard Error
SD: Standard Deviation
SAVI: Sheffield Accelerate Value of Information
VOI: Value of information analysis
WTP: Willingness to pay

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Introduction

In this first chapter, we will introduce the characteristics of the disease concerned in this thesis, inherited retinal dystrophies (IRD) caused by RPE-65 gene mutations and the reimbursement of Voretigene Neparvovec (Luxturna) in Norway will be given. Furthermore, the chapter presents uncertainties, ethical and monetary implications within the topic serving as a foundation for the scope and relevance of this thesis. Moreover, the research question will be outlined at the end of the chapter.

1.1 Characteristics of RPE65 associated inherited retinal dystrophies

Inherited retinal dystrophies can be considered an umbrella-term covering the spectrum of gene mutations causing rare vision impairment conditions (Chung et al., 2019). RPE65 associated gene mutations can be therefore classified as several clinical diseases.

RPE65 associated IRD develops between birth and the age of 5 years and causes vision impairment progressively progressing to blindness. The disease is characterized by severe retinal deterioration whereby patients diagnosed with RPE65 associated IRD experiences visual deficiency, which affects the ability to see in the dark, leads to lack of color vision, and a gradually constriction of their peripheral sight and visual acuity. Chung et al. (2019) examined the natural history of the disease and concluded, although there was some variation among patients, that the gradual worsening of vision loss started around age 15-20 and subsequently progressed rapidly after the age of 20. Hence, RPE65 associated IRD can be considered a severe health condition with substantial impact on the individual health related quality of life (HRQL) (Chao, Burr & Pennesi, 2019).

The severity of the disease is supported by The Norwegian Medicine Agency (NOMA) absolute shortfall calculations. The absolute shortfall for patients with RPE65 associated IRD is estimated to be 28,2 quality adjusted life years (QALY). The absolute shortfall calculations would be defined as the difference between the expected QALYs in the general population, and the expected total QALYs for the population with RPE65 associated retinal dystrophy, with best supportive care in Norway (NOMA, 2019).

However, the prevalence associated with retinal dystrophy caused by mutations in the RPE65 gene worldwide is low. Gene mutations in the RPE65 gene can both cause Retinitis pigmentosa and Leber congenital amaurosis. Published literature suggests that 2.5 million patients are suffering from IRD worldwide, whom of 21% to 24% suffer from retinitis pigmentosa and 2.5% to 22% suffer from Leber congenital amaurosis (LCA) (Aoun et al., 2021; Chao, Burr & Pennesi, 2019). In Norway, a total of eight people has been identified with this condition, and it is estimated that there are between 1,000 and 2,000 individuals in the United States. In the UK, an estimated prevalence is tough to be around 57 to 564 individuals (NOMA, 2019; NICE, 2018). Consequently, RPE65 associated IRD can be considered an orphan disease (Franco, 2012).

1.2 Voretigene Neparvovec (Luxturna) reimbursement process in Norway

Luxturna gained Food and Drug Administration (FDA) approval on December 19, 2017, making it the first ever FDA approved gene therapy and the only available treatment for RPE65

associated IRD. The European Medicine Agency (EMA) followed with an approval on November 23, 2018 (Gao, Hussain & Weng, 2020).

In 2019, Novartis submitted their technology appraisal for Luxturna in Norway with an economic evaluation of Luxturna compared to best supportive care which resulted in an incremental cost-effectiveness ratio (ICER) of 1,109,132 Norwegian Kroner (NOK) per QALY gained. However, in 2020, the National System for Managed Introduction of New Health Technologies decided that Luxturna should not be included in the Norwegian clinical practice based on NOMA's cost-effectiveness analysis and recommendations. More specifically, NOMA changed some of the assumptions in the cost-effectiveness analysis of Luxturna submitted by the manufacturer and estimated an ICER of 2,374,253 NOK per QALY which exceeds the willingness to pay (WTP) threshold of NOK 825,000 per QALY gained, suggested to be used for the most severe diseases (SLV, 2019; HOD, 2015-16).

As previously mentioned, Luxturna is considered an orphan-drug and its clinical efficacy is thus subject to uncertainty due to lack of data. The outcome of the health economic model would consequently rely on modelling assumptions. Some of the most important modelling assumption discrepancies gathered from NOMA (2019) is now highlighted below.

In the cost-effectiveness evaluation, NOMA opted for different long-term treatment effect, relative risk reduction (RRR) and utility weights compared to the base-case analysis submitted by Novartis. NOMA had received 4 years of additional effectiveness data from the phase 3 study. This showed that after these four years additional years, 5 out of 20 patients experienced deterioration. The long-term effect was thus considered to be speculative. While Novartis assumed a 50-year constant treatment effect, NOMA adjusted this to 15 years. However, it should be noted that the 15-year treatment effect also was arbitrarily chosen and therefore uncertain and that no empirical evidence for such assumptions existed. Novartis assigned the Voretigene Neparvovec-arm with a 25% RRR, because 25% of the retina is treated with Luxturna. NOMA adjusted this RRR to 50% to persevere some of the treatment effect. Novartis conducted a literature review to assign health related utility weights to their model- wherein no such values were collected for patients with RPE65 associated IRD. Novartis consequently decided that the utility weights in the literature should not be used in the health economic model because it was deemed unfit due to structural differences with the diseases in question. Eventually, Novartis opted for an expert elicited vignette study by Acaster Lloyd Consulting assigned by Spark Pharmaceuticals. However, NOMA had concerns regarding this study and decided to apply for utility values from both Brown et al. (1999) and Rentz et al. (2014), which were also used by the National Institute of Clinical Excellence (NICE) in their evaluation (NOMA, 2019; NICE, 2017).

Although NOMA found Luxturna to be cost-ineffective and recommended against its approval, other countries such as the Unite Kingdom and Germany concluded that Luxturna was cost-effective in their country specific settings and approved its implementation in clinical practice (Viriatio et al., 2020; Uhrmann, Lorenz & Gissel., 2020).

One year after the decision of the National System of Managed Introduction of New Health Technologies to not implement Luxturna, NOMA reconsidered their evaluation and recommended to reimburse Luxturna. More specifically, the National System for Managed Introduction of New Health Technologies decided to give Luxturna a so-called conditional reimbursement, requiring that every treated individual was to be registered into a quality registry over a four-year period. After four years, NOMA would perform a new evaluation

using gathered additional evidence from the manufacturer and the decision about Luxturna's reimbursement would yet again be evaluated.

NOMA estimated that Luxturna would have a budget impact of around NOK 35,5 million per year, in the first two years. And NOK 8,8 million in the third and fourth year. Accumulated, the total cost of IRD would surpass 97,7 million NOK. This estimation was based on the incidence and assumed prevalence of LCA in Norway as there are 8 eligible patients with and incidence rate between 0.5 and 1 new patient per year.

1.4 Previous literature

As Luxturna gained FDA's and EMA's approval in 2017 and 2018, respectively, available clinical evidence and literature is still limited. To the authors knowledge, the most relevant clinical trials, as well as previously performed CEAs are now briefly outlined below.

In the phase I trial by Maguire et al. (2009), twelve patients were included to examine Luxturna's safety and efficacy. The patients age ranged from 8 to 44 years and no patients experienced any severe adverse event. All included patients showed improvement in retinal function; however, the effect was observed best in younger patients.

The phase III trial by Russell et al. (2017) compared treatment effectiveness of Luxturna compared to no treatment. A total of 31 patients with a mean age of 15.1 years were included in this trial, 21 were given Luxturna and ten patients were assigned to no treatment. Whereas one patient from each group withdrew after consent. Effectiveness was compared at 30, 90, 180 and 365 days after administration. Primary endpoint was multi-luminance mobility test (MLMT) change (i.e., change in luminance (lux) score, see Figure 2.3) whereas a positive change indicates passing the MLMT at a lower light level. 13 out of 20 participants in the intervention group passed the MLMT at the lowest tested level, non from the control group. The most common adverse events experienced were mostly mild and transient and included elevated intraocular pressure, cataract, and retinal tear.

As for previously conducted CEAs, five unique analyses are recognized. The Institute of Clinical and Economic Review (ICER) developed a two-state Markov model. The two possible states were 'alive' and 'dead'. The model outcomes were visual acuity, visual field, and quality of life. Age-related mortality rates allowed for the modelling of life expectancy. A US health care system perspective was used. The analysis resulted in an ICER of $643.813 per QALY gained in a US healthcare system perspective, and of $480.130 per QALY gained in a societal perspective (ICER, 2018).

Zimmermann et al. (2019) developed a decision-analytical model and performed a CEA. The results they obtained were in line with the results presented by the ICER Institute mentioned above.

Uhrmann et al. (2020) had a similar modeling approach as ICER Institute and Zimmermann et al. as well, however, they performed their CEA from a German perspective. Luxturna led to an additional incremental QALY gain of 4.82 which resulted in a ICER of €156,853 per QALY. Based on these results, the authors stated that Luxturna will have important implications for future gene therapies and thus considered it to be cost-effective from a societal perspective over a lifetime horizon.

Johnson et al. (2019) developed a decision-analytical model with 5 health states. The authors informed transition probabilities for Luxturna using data on treatment efficacy progression. Transition probabilities in the standard of care-arm were based on natural history data. Furthermore, they used an expert elicitation for utility weights. Patients were modelled trough a lifetime horizon with 1000 Monte Carlo simulations. Several sensitivity analyses were performed, resulting in a variety of ICER. However, at a WTP threshold of $150.000, Luxturna was suggested cost-effective.

As with Johnson et al. (2019), Viriatio et al. (2020) utilized a Markov state transition model with five disease specific health states. A lifetime horizon with 1 year cycle lengths was implemented. The model consisted of two phases; the initial states based on transition specific count data from the phase III trial by Russell et al. (2017) and a long-term phase with multistate survival data from the natural history data by Chung et al. (2019). Quality of life (QoL) data was elicited from specialists with both EQ-5D and HUI3 instruments. As a PSA they ran 10,000 iterations resulting in an incremental QALY gain of 6.4 and an ICER of £95,072 per QALY gained. Because of significant improvement from standard care, Luxturna was ought to be eligible for WTP threshold valuation under the NICE highly specialist technology framework and was thus inferred cost-effective.

As portrayed, several modelling approaches has been previously performed. There has been some conflicting inference whether Luxturna is considered cost-effective or not. This is a result of the respective countries policies or which perspective the researchers have chosen. However, going forward with this thesis, a model based on clinical data progression with multiple states as Johnson et al. (2019) and Viriatio et al. (2020), will be utilized.

1.5 Scope, aims and contribution

All decisions are subject to uncertainty. This is also the case when conducting a cost-effectiveness analysis to determine the optimal medical intervention. Value of information analysis (VOI) is a set of methods used to quantify uncertainty. VOI allows researchers to evaluate the uncertainty in the decision made, based on the currently available evidence and to determine if the currently available evidence is sufficient to make the decision, or if there is a high value in collecting additional evidence before making the decision (Claxton & Sculpher, 2006). VOI results helps to determine the need and focus of future research studies to improve decision-making.

When assessing a new health technology, monetary criterions are not always exhaustive. When deciding on an individual's health, there would always be ethical and equity implications to account for. Ideally, health technology assessments and its constraints should capture these aspects. Whether these constraints are always followed is however debatable. Health technologies used to treat rare disease will naturally serve different prerequisites. As the first gene-therapy, Luxturna could contribute to technological advancement and as it is the only available treatment option for patients with IRD, it could ensure mental stability in the form of hope (Lakdawalla et al., 2018). Moreover, the health technology assessment framework should work as a consistent and reliable guideline for decision makers to make technology appraisals. The framework should thus, ought to be as exhaustive as possible to safeguard patients from both technical modelling discrepancies, but also – more interpersonal inconsistencies. This is especially relevant for technologies that is considered an orphan drug as the model might be subject to considerably uncertainties, the price would likely be considered high and both

patients and caretakers tend to have strong emotions regarding whether or not the technology are implemented within clinical practice.

Given that Luxturna is a novel and orphan drug with a scarcity of available evidence of effectivity, it is important to highlight the need to evaluate the decision uncertainty in the health economic evaluation of Luxturna. Especially, as there are to the authors knowledge no previous studies that have performed a value of information analysis on implementation of Luxturna in clinical practice will be conducted. A VOI analysis can thus help identify parameters that drive the uncertainty and should be targeted in further research.

Consequently, VOI analysis can be used to examine the evidence available at the time of Luxturna's cost-effectiveness evaluation in Norway and to quantify the expected value of additional information that could be gathered if NOMA would recommend a conditional reimbursement and whether this is justified by the estimated budget impact. To infer whether the conditional reimbursement could be vindicated, a prerequisite for this study is to assume that that I have the same information as NOMA had been portrayed back in 2019 when the reimbursement application form Novartis was provided to NOMA.

1.6 Research question

The evidence on Luxturna's effectiveness is limited and it is an expensive treatment with a list price of NOK 7,1 million for two injections. A VOI analysis has the potential to help improve decision-making on the implementation of Luxturna in clinical practice.

The research question of this thesis is as follows:

"Does value of information analysis support NOMA's decision to gather more evidence on Luxturna for patients with RPE65 associated IRD, eligible to be treated with Voretigene Neparvovec (Luxturna) in Norway before providing Voretigene Neparvovec (Luxturna) with a full reimbursement and implementing it in the clinical practice?"

1.7 Thesis structure

This thesis consists of five additional chapters. Chapter one has served as an introduction to the problem framework which this thesis operates within. Chapter two outlines further background information on the disease in question and the theoretical framework surrounding economic evaluation. Chapter three explains the applied method referring to the theory outlined in Chapter two. Chapter four presents the result from the performed economic evaluation, including both the cost-effectiveness analysis and the value of information analysis. Chapter five discusses the findings, study limitations, and potential policy implications. Finally, Chapter six provides a concluding remarks, as well as an answer to the research question.

Background and Theoretical framework

In this chapter, relevant information on gene mutated RPE65 associated IRD, the disease concerned in the present study will be provided. Furthermore, we outline the theoretical framework for the decision-analytical methods used in this thesis will be presented.

In Chapter 2.1 to 2.4, we provide some information on how RPE65 gene mutation and its impact on the visual cycle, and how clinicians can effectively and accurately diagnose RPE65 associated IRD, how Voretigene Neparvovec is administrated and possible ways to measure the effect of Voretigene Neparvovec through MLMT scores. Chapter 2.5, we provide insights on the characteristics of diseases that are classified as orphan diseases. In chapter 2.6 to 2.11, we provide the theoretical framework for health economic evaluation and theoretical concepts applied in the present thesis.

2.1 RPE65 associated Inherited Retinal Dystrophy

The RPE65 gene can be found on chromosome 1 and it specifically codes the retinal pigment epithelium-specific 65 kDa protein (Aoun et al., 2021). The RPE65 gene is what affects the visual cycle through a series of processes. More specifically, when the eye is exposed to light it is converted into electrical signals transmitted to the brain. When the light reaches the photosensitive pigments in the retina it converts 11-cis-retinal to all-trans-retinal. RPE65 is then acting as an isomerase (i.e., converting one isomer to another) that re-converts all-trans-retinal back to 11-cis-retinal making it ready for a new photoisomerization (i.e., absorption of light) event (Ciulla et al., 2020; Ripamonti et al., 2014). A graphical presentation of the visual cycles is presented in Figure 2.1 below. RPE65 is thus essential for regeneration of the visual pigmentation after exposure to light. A non-functioning RPE65 gene will not respond to the exposure of light and hence leave the individual with visual impairment.

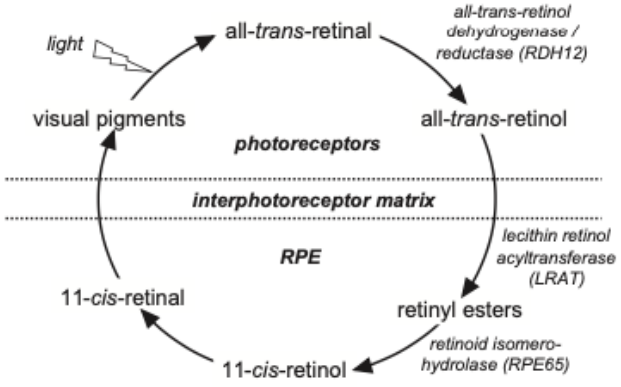

Figure 2.1: Visual cycle RPE65 (Hollander et al., 2008).

2.2 Diagnosis of RPE65 Associated Inherited Retinal Dystrophy

To be eligible for treatment with Voretigene Neparvovec, mutations in the RPE65 must be biallelic (i.e., in both alleles) and the patients must have viable photoreceptors (NOMA, 2019). As there are more than 300 variations of RPE65 mutations identified, diagnosis is key to distinguish viable patients. Although clinicians can attempt to establish the diagnosis using some specific criteria, gene testing is the only procedure that is considered a reliable way to diagnose RPE65 associated IRD with certainty. However, gene testing is associated with high

cost as it requires avant-garde technology. Nevertheless, segregation studies are seen as the most appropriate to conduct alongside genetic testing since by testing all relevant relatives, determining the pathogenicity is considered eased (Aoun et al., 2021).

2.3 Administration Voretigene Neparvovec

Voretigene Neparvovec is administrated under general anesthesia with a subretinal injection of 1,5 x10^{11} vg Voretigene Neparvovec for a total of subretinal volume of 0,3 mL on the worst functioning eye or based on patients' preferences. Voretigene Neparvovec is a genetically modified non-replicating adeno-associated virus serotype 2 (AAV2) vector containing RPE65 cDNA. The vector is purified, and a surfactant is added to prevent subsequent vector loss during storage and administration. Patients receive 1 mg/kg of prednisone orally for 7 days, however at a maximum dose of 40mg/day regardless of weight, whereas the prednisone is given three days before the procedure. The second eye are treated after 6 to 18 days after the first initial treatment. A standard vitreoretinal technique for subretinal surgery is utilized (i.e., the surgeon performs a vitreous detachment) including a three-port pars plana posterior cortical vitrectomy (Russell et al., 2017; NOMA, 2019; Ciulla et al., 2020; Aoun et al., 2021).

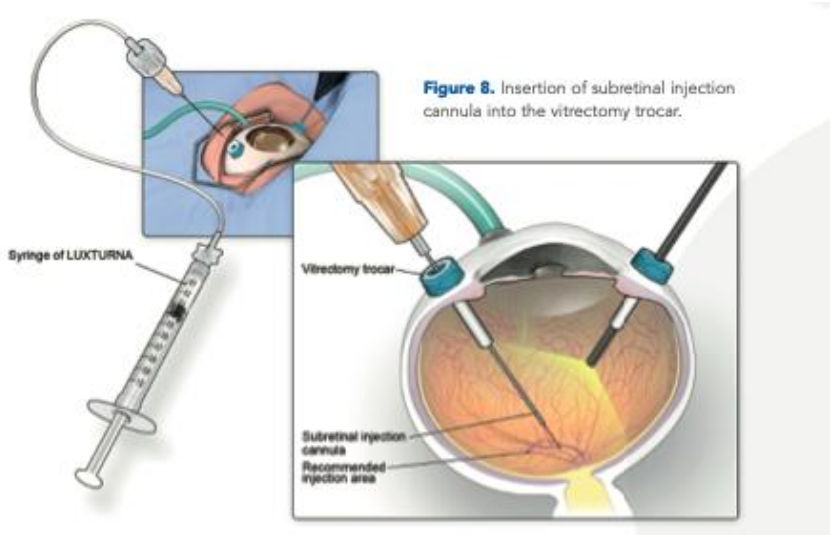

Figure 2.2: Graphical representation of the administration of Voretigene Neparvovec.

2.4 Measuring the effect of Voretigene Neparvovec

Visual field and visual acuity measures have long been widely recognized as suitable visual predictors of mobility performance. These measures construct the patient's mobility performance as a percentage of the preferred walking speed on a controlled surface. However, Chung et al (2016) argue that these tests have been subject to heterogenic residuals. As there is little evidence on the effect on mobility performance during varying lightning conditions, to account for this, Chung et al (2016) developed the multi-luminance mobility test.

Contrary to other mobility tests which is performed on controlled surfaces, patients assigned with multi-luminance mobility test scores are informed to follow designated paths indicated by arrows throughout the course as they are trying to avoid hurdles on or alongside their trace, additionally they must keep an eye out for elevated steps and finally to identify their exit. A visual example of such course is provided in Figure 2.4. This is repeated several times, each time with different lightning conditions listed in Figure 2.3. Furthermore, which eye the patients

can use will be differing whereas one is patched and finally, with both un-patched (Chung et al., 2016)

Illuminance (lux)	Luminance (cd/m^2)	Corresponding environment
1	0.32 mesopic vision	Moonless summer night; or indoor nightlight
4	1.3 mesopic vision	Cloudless summer night with half moon; or outdoor parking lot at night
10	3.2 mesopic vision	60 min after sunset in a city setting; or a bus stop at night
50	15.9 photopic vision	Outdoor train station at night; or inside of illuminated office building stairwell
125[†]	39.8 photopic vision	30 min before cloudless sunrise; or interior of shopping mall, train or bus at night
250[‡]	79.6 photopic vision	Interior of elevator, library or office hallway
400	127.3 photopic vision	Office environment; or food court

Figure 2.3: Lightning conditions (Chung et al., 2016).

Patients who are tested for multi-luminance test score are to be tested three times over the course of one year to identify any change. Twelve distinct configurations of the course were developed, and the assigned course was randomized before each visit (Chung et al., 2016)

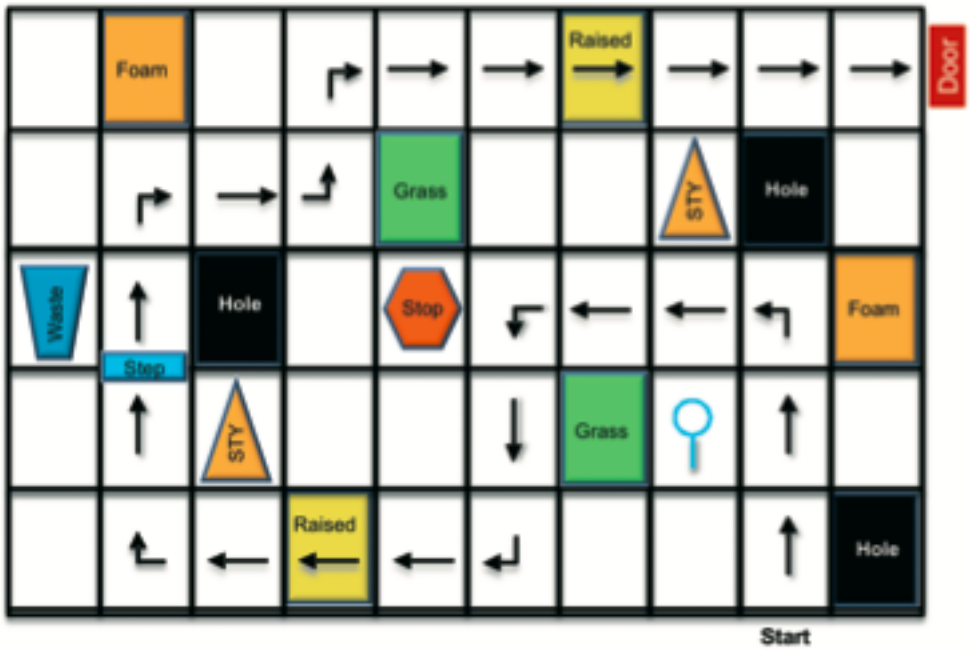

Figure 2.4: Example of MLMT course design (Chung et al., 2016).

Independent graders are used to assess when the participant passes or fail the course. To pass, the patients could maximum commit three fouls (i.e., touching obstacles, falling etc.) to serve as a test of accuracy. Moreover, the course had to be done within a total time of 180 seconds. MLMT score are then being evaluated between the difference in baseline score, at the lowest light level passed, and the lowest light level passed at the last – one year visit (Chung et al., 2016)

	Lux							
	1	4	10	50	(100 and 150)	(200 and 250)	400	>400[†]
Score code	6	5	4	3	2	1	0	−1

Figure 2.5: MLMT change score (Chung et al., 2016).

2.5 Orphan diseases and its elements of value

Much of the research is funded by pharmaceutical companies (DiMasi, Grabowski & Hansen, 2016). Given that these companies invest substantial resources on research and development of new drugs, they often prefer to invest in the development of drugs that can be expected to provide the highest return on investment. Consequently, pharmaceutical companies prefer to invest in developing drugs that would treat, for example, high-prevalence diseases, diseases with high severity and diseases with few treatment options. Given the high costs these new drugs are protected by patents to ensure that the companies receive the return on investment in developing new drugs. The general term of a patented drug is 20 years. By the time the companies have discovered, developed, tested, and registered their new product an estimated cost between $60 million and $2.6 billion has accrued (van der Gronde, Uyl-de Groot & Pieters, 2017). After the new compound has been marketed the company has only a limited time left to recoup a profit from sales while the product still has monopoly because of the patent protection. The income is only affected by two factors, volume, and price. Depending on the target population the price is likely to decrease or increase (Gregson, Sparrowhawk, Mauskopf & Paul, 2005).

Orphan drugs is a classification of a set of health technologies which aim is to benefit patients with rare diseases. As already established, pharmaceutical industry is interested in investing in interventions that have high potential for return on investment. Consequently, orphan drugs are not prioritized because the number of people to be treated is small. There is no clear-cut definition to the term "rare disease", however both prevalence and severity are common factors (Franco, 2012). Furthermore, as outlined in Franco (2012), the European Union defines an orphan disease as *"a life threatening or chronically debilitating condition affecting no more than 5 in 10,000 persons in the community…"* while the United States defines it only on the basis of prevalence, *"a disease or a condition, which affects fewer than 200,000 patients in US"*.

Hughes-Wilson et al (2012) states that the legislation from 2000 (i.e., EC No.141/2000) has been widely considered a success. Which is an orphan drug legislation to incentivize orphan drug discovery which includes accelerated reimbursement processes, additional market exclusivity and additional research funds. However even though a company acquire orphan designation, the drug can fail in development (Franco, 2012; Joppi, Bertele & Garattini, 2013). As more orphan drugs are being approved and included in the market, patients with previously unmet need gains thus a possibility to get treated. Even though the drug itself initiates high costs, the overall budget impact could sometimes be considered relatively low since orphan drugs seek to cover diseases with low prevalence. However, with the increased focus on orphan drugs, governments and decision makers are worried for the future impact it may pose. More specifically, given that the resources are scarce, it is essential to allocate them with caution. Luzzatto et al. (2018) gives merit to possible solutions between the government and manufacturer such as market access agreements as risk sharing and performance-related payments.

However, monetary thresholds may not be an exhaustive criterion when considering orphan drugs. Since the price of the drug can be significant, it may not be possible to meet a cost-effectiveness threshold established for treatments of more common diseases. Health technology assessments (HTA) bodies should thus strive for a pre-determined, orphan drug-specific framework when considering reimbursement dossiers. Lakdawalla et al (2018) has defined

other elements of value than only cost-effectiveness which could be taken into consideration when performing economic evaluations.

As beforementioned, IRD with associated RPE65 mutations has substantial impact on an individual's life. A study by Taylor et al. (2017) suggests that individual place a substantially higher weight on improvements for worse health states than health states which are less severe. Moreover, Lakdawalla et al., (2018) argues that patients will implicitly gain a benefit in terms of value of hope. Even though the effectiveness of the intervention is surrounded by uncertainty, people suffering from the disease are more willing to take the chance for an improvement in their health-related quality of life. Hope also relates to the fact that a new treatment may be their only real option. As there are currently no other effective treatments for patients with RPE65 associated IRD, Luxturna represents the only drug that has the potential to treat this disease. Furthermore, rarity and unmet need can be considered closely related to equity. From a patient with a rare disease stance, they can feel alienated and unfairly treated, if viable treatments for them are considered unwarranted based on just costs. Moreover, as the first approved gene therapies, Luxturna poses substantial impact on future technological advancements. By approving novel drugs, researchers can gather evidence and gain further knowledge in how this technology works such that the current approved drug could clear the path of new innovative drugs in the future (Lakdawalla et al., 2018).

2.6 The basics of Economic Evaluation

The Norwegian healthcare system is a universal system funded through taxation (Ringard, Sagan, Saunes & Lindahl, 2013). Thus, allocation of resources should arguably be distributed equally and non-discriminatory. For this reason, as public health authorities operate within a finite health care budget, all new treatments must undergo a cost-effectiveness evaluation and only those treatments that are considered cost-effective should be approved and included in clinical practice. Cost-effectiveness analysis is a type of full economic evaluation examining costs and effects of at least two interventions. Cost-effectiveness is something which should then be endeavored. By opting for one alternative, you explicitly forgo the second option, in economic theory this is referred to as opportunity costs. When considering several health technologies this opportunity cost may create a gap between what is medically possible, and what is economically reasonable. The purpose of economic evaluation is to identify the interventions which diminish this gap. Moreover, it possesses two distinct features. Economic evaluations aim to estimate both costs and health effects associated with the interventions considered. The second characteristic is that economic evaluation scrutinizes and compare choices (Drummond et al., 2015). Hence, it is crucial to understand that the choice of comparator and the economic evaluation assumptions is paramount, using different comparators and assumptions could result in contrasting results.

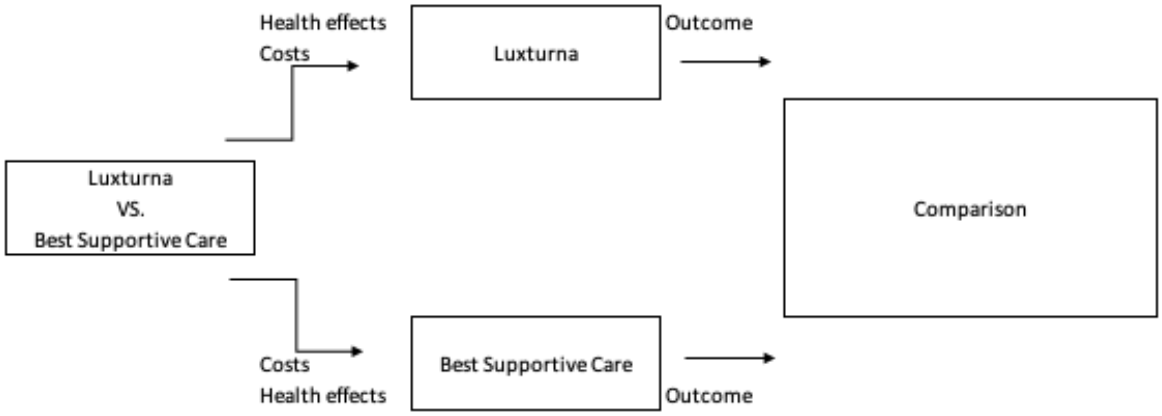

Figure 2.6: Simplified Economic Evaluation Schematic.

2.6.1 Types of Costs-effectiveness analysis

Depending on the type of health outcomes considered, four types of an economic evaluation can be distinguished. A brief outline of these four types is provided below.

In CEA health outcomes are expressed in health natural units. Natural units in this case can be described as consequences with more natural impact. Examples of such natural units are life years, number of days with vision or numbers of days that the patient can work. The CEA is most applicable when a decision maker is to choose between interventions within a limited field. However, when assessing interventions on such specific endpoints it could fail to asses' other aspects in the patient's life because it forgoes all other implications from the intervention (Drummond et al., 2015).

Instead of using natural units as health outcomes, a cost-utility analysis (CUA) utilizes a generic measurement of health. Such generic measurement is often measured in QALYs. Given that many economic evaluations use QALYs as the analyzed health outcome, the results can be compared across different studies, subpopulations, and if relevant across different disease and other settings. (Drummond et al., 2015). The concept of QALYs is further explained in Chapter 2.6.2 below.

CEAs and CUAs can be explained as research which seek to optimize the allocation of resources within an already existing and finite budget. However, in cost-benefit analysis (CBA) the research seeks to assess whether a budget should be increased. As with CUAs, CBAs utilizes effects in terms of generic measurements. The differentiation is that the CBA seeks to translate the effects into a monetary value. This could either be done by presenting the result as a ratio of costs to benefits or presenting the sum of costs and benefits (Drummond et al., 2015).

When there are more than two viable options that are homogenous in terms of consequences a cost-minimization analysis (CMA), could be conducted. Thus, a CMA evaluates only the costs associated with the interventions considered. However, estimates are always subject to uncertainty which should make the researcher questioning whether such analysis is appropriate (Drummond et al., 2015).

2.6.2 Perspective, costs, health effects and outcomes

Before collecting information about costs and effects the researcher should determine the perspective of the analysis. This is dependent on the analysis settings such as country and health system. For a societal perspective the researcher should collect information about all possible costs (both direct and indirect costs) associated with the interventions considered. When opting for a health care perspective, only direct costs and effects explicitly borne by the health care system should be accounted for (Brouwer & Koopmanschap, 1999; Drummond et al., 2015).

As beforementioned, a QALY is a generic measure which can be compared across different diseases. The concept of a QALY is that it is a measure with a multi-dimensional perspective. A QALY considers both time and a valuation of each health state included in the decision-analytical model, the valuation is thus based on the health-related quality of life in question. A QALY can take on a value in the range from zero to one, with zero representing the worst possible state, i.e., death, and one representing perfect health. For some cases, the QALY could be negative if the health state is considered worse than death (Weinstein Torrance & McGuire, 2009; Drummond et al., 2015).

As researchers often investigates interventions with future implications it is also important to adjust the results for time preferences. As both individuals and as societies we tend to prefer gains now, instead of sometime in the future. Discounting is often thought of as a strictly financial term and utilizes to present a monetary value in its net present form. However, this is not necessarily the case. As society we invest resources in health today to gain health benefits in the future. Discounting both costs and effects allows researchers to assess future gains in today's valuation (Drummond et al., 2015).

After gathering data on all the costs and effects, the result of an economic evaluation analysis is presented in form of an ICER. The ICER represents the incremental change in costs and effects when comparing the intervention to the comparator. By dividing the incremental costs with the incremental effects, hence – the ICER presents a measure which consists of costs per effect gained.

$$Incremental\ Cost\ Effectiveness\ Ratio\ (ICER) = \frac{Costs\ A - Costs\ B}{Effects\ A - Effects\ b}$$

This allows decision makers to assess whether an intervention is cost-effective towards what society is willing to pay. The WTP threshold is thus a societal criterion based on what society deems an additional effect, or QALY is worth.

The WTP threshold are thus varied due to pre-specified criteria. For instance, in Norway severity is one of the criteria that the WTP threshold is dependent on. This disease severity is calculated based on the absolute shortfall, i.e., how many quality-adjusted life years are lost due to early death or reduced quality of life due to sickness. While for diseases with the lowest severity suggested WTP threshold is NOK 275.000, for diseases with the highest severity this WTP increases to NOK 825.000 (HOD, 2015).

Another way to present the results of an economic evaluation is in form of incremental net monetary benefits. Using the estimated incremental effects (e.g., QALYs) and incremental costs in addition to the WTP threshold, the incremental net monetary benefit (INMB) can be calculated (Briggs, Schulpher & Claxton, 2006).

$$INMB = (WTP * \Delta Effects) - \Delta Costs$$

2.7 Modelling in economic evaluation

To make it possible for researchers to investigate whether an alternative intervention is superior to another intervention, which is often currently used in clinical practice, modelling techniques are often utilized. Modelling techniques makes it possible to determine health and cost consequences for interventions considered over a long perspective of time. This time is often referred to as the time horizon and should reflect the natural characteristics of the disease. The extrapolated parameters can then be iterated several times to account for any uncertainty in the estimates. In health economic modelling there are many types of decision analytical models, however two main ways to structure your model are through decision trees and Markov models.

The decision tree will portray all the possible prognoses for a certain individual after a specific or several interventions. For each prognosis there is a pathway with a given probability which connects both costs and effects. This makes it possible for the researcher to calculate the expected value for each possible outcome. Decision trees suffer nevertheless under the limitation that everything that is happing in the model is given by a discrete instantaneous time periods. Furthermore, some diseases consist of an array of possible interventions and health states, a decision three could thus be immensely complicated. Implementing time dependencies such as, discounting and calculating the overall survival will thus be cumbersome (Drummond et al., 2015).

A Markov model consists of a set of possible mutually exclusive 'health states' which a patient can occupy over the course of the disease. Researchers can consult clinical experts to elicit these health states to somewhat portray the natural disease progression. How the simulated patient moves between the health states is determined by transition probabilities. The frequency of simulated patients moving between the health states in are decided by a series of discrete time periods which is called cycles. Cycles should, as with the health states and transition probabilities, reflect the natural history of the disease. More precisely, it should be short enough to capture all important events, but not too short to not make the model too complex and ease computational burden. A Markov model allow us to analyse a longer time perspective and account for risk of various health states over time, reflecting the continuous risk of transition between health states, which is typical progressive diseases. Costs and effects are assigned to each health states and implemented in each cycle and varied accordingly to the number of simulated patients in each specific health state (Briggs, Sculpher & Claxton, 2006; Drummond et al., 2015). Figure 2.7 below, visualizes a simplified Markov model, with three identified health states with death as a naturally absorbing state.

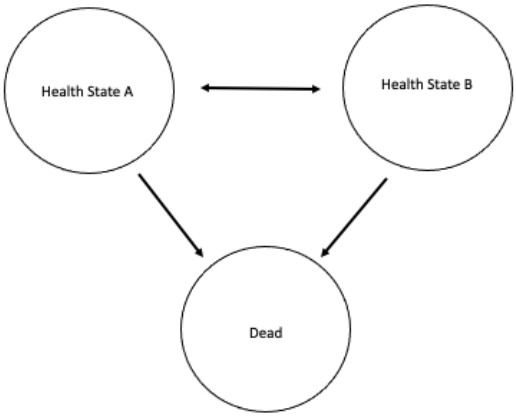

Figure 2.7: Markov Model.

2.8 Uncertainty in economic evaluation

Though researchers strive to include all relevant parameters in their economic evaluation, such analysis will always be subject to uncertainty. Patients are unique, how a patient experience quality of life and responds to a treatment will always differ. This is a consequence of that there are only samples of the population of interest that are included in research studies and not the total population, which eventually leads to uncertainty in obtained estimates. Parameters collected and estimated will never be known, the parameters will always be an estimated mean on the observed sample. However, there are several techniques to account for this structural uncertainty within an economic evaluation.

A scenario analysis, also called deterministic sensitivity analysis, is used to assess structural uncertainty within the model (Drummond et al., 2015). The researcher chooses a base case assumption which is deemed the most appropriate. By explicitly changing certain assumptions or parameters the researcher could assess the impact of such change on the obtained results. However, this way to explore uncertainty is a rather stepwise approach, since the researcher can only change few parameters to know exact what's causing the impact. Some structural changes could include the use of different discount rates or different values for utility weights.

Over the recent years the probabilistic sensitivity analysis (PSA) has grown in importance. In a PSA each parameter is assigned with a statistical probability distribution to represent the uncertainty within the parameter estimation. Thereafter a Monte Carlo simulation is ran which will draw random samples within the distributional range for each parameter. After running a given number of iterations (e.g., a thousand of iterations), the mean average within the distributional uncertainty range could be estimated (Drummond et al., 2015). The researcher is thus left with the expected mean value for each parameter. The economic evaluation will after a performed PSA account for the propagated uncertainty effect for all parameters and estimate the mean expected result.

Through a scatterplot, popularly called a cost-effectiveness plane each simulated expected mean result can be graphically presented in a two-dimensional chart which shows the relationship between the two variables. The more scattered the plots are, the more uncertainty in the estimates. However, to present uncertainty in cost-effectiveness estimates a cost-effectiveness acceptability curve (CEAC) is often utilized. The CEAC show the probability at which WTP threshold the intervention is considered cost-effective. The CEAC is constructed by estimating the proportion of all interventions considered cost-effective for a range of WTP

thresholds. This makes the CEAC to take a cumulative distributional shape, representing probability values for being cost-effective ranging from zero to one over several WTP thresholds. By reading of the WTP thresholds one can infer at which likelihood the intervention is considered cost-effective over the simulated outputs. Since a CEAC only infer on the probability that the intervention is considered cost-effective at a given threshold, it is not suitable to assess whether the intervention is considered optimal (Barton, Briggs & Fenwick, 2008; Fenwick & Byford, 2005; Fenwick, O'Brien & Briggs, 2004).

To determine which options is the better option it is necessary to calculate the option with the highest expected net monetary benefit (NMB). The cost-effectiveness acceptability frontier (CEAF) portrays the strategy with the highest expected NMB at each given WTP threshold. This makes it possible for decision makers to choose the optimal economic strategy (Barton, Briggs & Fenwick, 2008; Fenwick, Claxton & Schulpher, 2001).

2.9 Value of information analysis

Scenario analysis, PSA, CEAC and CEAF are useful to handle and present uncertainty in economic evaluations. However, for decision makers it is hard to determine whether the uncertainty in the underlying evidence is too substantial to make the decision now and eventually what type of evidence is needed to make more informed choices. As already established, clinical studies and research are associated with high costs and there will always be a consideration of conducting further study or allocate money somewhere else. Hence by using VOI as a tool to guide decision maker it will ensure coherent, transparent, and educated decisions. VOI analysis could thus be considered key for society to make better judgements for the future.

A VOI analysis is an analytical framework to inform decision makers on whether additional research is worthwhile. VOI quantifies the degree of uncertainty in the economic evaluation and assigns a monetary value or benefit on the reduction of this particular uncertainty. The output from the PSA can be used to perform VOI and to determine the expected value of hypothetical elimination or reduction of the uncertainty and to identify parameters that drives the uncertainty (Minelli & Baio, 2015). The VOI framework is rooted in Bayesian decision theory and statistical theory and is also used in other sectors than healthcare. VOI measurements are dependent on what the researchers assigns as a WTP threshold and is thus consistent with the objectives of health care resource allocation (Claxton & Schulpher, 2006). There are three important steps in VOI analysis: 1) calculation of expected value of perfect information (EVPI), 2) expected value of perfect partial information (EVPPI) and 3) expected value of sample information (EVSI).

EVPI calculates the expected net monetary gain in eliminating all uncertainty for all parameters in the model. Thus, EVPI is the difference between the expected value of the decision made with hypothetical perfect information and the decision made with current information. By aggregating the EVPI with the discounted incidence of the disease over a pre-specified time-horizon, we estimate EVPI on a population level. If the expected value of removing all uncertainty on the population level exceeds the expected costs of further research, the research is potentially deemed justified (Rothery et al., 2020; Briggs, Schulpher & Claxton, 2006; Wilson, 2014; Tuffaha, Gordon & Scuffham, 2014). However, because removing all possible uncertainty is not feasible, EVPI represents only the first step in VOI analysis. The parameters that drive the uncertainty also needs to be identified, to further elaborate on the preferred study design.

$$EVPI = \mathbb{E}_{\Theta}\big(max\mathcal{U}(d,\theta)\big) - \ max\mathbb{E}_{\Theta}(\mathcal{U}(d,\theta))$$

$\mathcal{U}(d,\theta) = Utility\ function\ of\ the\ decision\ given\ a\ vector\ of\ uncertain\ parameters$

$$populationEVPI = EVPI * \sum_{t=0}^{T} \frac{I_t}{(1+r)^t}$$

$I_t = Incidence$
$T = Time - horizon$
$r = Rate\ of\ discount$

After establishing whether further research is justified, it is of importance to identify the focus of further study. The researcher has a choice of investigating one parameter at a time or combine specific parameters in groups – if additional data to inform these parameters can be collected in one study. Essentially, when conducting EVPPI the researcher isolates selected parameters of interests to identify whether the respective parameters drive the uncertainty within the model. Thus, the estimated EVPPI is the difference in the maximum expected net benefit with perfect parameter information subtracted the expected value of current, uncertain, information (Rothery et al., 2020; Briggs, Schulpher & Claxton, 2006). As with EVPI, the EVPPI can be multiplied with the discounted incidence to get the population EVPPI serving as an upper bound of benefit for reducing uncertainty in the parameters of interest.

$$EVPPI(\theta_i) = \mathbb{E}_{\theta_i}\left(\max\mathbb{E}_{\theta_c|\theta_i}(\mathcal{U}\big(d,\theta_{i,}\theta_c\big)\right) - \ max\mathbb{E}_{\Theta}(\mathcal{U}(d,\theta))$$

$\theta_i = Vector\ of\ parameter\ of\ interest$
$\theta_c = Set\ of\ remaining\ complementary\ parameters$

As already established, reducing uncertainty completely is irrational to believe is possible. With EVSI, we estimate the value of reducing uncertainty through the collection of sample data through pre-specified sample sizes. EVSI calculates the expected difference between a decision made after collecting sample data on a subset of identified parameters and the expected value of a decision with current information, i.e., the net benefit with current information. EVSI framework is thus highly dependent on a 2-level Monte Carlo simulation and impose a computational burden. The outer loop creates plausible sample sets, conditional on these sets, the inner loop generates samples from a posterior distribution. The expected net monetary benefit is then calculated for each loop (Tuffaha et al., 2016; Tuffaha et al., 2014). However, several approximation methods have been developed and these methods ease the computation burden. For example, with output from a PSA, it is possible to run a non-parametric regression based EVSI method proposed by Strong et al. (2015). By calculating EVSI for a vector of sample sizes it eventually converges towards the already calculated population specific EVPI as uncertainty in the model is being reduced, as with other VOI measure the researcher can obtain population EVSI by multiplying the per patient calculated EVSI with the population of interest (Tuffaha et al., 2016; Strong et al., 2015; Tuffaha et al., 2014).

$$EVSI = \ \mathbb{E}_x(max\mathbb{E}_{\theta|x}\big(NB(d,\theta)\big) - \ max\mathbb{E}_x(\mathbb{E}_{\theta|x}\big(NB(d,\theta)\big)$$

$NB(d,\theta) = Net\ benefit\ of\ the\ decision\ given\ a\ vector\ of\ uncertain\ parameters$
$X = \ Vector\ of\ data\ from\ random\ variables\ within\ the\ distribution$

After calculating EVSI we can estimate the expected net benefit of sampling (ENBS). This is done by subtracting the expected research cost on the population EVSI. By calculating ENBS for a vector of sample sizes the researcher will figure out at which sample size that maximizes the expected benefit (Ades & Claxton, 2004).

$$ENBS(n) = Population\ EVSI - Research\ cost$$

2.10 Time to event analysis

For researchers to extrapolate parameters to simulate future results, statistical analysis must be applied. Clinical studies often seek to gather information on an unambiguous and pre-defined endpoint over a transient period. Time-to-event analysis requires the researchers to follow up a sample of patients over a series of established time intervals, over the course of the whole follow-up the researcher notes when or if patients are experiencing the already defined endpoint of interest. It is of importance that both the event and the time is noted as the goals is to get information on how the endpoint progresses over time. After collecting binary endpoint and continuous time events a non-parametric Kaplan-Meier (KM) curve could be constructed to visually portray how the disease evolves. This allows the researcher to estimate a survivor function (i.e., probability that the event has not yet occurred) and the hazard rate (i.e., the endpoint rate over the given time interval). To simulate the outcome over the finite and already observed follow-up researchers can fit parametric curves onto the already constructed KM curve through regression analysis. This allows the researcher to analytically and visually present and infer how the disease would progress over a longer time frame (Schober & Vetter, 2018).

It is, however, important to choose the parametric distributions carefully as each parametric distribution holds their own unique characteristics (i.e., survivor function and hazard rate). As Latimer (2013) portrays this could change the results of an CEA substantially. It is therefore essential to follow selection criteria in a transparent and coherent manner. The most basic way to assess whether the parametric distribution suitability is by visual inspection. By comparing the KM curve to the parametric distribution, one could infer whether there are any discrepancies. Nevertheless, curves could occur similar at one time interval and vary at another, and visual inspection only is thus deemed insufficient.

Through statistical analysis Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) values can be calculated to serve as a statistical test of the relative fit of parametric curves on the nonparametric KM curve where a lower value indicates the better fit (Latimer, 2011).

Furthermore, it is indicative that the researcher assesses whether the curve seems plausible from a clinical point of view. Controlling for clinical validity could be key to identify discrepancies from extrapolated outcome to what experts deem biological plausible. Furthermore, comparing previously estimated clinical data from other external sources could be a useful tool when evaluating the parametric distributional choice, however – it is then of importance that heterogeneity between the study samples is carefully examined to assess whether the results are transferable or not (Latimer, 2011).

2.11 Transition probabilities in multistate models with competing risk

In longitudinal studies such as time-to-event analysis patients can experience several intermediate health states or endpoints over the study period. Modelling a multi-state model (MSM) is then often utilized for simulating patients to transition through a finite number of states. In MSM the transition between states is referred to as intensities and provides the hazard rate from moving from one state to another (Meira-Machado et al., 2009). As all transient and absorbing health states competes against each other for the event, MSM models is causing competing risk situations. MSM models with competing risks violates the time-independence a Kaplan-Meier curve assume. It would be erroneously to assume that the hazard rate for one patient who had experienced the event of interest is the same as one patient who had experienced a competing event. A patient who had experienced a competing event would certainly not have experienced the event of interest at the same point in time (Putter, Fiocco & Geskus, 2007).

Hazard rates from MSM models represent the instantaneous incidence of transition to one state to another, rate to probability conversions is necessary as Markov models utilizes transition probabilities to reflect the movement between health states. This is often calculated using the "simple" formula whereas *t* represents time, *r* refers to the rate and *e* is the mathematical constant, Euler's number (Briggs, Schulpher & Claxton, 2006; Jones, Epstein & Garcia-Mochon, 2017).

$$p(t) = 1 - e^{-rt}$$

However, Jones et al. (2017) argues that this conversion is unprecise when dealing with MSM models as the individual could experience two or more transitions within one discrete time-period. They propose a method to solve the Kolmogorov equations through the diagonalization approach. The aim is to calculate the n x n transition-probability matrix P(t) given a transition-rate matrix Q. The forward solution would thus have the unique solution:

$$P(t) = Exp(Qt) = \sum_{r=0}^{\infty} Q^r \frac{t^r}{r!}$$

However, to simplify P(t) if Q has an eigen-decomposition the matrix exponential could be expressed as:

$$Exp(Qt) = U\, Exp(Dt) U^{-1}$$

Whereas D is a diagonal matrix of the eigenvalues of Q, and U is the corresponding matrix of eigenvectors.

$$Q = UDU^{-1} \; and \; Qt = UDtU^{-1}$$

By using algebraic software such as wxMaxima for the calculation of eigenvalues, eigenvectors and the algebraic formulas for transition probability conversion could effortlessly be implemented into spreadsheets for transparent utilization in PSA (Jones, Epstein & Garcia-Mochon, 2017).

Method

In this third chapter, we will outline and delineate the method applied to replicate the cost-effectiveness of Voretigene Neparvovec in Norway. Patients, intervention, comparator, and outcome (PICO) is presented for the reader to provide an overview of settings and assumptions of the economic model. The model and its prerequisites will therefore be accounted and justified for, as a more thorough description of the framework of the model are provided. This includes, how transition probabilities, costs and effects are utilized and applied within the model. An overview of every parameter base case value, its confidence interval, chosen distribution and source is presented to ensure transparency for the reader. To validate the results and to ensure credibility and accountability an internal validation will be provided and discussed.

3.1 PICO

PICO is the abbreviation of population of interest, intervention of interest, which comparator deemed fit and what the outcome is measured by. As in this thesis, we are replicating the HTA dossier provided to NOMA by Novartis, the choice of PICO correlates in exact fashion to what is outlined in NOMA (2019).

The population considered is Norwegian patients with biallelic RPE65 mutations with substantially viable retinal cells left before treatment. From the phase III trial, this is defined as retinal thickness of > 100 μm in posterior pole, ≥ 3 pupil diameters without atrophy or pigment deterioration in posterior pole and remaining peripheral sight of > 30 degrees (NOMA, 2019).

Intervention of interest is considered a subretinal injection of 1,5 $x10^{11}$ vg Voretigene Neparvovec. While the comparator of interests is best supportive care (BSC), as no other viable option exists.

However, as the clinical studies are focused on endpoints such as MLMT, visual acuity and visual field scores, the analysis performed in the present work is focused on health economic evaluation results including QALYs, costs, ICER, population EVPI, EVPPI, EVSI and ENBS.

Population: Norwegian patients with biallelic RPE65 mutation associated IRD
Intervention: Subretinal injection of 1,5 $x10^{11}$vg of Voretigene Neparvovec for a total 0,3 mL
Comparator: Best supportive care
Outcome: QALY, costs, ICER, population – EVPI, -EVPPI, -EVSI and -ENBS.

3.2 Model structure

As this thesis aims to replicate the Novartis submitted HTA to NOMA and extend it with a VOI analysis, the structure of the model relies heavily on the assumptions and documentation provided in that submission. However, the committee report by the National Institute of Clinical Excellence (NICE) is more comprehensive with information, it is thus used to gather complementary data.

The model is a multistate Markov cohort model. It includes six identified health states whereas the sixth and final state is seen as an absorbing state, “death”, description of the other health states are assigned through valuation of visual acuity and visual field are outlined in Table 3.1. It is considered that the model consists of three phases – the initial phase, the stabile phase, and

the progressive phase. The patients are modelled through lifetime, which is considered 85 cycles, with a cycle length of one year as patients are assumed 15 years at baseline, this correlates with the mean age in the phase III study by Russell et al (2017). Half cycle-correction is only applied the first cycle.

Health states					
			VA (LogMar)		VF (degrees)
HS1	Moderate VI	Moderate	Better than 1,0	Or	>240
HS2	Severe VI	Severe	1,0 - 1,4	Or	<240 to >144
HS3	Profound VI	Profound	1,4 - 1,8	Or	<144 to >48
HS4	CF	Counting fingers	1,8 - 3,0	Or	<48
HS5	HM, LP, NLP	Hand motion, light perception, no light perception	Worse than 3,0	Or	NA
HS6	Dead		NA		NA

Table 3.1: Health state description.

In the initial phase, it is assumed that the distribution of patients starting at baseline (i.e., in cycle 0), follows the same distribution as the clinical data from the phase III study relies on. As the patients can experience a positive treatment effect from the administration of Voretigene Neparvovec it is assumed that the patients are allowed to transition to better health states during the initial phase. Thus, for this exact phase the transition probabilities are provided by the transition count data gathered from the phase III study. The initial phase is only set to last one cycle.

The stable phase is seen as the phase where the effect obtained from Voretigene Neparvovec has a constant effect, this lasts for 15 cycles for the Voretigene Neparvovec-arm and are naturally non existing for the BSC-arm, as they are not treated with the intervention.

The progressive phase, or the long-term phase is where the effect from Voretigene Neparvovec is considered uncertain, and this is where patients start to progress. This phase lasts from cycle 16 (i.e., where patients are assumed 31 years) for patients modelled with Voretigene Neparvovec and cycle 2 for patients simulated with BSC. From the regression output from the natural disease history by Chung et al (2019) provided in the committee report by NICE, transition probabilities were calculated by applying the proposed procedure by Jones et al (2017). A 50% relative risk reduction (RRR) should have been applied to the patients receiving Voretigene Neparvovec to prevail some treatment effect as the assumed constant effect was shortened. However, in the present analysis, we decided to not implement the 50% RRR assumption and will provide a justification for this choice in the model validation in Chapter 3.7.2.

The structure of the Markov model is presented in Figure 3.1 and is provided below. As the patients are expected to gain effect from Voretigene Neparvovec administration in the first phase, arrows between the health states indicate that transition to better health states is possible. However, do note that this is only relevant for the first initial phase. As patients do not naturally die from RPE65 associated IRD mortality probabilities is calculated separately with age-specific mortality rates gathered from the Norwegian population.

Naturally, all costs and effects are applied to each health state for cycles deemed relevant, outlined in the HTA submission to NOMA (2019).

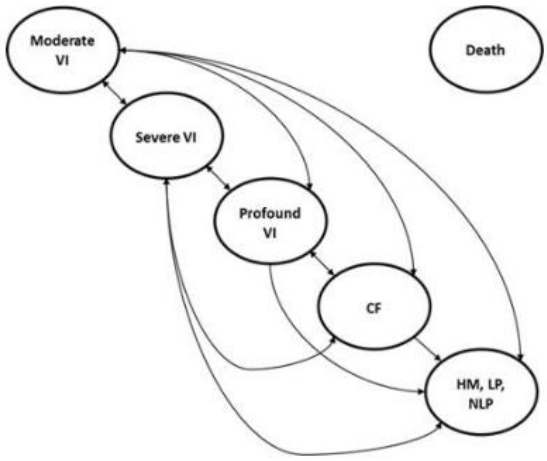

Figure 3.1: Markov model structure. With associated health states: Moderate, Severe, Profound, CF (Counting Fingers), HM, LP, NLP (Hand Movement, Light Perception, No Light Perception) and the absorbing state, Death.

3.3 Modelling guidelines in Norway

As HTA submission follows different procedures, these guidelines should be scrutinized and followed accordingly to the respective country the economic evaluation should take place. In Norway, there are at least two official bodies which provides HTA submission guidelines. NOMA is the official body which is in charge market legislation and reimbursement of new drugs in Norway and have provided guideline since 2002, whereas the most recently was updated in 2020. However, the most recently updated is from the National Institute of Public Health (NIPH) from 2021. The discrepancies between these two guidelines are deemed insignificant, however as it is NOMA's decision this present work seek to investigate the guidelines provided by NOMA is chosen as the most appropriate guideline to follow. Prerequisite requirements for HTA submission in Norway from NOMA (2021) are hence briefly outlined below.

The population should be described precisely according to patient characteristics in Norway. Furthermore, the intervention evaluated should be outlined with the characteristics and mechanisms of action. The choice of comparator, as a main rule, should be the intervention currently practiced. If there are several interventions performed in clinical practice, all relevant interventions should be included and evaluated accordingly.

A CUA is the recommended type of economic evaluation in Norway, this is to obtain a generic measurement of the clinical and economically effectiveness. This is to ensure comparability across diseases and interventions. When a CUA is performed, severity calculations should be calculated by using absolute shortfall estimations. And the time horizon should be long enough to capture all relevant future costs and effects between the alternatives.

The analysis should follow an extended healthcare perspective. More specifically, it should include effects over the patient's lifespan, the patients, and caregiver(s) HRQoL must be included. Moreover, treatment or prevention costs covered by a healthcare provider or caregiver, transport costs linked to treatment and patients and caregivers associated time-costs should also be included in the analysis. As HRQoL measure, QALYs should be used as a group measurement and should be based on an EQ-5D questionnaire reported by patients directly

from the clinical study. If other questionnaires or methods are applied a justification should be provided. Uncertainty should be examined through sensitivity, scenario analysis and a PSA.

Resource use and costs should preferably follow the private sectors market prices and should be given in the Norwegian currency, NOK. If conversion is needed, converting calculations should be provided.

To compare future benefits and costs in their present value, discounting procedures should be employed. For long time-horizons the rate should be 4% for year 0 – 39, in the years 40 – 75 the rate is decreased to 3% and from year 75 and onwards, 2% discount rate should be applied. The rates and when they are applied is equal for effects and costs.

Uncertainty must be investigated and discussed. This can be done with a deterministic sensitivity analysis (DSA) whereas selected variables are changed to explore the sensitivity the outcomes are with respect to selected variables. However, a DSA is not sufficient and thus a PSA should therefore also be conducted to explore the propagated parameter uncertainty and must be presented with a CEAC. VOI analysis can be conducted to quantify the value of further investigation. Finally, the results should be presented with and ICER, with cost per QALY gained.

3.4 Willingness to pay threshold in Norway

The outcome from the economic model in the HTA submission is used as a prerequisite to decide whether the intervention is considered cost-effective. This is done by comparing the estimated ICER towards the WTP threshold in the given country.

In a note from NOMA, a working group from different decision makers in Norway outlined important decision criteria when assessing new health technologies. They argued that both utility, resources and severity should be considered. The new health technology is to be given higher priority, if the intervention is associated with increased utility, the budget impact is considered incremental and finally, priority should be according to the severity associated with the disease (NOMA, 2018).

However, the priority could decrease if the uncertainty associated with the clinical evidence or estimation is considered substantial, nevertheless, for orphan disease more uncertainty could however be accepted. Furthermore, for orphan diseases a larger ICER could be accepted (NOMA, 2018). However, this is not as clearly defined, such as in NICE Highly Specialised Technology appraisal guidelines – where they have specified a ten-fold WTP threshold for highly specialized treatments providing a WTP threshold from £200.000 to £300.000 (Powell, O'Donnell., 2019).

As mentioned, in Norway the WTP threshold is defined by a severity specific threshold delineated from the Norheim-committee from 2015 assigned by the Ministry of Health and Care Services (HOD) Norway. They proposed a stepwise approach with six unique threshold values. These steps are identified and specified according to how severe the disease is calculated to be, according to absolute shortfall estimations. Even though there are six steps, the most severe is threshold is only a threefold of the baseline WTP threshold (HOD, 2015).

Group	1	2	3	4	5	6
Absolute shortfall	0 - 3.9	4.0 - 7.9	8.0 - 11.9	12.0 - 15.9	16.0 - 19.9	20.0 +
Weight	1	1.4	1.8	2.2	2.6	3
Upper limit per QALY (1000 KR)	275	385	495	605	715	825

Table 3.2: Norwegian threshold values.

3.5 Model parameters

In the following chapter, an overview over all parameters included in the model is provided. As parameters are assigned distributions to propagate for uncertainty a justification for the distributional choice will be provided. Base case values with available standard errors (SE), standard deviation (SD) or alphas, betas and the sample size will be included. Where quantification of the uncertainty was unknown and rather assigned arbitrary a rationalization for the exact values will follow. For parameters where conversion was necessary for model implementation a delineation of the procedure will be given and any hard calculations will be provided in the appendix.

3.5.1 Miscellaneous parameters

As some of the parameters are not subject to variation, these values were clustered together for transparency purposes. All patients are not assumed to start in in health state 1 (HS1) at the beginning of the model. They are rather expected to follow the distribution that is the equivalent distribution of patients in the phase III trial by Russell et al (2017). Hence, the proportion of patients identified in HS1 are as in the phase III trials, set to 23%, giving us 230 patients of the assumed 1000 in total. The parameters for the distribution of patients are identified by the abbreviation "dist" for distribution.

As previously mentioned in Chapter 3.3, modelling in Norway requires several values when discounting for longer time periods. These are indicated by "dr" for discount rate. "Mid" is for year 40 – 79 and "Low" is for the following years, the one without any unique identification is thus for the first 0 – 39 years. Even though the values are equal for benefits and costs, two identical set were employed for distinction purposes.

WTP threshold is not listed are not listed below, however, this was set to 2,200,000 NOK per QALY.

Miscellaneous parameters

Parameter name	Base case value	Source
distHS1	230	NICE
distHS2	320	NICE
distHS3	230	NICE
distHS4	190	NICE
distHS5	30	NICE
drBenefit	0.04	NIPH
drBenefitMid	0.03	NIPH
drBenefitLow	0.02	NIPH
drCosts	0.04	NIPH
drCostsMid	0.03	NIPH
drCostsLow	0.02	NIPH

Table 3.3: Miscellaneous parameters.

3.5.2 Treatment efficacy and NHx progression parameters

In this section parameters for both treatment transition and natural history disease progression are listed.

3.5.2.1 Treatment efficacy parameters

This section includes transition probabilities used in the initial phase and held constant in the stabile phase and was gathered from transition count data from the phase III study by Russell et al. (2017). In the Voretigene Neparvovec - arm 20 individuals were included whereas in the BSC-arm nine individuals was registered. These tables were reported in the NICE committee report (NICE, 2017).

Health state transition count data - VN arm

	HS1	HS2	HS3	HS4	HS5
HS1	4	0	0	0	0
HS2	5	1	0	0	0
HS3	3	3	0	0	0
HS4	2	0	1	1	0
HS5	0	0	0	0	0

Health state transition count data - BSC arm

	HS1	HS2	HS3	HS4	HS5
HS1	3	0	0	0	0
HS2	1	2	0	1	0
HS3	0	0	1	0	0
HS4	0	0	1	0	0
HS5	0	0	0	0	0

Table 3.4: Transition count Voretigene Neparvovec (VN) & BSC arm.

Patients are assumed to move with a probability equal to the total number observed in each health state divided upon the total number transitioned from that exact health state. Furthermore, Novartis assumed that patients without any transition data could transition the same amount of health states as the patients could in the next least severe health state, creating some transition probabilities that where not observed with any counts, this resulted in what Novartis called “Exact TP matrix”. These probabilities were also provided in the NICE committee report as above.

Exact TP matrix VN arm

	HS1	HS2	HS3	HS4	HS5
HS1	1.00	0.00	0.00	0.00	0.00
HS2	0.83	0.17	0.00	0.00	0.00
HS3	0.50	0.50	0.00	0.00	0.00
HS4	0.50	0.00	0.25	0.25	0.00
HS5	0.00	0.50	0.00	0.25	0.25

Exact TP matrix BSC arm

	HS1	HS2	HS3	HS4	HS5
HS1	1.00	0.00	0.00	0.00	0.00
HS2	0.25	0.50	0.00	0.25	0.00
HS3	0.00	0.00	1.00	0.00	0.00
HS4	0.00	0.00	1.00	0.00	0.00
HS5	0.00	0.00	0.00	1.00	0.00

Table 3.5: Transition probability matrices for Voretigene Neparvovec (VN) & BSC arm.

The matrices presented in Table 3.5, do not include all possible transition included in the Markov model. These values were only used in the base-case deterministic analysis. For PSA purposes a 0.1 prior was added to each possible transition count. This allowed patients to move through every health state possible. Furthermore, it allowed us to assign a probability distribution to all input parameters associated with transition probabilities to propagate the parameter uncertainty. As these parameters represents multinominal probabilities which naturally should sum to 1 for each health state, Dirichlet was the distributional choice. This resulted in possible transition parameters in the initial stage as given below in Table 3.6.

The created abbreviations were structured as follows, “tp” indicated that it was a transition probability, “VN” or BSC” indicated which arm, hence either Voretigene Neparvovec or BSC. Moreover, the first Hs number indicate the current state, the second Hs in the naming regime, indicated which health state the simulated patient transitioned to.

Transition probabilitites VN and BSC arm

Parameter name	Base case value	Alpha	Beta	95% CI Lower	95% CI Upper	Distribution	Source
tpVN_hs1hs1	0.91	4.1	3.250	0.207514	1.000000	Dirichlet	NICE Table 40
tpVN_hs1hs2	0.02	0.1	0.007	0.000000	0.661716	Dirichlet	NICE Table 40
tpVN_hs1hs3	0.02	0.1	0.000	0.000000	0.726664	Dirichlet	NICE Table 40
tpVN_hs1hs4	0.02	0.1	0.000	0.000000	0.616300	Dirichlet	NICE Table 40
tpVN_hs1hs5	0.02	0.1	0.023	0.000000	0.674638	Dirichlet	NICE Table 40
tpVN_hs2hs1	0.78	5.1	5.524	0.220115	0.999288	Dirichlet	NICE Table 40
tpVN_hs2hs2	0.17	1.1	1.814	0.000221	0.760622	Dirichlet	NICE Table 40
tpVN_hs2hs3	0.02	0.1	0.013	0.000000	0.430895	Dirichlet	NICE Table 40
tpVN_hs2hs4	0.02	0.1	0.000	0.000000	0.389401	Dirichlet	NICE Table 40
tpVN_hs2hs5	0.02	0.1	0.072	0.000000	0.538187	Dirichlet	NICE Table 40
tpVN_hs3hs1	0.48	3.1	3.019	0.025371	0.966855	Dirichlet	NICE Table 40
tpVN_hs3hs2	0.48	3.1	4.491	0.029273	0.974483	Dirichlet	NICE Table 40
tpVN_hs3hs3	0.02	0.1	0.002	0.000000	0.409092	Dirichlet	NICE Table 40
tpVN_hs3hs4	0.02	0.1	0.000	0.000000	0.420442	Dirichlet	NICE Table 40
tpVN_hs3hs5	0.02	0.1	0.000	0.000000	0.396680	Dirichlet	NICE Table 40
tpVN_hs4hs1	0.47	2.1	3.510	0.023163	0.958079	Dirichlet	NICE Table 40
tpVN_hs4hs2	0.02	0.1	0.000	0.000000	0.727623	Dirichlet	NICE Table 40
tpVN_hs4hs3	0.24	1.1	2.166	0.000759	0.874303	Dirichlet	NICE Table 40
tpVN_hs4hs4	0.24	1.1	0.217	0.000575	0.869399	Dirichlet	NICE Table 40
tpVN_hs4hs5	0.02	0.1	0.020	0.000000	0.557985	Dirichlet	NICE Table 40
tpVN_hs5hs1	0.20	0.1	0.000	0.000000	0.999995	Dirichlet	NICE Table 40
tpVN_hs5hs2	0.20	0.1	0.009	0.000000	0.999998	Dirichlet	NICE Table 40
tpVN_hs5hs3	0.20	0.1	0.000	0.000000	0.999997	Dirichlet	NICE Table 40
tpVN_hs5hs4	0.20	0.1	0.059	0.000000	0.999999	Dirichlet	NICE Table 40
tpVN_hs5hs5	0.20	0.1	0.000	0.000000	1.000000	Dirichlet	NICE Table 40
tpBSC_hs1hs1	0.89	3.1	4.031	0.202005	1.000000	Dirichlet	NICE Table 39
tpBSC_hs1hs2	0.03	0.1	0.004	0.000000	0.661099	Dirichlet	NICE Table 39
tpBSC_hs1hs3	0.03	0.1	0.000	0.000000	0.645332	Dirichlet	NICE Table 39
tpBSC_hs1hs4	0.03	0.1	0.000	0.000000	0.700911	Dirichlet	NICE Table 39
tpBSC_hs1hs5	0.03	0.1	0.000	0.000000	0.791563	Dirichlet	NICE Table 39
tpBSC_hs2hs1	0.24	1.1	0.926	0.000130	0.873824	Dirichlet	NICE Table 39
tpBSC_hs2hs2	0.47	2.1	0.656	0.020322	0.970776	Dirichlet	NICE Table 39
tpBSC_hs2hs3	0.02	0.1	0.000	0.000000	0.844963	Dirichlet	NICE Table 39
tpBSC_hs2hs4	0.24	1.1	0.567	0.000025	0.930622	Dirichlet	NICE Table 39
tpBSC_hs2hs5	0.02	0.1	0.025	0.000000	0.682483	Dirichlet	NICE Table 39
tpBSC_hs3hs1	0.07	0.1	0.046	0.000000	0.991523	Dirichlet	NICE Table 39
tpBSC_hs3hs2	0.07	0.1	0.249	0.000000	0.981069	Dirichlet	NICE Table 39
tpBSC_hs3hs3	0.73	1.1	0.591	0.004322	1.000000	Dirichlet	NICE Table 39
tpBSC_hs3hs4	0.07	0.1	0.000	0.000000	0.988201	Dirichlet	NICE Table 39
tpBSC_hs3hs5	0.07	0.1	0.003	0.000000	0.990163	Dirichlet	NICE Table 39
tpBSC_hs4hs1	0.07	0.1	0.000	0.000000	0.992411	Dirichlet	NICE Table 39
tpBSC_hs4hs2	0.07	0.1	0.000	0.000000	0.967009	Dirichlet	NICE Table 39
tpBSC_hs4hs3	0.07	0.1	0.000	0.000000	0.975281	Dirichlet	NICE Table 39
tpBSC_hs4hs4	0.73	1.1	0.347	0.007407	1.000000	Dirichlet	NICE Table 39
tpBSC_hs4hs5	0.07	0.1	0.075	0.000000	0.989560	Dirichlet	NICE Table 39
tpBSC_hs5hs1	0.20	0.1	0.000	0.000000	1.000000	Dirichlet	NICE Table 39
tpBSC_hs5hs2	0.20	0.1	0.000	0.000000	1.000000	Dirichlet	NICE Table 39
tpBSC_hs5hs3	0.20	0.1	0.000	0.000000	1.000000	Dirichlet	NICE Table 39
tpBSC_hs5hs4	0.20	0.1	0.000	0.000000	0.999999	Dirichlet	NICE Table 39
tpBSC_hs5hs5	0.20	0.1	0.000	0.000000	1.000000	Dirichlet	NICE Table 39

Table 3.6: Transition probabilities Voretigene Neparvovec & BSC arm for PSA usage.

3.5.2.2 NHx disease progression parameters

Transition intensity rates from the natural history (NHx) of RPE65 mutated associated IRD are calculated from the transition counts by Chung et al (2019) and are provided by the NICE (2017). These counts are based on an observational study on 283 patients whereas 28 transitions counts were observed. These intensity rates are important model parameters since they serve as the extrapolated transition probabilities in the long-term phase. They have been calculated using the procedure by Crowther & Lambert (2016) MSM procedure. These transitional intensity rates are converted through the procedure by Jones et al (2017). The wxMaxima output for the calculation of eigenvalues, eigenvectors, and algebraic conversion formulas will be provided in the appendix. By implementing these conversion formulas directly into Excel, variation within a PSA analysis was allowed. The transition intensities rates provided in Table 3.8, had to be converted to hazards to allow the conversion between hazards and probabilities. This was done by calculating the hazard function for the respective distribution. For transparency, the rates listed are rates calculated when extrapolating using a Gompertz distribution. The complete list where rates for Exponential, Weibull etc. will also be provided in the appendix.

For Gompertz the hazard function is: $h(t)$: $\lambda e^{\theta t}$.

The positive scale value λ, is the natural logarithm of the parameter named "constant", which represents HS2 in the present model. For each respective health state calculation after HS2, it is calculated through use of the natural logarithm of for example "constant" + "Hs1Hs3" for HS3 etc. As there are no values for HS1, HS1 is thus equal to 1 – HS2 + HS3 + HS4 +HS5. The shape parameter, θ, is the exponential of "gamma", which is multiplied with the cycle length (i.e., one year or 365.25 days). To get the yearly rate, the complete formula is multiplied yet again with 365.25. To calculate the hazards for other distributions the same reasoning applies. All possible transitions can be viewed in the transition matrix in Figure 3.2.

$$\begin{pmatrix} HS1 & HS2 & HS3 & HS4 & HS5 \\ 0 & HS2 & HS3 & HS4 & HS5 \\ 0 & 0 & HS3 & HS4 & HS5 \\ 0 & 0 & 0 & HS4 & HS5 \\ 0 & 0 & 0 & 0 & HS5 \end{pmatrix}$$

Figure 3.2: Transition Matrix.

Even though Weibull was considered to have the best statical fit based on AIC and BIC tests as shown in Table 3.7, NOMA considered Gompertz to have more clinical plausibility because of a more rapid deterioration of visual function and was thus applied to simulate natural disease progression in the model.

Model	AIC	BIC
Weibull	138.3	176.6
Gompertz	139	177.3
Exponential	146.3	181.1
Log-normal	141.2	179.4
Log-logistic	140.5	178.7

Table 3.7: AIC/BIC values NHx data.

As mentioned, transition counts through all identified health states were not observed within the NHx study; however, these were generated through the Jones et al (2019) procedure. Normal distribution was used to assign uncertainty to the estimates as this was done by NICE (2017). For some of the values, Hs1Hs5, Hs2Hs5 and Hs3Hs5 the standard errors were so substantial that these values were held constant to not cause errors within the simulations in Excel. The naming structured for the NHx transitional probabilities followed from the statistical output. However, Hs1Hs3 indicates the health states the transition starts at and where the patients are transitioning to.

Natural history transition rates

Parameter name	Base case value	Standard Error	95% CI Lower	95% CI Upper	Distribution	Reference
Hs1Hs3	-2.485	1.041	-4.5253	-0.044464	Normal	NICE Committee NHx MSM statisical output
Hs1Hs4	-2.485	1.041	-4.5253	-0.044464	Normal	NICE Committee NHx MSM statisical output
Hs1Hs5	-17.25	1609.5	-3171.87	3137.37	-	NICE Committee NHx MSM statisical output
Hs2Hs3	-0.513	0.419	-1.3342	0.30824	Normal	NICE Committee NHx MSM statisical output
Hs2Hs4	-2.91	1.042	-4.9523	-0.86768	Normal	NICE Committee NHx MSM statisical output
Hs2Hs5	-17.28	1319.0	-2602.5	2567.96	-	NICE Committee NHx MSM statisical output
Hs3Hs4	-1.404	0.535	-2.4526	-0.3554	Normal	NICE Committee NHx MSM statisical output
Hs3Hs5	-17.37	1194.3	-2358.2	2323.46	-	NICE Committee NHx MSM statisical output
Hs4Hs5	-1.555	0.666	-2.86036	-0.24964	Normal	NICE Committee NHx MSM statisical output
constant	-9.211	0.355	-9.9068	-8.5152	Normal	NICE Committee NHx MSM statisical output
gamma	0.000316	0.0000825	0.0001534	0.0004777	Normal	NICE Committee NHx MSM statisical output

Table 3.8: NHx transition intensity rates – Gompertz.

3.5.2 Adverse event and mortality parameters

Parameters for adverse events were elicited from the phase 3 trial by Russell et al (2017) are given in Table 3.9. The main adverse events included cataracts eye inflammation and increased intraocular pressure. Of the 20 participants enrolled in the Voretigene Neparvovec arm three patients experienced cataracts, two were subject to eye inflammation and four sustained increased intraocular pressure. These parameters correspond to what is reported in the HTA submission from NICE (2017). However, these were not used to add disutility. In the report by NOMA (2019), disutility for adverse events were added as a one-off which will be explained further in the coming sections. However, these proportions are used to include adverse events related cost into the model. Beta distribution was chosen as the distribution to propagate the uncertainty as recommended by Briggs et al (2006) for probability parameters. To distinguish the parameters in the model the lowercase p indicates that it is a probability and "AE" is an abbreviation for adverse event.

Probability adverse events phase 3 study

Parameter name	Base case value	95% CI Lower	95% CI Upper	Alpha	Beta	Distribution	Source
pAECataract	0.15	0.002613	0.460693	3	17	Beta	Russell et al
pAEEyeInflam	0.1	0.002591	0.375691	2	18	Beta	Russell et al
pAEInclOP	0.2	0.009298	0.526600	4	16	Beta	Russell et al

Table 3.9: Probability adverse event.

As patients with RPE65-associated IRD does not affect mortality, age specific mortality probabilities from the mean population can be used to simulate mortality risk within the model. NOMA used death-specific data gathered from Norway's mean population from year 2017 to calculate their expected remaining lifetime when calculating absolute shortfall. To include the same mortality risk within my model, and to replicate their model, 2017 was naturally selected as my reference. The numbers were elicited from Statistisk Sentralbyrå (SSB) Table 05381 (SSB, 2022) and are presented below in Table 3.10. Data was collected for both woman and men and from the age of 15 to 90 plus. For the purpose to be used within the model these mortality rates had to be converted to probabilities. As with the probability for adverse events, the beta distribution was utilized for the age specific mortality probabilities. To keep transparency while modelling, "Mort" is used as an abbreviation for mortality and the numbers indicate which age interval these probabilities was relevant for.

Age specific mortality probabilitites

Parameter name	Base case value	Alpha	Beta	95% CI Lower	95% CI Upper	Distribution	Source	Year
pMort15-19	0.0005	46	99954	0.0003379	0.0005997	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort20-24	0.0008	80	99920	0.0006449	0.0009761	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort25-29	0.0008	81	99919	0.0006425	0.0010015	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort30-34	0.0009	92	99908	0.0007316	0.0011314	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort35-39	0.0012	116	99884	0.0009668	0.0013808	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort40-44	0.0016	164	99836	0.0014145	0.0018848	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort45-49	0.0027	271	99729	0.0024054	0.0030598	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort50-54	0.0046	460	99540	0.0041992	0.0050040	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort55-59	0.0077	766	99234	0.0070087	0.0082108	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort60-64	0.0122	1220	98780	0.0115781	0.0129053	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort65-69	0.0212	2124	97876	0.0203511	0.0220965	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort70-74	0.0344	3435	96565	0.0330614	0.0354113	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort75-79	0.0604	6035	93965	0.0589341	0.0618551	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort80-84	0.1144	11439	88561	0.1124052	0.1162272	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort85-89	0.2202	22016	77984	0.2175919	0.2226451	Beta	SSB: Table 05381 Deaths per mean population	2017
pMort90plus	0.4699	46986	53014	0.4666636	0.4727691	Beta	SSB: Table 05381 Deaths per mean population	2017

Table 3.10: Age specific mortality probabilities.

3.5.3 Utility parameters

In the base case model, we used utility parameters that are in line with the parameters used by NOMA (2019). These utility weights are taken from Brown et al (1999) and not by from the vignette study by Acaster Lloyd which Novartis used in their analysis. These utility weights are gathered from a study population of 325 individuals with a mean age of 68. These were elicited by using time trade off and standard gamble and measures only visual acuity. Utility values are multiplied with the proportion of patients in each health state throughout the model. As utility values are binominal data constrained within [0, 1], the Beta distribution is assigned as distribution to the utility weights to represent the uncertainty. As these weights are gathered from an external source and do not include counts but standard deviations, fitting the Beta distribution must be done through methods of moments (Briggs et al, 2006). Parameters are structured as "qol" as a short-term for quality of life followed by the health state in question.

As previously mentioned in Chapter 3.5.2, disutility for AE was added as a one off in the first cycle of treatment. The utility decrement was 0.12, in line with assumptions made by NOMA and was not subject to any change. This is because NOMA conveyed that the disutility caused by AE negligibly changed the outcome. Moreover, additional disutility for young relatives was included (i.e., for individuals aged 18 or younger) in the model. The values were gathered from Wittenberg et al (2013) which investigated HRQoL for individuals with activity limitations through EQ-5D questionnaires. As with the QALY weights, the Beta distribution was applied, and the uncertainty range was calculated through method of moments.

HRQoL Utility Weights

Parameter name	Base case value	Standard Deviation	95% CI Lower	95% CI Upper	Alpha	Beta	Distribution	Source
qolHS1	0.75	0.21	0.711748	0.785475	2.44	0.81	Beta	Brown et al
qolHS2	0.65	0.20	0.609372	0.687779	3.05	1.64	Beta	Brown et al
qolHS3	0.54	0.17	0.512499	0.57528	4.10	3.49	Beta	Brown et al
qolHS4	0.52	0.29	0.468610	0.572217	1.02	0.94	Beta	Brown et al
qolHS5	0.35	0.29	0.295004	0.406936	0.60	1.11	Beta	Brown et al
sSizeBrown	325	-	-	-	-	-	-	Brown et al

HRQoL Disutility Weights

Parameter name	Base case value	Standard Deviation	95% CI Lower	95% CI Upper	Alpha	Beta	Distribution	Source
qolAE_agg	0.12	-	-	-	-	-	Beta	SLV
qolRelatives_young	0.08	0.82	0.037022	0.155202	22.88	241.97	Beta	Wittenberg et al
sSizeWittenberg	2412	-	-	-	-	-	-	Wittenberg et al

Table 3.11: Utility weights.

3.5.4 Costs parameters

Cost parameters were implemented into the model in accordance with assumptions made by NOMA (2019). Voretigene Neparvovec administration associated costs was implemented in the initial cycle for all patients in the Voretigene Neparvovec arm. This includes the cost of the drug administration, surgery, prednisolone, and admission to surgery costs. Furthermore, AE-associated costs are only applicable for the first initial cycle. The probability of experiencing an AE was multiplied with the total population and its associated cost.

Moreover, some costs were identified by the company to follow the patient throughout their entire life. These are costs regarding hospital admission, general ophthalmologic services, technical assistance for both children and adults (i.e., the abbreviation "Ext" indicates extended help, and is thus considered for children aged 18 or younger), treatment from depression and continuously follow up by the health care services. However, all costs were not necessarily included in every health state. Hospital admission was relevant from HS2 to HS5, ophthalmologic services and follow up was provided in all health states, technical assistance was issued for HS4 and HS5 for both children and adults and treatment from depression were issued for patients identified in HS3 to HS5.

In accordance with Briggs et al (2006), Gamma distribution was assigned to cost parameters to represent the uncertainty. However, as no standard error was provided, an arbitrary of 10% was chosen. Even though drug discounts are possible and highly likely, Voretigene Neparvovec administration costs was held constant as an arbitrary value in as the gamma distribution would cause it to fluctuate to higher amounts which would cause an erroneously large discrepancy as it is irrational to believe that the Norwegian health care services would pay above list price.

Costs parameters

Parameter name	Base case value	Standard Error	95% CI Lower	95% CI Upper	Alpha	Beta	Distribution	Source
cVNadministration	7108878.0	710887.8	-	-	100	71088.78	-	SLV
cSurgery	129854.0	12985.4	87854.59	178291.46	100	1298.54	Gamma	SLV
cPrednisolon	173.0	17.3	123.22	224.66	100	1.73	Gamma	SLV
cAdmissionSurgery	28482.0	2848.2	20173.16	39226.54	100	284.82	Gamma	SLV
cFollowUp	1206.0	120.6	849.22	1671.27	100	12.06	Gamma	SLV
cAEcataract	40724.5	4072.4	29264.19	54273.88	100	407.24	Gamma	SLV
cAEeyeInflam	70464.0	7046.4	50165.27	92567.00	100	704.64	Gamma	SLV
cAEincIOP	10136.5	1013.6	7132.88	14110.73	100	101.36	Gamma	SLV
cHospAdmis	8332.0	833.2	5935.5	10997.38	100	83.32	Gamma	SLV
cOftaHelp	1206.0	120.6	844.67	1602.52	100	12.06	Gamma	SLV
cTechAssistance	14748.0	1474.8	10159	19817.7	100	147.48	Gamma	SLV
cTechAssistanceExt	58992.0	5899.2	41951.66	77000.43	100	589.92	Gamma	SLV
cDepression	1741.0	174.1	1261.47	2364.76	100	17.41	Gamma	SLV

Table 3.12: Cost's parameters.

3.6 Half-cycle correction

As time-to-event analysis analyze patients at pre-determined points in time it is difficult to assess exactly when the patient moves. As the cycle length is set to be one year, the patients could move whenever within that timeframe. By taking the average between the first two cycles. This causes the events to happen at year 1.5 rather than year 1.

3.7 Model Uncertainties

To cope with both structural uncertainty and parameter uncertainty in the model we performed several analyses. Scenario analysis (i.e., deterministic sensitivity analysis) are used for handling structural uncertainty. As the true values of parameters cannot be known with certainty, a PSA propagates parameters uncertainty from input parameters to the model outputs.

3.7.2 Probabilistic sensitivity analysis

To propagate parameter uncertainty utilized within the model, a PSA was conducted. This is done by drawing and storing sampling values within each parameters distribution that was already assigned appropriately and within their given uncertainty range. Our Monte Carlo simulation was iterated 1000 times where the main outcome is represented by the mean value over all iterations. Additionally, by storing all the values for all simulations, we estimated a range of outcomes which will be represented within the CE-plane. By calculating the NMB from every iteration, a CEAC and CEAF can also be visualized.

3.7.3 Value of Information

As previously noted, value of information measurements is a set of methods used quantify the decision uncertainty. VOI provides a monetary estimate which can be used by decision makers to decide whether it is worthwhile to conduct further research to reduce this uncertainty and could thus be used as a tool to design and prioritize by decision makers. After the PSA was conducted NMB can be estimated for each iteration by using a defined WTP threshold (i.e., 2,200,000 NOK). The EVPI can manually be calculated within different software programs using the calculated NMB of every iteration. By aggregating the EVPI by the discounted population prevalence and incidence over the defined time horizon we get population EVPI.

EVPPI and EVSI is rather cumbersome to calculate manually, so this was done within the "voi" R package which is developed by Christoffer Jackson as a project of the Collaborative Network for Value of Information group (ConVOI) (Jackson, 2022). Within the voi R package there are several different procedures to calculate EVPPI and EVSI. However, for EVPPI the Gaussian process regression method by Strong et al. (2013) was utilized. To calculate the EVSI the nonparametric regression method by Strong et al. (2015) was applied.

The model parameters will be clustered into relevant groups before being investigated through EVPPI and EVSI. This makes it possible to make an informed choice when opting for study design when collecting information on fixed and variable costs for the calculation of ENBS.

Estimates for research associated costs for randomized controlled trials (RCT) for the construction of ENBS, we utilized cost gathered from Kunst et al. 2019. As the cost were reported in 2019 US dollars, we converted it to NOK by using the average exchange rate for US dollar to NOK in 2019 gathered from Norway's Central Bank (Norges Bank).

3.7.4 Scenario analysis

To test the model for structural uncertainty several selected scenario analyses will be performed. The clinical effectiveness in the long-term phase is thought to have substantial impact on the model outcome. Therefore, as Weibull distribution was chosen by Novartis as the base-case distribution to extrapolate disease progression, we investigated how using this

distribution would affect the model outcomes. Their AIC/BIC values indicated a rather similar statistical fit; however, Weibull was associated with longer distributional tales (i.e., slower disease progression) (NOMA, 2017), which could alter the outcome.

Another assumption that should be examined was the constant treatment effect. NOMA opted for 15 years of constant treatment effect of Voretigene Neparvovec administration whereas Novartis used 50 years as their constant effect. This change is thought to have paramount effect on the model outcomes. As previously established, disease progression with RPE65 gene mutation associated IRD is rapid, postponing such progression would cause the patients to stay much longer in healthier health states associated with higher HRQoL valuation.

A third and final scenario analysis is to use utility weights from the Acaster Lloyd vignette study implemented by Novartis.

3.8 Model validation

As data for RPE65 associated IRD is rather scarce, and due to a replication of an already existing method, parameters were predominantly gathered from the method evaluation by NOMA (2019). However, additional information was gathered from the more exhaustive report by NICE (2017). Nevertheless – to infer whether the analysis is precise outcomes from both these evaluations can be used for comparison. Moreover, as the CEA authored by Johnson et al. (2019) and Viriatio et al. (2020) utilizes similar approaches as the present work so these can also be used to control for similarity.

3.8.1 Transition validation

Clinical effects for the initial phase are publicly available, i.e., the exact transition probabilities given in Table 3.5, from almost all sources, (NOMA, 2019; NICE, 2019; Viriatio et al., 2020). However, as transition probabilities for the long-term phase are to be calculated some variation could occur. These values are not given explicitly, however – the statistical output from the NHx trial is given by NICE (2017) and provided in the supplementary material from Viriatio et al. (2020) and Johnson et al. (2019). There are some discrepancies between the values reported. We opted however for the values given by NICE (2017) and Viriatio et al. (2020), as these values are comparable, the sample size is larger, and the values are collected directly from the HTA submission by Novartis since they are reported by NICE (2017). To determine whether the calculations are accurate a comparison of the Markov traces can be done.

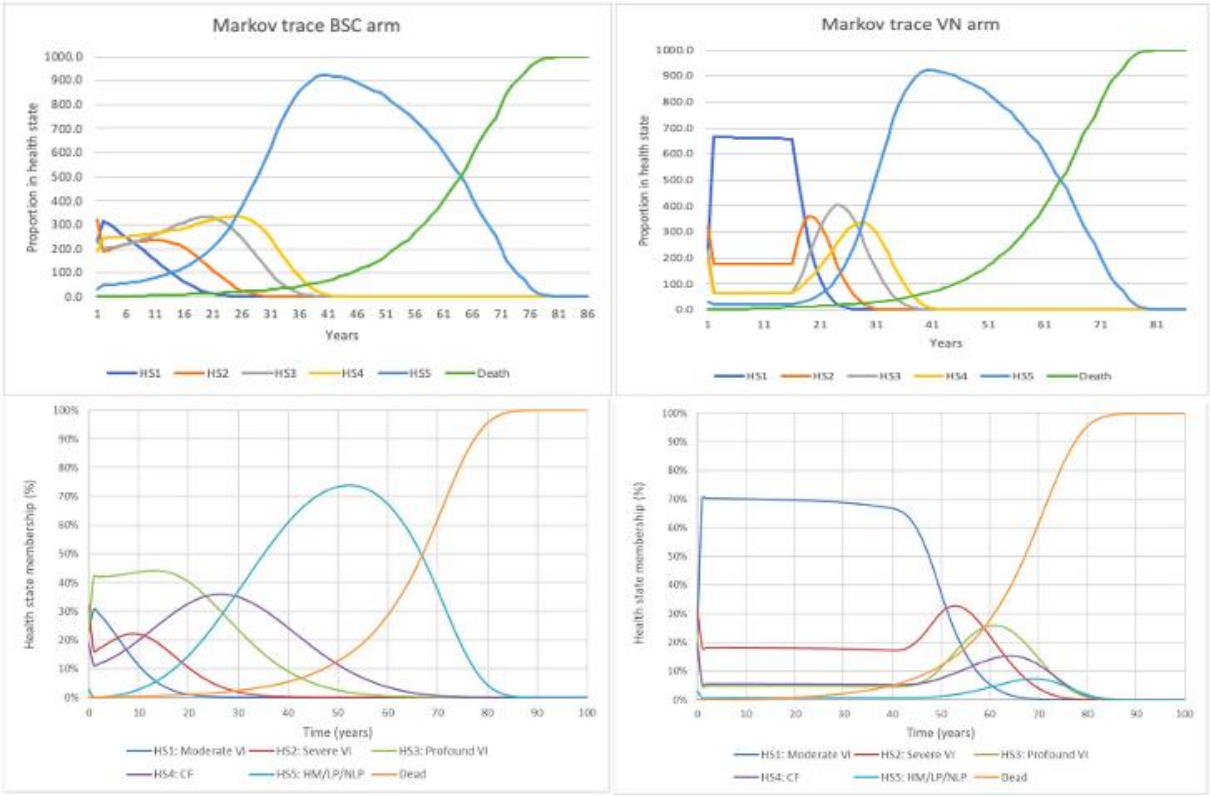

Figure 3.3: Markov traces. Markov traces from this analysis is presented on top whereas Markov traces from NICE (2017) is presented on the bottom.

By comparing our estimated Markov traces, to the Markov traces given in NICE (2017) in Figure 3.3, we could infer that these traces seem to match quite reasonably, and we could thus conclude that the conversion of transition intensity rates to transition probabilities were done satisfactory.

3.8.2 Outcome validation

As we replicated the method assumptions for this analysis it would naturally be of importance to compare outcomes such as effects and costs with NOMA (2019). Parameter values that are gathered directly from NOMA (2019) and are not subject to any conversion nor indexing and should thus be accurate. Since this thesis evaluate the decision made by NOMA in 2019, more recent information on values must be discarded as this was not available at that time.

The results will be provided in the Result section, however for comparison purposes our model calculated an incremental discounted result of 7,204,660 NOK in terms of costs and 3.273 incremental QALYs gained, which in turn resulted in an ICER of NOK 2,200,934. By comparison, NOMA in their base case analysis the incremental cost is simulated to be NOK 7,117,688 with 3,0 QALYs gained and resulting in an ICER of NOK 2,374,253.

Here, our analysis is slightly overestimating the incremental costs and QALYs gained. However, since both the costs and QALYs are slightly larger, the ICER remains accurate in comparison to the result given by NOMA (2019), with a variation in calculated ICER of only 1.21%. Because of this, it is not expected that the variation in results have any negative impact on the VOI results.

One important aspect to mention is that RRR was not implemented within the model in accordance with the model assumptions made by NOMA (2019). Although this is a flaw in the method applied within our model, the RRR is not subject to variation in PSA and because it is held constant it does not affect the VOI estimates. It is believed that the accuracy in outcomes in this analysis, compared to NOMA's estimates is crucial to get valid VOI estimates. Which in turn is achieved by omitting the RRR implementation.

To validate VOI estimations comparative validation are going to be performed to check whether estimates are equal by utilizing different approaches. As established, only EVPI is calculated within a spreadsheet (Microsoft Excel) for the purpose of a simple aggregation to the population EVPI. EVPPI and EVSI outcomes are going to be gathered from the "voi" package in R.

However, by using the Sheffield Accelerate Value of Information (SAVI) tool by the University of Sheffield and the EVPI estimation within R, a cross validation is allowed. This makes it possible to assess whether EVPI estimations are similar. For EVPPI and EVSI, a Monte Carlo error will occur, since collecting sample data will cause different estimations each time the analysis is run, however it will be possible to scrutinize common trends.

Results

In this fourth chapter, the main findings will be presented. This will include the incremental probabilistic discounted outcomes such as costs, QALYs and ICER. This is followed by a representation of the variation of results within the PSA visualized by a CE-plane. Furthermore, the CEAC and CEAF will be presented to showcase the probability of cost-effectiveness and the suggested optimal strategy, at different WTP thresholds. Thereinafter the results from the conducted VOI analysis will be presented. To conclude this chapter results from the scenario analysis will be given to portray the impact the selected structural changes provide. The base case costs and health outcomes are represented in the Table 4.1 below.

	Voretigene Neparvovec	BSC	Increment
Total Costs	kr 7 717 797.94	kr 513 137.81	kr 7 204 660.13
Total QALYs	21.66	18.38	3.27
ICER	-	-	kr 2 200 934.82

Table 4.1: Base-case cost-effectiveness results.

The strategy with Voretigene Neparvovec was associated with 21.66 QALYs were accrued over a lifetime horizon and total cost accumulated to a total of NOK 7,717,797. The strategy with BSC was associated with 18.38 QALYs and total costs of NOK 513,137.

This resulted in incremental QALYs of 3.27, incremental costs of NOK 7,204,660.13 which resulted in an ICER of NOK 2,200,934 per QALY gained for Voretigene Neparvovec compared to BSC.

4.1 Cost-effectiveness – plane

Results for health and costs outcomes of each iteration of the 1000 Monte Marlo simulations are presented in an incremental CE-plane (Figure 4.1). Each dot represents an ICER per QALY gained result, which is the product of the incremental cost and incremental QALYs gained. These dots are thus representing all simulated ICER's in the model.

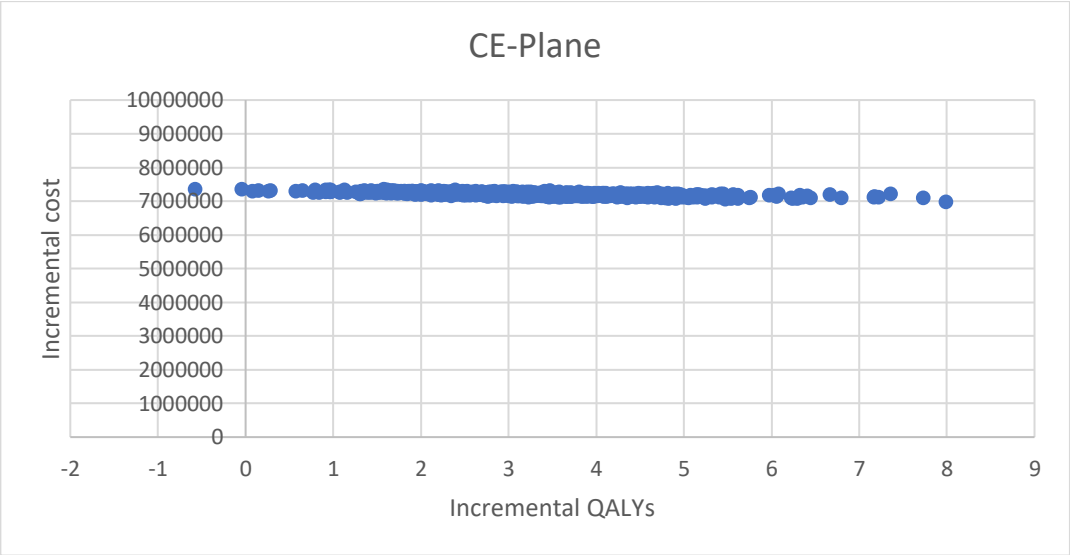

Figure 4.1: CE-plane.

As seen from Figure 4.1, the variation between incremental QALYs gained with Voretigene Neparvovec administration compared to BSC is substantial. Almost exhaustively every iteration is in the north-eastern quadrant. This indicates that Voretigene Neparvovec administration is associated with both higher cost and QALYs. Whether it can be considered a cost-effective strategy depends however on the WTP threshold. The density of dots seems to be between one and five incremental QALYs, with outliers stretching from almost negative one, to eight incremental QALYs. This indicates uncertainty in either the transitions or the utility weights. The reason why transition probabilities are considered uncertain is because QALYs are subject of utility weight, and the time spent with that exact utility. In this model, time spent in health states which are object for their own unique utility weight is determined by how fast the patients transition through the health states. The discrepancy between incremental costs is deemed to be narrow and thus rather an exact estimate which could be a result of using an arbitrary 10% variation for costs parameters.

4.2 Cost-effectiveness acceptability curve

The CEAC is presented in Figure 4.2, presents the probability of Voretigene Neparvovec and BSC to be cost-effective at each WTP threshold considered.

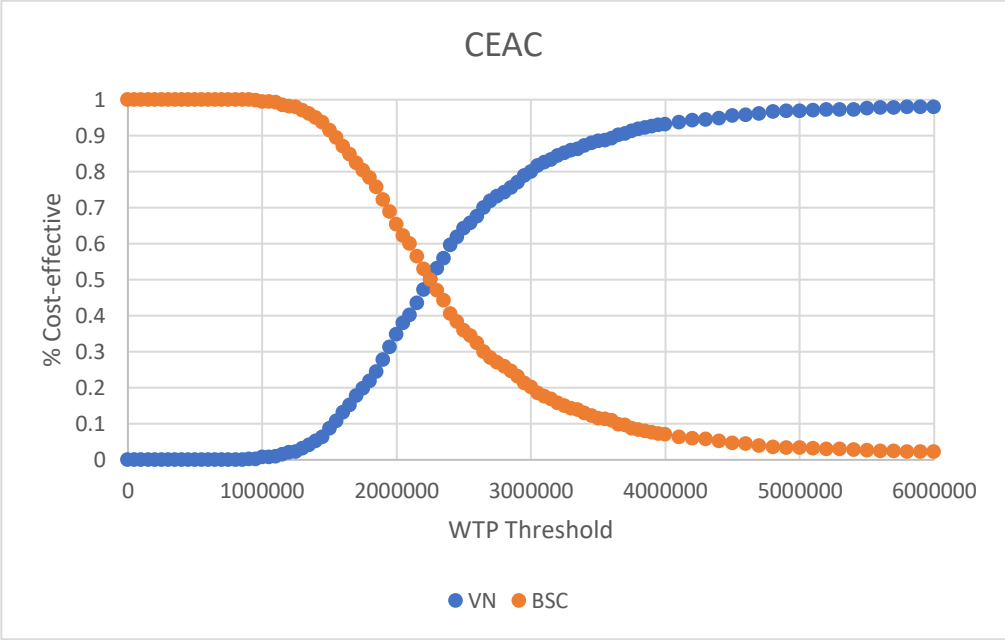

Figure 4.2: CEAC.

BSC has the highest probability of being cost-effective when the WTP thresholds are below 2,200,000 NOK. Furthermore, the strategy with the highest probability of being cost-effective switches around approximately this exact threshold value of 2,200,000 NOK, hence from thereon out Voretigene Neparvovec is considered to have the highest probability of being cost-effective.

4.3 Cost-effectiveness acceptability frontier

Since the CEAC can only provide information on strategies' probability of being cost-effective, a CEAF is considered essential when deciding on the optimal strategy since it presents the strategy with the highest NMB. Hence, a CEAF presents the optimal strategy and thus the intervention with the highest NMB for every WTP threshold.

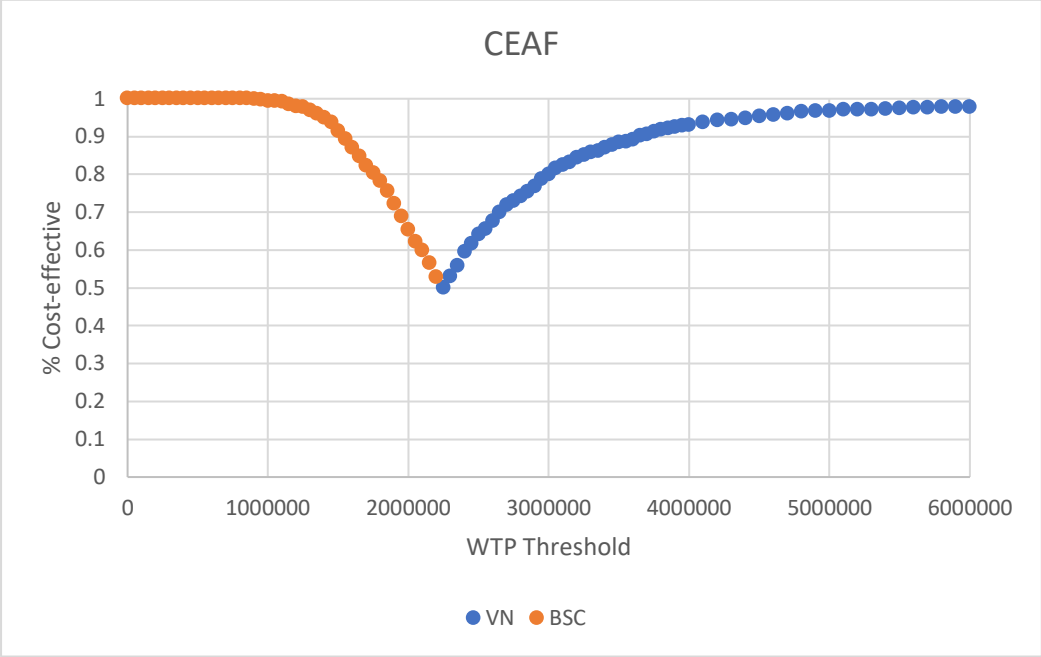

Figure 4.3: CEAF.

Figure 4.3 indicates that Voretigene Neparvovec is associated with the highest NMB at WTP thresholds above 2,200,000 NOK.

4.4 Value of Information

As value of information analysis consists of several calculations the results will be presented in this following order: individual EVPI, population EVPI, population EVPPI, population EVSI and population ENBS.

By comparing the CEAF from Figure 4.3 with the results from Figure 4.4, we can see that the highest EVPI is at the WTP threshold where the optimal strategy switched from BSC to Voretigene Neparvovec. This point represents the point with greatest uncertainty because both Voretigene Neparvovec and BSC are associated with 50% chance of being cost-effective and is thus naturally the point where it is most valuable to gain additional knowledge. As we can see from Figure 4.4 this is at the WTP threshold of 2,200,000 NOK.

At the WTP threshold of 2,200,000 NOK, the individual EVPI was calculated to be NOK 927,800. When aggregating the individual EVPI over a prevalence of 8 patients and an incidence of one patient per year over a time horizon of 10 years the population EVPI is estimated to be NOK 9,941,417.

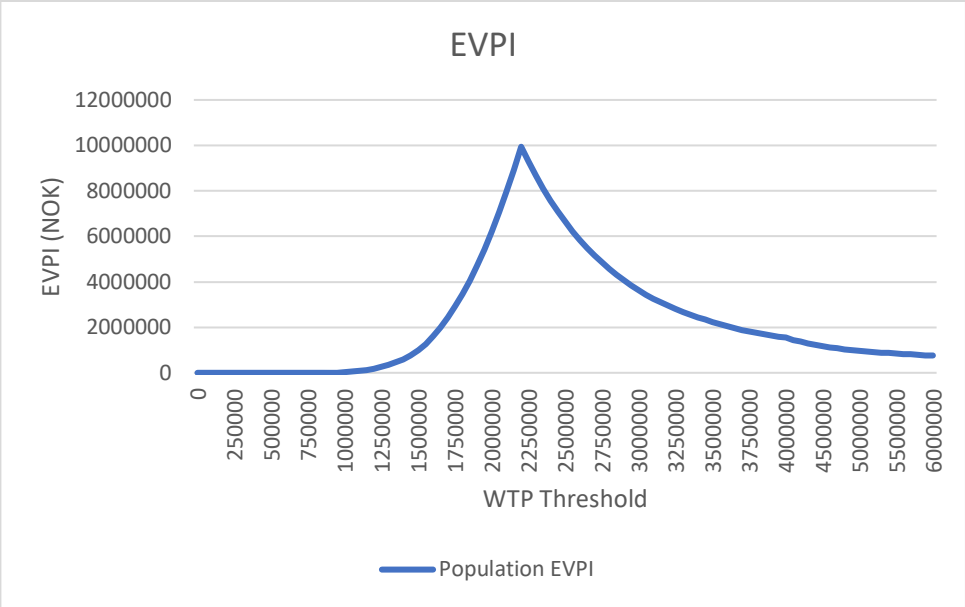

Figure 4.4: Population EVPI.

For the calculation of EVPPI, we created groups of parameters that shared common purpose within the model. This was to enable having grouped parameters that we could collect additional data for in one research study. This included a group for the natural history of disease progression transitional parameters which was labelled "NHx RPE65" (see Table 3.8 in Chapter 3.5.2 for the list of all parameters included). One group called "Clinical Efficacy" included clinical effectiveness parameters from the phase III study by Russell et al. (2017) (see Table 3.6 in Chapter 3.5.2).

Utility weight measurements gathered from Brown et al (1999) was clustered under "HRQoL" and a complete list of the parameters can be found in Table 3.11 in Chapter 3.5.3, including parameters concerning disutility. Age specific mortality parameters was congregated into one group named "Mortality" (see Table 3.10.) Finally, cost parameters were named "Costs" and are provided in Table 3.12 in Chapter 3.5.4.

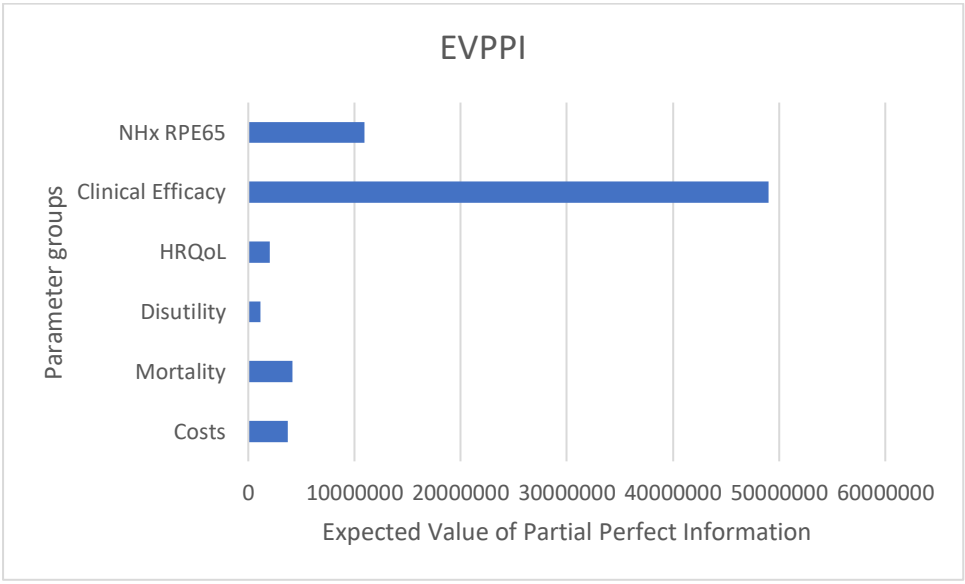

Figure 4.5: EVPPI with associated parameter groups.

A parameter group with higher EVPPI value naturally implies that the group is associated with higher decision uncertainty. As displayed in Figure 4.5, we can infer that the groups: NHx RPE65 and especially Clinical Efficacy has large discrepancies in their parameter interval after running the PSA and is thus causing uncertainty within the model. Hence, indicating that further research might be worthwhile for parameters within these groups. This is seemed to be a logical estimate as we have already established that data regarding RPE65 associated IRD is prone to large variability as both Russell et al. (2017) and Chung et al. (2019) suffers from small study populations and or few observed events.

Naturally, the other groups cause some level of decision uncertainty, however, in comparison this is determined negligible.

We estimated population EVSI and ENBS for the group "Clinical Efficacy" given that this group was associated with the highest decision uncertainty where the results is represented in Figure 4.6. The results represent the aggregated population EVSI through the discounted prevalence and expected incidence. The optimal sample size can be identified as the highest point on the ENBS curve, indicating that the optimal sample size for the proposed research was 10 individuals. Even though EVSI is positive, it is important to note that ENBS valuation is considered negative (i.e., ENBS curve do not cross the horizontal zero line) for the complete interval. This indicates that the expected cost of further research exceeds the expected value of additional information. Therefore, collecting additional data on clinical efficacy of Voretigene Neparvovec is considered potentially not worthwhile.

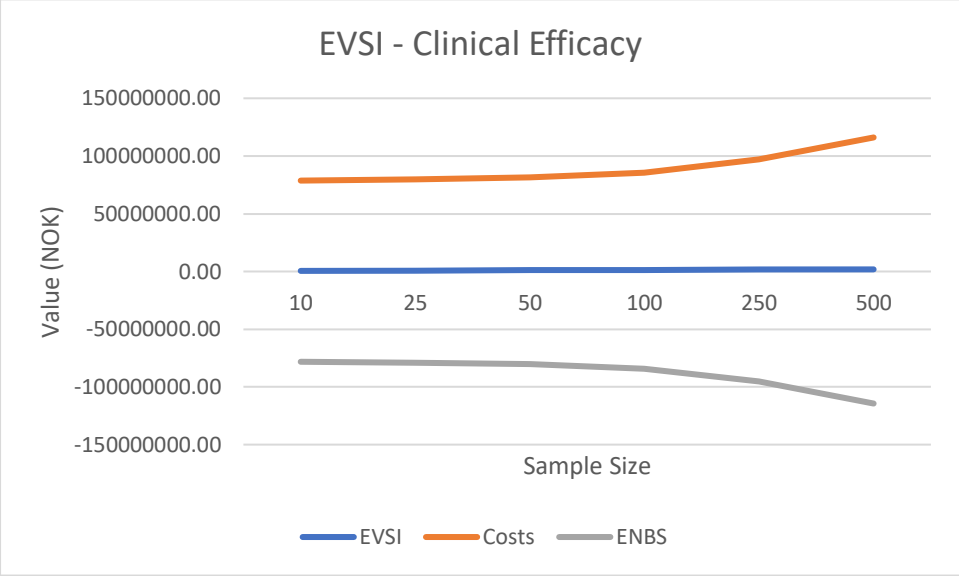

Figure 4.6: Clinical Efficacy population EVSI.

4.5 Scenario analysis

In the first sensitivity analysis, we extrapolated natural history disease progression using Weibull distribution instead of Gompertz distribution, as Novartis opted for in their submission. As seen in Table 4.2, this resulted in a lower ICER. The structural change did not affect the costs that much, however – the incremental gain in QALYs increased as expected given that Weibull distribution is associated with longer tales than Gompertz distribution.

	Voretigene Neparvovec	BSC	Increment
Total Costs	kr 7 698 598.13	kr 509 469.67	kr 7 189 128.46
Total QALYs	25.44	20.65	4.79
ICER	-	-	kr 1 500 198.93

Table 4.2: Scenario analysis: Weibull distribution.

In the second scenario analysis, we increased the Voretigene Neparvovec constant clinical effect from 15 years (i.e., as NOMA assumed in their base case analysis), to 50 years which was reported in the manufacturer's base-case analysis. Similarly, to the previous scenario analysis, this change did not affect the costs to large extent, however, because of the paramount change in incremental QALYs gained, the ICER substantially decreased as portrayed in Table 4.3.

	Voretigene Neparvovec	BSC	Increment
Total Costs	kr 7 558 713.13	kr 509 368.00	kr 7 049 345.13
Total QALYs	34.61	18.43	16.18
ICER	-	-	kr 435 702.13

Table 4.3: Scenario analysis: 50 years constant treatment effect.

The third structural change that was applied as a scenario analysis concerned the utility weights. NOMA originally utilized utility weights elicited from Brown et al. (1999), whereas Novartis applied their expert elicited values from Acaster Lloyd vignette study. As presented in Table 4.4, as with the other structural changes, this change did not alter the costs so much. Moreover, the incremental QALYs also stayed rather similar compared to base-case values. Hence, resulting in an ICER not that far from the base-case result.

	Voretigene Neparvovec	BSC	Increment
Total Costs	kr 7 715 704.47	kr 512 399.59	kr 7 203 304.88
Total QALYs	18.36	14.37	3.98
ICER	-	-	kr 1 808 735.23

Table 4.4: Scenario analysis: Outcomes Acaster Lloyd vignette study QALY weights.

4.5.1 Population EVPI Sensitivity

In the base-case estimation of population EVPI, we assumed a time horizon of 10 years. By changing the time horizon to 5 years, a population EVPI resulted in a value of 9.482.081 NOK. Thus, resulting in a difference NOK 459,336 less than compared to base-case results. By increasing the time horizon to 15 years the population increases to NOK 10,043,855, an increase of NOK 102,438. Visually, as portrayed in Figure 4.7, population EVPI values across different years are substantially overlapping as the results are quite similar. Indicating that this assumption did not have a substantial effect on the obtained VOI results.

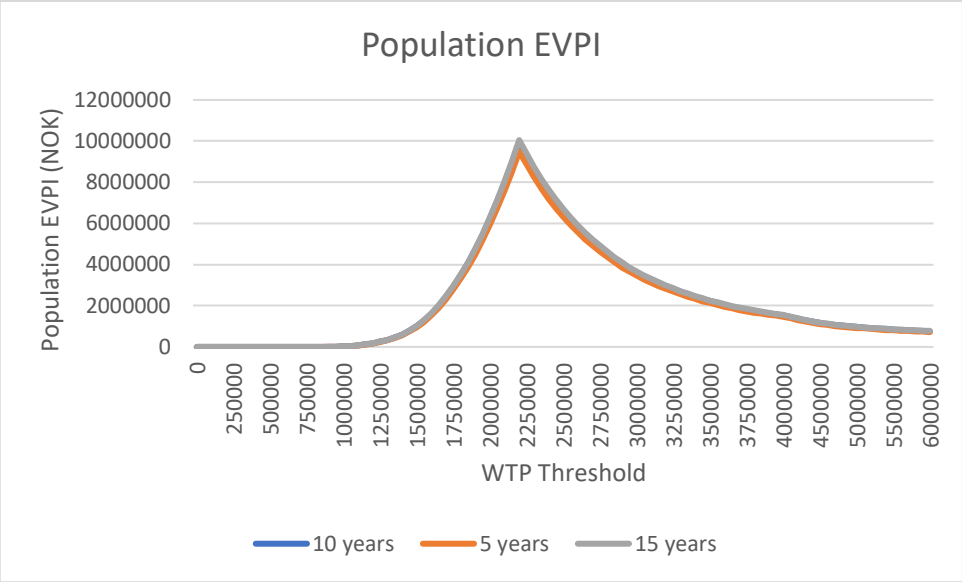

Figure 4.7: Population EVPI over different time horizons.

Discussion

In this chapter, the main findings from our analysis will be discussed. These results will be used as consideration when answering the research question of this thesis. Thus, we ought to interpret the results, evaluate the method applied and discuss model assumptions. Finally, we will ventilate possible contributions this thesis yield and recommend areas where further research is deemed necessary.

Chapter 5.1 presents the main results gathered from this thesis. In subsection 5.1.1, the justification of the conditional reimbursement is discussed, whereas in subsection 5.1.2, the value of quantified uncertainty is considered. Chapter 5.2 will assess the model's validity and its limitations whereas in Chapter 5.3, the strengths of the model are highlighted. Chapter 5.4 discusses this thesis' findings transferability. Finally, in Chapter 5.5, proposed policy implications and suggested new research are outlined.

5.1 Main results

This thesis found that Voretigene Neparvovec could be regarded as cost-effective for clinical practice implementation in Norway, if the WTP threshold would be above 2,200,000 NOK.

With the already assumed WTP threshold of 2,200,000 NOK, the population EVPI, i.e., the value of removing all decision uncertainty within our model, would accrue to 9,941,417 NOK over a time horizon of 10 years. This value does not seem to be affected when changing the time horizon. The obtained EVPI value is substantially lower than the 97,7 million NOK estimated by NOMA, which is the expected budget impact of including the eligible Norwegian patient into the quality register. Furthermore, it exceeds the expected research cost estimated in this present work to construct ENBS, where a fixed cost of 77,967,300 NOK and a variable cost of 76,209 NOK per patient (Kunst et al., 2019), were utilized as RCT associated research cost. If this expected cost of further research is correct, we can see already based on the EVPI results that the conditional reimbursement should not be considered justified given that the expected costs of additional research extend the maximum value that can be gained from that additional data collection. Still, to gain a better insight into the decision uncertainty, its drivers, and the expected value of additional research we estimated EVPPI, EVSI and ENBS.

We clustered parameters that could represent target outcomes of separate research studies and estimated population EVPPI. Parameters related to natural disease progression and clinical efficacy were identified to be prone to more decision uncertainty and could thus need more research. Furthermore, as identified through the second scenario analysis, the arbitrary constant treatment effect applied within the model, precipitate substantial impact on the final outcomes and should thus be further evaluated for more accurate estimates.

Parameters within clinical efficacy were chosen for further investigation through EVSI. RCT were deemed the best research design as it would require an intervention and comparator to gather further relevant clinical evidence. Furthermore, as Voretigene Neparvovec was novel back in 2019 it is reasonable to believe that viable quality registers would not exist which discard retrospective observational studies. ENBS is maximized at 10 patients, however, ENBS was considered negative for the complete sample size interval, indicating that research is potentially not worthwhile as the research cost associated is considered too high.

5.1.1 NOMA's conditional reimbursement decision

Using a model analytical approach, our findings suggests that the conditional reimbursement given by the National System for Managed Introduction of New Health Technologies in Norway is not supported by VOI measurements with an explicit monetary reasoning. Even when the WTP threshold were assumed to be 2,200,000 NOK (i.e., the intersection between optimal treatment strategy choice where the uncertainty is at its peak and thus the value of additional information is considered most significant). The Norwegian health services is therefore set out to spend excessive amounts of money over a four-year period, compared to the possible additional information collected. Furthermore, portrayed by ENBS, the information acquired by the eligible Norwegian population, nor any other larger sample, is not considered worthwhile because of the large research cost associated with collecting the additional information for clinical efficacy.

The Norwegian National System for Managed Introduction of New Health Technologies applies a severity specific WTP threshold to assess whether they regard implementation of new health technologies as cost-effective. Arguably, for rare diseases, these thresholds are considered low for several reasons including that collecting additional data is difficult and costly. As earlier recognized, in Chapter 3.4, NOMA (2018) conveyed that a higher WTP threshold for orphan specific diseases could be applied. However, this is clearly an ambiguous statement from the Norwegian governmental agency which in turn leaves room for decision-discrepancies when applied to different orphan drug prospects. Health economic evaluations is an applied framework that should aid decision makers to make more informed and reliable judgements based on what the society value, or another stakeholder depending on the perspective, values and deems beneficial. Even though applying an exhaustive framework that covers all aspects might be too optimistic or not feasible. Given that the resources are scarce, and they need to allocate wisely, health economic modelling and evaluation can help to make more informed decisions. However, it is important that health economic modelling highly depends on the assumptions taken in the analysis and those should be chosen carefully so that the analysis provides reliable results.

In the United Kingdom, NICE allows for highly specialized treatments, a WTP threshold that is a ten-fold of their original £20.000 - £30.000 threshold range (Powell, O'Donnell., 2019). This policy will not make the decision making totally explicit, yet it will provide decision makers with some guidance towards what society deems as cost-effective within highly specialized orphan disease treatments. A similar valuation and guideline could be considered implemented into the Norwegian HTA evaluation practice. The society will then provide a resource-cap for what is deemed beneficial and affordable for highly specialized treatments which perhaps is not captured sufficiently in the already established guidelines. It will ensure that society does not overspend and in turn, give manufacturers and patients a more reliable reimbursement process.

Moreover, it is outside of this thesis' scope to valuate different criteria, however, as introduced, monetary valuation alone might not be sufficient with regards to orphan drugs. Intangible aspects can be hard to value and thus difficult to include and to simulate within an economic model. Nonetheless, it should not be underestimated the individual value of having a sense of futuristic hope, by having an actual treatment available. Primarily, the true value is associated with having a real possibility of postponing the visual deterioration, even though the long-term effect is considered uncertain.

Gene mutated RPE65 associated IRD is associated with serious future difficulties and QoL implications from a young age. This can be expected to require a frequent follow up from the Norwegian health bodies and thus imply continuous costs throughout patients' remaining life. As Norway operates with universal health care, treatments that can possibly stagnate future health care and societal costs associated with care for these explicit individuals should be sought after. NOMA (2019) calculated a budget impact of 97,7 million NOK covered over four years. The Norwegian government health care budget was 210,592 million NOK in 2019 (Prop. 1S, 2018-2019) and could thus be considered rather bijou in comparison. However, by allowing these small "budget adjustments", to every possible treatment for orphan diseases, net spend would promptly accumulate and is thus not regarded as a viable argument. However, by treating patients with Voretigene Neparvovec, it would allow researchers to gather more information. Technological advancements would only be possible if the technology is getting tested. As gene therapies represents novel procedures in health care, their benefits are yet to be fully discovered.

We were therefore unsure over why Novartis did not include a more thorough cost analysis. Technical assistance was the only parameter that is not strictly health service associated. Mutated RPE65 associated IRD is thought to have severe impact on a person life. Conceivably more societal costs could have been identified and included, as Norway utilizes an extended health care perspective that allows indirect costs, it is naturally to conclude that the Voretigene Neparvovec-arm would benefit if more cost variables were included – as patients within the BSC arm would require societal associated costs for a longer time.

Arguably, as a last notation, the population with 8 eligible patients and an incidence rate of 0.5 – 1 patient a year, Norway is not sufficient to justify an additional collection of information. Hence, the need for international cooperation should be desired. Partnership across borders for countries with similar patient populations should especially be more relevant for orphan diseases as these diseases typically are subject to less reliant data.

5.1.2 Quantification of the expected value of additional information

EVPPI measures presented in Chapter 4.4 can help understand what parameters included in the health economic model contributed to the decision uncertainty. From Figure 4.5, it can be deduced that clinical data regarding the natural disease progression and clinical efficacy of Voretigene Neparvovec are the main drivers for current decision uncertainty. This is not perplexing as the natural history study by Chung et al (2018) contains an arguably small sample size of 70 individuals as this study serves as material for calculation of transition probabilities in the long-term phase. Moreover, provided in the committee report by NICE (2019), transition count data are only observed 28 times over 20.78 years, which is deemed insufficient to extrapolate accurate disease progression probabilities estimates, which is also reflected in the parameter's standard errors portrayed in Table 3.9 and the appendix.

Even though, there are variability in the other parameters, these were deemed insignificant. For instance, variation within the cost's estimates was chosen at an arbitrary level of 10% whereas administration costs for Voretigene Neparvovec were held constant as the "real" price is not known. Furthermore, the parameters within "disutility" are not causing any major model outcome impact, as they pose such a trivial part of the model with only five parameters, where one is held constant.

One aim of this thesis was to evaluate the required sample size required to obtain adequate additional information through EVSI and ENBS estimates. By assigning relevant parameters

into groups that had the characteristics to be evaluated through the same study design, natural disease progression and treatment efficacy were established as main drivers of uncertainty within the model. However, clinical efficacy was the only group that were analyzed through further VOI measurements. Natural disease progression data could be collected through a retrospective observational study. However, this would require removing patient's possibility to get treated with Voretigene Neparvovec. As Voretigene Neparvovec has been approved by both FDA and EMA, this would deprive the patients of an opportunity. We perceived this as unethical and deemed such a study as unfeasible.

Moreover, there are some structural uncertainties that are not being captured by EVPPI nor scenario analysis, which may be worth investigating further. HRQoL values elicited from Brown (1999) consists of gathered utility weights from 325 individuals using a disease specific questionnaire to test visual acuity. The mean age of the population is 68 years and the patients had other retinal diseases than mutated RPE65 gene associated IRD, whereas assumed mean population age in question for this thesis is 15 years. This results in an unequal patient population. Losing the peripheral functionality at a young age can arguably be considered worse. They will be confronted with prolonged life challenges. For instance, these patients could struggle or lose the possibility to get an education and start a family which would impact their perceived QoL considerably.

Furthermore, as explored in the scenario analysis in Chapter 4.5, the constant treatment effect has a substantial impact on the analysis outcome. The efficacy of Voretigene Neparvovec was determined from Russel et al. (2017) phase III trial. NOMA assumed that the treatment effectiveness was expected to be constant for 15 years. However, in the HTA submission by Novartis, they opted for 50 years constant effect, whereas in their submission to NICE (2017) they assumed 40 years. It would be erroneously to hypothesize which assumptions is most accurate as there are no available data. However, the early follow up from patients enrolled within the phase III trial indicates that the treatment effectiveness should not be expected to be constant in their remaining life, where 5 of 20 (i.e., 25%) patients have experienced at least one point deterioration in MLMT score after 4 years after administration (NOMA, 2019).

5.2 Model validity

It is of importance to examine a models' validity, when developing a health economic model, assumptions are being made which makes it viable to assumption fallacies. Furthermore, as modelling relies on simulation, only the mean outcome is reported and not necessarily the truth. As researchers we are obliged to discuss our own work carefully and address any limitations. This philosophical act can help us identify questions that could be answered in the future and is a vital part of keeping research reliable.

5.2.2 Limitations

As this present work is a replication of an already submitted HTA, access to all relevant data and assumptions would be unreasonable to presume. This may lead to some model assumption discrepancies compared to the original submission. However, by getting in touch with NOMA and Novartis we were privileged with information and help we are therefore confident that this present replication results are accurate.

After estimating EVSI several times through the R package "voi" by Christopher Jackson (Jackson, 2022). In our estimations we experienced a Monte Carlo error (i.e., estimation

inaccuracy) which caused some fluctuations in the EVSI results. Furthermore, after running EVSI several times using the same assumptions, we noticed that in some runs, the EVSI results did not increase with the increasing sample size as we would otherwise expect. This may be caused by a shortcoming in our R code or in the used R package and should be further investigated. However, we do not expect this limitation to have any impact on the conclusions of this thesis given that our EVPI results indicated that further research to collect additional information would not be worthwhile. We still performed a full VOI analysis to determine the drivers of uncertainty and illustrate how VOI framework could be used in reimbursement decisions.

Moreover, this thesis applies an arbitrary WTP threshold of 2,200,000 NOK per QALY gained. However, this is well above what Norway recognizes as the highest severe specific WTP threshold of 825,000 NOK per QALY. This causes the model to overestimate the uncertainty between which interventions is considered the optimal choice. This was however done for illustrative purposes only as we wanted to utilize the WTP threshold to maximize the VOI measurements. The sole purpose for this is if VOI do not justify NOMA's conditional reimbursement with max values, it could be inferred as an exhaustive conclusion for any other WTP threshold levels. However, WTP thresholds for orphan diseases should arguably be valued differently. As the United Kingdom utilizes upwards of a ten folded ICER for their evaluations of highly specialized technologies whereas Norway has no clear guideline, we thus consider it justified to use a higher WTP threshold.

Furthermore, we acknowledge the discrepancies when performing the scenario analysis, compared to scenario results reported in HTA submission provided by NOMA (2019). Especially, we were quite perplexed with the substantial different estimated outcome with 50-years constant treatment effect and extrapolating with Weibull distribution. We calculated the 50-yeaer constant treatment effect ICER to be 435,702 NOK, whereas NOMA reported 1,555,654 NOK per QALY gained. Moreover, when extrapolating natural disease progression with Weibull distribution, NOMA calculates an ICER of 2,355,831 NOK per QALY gained, whereas our model computes an ICER of 1,500,198 NOK per QALY gained. In both cases our estimated ICER seems to get reduced compared to what's reported by NOMA. This is believed to be caused by an increase in expected incremental QALY gain for Voretigene Neparvovec in the scenario analysis compared to base-case (see Table 4.1, 4.2 and 4.3). These inconsistencies caused us some bewilderment. However, longer constant treatment effect and extrapolating disease progression with Weibull distribution that cause slower disease progression, it is arguably natural that the incremental QALY gain for Voretigene Neparvovec in fact should increase and thus decrease the estimated ICER. Nevertheless, as the base-case values computed accurately in such great extent, this fallacy is believed to not cause any VOI estimation errors.

Finally, it is worth mentioning that we may not be aware of possible discounts, risk sharing agreements, or other market access agreements commonly negotiated for orphan drugs (Garrison Jr. et al., 2013). As the acquisition cost of Voretigene Neparvovec is predominantly the main cost driver, a potential discount could alter the cost-effectiveness and VOI outcome substantially.

5.3 Strengths

As any model are notwithstanding any limitations, some strengths are as well present. Primarily, the strength of this thesis is the modelling base-case accuracy compared to NOMA's results. With a calculated ICER per QALY gained that only differ with 1.21%, the results can

therefore be appraised precise. This is deemed a fundamental element to this thesis as the pivotal aim was to replicate their model in exact fashion. This is achieved by utilizing the same procedure as Novartis' and NOMA applied to convert their transitional intensity rates to probabilities. By using the same procedures, the structural margin of error gets restricted.

This is achieved by having all relevant parameters publicly available from two official bodies (i.e., NOMA and NICE) which is considered beneficial. All relevant information on costs were gathered from NOMA and is thus not prone to any transferability issues. Moreover, cost estimates are also gathered from the year NOMA made their decision and are given in NOK, these estimates are thus not subject to any indexing or conversion issues. Disease specific data such as utility weights, distribution of patients and transitional probabilities and NOMA's modelling methods are publicly obtainable and is considered not viable to any transparency issues as with costs.

EVPI results are equal when simulating the results through Microsoft Excel, SAVI Web Tool (SAVI, 2021) and "voi" package in R and is thus considered accurate. As EVPPI results are subject to variation because of Monte Carlo error, equality is not expected. However, SAVI Web Tool (SAVI, 2021) determines "Clinical Efficacy" and NHx RPE65" as the main drivers of uncertainty within the model as obtained from the "voi" R package.

5.4 Transferability

In its entirety, this thesis is not to be viewed to have global applicability. The conditional reimbursement made by the National System for Managed Introduction of New Health Technologies in Norway is in its whole purpose made for a Norwegian setting. Hence, estimates regarding population VOI results would thus differ. Furthermore, as cost associated questions can alter VOI considerations, costs must be considered carefully when contemplating whether this thesis' contribution is transferable, or not. Furthermore, the findings of this thesis are tailored to maximize the uncertainty by using the WTP threshold that identifies the switch between optimal treatments. However, in real world decision making this exact WTP threshold may arguably not be relevant. We therefore acknowledge that this thesis may overestimate the value of additional information.

However, as this thesis foundational framework (i.e., parameter valuation and bias) is based upon Novartis' HTA submissions to both Norway and the UK, the individual VOI measurements could be reproduced to pertain in other countries. Nevertheless, as aggregated population measurements are dependent upon the incidence and prevalence of the disease for the country in question, this must be adjusted.

Nevertheless, EVPPI measurements is considered to have globally relevance. At least, if the same assumptions and measurements are utilized in the same manner as in this present thesis. We acknowledge that this thesis has made its assumptions on past knowledge, and that new knowledge may have already been discovered and could thus pose more reliable estimates. However, if this is not the case – areas of interests for the discovering of new additional knowledge, identified in this thesis, may still apply.

5.5 Policy implications and possible further research

We propose that the Norwegian government should adopt a similar approach to WTP threshold guidelines as what NICE utilizes in the UK. This would ensure a more reliant, coherent, and

thus ethical application of the health economic modelling framework. Moreover, as the intent with the conditional reimbursement was to assess additional information on treatment efficacy and long-term effect at a later stage, we suggest that the Norwegian government should take initiative for international co-operation.

Further research should focus on the focal point of determining the long-term treatment effectiveness as this cause a lot of outcome bias. Moreover, clinical efficacy – how patients transition through the disease, should also be examined more thoroughly. Finally, a more exhaustive cost examination should be conducted to establish both health service and societal related costs to gene mutated RPE65 associated IRD.

Conclusion

This chapter will serve as the last section where we give our final concluding remarks on the results and future possible contributions this thesis provides.

Based on our VOI results, the conditional reimbursement of Voretigene Neparvovec made by the National System for Managed Introduction of New Health Technologies in Norway cannot be justified as the assumed budget impact is considered too high compared to population EVPI. Moreover, our EVPPI results have provided us with information about the focus on additional research as we identified clinical efficacy measures to be the main driver of decision uncertainty using our decision-analytical model. However, the additional information provided by investigating clinical efficacy is considered to not be worthwhile because the research cost is considered too high compared to EVSI results as presented by the ENBS estimate.

However, as RPE65 associated IRD is considered an orphan disease it has been argued that monetary criteria should not be considered comprehensive in reimbursement processes. We consider this as a potential shortcoming of the health technology evaluation framework in Norway. As the framework is dealing with controversial and vulnerable topics for the patients' populations considered, it is considered an ethical abdication of not ensuring patients a reliable reimbursement process.

Therefore, we are hesitant based on this present work whether the actual reimbursement is, justified. However, our results indicate that the decision of the National System for Managed Introduction of New Health Technologies in Norway to gather additional information as potentially inappropriate. Our results indicate that the decision on reimbursing Voretigene Neparvovec should have been taken based on whether society actually values Voretigene Neparvovec, within a reliable framework that values orphan drug adequately.

For future considerations, we suggest that WTP thresholds in Norway should be revised to capture societies valuation of orphan drugs to ensure reliable reimbursement processes. Furthermore, as orphan disease is prone to small populations, we call for an international collaboration to ensure sufficient information to facilitate for future reliable research. Additionally, we suggest that VOI analysis should represent a fundamental part of reimbursement decisions that considers collecting additional information. Furthermore, it would have been interesting to investigate the VOI results from a model that replicated Novartis submission, to see whether this would change the conditional reimbursement justification.

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Appendix

wxMaxima – Jones et al. (2017) output

```
/*Step1: Define Q.*/
Q:matrix([a,b,c,d,e], [0,f,g,h,i], [0,0,j,k,l], [0,0,0,-m,m], [0,0,0,-0,0]);
```

(%o69)
$$\begin{pmatrix} a & b & c & d & e \\ 0 & f & g & h & i \\ 0 & 0 & j & k & l \\ 0 & 0 & 0 & -m & m \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

```
/*Step2: Get the eigen-decomposition and reorder and display the eigenvalues.*/
[evalues, evectors]: eigenvectors(Q);
evalues[1]: [evalues[1][4], evalues[1][3], evalues[1][2], evalues[1][1], evalues[1][5] ];
```

(%o70)
$$\left[\left[-m,j,f,a,0\right],\left[1,1,1,1,1\right]\right],\left[\left[\left[1,\frac{hm^2+(-gk+hj+ah)m-agk+ahj}{dm^2+(-ck+dj-bh+df)m+(bg-cf)k+(df-bh)j},\frac{km^2+(f+a)km+afk}{dm^2+(-ck+dj-bh+df)m+(bg-cf)k+(df-bh)j},-\frac{m^3+(j+f+a)m^2+((f+a)j+af)m+afj}{dm^2+(-ck+dj-bh+df)m+(bg-cf)k+(df-bh)j},0\right]\right],$$
$$\left[\left[1,\frac{gj-ag}{cj+bg-cf},\frac{j^2+(-f-a)j+af}{cj+bg-cf},0,0\right]\right],\left[\left[1,\frac{f-a}{b},0,0,0\right]\right],\left[\left[1,0,0,0,0\right]\right],\left[\left[1,-\frac{agl+agk+(-ai-ah)j}{(bg-cf)l+(bg-cf)k+(-bi-bh+(e+d)f)j},\frac{afl+afk}{(bg-cf)l+(bg-cf)k+(-bi-bh+(e+d)f)j},-\frac{afj}{(bg-cf)l+(bg-cf)k+(-bi-bh+(e+d)f)j},-\frac{afj}{(bg-cf)l+(bg-cf)k+(-bi-bh+(e+d)f)j}\right]\right]\right]$$

```
[a,f,j,-m,0]
```

(%o71) $\left[a,f,j,-m,0\right]$

```
/* Step 3: Re-order and scale the eigenvectors, combine them to make U, and redefine U with intermediate variables.*/
evectors: [evectors[4], evectors[3]*b, evectors[2]*(c*j+b*g-c*f), evectors[1]*(d*m^2+(-c*k+d*j-b*h+d*f)*m+(b*g-c*f)*k+(d*f-b*h)*j), evectors[5]*((b*g-c*f)*l+(b*g-c*f)*k+(-b*i-b*h+(e+d)*f)*j)];
U: transpose(matrix(evectors[1][1]));
for i: 2 thru 5 do U: addcol (U, evectors[i][1]);
expand(U);
U:matrix([1, b,n,o,p], [0,q,r,s,t], [0,0,u,v,w], [0,0,0,x,y], [0,0,0,0,z]);
```

(%o72)
$$\left[\left[1,0,0,0,0\right]\right],\left[\left[b,f-a,0,0,0\right]\right],\left[\left[cj+bg-cf,gj-ag,j^2+(-f-a)j+af,0,0\right]\right],$$
$$\left[\left[dm^2+(-ck+dj-bh+df)m+(bg-cf)k+(df-bh)j,hm^2+(-gk+hj+ah)m-agk+ahj,km^2+(f+a)km+afk,-m^3-(j+f+a)m^2-((f+a)j+af)m-afj,0\right]\right],$$
$$\left[\left[(bg-cf)l+(bg-cf)k+(-bi-bh+(e+d)f)j,-agl-agk-(-ai-ah)j,afl+afk,-afj,-afj\right]\right]$$

(%o73)
$$\begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

(%o74) *done*

(%o75)
$$\begin{pmatrix} 1 & b & cj+bg-cf & dm^2-ckm+djm-bhm+dfm+bgk-cfk-bhj+dfj & bgl-cfl+bgk-cfk-bij-bhj+efj+dfj \\ 0 & f-a & gj-ag & hm^2-gkm+hjm+ahm-agk+ahj & -agl-agk+aij+ahj \\ 0 & 0 & j^2-fj-aj+af & km^2+fkm+akm+afk & afl+afk \\ 0 & 0 & 0 & -m^3-jm^2-fm^2-am^2-fjm-ajm-afm-afj & -afj \\ 0 & 0 & 0 & 0 & -afj \end{pmatrix}$$

(%o76)
$$\begin{pmatrix} 1 & b & n & o & p \\ 0 & q & r & s & t \\ 0 & 0 & u & v & w \\ 0 & 0 & 0 & x & y \\ 0 & 0 & 0 & 0 & z \end{pmatrix}$$

```
/*Step 4: Invert U and redefine Uinverse with intermediate values*/
expand(invert(U));
```

(%o77)
$$\begin{pmatrix} 1 & -\frac{b}{q} & \frac{br}{qu} & -\frac{n}{u} & -\frac{brv}{qux}+\frac{nv}{ux}+\frac{bs}{qx}-\frac{o}{x} & \frac{brvy}{qux z}-\frac{nvy}{uxz}-\frac{bsy}{qxz}+\frac{oy}{xz}-\frac{brw}{quz}+\frac{nw}{uz}+\frac{bt}{qz}-\frac{p}{z} \\ 0 & \frac{1}{q} & -\frac{r}{qu} & \frac{rv}{qux}-\frac{s}{qx} & -\frac{rvy}{quxz}+\frac{sy}{qxz}+\frac{rw}{quz}-\frac{t}{qz} \\ 0 & 0 & \frac{1}{u} & -\frac{v}{ux} & \frac{vy}{uxz}-\frac{w}{uz} \\ 0 & 0 & 0 & \frac{1}{x} & -\frac{y}{xz} \\ 0 & 0 & 0 & 0 & \frac{1}{z} \end{pmatrix}$$

```
Uinverse: matrix([1,aa,ab,ac,ad], [0,ae,af,ag,ah], [0,0,ai,aj,ak], [0,0,0,al,am], [0,0,0,0, an]);
```

(%o78)
$$\begin{pmatrix} 1 & aa & ab & ac & ad \\ 0 & ae & af & ag & ah \\ 0 & 0 & ai & aj & ak \\ 0 & 0 & 0 & al & am \\ 0 & 0 & 0 & 0 & an \end{pmatrix}$$

```
/*Step 5: Define expDt and find P(t)*/
expDt: matrix([expat,0,0,0,0], [0,expft,0,0,0], [0,0,expjt,0,0], [0,0,0, expminusmt,0], [0,0,0,0,1]);
```

(%o79)
$$\begin{pmatrix} expat & 0 & 0 & 0 & 0 \\ 0 & expft & 0 & 0 & 0 \\ 0 & 0 & expjt & 0 & 0 \\ 0 & 0 & 0 & expminusmt & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

```
U. expDt. Uinverse;
```

(%o80)
$$\begin{pmatrix} expat & ae\,b\,expft+aa\,expat & ai\,expjt\,n+af\,b\,expft+ab\,expat & al\,expminusmt\,o+aj\,expjt\,n+ag\,b\,expft+ac\,expat & an\,p+am\,expminusmt\,o+ak\,expjt\,n+ah\,b\,expft+ad\,expat \\ 0 & ae\,expft\,q & ai\,expjt\,r+af\,expft\,q & al\,expminusmt\,s+aj\,expjt\,r+ag\,expft\,q & an\,t+am\,expminusmt\,s+ak\,expjt\,r+ah\,expft\,q \\ 0 & 0 & ai\,expjt\,u & al\,expminusmt\,v+aj\,expjt\,u & an\,w+am\,expminusmt\,v+ak\,expjt\,u \\ 0 & 0 & 0 & al\,expminusmt\,x & an\,y+am\,expminusmt\,x \\ 0 & 0 & 0 & 0 & an\,z \end{pmatrix}$$

R knit I

```
library(devtools)

## Loading required package: usethis

library(voi)

set.seed(1)
psa <- read.csv("PSA2.csv", header = TRUE)

is.data.frame(psa)

## [1] TRUE

lambda <- 2200000
option1 <- psa$effectsVN * lambda - psa$costsVN
option2 <- psa$effectsBSC * lambda - psa$costsBSC
nb <- data.frame(option1, option2)

evpi(nb)

## [1] 927800.1

evppi(nb, psa, pars = list("Hs1Hs3", "Hs1Hs4", "Hs2Hs3", "Hs2Hs4", "Hs3Hs4",
"Hs4Hs5", "Constant", "Gamma"), method = "gp", nsim = 1000)

##       pars     evppi
## 1   Hs1Hs3 103703.08
## 2   Hs1Hs4  29513.28
## 3   Hs2Hs3  53239.75
## 4   Hs2Hs4  40388.23
## 5   Hs3Hs4  39269.47
## 6   Hs4Hs5 233741.26
## 7 Constant 142558.48
## 8    Gamma 376266.96

evppi(nb, psa, pars = list("tpVN_hs1hs1", "tpVN_hs1hs2", "tpVN_hs1hs3",
"tpVN_hs1hs4", "tpVN_hs1hs5", "tpVN_hs2hs1", "tpVN_hs2hs2", "tpVN_hs2hs3",
"tpVN_hs2hs4", "tpVN_hs2hs5", "tpVN_hs3hs1", "tpVN_hs3hs2", "tpVN_hs3hs3",
"tpVN_hs3hs4", "tpVN_hs3hs5", "tpVN_hs4hs1", "tpVN_hs4hs2", "tpVN_hs4hs3",
"tpVN_hs4hs4", "tpVN_hs4hs5", "tpVN_hs5hs1", "tpVN_hs5hs2", "tpVN_hs5hs3",
"tpVN_hs5hs4", "tpVN_hs5hs5"), method = "gp", nsim = 1000)

##           pars      evppi
## 1  tpVN_hs1hs1 176315.679
## 2  tpVN_hs1hs2  12370.465
## 3  tpVN_hs1hs3  47979.964
## 4  tpVN_hs1hs4  44343.783
## 5  tpVN_hs1hs5 127457.737
```

R knit II

```
## 6  tpVN_hs2hs1 121918.343
## 7  tpVN_hs2hs2  25481.144
## 8  tpVN_hs2hs3   4940.221
## 9  tpVN_hs2hs4  52033.983
## 10 tpVN_hs2hs5 157121.556
## 11 tpVN_hs3hs1 125121.090
## 12 tpVN_hs3hs2  23102.221
## 13 tpVN_hs3hs3  29992.046
## 14 tpVN_hs3hs4  32365.517
## 15 tpVN_hs3hs5 127113.079
## 16 tpVN_hs4hs1 232479.359
## 17 tpVN_hs4hs2   2545.326
## 18 tpVN_hs4hs3  85727.203
## 19 tpVN_hs4hs4 141391.893
## 20 tpVN_hs4hs5  55304.193
## 21 tpVN_hs5hs1  97144.819
## 22 tpVN_hs5hs2  28845.651
## 23 tpVN_hs5hs3  28943.128
## 24 tpVN_hs5hs4   6151.967
## 25 tpVN_hs5hs5  67940.512
```

```
evppi(nb, psa, pars = list("tpBSC_hs1hs1", "tpBSC_hs1hs2", "tpBSC_hs1hs3",
"tpBSC_hs1hs4", "tpBSC_hs1hs5", "tpBSC_hs2hs1", "tpBSC_hs2hs2",
"tpBSC_hs2hs3", "tpBSC_hs2hs4", "tpBSC_hs2hs5", "tpBSC_hs3hs1",
"tpBSC_hs3hs2", "tpBSC_hs3hs3", "tpBSC_hs3hs4", "tpBSC_hs3hs5",
"tpBSC_hs4hs1", "tpBSC_hs4hs2", "tpBSC_hs4hs3", "tpBSC_hs4hs4",
"tpBSC_hs4hs5", "tpBSC_hs5hs1", "tpBSC_hs5hs2", "tpBSC_hs5hs3",
"tpBSC_hs5hs4", "tpBSC_hs5hs5"), method = "gp", nsim = 1000)
```

```
##            pars      evppi
## 1  tpBSC_hs1hs1 134939.947
## 2  tpBSC_hs1hs2   1444.434
## 3  tpBSC_hs1hs3  18185.410
## 4  tpBSC_hs1hs4  56215.721
## 5  tpBSC_hs1hs5 100760.342
## 6  tpBSC_hs2hs1 236747.418
## 7  tpBSC_hs2hs2 144460.542
## 8  tpBSC_hs2hs3      0.000
## 9  tpBSC_hs2hs4 337725.731
## 10 tpBSC_hs2hs5 150299.354
## 11 tpBSC_hs3hs1 135707.396
## 12 tpBSC_hs3hs2  54702.238
## 13 tpBSC_hs3hs3 103988.134
## 14 tpBSC_hs3hs4  69976.571
## 15 tpBSC_hs3hs5 260584.912
## 16 tpBSC_hs4hs1 119053.203
## 17 tpBSC_hs4hs2  98922.336
## 18 tpBSC_hs4hs3  81773.344
## 19 tpBSC_hs4hs4 115220.076
## 20 tpBSC_hs4hs5 147521.889
```

R knit III

```
## 21 tpBSC_hs5hs1  74000.682
## 22 tpBSC_hs5hs2  82740.448
## 23 tpBSC_hs5hs3  41979.569
## 24 tpBSC_hs5hs4  19681.930
## 25 tpBSC_hs5hs5 127798.594
```

```
evppi(nb, psa, pars = list("qolHS1", "qolHS2", "qolHS3", "qolHS4", "qolHS5"),
method = "gp", nsim = 1000)
```

```
##     pars     evppi
## 1 qolHS1 104944.71
## 2 qolHS2  18273.60
## 3 qolHS3  35285.36
## 4 qolHS4  13939.68
## 5 qolHS5  16314.38
```

```
evppi(nb, psa, pars = list("pAECataract", "pAEEyeInflam", "pAEInclOP",
"qolRelatives_young"), method = "gp", nsim = 1000)
```

```
##                 pars        evppi
## 1        pAECataract 34058.149265
## 2       pAEEyeInflam  7407.147973
## 3          pAEInclOP 62480.392119
## 4 qolRelatives_young     8.224409
```

```
evppi(nb, psa, pars = list("cSurgery", "cPred", "cAdmSurg", "cFollowUp",
"cAECataract", "cAEEyeInflam", "cAEInclOP", "cHospAdm", "cOftaHelp",
"cTechAss", "cTechAssExt", "cDepression"), method = "gp", nsim = 1000)
```

```
##            pars      evppi
## 1      cSurgery  7230.3828
## 2         cPred   849.3707
## 3      cAdmSurg 35434.2935
## 4     cFollowUp 11041.0971
## 5   cAECataract 29124.8428
## 6  cAEEyeInflam 72296.3851
## 7     cAEInclOP 91820.7403
## 8      cHospAdm 47508.5230
## 9     cOftaHelp 26192.2561
## 10     cTechAss 25032.1215
## 11  cTechAssExt 37370.5764
## 12  cDepression 66403.2742
```

```
evppi(nb, psa, pars = list("pMort15.19", "pMort20.24", "pMort25.29",
"pMort30.34", "pMort35.39", "pMort40.44", "pMort45.49", "pMort50.54",
"pMort55.59", "pMort60.64", "pMort65.69", "pMort70.74", "pMort75.79",
"pMort80.84", "pMort85.89", "pMort9plus"), method = "gp", nsim = 1000)
```

```
##          pars        evppi
## 1  pMort15.19 5.848586e+04
## 2  pMort20.24 5.443670e+04
## 3  pMort25.29 1.038191e+04
```

R knit IV

```
## 4  pMort30.34 2.428417e+03
## 5  pMort35.39 1.138262e+04
## 6  pMort40.44 3.625093e+04
## 7  pMort45.49 5.508138e+04
## 8  pMort50.54 2.561154e+04
## 9  pMort55.59 6.364413e+04
## 10 pMort60.64 6.772367e+04
## 11 pMort65.69 4.888420e+04
## 12 pMort70.74 2.932671e-01
## 13 pMort75.79 2.642072e+04
## 14 pMort80.84 5.014410e+04
## 15 pMort85.89 5.407737e+04
## 16 pMort9plus 4.547347e+04
```

```
evsi(nb, psa, study = "normal_known", n=c(10,25,50,100,250,500), pars =
c("tpVN_hs1hs1", "tpVN_hs1hs2", "tpVN_hs1hs3", "tpVN_hs1hs4", "tpVN_hs1hs5",
"tpVN_hs2hs1", "tpVN_hs2hs2", "tpVN_hs2hs3", "tpVN_hs2hs4", "tpVN_hs2hs5",
"tpVN_hs3hs1", "tpVN_hs3hs2", "tpVN_hs3hs3", "tpVN_hs3hs4", "tpVN_hs3hs5",
"tpVN_hs4hs1", "tpVN_hs4hs2", "tpVN_hs4hs3", "tpVN_hs4hs4", "tpVN_hs4hs5",
"tpVN_hs5hs1", "tpVN_hs5hs2", "tpVN_hs5hs3", "tpVN_hs5hs4", "tpVN_hs5hs5",
"tpBSC_hs1hs1", "tpBSC_hs1hs2", "tpBSC_hs1hs3", "tpBSC_hs1hs4",
"tpBSC_hs1hs5", "tpBSC_hs2hs1", "tpBSC_hs2hs2", "tpBSC_hs2hs3",
"tpBSC_hs2hs4", "tpBSC_hs2hs5", "tpBSC_hs3hs1", "tpBSC_hs3hs2",
"tpBSC_hs3hs3", "tpBSC_hs3hs4", "tpBSC_hs3hs5", "tpBSC_hs4hs1",
"tpBSC_hs4hs2", "tpBSC_hs4hs3", "tpBSC_hs4hs4", "tpBSC_hs4hs5",
"tpBSC_hs5hs1", "tpBSC_hs5hs2", "tpBSC_hs5hs3", "tpBSC_hs5hs4",
"tpBSC_hs5hs5"))
```

```
##     n      evsi
## 1  10  30094.32
## 2  25  93952.69
## 3  50 104131.61
## 4 100 103481.34
## 5 250 161608.80
## 6 500 190840.74
```

Statistical output NHx (NICE, 2017)

Table 19: Revised statistical models (average eye)†

	Weibull	Gompertz	Exponential	Log-logistic	Log-normal
HS1 to HS3	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.407** (0.531)	1.418** (0.487)

HS1 to HS4	-2.485* (1.041)	-2.485* (1.041)	-2.485* (1.041)	1.392** (0.532)	1.086** (0.420)
HS1 to HS5	-18.30 (2711.3)	-17.25 (1609.5)	-17.31 (1655.3)	8.476 (1003.5)	5.385 (476.2)
HS2 to HS3	-0.601 (0.420)	-0.513 (0.419)	-0.342 (0.417)	0.514* (0.261)	0.528 (0.285)
HS2 to HS4	-2.999** (1.042)	-2.910** (1.042)	-2.740** (1.041)	1.689** (0.524)	1.636*** (0.451)
HS2 to HS5	-18.32 (2122.2)	-17.28 (1319.0)	-17.31 (1457.1)	8.559 (821.1)	5.438 (419.7)
HS3 to HS4	-1.372** (0.517)	-1.404** (0.535)	-0.805 (0.500)	0.936** (0.304)	0.959** (0.336)
HS3 to HS5	-18.36 (1990.8)	-17.37 (1194.3)	-17.31 (1565.6)	8.769 (888.2)	5.749 (496.0)
HS4 to HS5	-1.553* (0.658)	-1.555* (0.666)	-1.008 (0.646)	1.003** (0.377)	1.075* (0.419)
Constant	-14.95*** (1.859)	-9.211*** (0.355)	-8.588*** (0.289)	7.986*** (0.190)	8.018*** (0.203)
ln (p)	0.586*** (0.125)				
gamma		0.000316*** (0.0000825)			
ln (gamma)				-0.785*** (0.132)	
ln (sigma)					-0.143 (0.120)
N	283	283	283	283	283

† Standard errors in parentheses.
* p < 0.05, ** p < 0.01, *** p < 0.001
Key: HS1, moderate visual impairment; HS2, severe visual impairment; HS3, profound visual impairment; HS4, counting fingers; HS5, hand motion, light perception to no light perception.