Research report

Cost-effectiveness of pegaspargase compared to asparaginase for treating standard-risk acute lymphoblastic leukaemia in children under 18

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Abstract

Title: Cost-effectiveness of pegaspargase compared to asparaginase for treating standard-risk acute lymphoblastic leukaemia in children under 18.

Project description: This project is a research report that focuses on economic modelling.

Background: The most common type of childhood cancer is acute lymphoblastic leukaemia (ALL). Each year, almost 120 new cases of childhood ALL are diagnosed in the Netherlands. Luckily, the survival rates of this childhood blood cancer increased to 80-85% in the last decades due to improved treatment. The degree to which leukaemia can be treated depends on the variety of different factors which classify the child's acute lymphoblastic leukaemia into a certain risk category: low-risk, standard risk, high-risk or very high-risk. The treatment of acute lymphoblastic leukaemia consists of induction, consolidation (also known as intensification) and continuation phases. Within each phase of treatment, certain medications are administered on a frequent basis. Escherichia coli derived L-asparaginase (also referred as E. coli asparaginase or asparaginase), PEGasparginase and Erwinia asparaginase are the key drugs in the treatment of ALL. Although these drugs have good outcomes regarding the overall survival, mild to severe allergic reactions may be associated with these drugs. This can lead to a lower utility and a higher cost.

Aim: The aim of this study is to give insight in the cost-effectiveness of pegaspargase compared to asparaginase by employing a model. The results are used in order to provide advice on the reimbursement of pegaspargase.

Methods: A cost-effectiveness model was built in order to assess the cost-effectiveness of pegaspargase compared to asparaginase with Erwinia asparaginase as second-line treatment. The setting of the study was the Netherlands, because no previous Dutch cost-effectiveness models could be found. For this model a healthcare payers' perspective was chosen. A five-year time horizon has been applied so that all narrowly defined costs and consequences could be included in the model. The costs and the utilities were estimated per treatment phase. In the case of pegaspargase, the costs and disutility related to adverse events were taken into account in the delayed intensification phase. For asparaginase was this the case during the induction phase. With all the values of the different input parameters (utilities, costs, etc.) and their distributions and standard errors, an incremental cost-effectiveness ratio could be calculated. Subsequently, a probabilistic sensitivity analysis was run by the use of a simulation.

Conclusion: The analysis showed that pegaspargase is less expensive and more effective compared to asparaginase. Approximately 90% of the cost-effect pairs could be found in the southeast quadrant of the cost-effectiveness plan. This says that asparaginase is dominated by pegaspargase.

Acknowledgements

In front of you lies my thesis as a final proof of competence for obtaining the European Master in Health Economics and Management at the University of Oslo, Norway. It already showed my competence for the master degree in Health Economics, Policy and Law at the Erasmus University Rotterdam, the Netherlands. These two masters combined form the European Master in Health Economics and Management, with the specialisation in economic evaluation in health care.

This thesis, "Cost-effectiveness of pegaspargase compared to asparaginase for treating standard-risk acute lymphoblastic leukaemia in children under 18", was a big challenge. During the writing process of the thesis a family member passed away. Unfortunately, this delayed the completion of my thesis. During this period, I got much support from my supervisor in the Netherlands, Maiwenn All, who encouraged me to persevere. Of course, my parents have also been there for me and they were the reason for me to continue. In addition, I am grateful that Elina Aas as my supervisor from the University of Oslo was willing to give extensive feedback on my thesis in order that I could align it with the guidelines and requirements of the University of Oslo.

Claire de Vos
November 13, 2016

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List of abbreviations

ALL	Acute Lymphoblastic Leukaemia
CNS	Central Nervous System
MRD	Minimal Residual Disease
EFS	Event-Free Survival
PFS	Progression-Free Survival
PEG	Polyethylene Glycol
FDA	Food and Drug Administration
EMEA	European Medicines Agency
ICER	Incremental Cost-Effectiveness Ratio
QALYs	Quality-Adjusted Life Years
CE	Cost-Effectiveness
PSA	Probabilistic Sensitivity Analysis
RCT	Randomized Controlled Trials
ELISA	Enzyme-Linked Immunosorbent Assay
COG	Children's Oncology Group
MR	Medium-Risk
CCG	Children's Cancer Group
NHCI	National Health Care Institute
HIA	Health Insurance Act
LCA	Long-term Care Act
NICE	National Institute of Health and Care Excellence
WBC	White Blood Cell
IM	Intramuscularly
IV	Intravenously
PO	Oral
IT	Intrathecal
SC	Subcutaneous
OS	Overall Survival
HRQL	Health-Related Quality of Life
HUI	Health Utilities Index
CPI	Consumer Price Index
LY	Life Year

CEAC	Cost-Effectiveness Acceptability Curve
UK	United Kingdom

1 Introduction

Resource allocation is a central part of the decision-making process in any health care system (Calman, 1994). Resources have always been finite. This is in contrast with the infinite nature of human demands. Considering the scarcity of resources in health care, regulatory choices imply dealing with person trade-offs in terms of value.

In times of scarcity, it is essential that resources are used as efficiently as possible. The society should make the most of the resources available by comparing what is gained from using those resources with the gain from alternative uses (Brouwer & Georgiou, 2012). Economic evaluations have become an important and much used tool in aiding decision makers in deciding on which technologies are eligible for reimbursement and which ones not (Stolk, Van Donselaar, Brouwer & Busschbach, 2004). With the use of an economic evaluation, information on cost-effectiveness can be gathered and alternatives are compared in terms of both their costs and consequences (Drummond, Sculpher, Torrance, O'Brien & Stoddart, 2005).

Acute lymphoblastic leukaemia (ALL) is a rapidly progressive malignant blood disease. Several treatments and technologies exist in order to improve the survival rate for ALL. The main treatment for acute lymphoblastic leukaemia is the use of chemotherapy. PEGasparaginase (pegaspargase) and native Escherichia Coli L-Asparaginase (asparaginase) are both chemotherapy drugs for the first-line treatment of acute lymphoblastic leukaemia will be assessed. These drugs differ both in effectiveness and costs. An economic evaluation will give insight in the cost-effectiveness and will influence the decision on the reimbursement of the drugs.

This chapter will first give information on the background of ALL, the different drugs and the objective of this modelling study. Subsequently, the theory on economic evaluation will be discussed in more detail in Chapter 2.

1.1 Background

Cancer in children is a rare disease. Nevertheless, it is still the leading cause of death among children behind accidents. Annually, 550 children aged 0 to 18 years are diagnosed with cancer (Kanker.nl, 2013). Despite a dramatic increase in the survival rate for children -currently more than 75%- yet every two-three days a child dies from cancer (VOKK, n.d.). The most common type of childhood cancer is acute lymphoblastic leukaemia. Each year, almost 120 new cases of childhood ALL are

diagnosed in the Netherlands. Luckily, the survival rates of childhood ALL have improved over the last decades to 80-85%, a result largely due to improved treatment (Tong et al., 2013).

The degree to which leukaemia can be treated depends on the various factors used in classifying a child's acute lymphoblastic leukaemia into a certain risk category: low-risk, standard risk, high-risk or very high-risk (Truong, Zupanec, Naqvi & Able, 2010). The risk group is influenced by several different features that are already known at diagnosis such as age, white blood cell count, a positive central nervous system (CNS) status, leukemic cells in the testes of boys, ALL subtype (precursor B-cell, T-cell or B-cell ALL) and chromosome changes inside leukemic cells. Another essential factor that determines the risk category is the response to the treatment (Truong et al., 2010). In order to monitor how well the child is responding to the treatment, the amount of leukemic cells that are left inside the child's blood and bone marrow are checked. This is called minimal residual disease (MRD). The samples of the child's blood and bone marrow are tested at different times during the first phase of chemotherapy. A certain MRD cut-off value is used to guide treatment. Finding leukemic cells below or above this value gives information about the procedure and the likely outcome of the child's treatment (Truong et al., 2010). The risk categorization of children with acute lymphoblastic leukaemia is displayed in Table 1.

The estimated event-free survival (EFS) for the four risk groups is 91%, 86%, 76% and 46% respectively (Bhojwani, Howard & Pui, 2009). Event-free survival is in this case defined as the time from randomization to disease progression, death or discontinuation of treatment for any reason. That reason can be toxicity, patient preference or introduction of a new treatment without documented progression. This efficacy endpoint is similar to progression-free survival (PFS), which is the time from randomization until disease progression or death. However, EFS may be more useful in evaluation of highly toxic therapies (Genentech, 2016). Nowadays, with improved insights into molecular defects and precise MRD measurement, it is possible that some high or very-high-risk patients will be reclassified as standard-risk (Bhojwani et al., 2009). This reclassification will give another indication to the prescribed treatment.

Table 1. Risk categorization of acute lymphoblastic leukaemia (Truong et al., 2010)

Risk category	**Factors**
Low-risk	Age between 1 and 10
	< 50,000 white blood cells/mm^3 at diagnosis
	Leukaemia cells with chromosome changes that respond well to treatment: translocation of chromosome 12 and 21 or three copies of chromosomes 4, 10 and 17
	Negative CNS status (no leukemic cells in the cerebrospinal fluid (CSF))
	A good response to the first phase of chemotherapy (rapid early response (RER) treatment)
Standard risk	No features of low-risk or high-risk group (e.g. a child of 4 years old, CNS negative and a white blood cell count of <50,000, not having the low-risk features of leukaemia)
High-risk	Age < 1 or > 10
	> 50,000 white blood cells/mm^3 at diagnosis
	Positive CNS status (large amount of leukemic cells in the CSF)
	Leukemic cells with chromosome changes that are more difficult to treat (MLL gene rearrangement)
Very high-risk	Leukemic cells that have parts of chromosome 9 and chromosome 22 fused together (Philadelphia chromosome)
	Leukemic cells which have too few chromosomes (hypodiploid)

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The treatment of acute lymphoblastic leukaemia consists of induction, consolidation (also known as intensification) and continuation phases (Larson, Lowenberg & Connor, 2015). The induction of remission phase takes about four weeks and is almost always performed when patients are hospitalized. The treatment usually includes vincristine (Oncovin), a steroid hormone (like

prednisone) and may include an anthracycline (such as daunorubicin or doxorubicin). An enzyme called asparaginase is often given intravenously to starve malignant lymphoblasts of the essential amino acid asparagine in the plasma. The next phase is the consolidation phase. During consolidation it is attempted to reduce the number of leukaemia cells still in the body in order to avoid relapse. Most of this treatment is provided as outpatient care. Children are commonly treated with methotrexate, 6-mercaptopurine, vincristine, asparaginase or prednisone, either as a monotherapy or in combination. If the leukaemia remains in remission after induction and consolidation, the maintenance or continuation phase can start. The maintenance phase of acute lymphoblastic leukaemia treatment consists of daily 6-mercaptopurine and weekly methotrexate. Both administered in pill form. These drugs are often combined with vincristine, which is given intravenously, and a steroid like prednisone. Vincristine and prednisone are given either every four or every eight weeks. Most treatment plans also include one or two intensified treatments similar to the initial induction during the first few months of maintenance. These intensifications have a duration of four or eight weeks and are called re-induction or delayed intensification. Dependent on the chosen programme, the total length of therapy for ALL is two to three years (Larson et al., 2015; American Cancer Society; 2015).

Escherichia coli derived L-asparaginase (also referred as E. coli asparaginase or asparaginase) is one of the key drugs in the treatment of ALL. This non-human enzyme hydrolyses asparagine into aspartic acid and ammonia. Unfortunately, the drug can cause allergic reactions that lead to inactivation or silent inactivation (Bauters, Mondelaers, De Moerloose, Robays & Benoit, 2013). When these allergic reactions arise, antibodies will either degrade or inactivate the drug. This inactivation can also arise without the patient and doctor noticing, in other words without any clinical symptoms of an allergy. This is called silent inactivation. With silent inactivation the asparaginase level is 0. The allergic reactions to asparaginase products are diverse and can range from grade 1 to grade 5 (Shinnick, Browning & Koontz, 2013). In Table 2, an overview of the grading of allergic reaction/hypersensitivity is displayed.

Another main type of asparaginase that has been used to date is PEGasparaginase. Several studies have shown the effectiveness of PEGasparaginase (pegaspargase) in patients with ALL, including patients who were allergic to other drugs containing asparaginase. Through the conjugation of immunogenic E. coli asparaginase and polyethylene glycol (PEG), the duration of activity of the drug may be extended while reducing the potential for immunogenic reactions (NIHR, 2015). Additionally, due to the longer half-life of pegaspargase a similar anti-leukemic activity is achieved with a single pegaspargase dose compared to six to nine doses of native E. coli asparaginase (NIHR, 2015). Already a decade ago, the U.S. Food and Drug Administration (FDA) granted

approval to pegaspargase as a first-line treatment (National Cancer Institute, 2013). In the Netherlands, the drug has been used as well for many years as a second-line treatment. Nonetheless, it was only recently approved by the European Medicines Agency (EMEA) as a first-line treatment (European Medicines Agency, 2016).

Table 2. Grading of allergic reaction/hypersensitivity (Shinnick et al., 2013)

Grade	Symptoms of allergic reaction/ hypersensitivity
Grade 1	Transient flushing or rash
	Drug fever <38°C
Grade 2	Rash, flushing
	Urticaria
	Dyspnea
	Drug fever ≥38°C
Grade 3	Symptomatic bronchospasm with or without urticaria
	Parenteral medication or medications indicated
	Allergy-related edema/angioedema
	Hypotension
Grade 4	Anaphylaxis
Grade 5	Death

A third asparaginase preparation available on the market is Ewinia chrysanthemi or Erwinia asparaginase (erwinase) The FDA approval for Erwinia chrysanthemi derived L-asparaginase (Erwinia asparaginase) was gained in November 2011, and now serves as an alternative for ALL patients who become hypersensitive to E. coli asparaginase or PEGasparaginase (Pieter et al., 2012). Research showed that the antibody positive patients with allergic symptoms who switched to Erwinia asparaginase had a reduced hazard ratio for treatment failure. The group of patients (29%) still receiving E. coli asparaginase while having silent hypersensitivity had poorer outcomes. These results indicate the comparatively higher tolerability of the drug and its effectiveness in achieving asparaginase levels associated with efficacy in the treatment of ALL (Pieter et al., 2012).

Nevertheless, it goes without saying that paediatric cancer and its treatment has far-reaching implications for the children affected. In addition to the experienced health problems for children with acute lymphoblastic leukaemia, the psychosocial impact is also profound. Children struggle to cope with the stress of treatment, surgery, chemotherapy and radiation (Marcus, 2012). However,

the impact on the family and society is certainly an issue as well. Theory suggests that the role-functioning, caregiver burden and stress may have harmful effects on the health of caregivers (Litzelman, Catrine, Gangnon & Witt, 2011). Parents alter their responsibilities, roles and family functions to accommodate the child with cancer. These changes can cause significant stress for the family. Increased burden due to caregiving may lead to greater stress for parents. This will in turn negatively impact parents' mental quality of life (Litzelman et al., 2011). Families who care for a child with cancer incur substantial costs during the diagnostic, treatment and in the follow-up phases of the disease. Necessary travel and loss of income because of a reduction or termination of parental employment are two factors that can contribute to the economic burden of the disease. This burden can have long-term effects on quality of life, financial security and future well-being of the entire family (Miedema, Easley, Fortin, Hamilton & Mathews, 2008). Consequently, the economic impact on families also negatively impacts the society due to productivity loss and absenteeism (Marcus, 2012).

1.2 Objective and research question

Due to fewer side effects and a lower risk of allergic reactions, pegaspargase is expected to improve the health outcomes in children with acute lymphoblastic leukaemia. Pegaspargase therefore appears to be a good alternative to asparaginase as a first-line treatment of ALL. However, as previously described, there is still a risk on developing allergic reactions with the administration of pegaspargase. Therefore, Erwinia asparaginase is taken into account as the second-line treatment of the disease. Switching to Erwinia asparaginase after allergic reactions to asparaginase or pegaspargase can mitigate the adverse effects of silent hypersensitivity.

Due to the fact that pegaspargase has only recently been approved by the EMEA for the first-line treatment of ALL, no Dutch studies are available that both model the cost-effectiveness of pegaspargase compared to asparaginase and take into consideration the use of Erwinia asparaginase as second-line treatment. Therefore, the objective of this study is to give insight in the cost-effectiveness of pegaspargase compared to asparaginase by employing a model. The results are used in order to provide advice on the reimbursement of pegaspargase. Based on this objective, the research question will be as follows:

'What is the cost-effectiveness of treating children diagnosed with standard-risk acute lymphoblastic leukaemia up to the age of 18 with PEGasparaginase compared to Escherichia coli derived L-asparaginase from a societal perspective with a lifetime horizon?'

1.3 Overview of chapters

This research report consists of several chapters that describe the cost-effectiveness model and its results step by step. The next chapter is about the theoretical framework. This chapter will highlight what is already known about the clinical and cost-effectiveness research of the subject. Additionally, the theoretical perspective will be developed and subsequently the study will be positioned within the debate. The third chapter describes the research methods and is divided into two sections: one section about the framing of the study and the other about the decision analytic model. The different framing aspects and the features of the decision analytic model will be addressed in order to adequately explain the model structure used to calculate an incremental cost-effectiveness ratio (ICER). The next chapter reveals the results of the cost-effectiveness model. The final chapter will provide a discussion and conclusion. The main result of the study will briefly be summarized. Subsequently, the different strengths and limitations of this modelling study are discussed, thereby considering the consequences for the value of the results. Furthermore, several recommendations are provided. Lastly, concluding remarks are shared.

2 Theoretical framework

The chapter will start with a theoretical framework on economic evaluation. The need for cost-effectiveness studies, the different types of economic analyses, modelling, cost and quality-adjusted life years (QALYs) will be explained. Additionally, the relevant clinical and cost-effectiveness research on E. coli asparaginase, pegaspargase, acute lymphoblastic leukaemia and all the related concepts are explored.

2.1 Economic evaluation

Economic evaluation can be defined as the comparative analysis of alternatives in terms of both their costs and consequences (Drummond et al., 2005). This evaluation is about determining whether an intervention is an efficient use of society's resources (Brouwer & Georgiou, 2012). On the policy level, the government uses this evaluation to determine which programs are eligible for reimbursement and which ones not (Lapré, Rutten & Schut, 2001).

2.1.1 Types of economic evaluation

Various types of economic evaluation exist to identify the cost and consequences. Cost-effectiveness analysis is one type of economic evaluation that will be applied in this study. This type compares the relative costs and effects (or outcomes) of two or more alternatives. The most cost-effective option is identified as the one with the lowest present value of costs. With the use of this analysis the effects are not expressed in monetary terms, as is the case in cost-benefit analysis, but in health effects or outcomes either in natural units (Brouwer & Georgiou, 2012). The most commonly used outcome measure of cost-effectiveness is quality-adjusted life years. This type of analysis is called cost-utility analysis. QALYs combine changes in quantity and quality of life (mortality and morbidity) in a common measure and, basically, by the use of QALYs the cost-effectiveness of different interventions is comparable (Van den Berg et al., 2008). In the Netherlands, a maximum amount to €80,000 per QALY is often considered to be cost-effective (Krabbe – Lugnér, 2011).

2.1.2 The process of economic evaluation

An economic evaluation consists of several steps. The process starts with defining the economic question and perspective. Subsequently, the alternatives to be evaluated are determined and the evaluation design is chosen. In addition, the costs which are in monetary terms will be identified,

measured and valued. The same is done for the consequences. Thereafter, the time horizon(s) over which costs and consequences are being evaluated are stated and the choice of discount rate(s) used are reported. After that, an incremental cost-effectiveness ratio (ICER) will be calculated. This ratio reflects how much one has to pay per extra unit of effect (Drummond et al., 2005). In other words, when calculating the ICER, the cost and effects of the intervention drug (pegaspargase) are compared with the cost and effects of the control drug (asparaginase). This leads to the following formula:

$$ICER = \frac{Cost_A - Cost_B}{Effect_A - Effect_B}$$

A = intervention

B = conventional care

Figure 1. Formula Incremental Cost-Effectiveness Ratio

The cost-effectiveness analysis results in a Cost-Effectiveness (CE) plane, observable in figure 2. This figure displays four different outcomes.

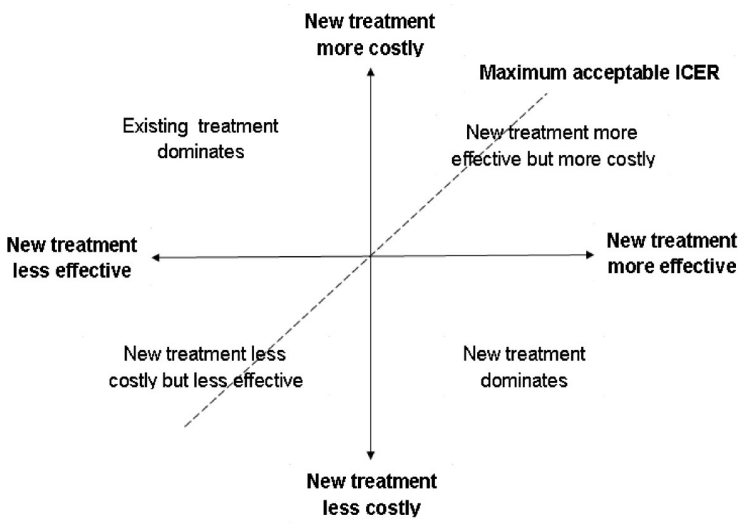

Figure 2. Cost-effectiveness plane with four different quadrants

A point estimate in the southeast quadrant is the most preferred outcome in which the intervention drug is more effective and less costly than the comparator drug. This outcome will lead to reimbursement of the new treatment. If the point estimate is placed in the northwest quadrant, then the comparator drug is more effective and less costly than the intervention drug. The northeast and southwest quadrant show questionable results. When the point estimate lays in one of these quadrants, more aspects like budget impact and disease severity come into play.

2.1.3 Sensitivity analysis

The ICER is a point estimate that is surrounded by uncertainty (Briggs, Sculpher & Claxton, 2006). The model calculations that are used to identify the cost-effectiveness of the drugs are based on assumptions about the effect in the longer term, the scope and the cost of an intervention This uncertainty causes a risk of making an inappropriate decision. A so-called sensitivity analysis estimates the margins of the calculated cost-effectiveness by taking into account the uncertainty about the assumptions (Hamberg – Van Reenen & Meijer, 2011). A sensitivity analysis is recommended to test the robustness of results in any type of economic evaluation. Several forms can be used in a cost-effectiveness analysis - such as one-way, multi-way, analysis of the extremes, stochastic, probabilistic – depending also on the extensive recourse to modelling (Garattini & Van de Vooren, 2011).

Stochastic uncertainty is related to the uncertainty associated to the different experienced effects of an intervention per patient (Briggs et al., 2012). Parameter uncertainty reflects the uncertainty related to the fact that the parameters (cost, utilities, effect of treatment) as used in in an economic evaluation are estimates (Briggs et al., 2012). A probabilistic sensitivity analysis (PSA) starts with the characterization of uncertainty in these estimates through a distribution fitted around the mean of each parameter (Drummond et al., 2005).

2.1.4 Two basic approaches of economic evaluation

An economic evaluation can either be based on a model or a trial. In trial-based studies, economic data are collected alongside a single clinical study often being in the shape of a controlled clinical trial. It has been well recognized that many trials exhibit weaknesses when these trials are the sole source of evidence on resource use and health effects that, together with external valuation data, forms the basis of the estimate of cost-effectiveness (Briggs et al., 2006). When executing a modelled study, data from a wide range of sources, such as observational studies and trials, are synthesized using an economic model (Drummond & Sculpher, 2005). Models are able to represent a simplified reality. This reductionist methodology calculates the expected cost and outcome of each option under evaluation and it allows for the variability and uncertainty associated with all decisions (Briggs et al., 2006; Caro, Briggs, Siebert & Kuntz, 2012).

A frequently-used model in economic evaluation is the Markov model. A Markov model can represent a stochastic process which is a random process that evolves over time. The model is useful when a decision problem involves risk that is continuous over time, when the timing of events is important and when important events may happen more than once. A Markov model can be

evaluated in several ways. Frequently used methods are cohort simulation and Monte Carlo simulation (Briggs & Sculpher, 1998).

Markov cohort simulation is the most straightforward way to present the Markov process. With this simulation, a hypothetical cohort of patients transit from one state to another for each cycle. During each cycle, it is recorded how many patients have stayed in different states. At the end, summary results can be presented on patients' spending in different states. With this approach it is assumed that transitions happen at the end of each cycle (Xin, 2007). Another simulation method is Monte Carlo simulation or so-called individual simulation. It is assumed that a large number of patients enter the model all individually. These patients go through the states in a random manner. The overall results, after repeating many cycles of the previously-described behaviour, are obtained by summing the outcomes for each patient who goes through the model. The most patients will be absorbed in this model when performing a Monte Carlo simulation (Xin, 2007).

So the biggest difference between cohort simulation and Monte Carlo simulation is that patients in cohort simulation move in a given path through the model, while patients in Monte Carlo simulation transit stochastically (Xin, 2007). This difference gives the latter simulation the advantage of producing distribution profiles of patients with random deviation. Additionally, the calculation methods for expected outcomes are different between these two approaches. In cohort simulation the total values for the cycle are obtained by summing the health outcomes and costs in different health states (Xin, 2007). On the other hand, in Monte Carlo simulation, the total health outcomes and costs of an individual are the addition of consequences and costs of states that the individual transiting through the model (Xin, 2007).

2.1.5 The process of decision-analysis modelling

A common route of performance is applied for decision-analytical modelling. The process is as follows (Xin, 2007):

1. Identify the objectives and develop the model. The design of the model is based on clinical judgement of the main aspects of the disease and treatment process.
2. Select inputs. The best available evidence to inform choice of data inputs is used. The probabilities are assigned to the model after the model is validated. The assignment of health utilities and costs is performed separately.
3. Analyse. The results are calculated and the robustness to changes in assumptions and data is tested.

4. Review. If not enough results are gathered, more information will be collected. Additionally, the assumptions will be checked if necessary. After this review the results are presented and interpreted.

2.1.6 Conceptual model

With the use of the theoretical framework, a conceptual model on economic evaluation is composed as can be observed in figure 3.

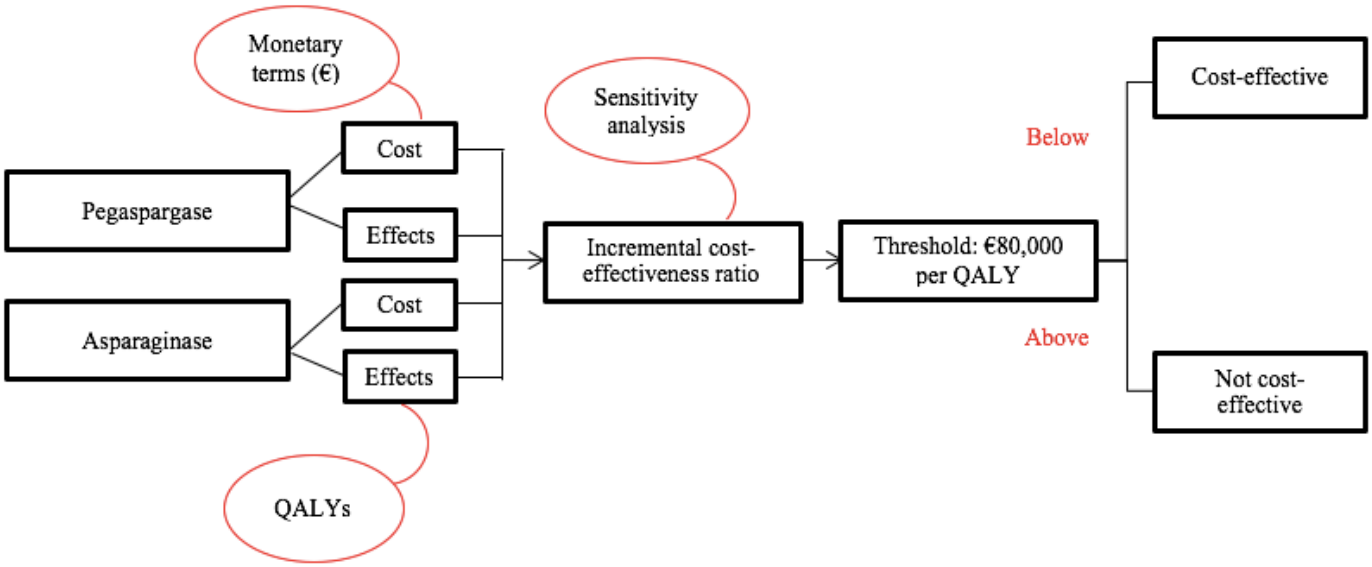

Figure 3. A conceptual model on economic evaluation

2.2 Relevant clinical research

Given that the FDA has approved pegaspargase already for more than ten years, one would expect to find several randomized controlled trials (RCTs) on the effects of the medication. However, not many RCTs are available. One study was found that compares native E. coli asparaginase and polyethylene glycol conjugated asparaginase for the treatment of children with newly diagnosed standard-risk acute lymphoblastic leukaemia. In the study conducted by Avramis and his colleagues (2002) 118 children with standard ALL were randomly assigned to receive either asparaginase or pegaspargase as part of induction and two delayed intensification treatment phases. The patients treated with pegaspargase had more rapid clearance of lymphoblasts and bone marrow aspirates. Additionally, more prolonged asparaginase activity was found in the group treated with pegaspargase than in those treated with native asparaginase. In the first delayed intensification phase, 26% of native asparaginase patients had high-titer antibodies. These antibodies are indicative of an

allergic response. Studies have shown that asparaginase activity is often low when the antibody titer is high (Holland et al., 1997; Kurtzberg et al., 1993). The authors define high-titer antibody initially as a ratio of serum antibody to the average control value of 2.5. This value corresponds to the enzyme-linked immunosorbent assay (ELISA) absorbance reported (Avramis et al., 2002). Many samples with antibody ratios of more than or equal to 2.5 had asparaginase activity in an ineffective range of less than 0.1 IU/mL. The abbreviation IU stands for International Unit and is a measure for the amount of a substance based on measured biological activity (or effect). One unit of asparaginase is the enzyme activity that under standard conditions cleaves 1 micromole per minute of ammonia from L-asparagine. This result is in line with what was expected for the native asparaginase arm. Antibody ratios of 1.5 and 2.0 were also associated with a low asparaginase activity. In contrast to the native asparaginase patients, only 2% of the pegaspargase patients had those levels similar to the asparaginase arm. These high-titer antibodies were associated with low asparaginase activity in the group treated with asparaginase, but not in the pegaspargase group (Avramis et al., 2002). The study does not show any difference in hospitalization, infections and adverse events between the two treatment arms. Furthermore, no disparity in event-free survival at three years was found in both treatment arms. The EFS was 82% at three years. Thereafter, the survival rate for the asparaginase patients decreases to 77% and remains constant for at least half a year, whereby the EFS of the pegaspargase arm remains constant at 82%. The event-free survival events contain induction death, no induction response, relapse at any site and second malignant neoplasm. The study also showed that the half-lives of asparaginase for pegaspargase are almost five times as long as those for native asparaginase. This prolonged half-life may be an important factor in improving the pharmacokinetic profile of the drug (Avramis et al., 2002).

In the article “Pegasparaginase: where do we stand?” the clinical aspects, tolerability and the side effects of pegaspargase are reviewed. Pegaspargase is documented to retain the enzymatic activity of asparaginase, yet is associated with a decreased immunogenicity. However, the pharmacokinetics of pegaspargase may be adversely affected by the development of antibodies to the asparaginase. Pegaspargase had a significantly lower half-life in patients who received asparaginase as first-line treatment with documented hypersensitivity reactions. Therefore, in this modelling study the choice has been made to have either PEGaspargase or native E. Coli asparaginase as first-line treatment. When allergic reactions arise, patients switch to Erwinia asparaginase as this drug has been documented not to cross-react with pegaspargase or asparaginase. Moreover, altered pharmacokinetics and increased anti-ASP antibody formation was observed in clinically hypersensitive patients as well as silent hypersensitive patients. This suggests that the frequency of pegaspargase administration may need to augmented from its currently recommended

bi-monthly administration (Zeidan, Wang, & Wetzler, 2009). In the States, the initial route of administration of pegaspargase has been intramuscular. Meanwhile, in Europe pegaspargase has been broadly administered intravenously. The latter administration method does not increase any apparent side effects when compared to either intramuscular administration or subcutaneous routes.

Preclinical trials in animals have shown a higher antitumor activity for pegaspargase when it is compared to unmodified asparaginase forms. Based on these trials and phase I and II trials, pegaspargase was already approved by the FDA in 1994 for treating patients with acute lymphoblastic leukaemia and who are hypersensitive to native asparaginase (Zeidan et al., 2009). Incorporation of pegaspargase into standard multi-agent chemotherapy regimes for relapsed ALL was found to be effective, safe and well tolerated in several trials. The substitution of pegaspargase for native asparaginase in those multi-agent chemotherapy treatments has been associated with similar efficacy in RCTs in children. Grade 3 or 4 toxicity reactions (as shown in Table 2) are rare in patients treated by pegaspargase. However, these patients should be monitored frequently for symptoms and signs that indicate the development of toxicity (Zeidan et al., 2009).

2.2.1 Adverse events

As previously mentioned, one of the biggest reasons for the interest in pegaspargase is that it seems to cause less adverse events than asparaginase. The FDA defines an adverse event as *"any undesirable experience associated with the use of a medical product in a patient"* (FDA, 2016). The hypersensitive reactions to asparaginase and pegaspargase are considered as adverse events. In this study, hypersensitivity and allergic reactions are used interchangeably. Allergic reactions can range from milder reactions like urticarial to severe including systematic anaphylaxis. There are several risk factors contributing to the occurrence of these allergic reactions, such as different formulations of the drug, the dose of the drug, repeated courses of treatment, administration of the drug after a break in cycles as well as concomitant chemotherapy (Woo et al., 2000).

According to Shinnick and colleagues (2013) the frequency of clinical hypersensitivity reactions to E. coli is rather variable and can range from 32.5% to 75%. A possible explanation of this variation is the chosen definition of hypersensitivity. For example, in the case of a 70% hypersensitivity, all allergic reactions (including silent inactivation) are taken into account, whereas in the case of 35% only grade 3 or 4 of allergic responses are included. Several studies found that hypersensitivity reactions are more likely to be associated with antibodies, which increases clearance of the drug, and are more likely to occur with repeat dosing (Avramis & Tiwari, 2006; Zalewska-Szewczyk et al., 2007). An increased incidence of hypersensitivity reactions and a shorter half-life

have been reported when E. coli asparaginase was administered intravenously instead of intramuscularly. Less asparagine depletion, understood as a surrogate maker of therapeutic benefit, may be achieved in patients that experiencing hypersensitivity (Avramis & Tiwari, 2006; Müller & Boos, 1998).

Pegaspargase appears to have a longer half-life, prolonged asparagine depletion and less immunogenicity (Avramis et al., 2002; Masetti & Pession, 2009). Given these advantages the antineoplastic effect, in other words the inhibition or prevention of the growth or development of malignant cells, is maintained. While allergic reactions to pegaspargase also occur, they do so to a lesser extent than with the use of native asparaginase. With the use of pegaspargase, the allergic reactions range from 2% after a single dose up to 50% in patients who receive post remission consolidation therapy after treatment with native E. coli asparaginase (Stock et al., 2011). In contrast to asparaginase, intravenous pegaspargase does not result in a significantly different incidence of hypersensitivity in comparison with intramuscular administration (Shinnick et al., 2013; Silverman et al., 2011; Pidparti & Bostrom, 2011).

Nowadays, the Children's Oncology Group (COG) ALL trials use pegaspargase instead of native asparaginase in their treatment protocols (Gaynon et al., 2010). Such is the case in the Netherlands, in which protocol ALL-11 is followed. ALL-11 is the newest treatment study protocol of the Childhood Oncology Group for children and adolescents (1-19 year) with newly diagnosed acute lymphoblastic leukemia (DCOG, 2016). In order to improve the asparaginase therapy, some changes have been made in protocol ALL-11 compared to the former protocol (ALL-10). The protocol states that the less immunogenic pegaspargase will be used instead of native asparaginase in order to prevent allergic side effects. Previously this drug was only prescribed during the induction phase, nowadays they recommend to prescribe it during the intensification phase as well. Based on high asparaginase levels found in the ALL-10 study, the starting dose is reduced to 1,500 IU/m^2 instead of 2,500 IU/m^2 (DCOG, 2014). This deviates from the prescribed dosage as stated in USA protocols, where they still adhere to a dose of 2,500 IU/m^2. Additionally, the Dutch protocol recommends the monitoring of serum asparaginase levels. These levels correlate well with the level of asparagine depletion. The monitoring leads to individualizing the dose schedule of asparaginase for each level. If high dose levels are found, the dose will be reduced. This reduction will ultimately lower costs (DCOG, 2016). Furthermore, even severe allergic reactions (e.g. anaphylactic shock) may be prevented. The gradation in severity is displayed in Table 2 in Chapter 1. Based upon the severity of the clinically allergic reaction and the route of administration, it is advised that in the case of a Grade 2 or higher reactions, a switch of asparaginase preparation is indicated without definite need for testing of asparaginase (Van der Sluis et al., 2016). When having a Grade 1 reaction

or a reaction that has occurred with a questionable significance, real-time monitoring of serum asparaginase activity levels is recommended. With an undetectable level, patients should switch to Erwinia asparaginase. If the level is detectable, a 14-day through level is advised and a subsequent dose of asparaginase should be carefully administered. However, identifying a clinical allergy is not straightforward (Van der Sluis et al., 2016). It can be difficult to distinguish a reaction as a true allergic reaction. In this case, there are two concerns: (1) the failure to positively identify the allergic reaction and act hereupon; (2) the failure of false positive identification and switching to Erwinia asparaginase. Due to this uncertainty, some studies suggest that even Grade 1 reaction can be associated with hypersensitivity (Tong et al., 2014).

When silent inactivation arises, continued asparaginase therapy with the same formulation will lead to poorer outcomes as witnessed in allergic reactions. Data suggest that the development of silent inactivation is clinically important and acting upon this subclinical allergy may improve the outcome of therapy in children with acute lymphoblastic leukaemia (Vrooman et al., 2013; Panoysan et al., 2004). These results highlight importance of switching from pegaspargase or asparaginase to Erwinia asparaginase (Van der Sluis et al., 2016). If silent inactivation is detected, the next dose of pegaspargase or asparaginase is not administered and patients will switch to Erwinia asparaginase. Detection of silent inactivation can only properly be done by the drug monitoring program (DCOG, 2016). The concern that patients could continue to be exposed to a drug that has been rendered ineffective when an alternative treatment exists is compelling. Therefore, Van der Sluis and her colleagues (2016) recommend to consider screening in all patients that undergo treatment for acute lymphoblastic leukaemia with administration of asparaginase.

2.3 Previous cost-effectiveness research

As was mentioned earlier, there are no Dutch studies that model the cost-effectiveness of pegaspargase compared to asparaginase. There exist, however, some cost-effectiveness studies conducted within the Netherlands.

Tong and others (2013) studied the costs of asparaginase in childhood ALL patients treated with PEGasparaginase or Erwinia asparaginase during the first 30 weeks of the intensification phase of the ALL-10 medium-risk (MR) protocol. The aim of the study was to assess whether there could be savings from using pegaspargase as the first-line drug compared to asparaginase within the intensification phase. Three scenarios were used in the study: in scenario 1 a dose of 2,500 IU/m^2 pegaspargase was administered every fourteen days with 20,000 IU/m^2 of Erwinia asparaginase as second-line treatment (Tong et al., 2013). In the other two hypothetical scenarios patients were

treated with 5,000 IU/m^2 asparaginase for a duration of 30 weeks. The costs were narrowly defined. The included costs were chemotherapy without asparaginase, costs of pegaspargase and asparaginase, cost of additional treatment, day care and inpatient care, blood products, laboratory and other hospital activities. The costs of treatment with asparaginase, followed by a switch to PEGasparaginase, and subsequently to Erwinia asparaginase after the occurrence of an allergic reaction, were $70,402. This amount was approximately the same as the costs of treatment with pegaspargase as the first-line drug. Both scenarios have more or less the same costs. Therefore, pegaspargase is preferred because it is administered less frequently. The use of pegaspargase is seen as the most patient friendly option as first line treatment, eventually resulting in a reduced burden for the patient and the family (Tong et al., 2013).

The pharmacoeconomic study of Kurre and his colleagues (2002) sought to compare pegaspargase with E. coli asparaginase in induction, delayed intensification 1 and delayed intensification 2. A subset of patients with newly diagnosed, standard- risk ALL enrolled in Children's Cancer Group (CCG) study gave consent and was enrolled in the study of Kurre et al. (2002). Both societal and payer costs were collected. The authors found, when taking all three phases into account, that the cost for pegaspargase therapy was $667 (2%) higher than native E. coli asparaginase. The societal costs were similar in both arms, with a difference in costs of $12 (1%) favouring asparaginase. The inpatient stays accounted for approximately 90% of the pegaspargase and asparaginase payer costs.

3 Research methods

The method chapter starts with the different framing aspects and on the basis of this study frame the decision analytic model will be given.

3.1 Framing

The series of decisions that collectively define and describe the study to be undertaken constitute the study frame. The purpose of framing a modelling study is setting the boundaries of the study in order to match the breadth of the research question posed (Torrance, Siegel & Luce, 1996). The different framing aspects of this modelling study will be discussed in the following paragraphs.

3.1.1 Perspective

The perspective of this modelling study should be related to its target audience. The study is targeted at the National Health Care Institute, NHCI (Dutch: Zorginstituut Nederland). This Dutch independent administrative body ensures that Dutch citizens are insured and remain insured under the Health Insurance Act, HIA (Dutch: Zorgverzekeringswet, Zvw), and the Long-term Care Act, LCA (Dutch: Wet langdurige zorg, Wlz). This ensures that everyone entitled to care receives it. Additionally, the institute is charged with improving the quality of care (Zorginstituut Nederland, n.d.). As NHCI is the target audience, the study perspective should be based on its guidelines. The guideline of the NHCI (2016) for economic evaluations in healthcare states that the adopted perspective should be societal. When applying this perspective, costs and consequences are broadly defined. In other words, this perspective considers the impact of an intervention on the welfare of the whole society and not just the individuals. For this study, a broad view would be important because acute lymphoblastic leukaemia impacts not only the children but also the the parents and eventually the society as a whole. Another reason for choosing a societal perspective is that the gained life years by treatment can be very costly for society. The incurred costs are for the greater part related to the late effects that the youngest population of the society will experience because of their past with ALL treatment. In all likelihood, this young population will live for many more years.

Despite this logical reasoning and recommendation of the institute, there has been taken a different choice. Instead of the societal perspective, a health payers' perspective is applied. This is more in line with the guidelines of the National Institute of Health and Care Excellence (NICE). When applying a health care payers' perspective, costs and consequences are narrowly defined. This

means that only those direct medical costs and consequences associated with the intervention and comparator are considered. One justification for this deviation is the lack of literature. Little research has been done on the quality of life of the parents of children with cancer. Furthermore, only some articles investigated the financial impact of having a child with cancer. Therefore, it was concluded that the existing literature was too limited to have a comprehensive societal perspective.

3.1.2 Time horizon

As is recommended by the National Health Care Institute, a lifetime horizon would be the most preferred time horizon. The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

However, as will be shown in the Markov model, the overall survival of children with acute lymphoblastic leukaemia is high. When verifying Figure 3 of the article of Vora and his colleagues (2013), an overall 5-years survival of 0.90 can be read from the figure. It is assumed that the overall survival for pegaspargase and asparaginase is equally high, therefore both drugs have the same overall survival. After the treatment completion (for both drugs), the treatment arm and the control arm of the hypothetical population will receive the same care with the same frequency. Consequently, it is assumed that this will not result in substantial differences in the ICER. This means that after the treatment program, the costs will be the same. Therefore, it is chosen to have a time horizon of 5 years instead of a lifetime horizon.

3.1.3 Discounting

A constant discount rate of 4% for costs was used and future effects were discounted at a discount rate of 1.5%. This is in line with the guideline on pharmacoeconomic research of the National Health Care Institute (Zorginstituut Nederland, 2016). A half-cycle correction is applied on both the costs and utilities in order to improve the accuracy of the results. The flow of patients between the different Markov states is assumed to be continuous. This means that if the number of patients, costs and effects are measured at the beginning or end of each cycle the result can be an overestimation or underestimation. By the use of half- cycle correction, the difference from real data can be diminished (Nemeth & Szeker, 2014).

3.1.4 Population

The (hypothetical) population being studied consists of children under the age of 18 who have acute lymphoblastic leukaemia. The population is enrolled in CCG protocol 1962 and is at standard-risk, Additionally, the enrolled patients have white blood cell (WBC) counts of less than or equal to 50,000/μL and less than or equal to 20% surface immunoglobulin(lg)-positive leukemic blasts (Avramis et al., 2002).

3.1.5 Intervention and comparator

The treatment of the population consists of four weeks of induction, four weeks of consolidation, eight weeks of interim maintenance, eight weeks of delayed intensification and it concludes with maintenance therapy. The total duration of the therapy is three years, from the start of the interim maintenance phase. The population receives either the intervention drug or the comparator drug.
The intervention drug is PEGasparaginase, which is a chemotherapy drug and the first-line treatment for acute lymphoblastic leukaemia. At the start of the induction, patients receive hypothetically 2,500 IU/m^2 intramuscularly (IM) at the third day of the 28-days lasting period. The dose depends on the age and body surface of the patient. The comparator drug is native E. coli asparaginase, also being chemotherapy. This treatment is administered intramuscularly every three days during the induction phase, at a dose of 6,000 IU/m^2. The drug administration of PEGasparaginase also applies to the delayed intensification phase. The administration of asparaginase changes. As asparaginase is administered for nine doses in the induction phase, it is administered for six doses in the delayed intensification phase.

As previously described, the population is susceptible to allergic reactions by the use of both pegaspargase and asparaginase. In the manifestation of an allergic reaction, pegaspargase and asparaginase are replaced by Erwinia asparaginase. The population will then receive 20,000 IU/m^2 of Erwinia asparaginase IM three times per week, as second-line treatment for ALL.

Of course, both chemotherapy drugs are not the only drugs in the treatment for ALL. Prednisone, vincristine, methotrexate and other drugs also belong to the treatment schema of ALL. The full schema is displayed in Table 3.

Table 3. Treatment schema for treating ALL in children under 18 (Avramis et al., 2002)

Intervention				**Comparator**			
Phase	**Medication**	**Dosage**	**Frequency**	**Phase**	**Medication**	**Dosage**	**Frequency**
Induction (4 weeks)	**Pegaspargase IM**	2,500 IU/m^2	Day 3	*Induction (4 weeks)*	**Asparaginase IM**	6,000 IU/m^2	Days 3, 5, 8, 10, 12, 15, 17, 19, 22
	Vincristine IV	1.5 mg/m^2	Days 0, 7, 14, 21		Vincristine IV	1.5 mg/m^2	Days 0, 7, 14, 21
	Prednisone PO	40 mg/m^2	Days 0 - 28		Prednisone PO	40 mg/m^2	Days 0 – 28
	Cytarabine IT	50 mg	Day 0		Cytarabine IT	50 mg	Day 0
	Methotrexate IT	10 mg	Days 7, 28		Methotrexate IT	10 mg	Days 7, 28
Consolidation (4 weeks)	Vincristine IV	1.5 mg/m^2	Days 0, 28	*Consolidation (4 weeks)*	Vincristine IV	1.5 mg/m^2	Days 0, 28
	6-mercaptopurine PO	75 mg/m^2	Days 1 - 28		6-mercaptopurine PO	75 mg/m^2	Days 1 - 28
	Methotrexate IT	10 mg	Days 7, 14, 21		Methotrexate IT	10 mg	Days 7, 14, 21
Interim maintenance (8 weeks)	Vincristine IV	1.5 mg/m^2	Days 0, 28, 56	*Interim maintenance (8 weeks)*	Vincristine IV	1.5 mg/m^2	Days 0, 28, 56
	Prednisone PO	40 mg/m^2	Days 0 – 4, 28 - 32		Prednisone PO	40 mg/m^2	Days 0 – 4, 28 - 32

	Methotrexate PO	20 mg/m^2	Weekly		Methotrexate PO	20 mg/m^2	Weekly
	6-mercaptopurine PO	75 mg/m^2	Daily		6-mercaptopurine PO	75 mg/m^2	Daily
Delayed intensification (8 weeks)	**Pegaspargase IM**	2,500 IU/m^2	Day 3	*Delayed intensification (8 weeks)*	**Asparaginase IM**	6,000 IU/m^2	Days 3, 5, 8, 10, 12, 15
	Dexamethasone PO	10 mg/m^2	Days 0 – 6, 14 - 20		Dexamethasone PO	10 mg/m^2	Days 0 – 6, 14 - 20
	Doxorubicin IV	25 mg/m^2	Days 0, 7, 14		Doxorubicin IV	25 mg/m^2	Days 0, 7, 14
	Cyclophosphamide IV	1000 mg/m^2	Day 28		Cyclophosphamide IV	1000 mg/m^2	Day 28
	Thioguanine PO	60 mg/m^2	Days 28 - 41		Thioguanine PO	60 mg/m^2	Days 28 - 41
	Vincristine IV	1.5 mg/m^2	Days 0, 7, 14		Vincristine IV	1.5 mg/m^2	Days 0, 7, 14
	Cytarabine IV or SC	75 mg/m^2	Days 29 – 32, 36 - 39		Cytarabine IV or SC	75 mg/m^2	Days 29 – 32, 36 - 39
	Methotrexate IT	10 mg	Days 7, 28		Methotrexate IT	10 mg	Days 7, 28
Maintenance (2,5 years = 130 weeks)	Vincristine IV	1.5 mg/m^2	Every 4 weeks	*Maintenance (2,5 years = 130 weeks)*	Vincristine IV	1.5 mg/m^2	Every 4 weeks
	Prednisone PO	40 mg/m^2	Days 0 – 4 every 4 weeks		Prednisone PO	40 mg/m^2	Days 0 – 4 every 4 weeks
	Methotrexate PO	20 mg/m^2	Weekly		Methotrexate PO	20 mg/m^2	Weekly

	6-mercaptopurine PO	75 mg/m^2	Daily		6-mercaptopurine PO	75 mg/m^2	Daily
	Methotrexate IT	10 mg	Every three months		Methotrexate IT	10 mg	Every three months

IV: intravenously; PO: oral; IM: intramuscularly; IT: intrathecal; SC: subcutaneous

3.2 The decision analytic model

In the next subsections, the different aspects related to the decision analytic model of this study will be elucidated. Furthermore, the assumptions, their underlying motivation and the possible alternatives will be discussed.

3.2.1 Markov structure

As it has been told in section 2.1.4, health economic evaluations can be performed based on either a trial or a model. A modelled economic evaluation is considered as the more appropriate approach to use in this case, because little information is available on costs and utility on patient level in order to assess the cost-effectiveness empirically. As previously-mentioned, no models on the cost-effectiveness of pegaspargase compared to asparaginase can be found in the literature. Therefore, a new model is necessary. A Markov model will be used in this modelling study, because of the advantage that the elapse of time can be made explicit compared to the use of a decision tree (Briggs et al., 2006).

Based on the randomized study of Avramis and others (2002) and several other studies, it would be relevant to include four different health states in the model namely 'disease progression', 'adverse events', 'event-free survival' and 'death'. Both disease progression and adverse events are substantial causes of adaptation of treatment, intermission of treatment and death, which consequently can influence the cost and effects. In the most ideal situation, the model as presented in Figure 4 would be used as structure.

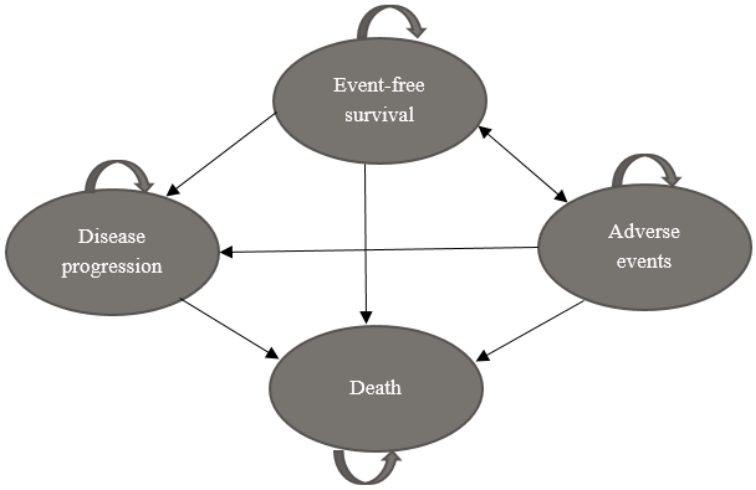

Figure 4. Model structure with four relevant health states

However, no data is available that reflects the transition probability from an adverse event back to the event-free survival or to the disease progression state. Therefore, the model structure as shown in Figure 5 was applied in this modelling study.

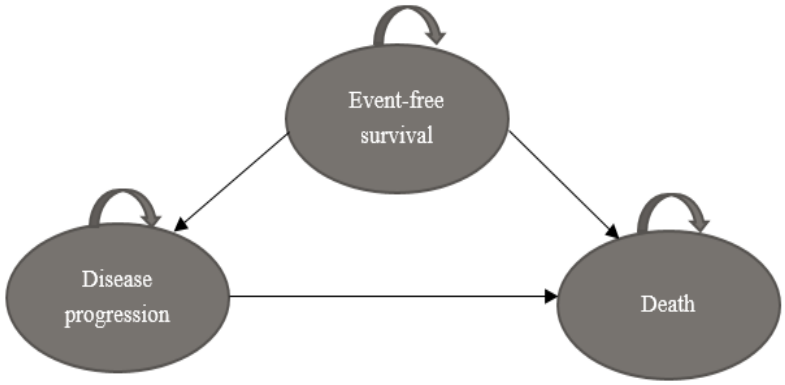

Figure 5. Markov model as used in the modelling study

The model displayed in Figure 5 is a closed cohort, probabilistic Markov model. The hypothetical patients will enter the model in the state 'event-free survival'. As can be observed in Figure 5, 'adverse events' is no longer a separate health state. To be clear, adverse events contain the allergic reactions or hypersensitivity that patients can experience during treatment. The costs and disutilities associated with the adverse events will be taken into account in the 'event-free' state. The cycle length is four weeks, because patients start their treatment in the induction phase which lasts for four weeks.

3.3 Input parameters

Within the section 'Data and analysis', the different input parameters of the Markov model are highlighted.

3.3.1 Treatment effect

The comparison between the treatments takes place by using clinical data from two studies. The main study being used is the article of Avramis and others (2002). This study performed a Kaplan-Meier analysis, showing a higher event-free survival for patients in the treatment arm (Avramis et al., 2002). The curve shows that 3-year EFS rates for pegaspargase and native asparaginase were 85% and 78% respectively. Figure 6 shows these EFS-curves. The other article that is used is the

article of Vora et al. (2013). In this article the overall survival (OS) is displayed. As previously-mentioned, it is assumed that the overall survival is equal for both the treatment group and control group. The 5-year overall survival for children with acute lymphoblastic leukaemia is 90% (Vora et al, 2013). In Figure 7, the OS-curve of the article of Vora and others (2013) is displayed.

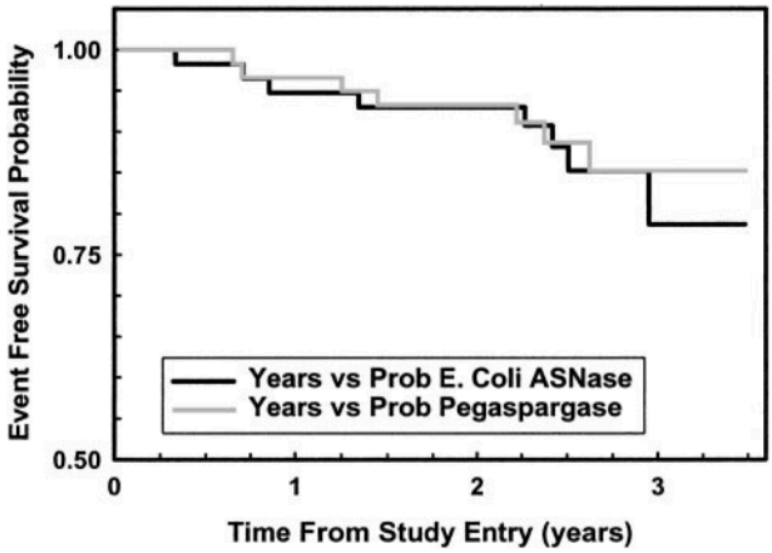

Figure 2. Kaplan-Meier plot of EFS for all randomly assigned patients. Solid line (black) shows data for 59 native ASNase patients; gray line for 59 pegaspargase patients, *P* = .773 log-rank.

Figure 6. EFS-curve of the article from Avramis et al. (2002)

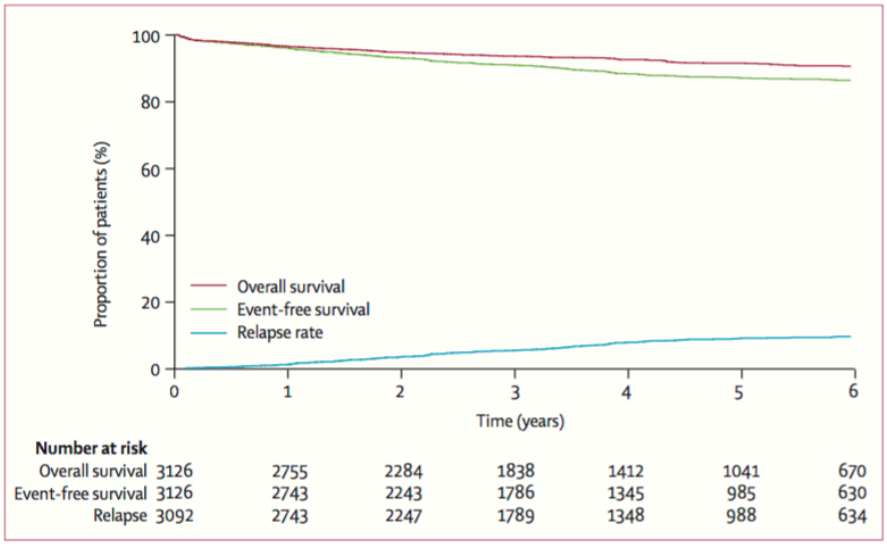

Figure 7. Event-free survival, relapse, and overall survival in the trial of Vora et al. (2013)

The curves of overall survival and event-free survival are used to estimate the transitions of the patients in the model. A time horizon of five years is chosen, however the Kaplan-Meier curve that

shows the data from the trial of Avramis et al. (2002) ceased after 36 months. Since patients were still alive after 36 months and the chosen time horizon is 5 years, the EFS-curve had to be extrapolated. In order to extrapolate, the following formulas were used:

$$\text{Rate} = -[\ln(1 - P)] / t$$

P = probability of the event

t = time

Now it is possible to calculate, for example, a one-year probability of the event with the following formula:

$$\text{Probability} = 1 - \exp\{-rt\}$$

In order to make the formulas more understandable, an example is given. To calculate the overall survival after three years (156 weeks), the proportion of patients at three years should be read from Figure 7. This proportion is 93%, giving a probability of 0.07 (= 1 – 0.93). The rate can now be calculated:

Rate = -[ln (1 – 0.07)]/156 = 0.000465…

4- week probability = 1 – exp (-0.000465… * 4) = 0.00186

When using these formulas, a (constant) instantaneous rate is assumed. The transition probabilities that are estimated are used to fill in the Markov trace.

3.3.2 Health related quality of life

Measuring the utilities and health-related quality of life (HRQL) in children is challenging. This is due to their changing developmental stages and their cognitive abilities (Litsenburg et al., 2014). HRQL is multidimensional and includes social, psychological and physical domains. In order to make the assessment of HRQL for children more reliable, autonomy, body image, cognitive functioning and family relationships might be included. Several questionnaires have been developed for the indirect measurement of utilities of the paediatric population. The Health Utilities Index (HUI) is chosen as questionnaire, because it seems appropriate for eliciting utilities in paediatric ALL and it has been proven to be reliable, responsive and valid to change for people of five years and older (Litsenburg et al., 2014).

PubMed was used to find literature giving information on utility values reflecting the health-related quality of life of the different health states in the model. Hence, the following search strategy was used:
("health"[MeSH Terms] OR "health"[All Fields]) AND state[All Fields] AND utilities[All Fields] AND ("acute lymphoblastic leukaemia"[All Fields] OR "precursor cell lymphoblastic leukemia-lymphoma"[MeSH Terms] OR ("precursor"[All Fields] AND "cell"[All Fields] AND "lymphoblastic"[All Fields] AND "leukemia-lymphoma"[All Fields]) OR "precursor cell lymphoblastic leukemia-lymphoma"[All Fields] OR ("acute"[All Fields] AND "lymphoblastic"[All Fields] AND "leukemia"[All Fields]) OR "acute lymphoblastic leukemia"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields])

This broad query translation gave three hits. These three articles were checked on appropriateness and after this check the articles did not seem to fit. So another search was performed with a focus on economic evaluation, because these evaluations address both costs and effects. Accordingly, the search strategy was as follows:
("cost-benefit analysis"[MeSH Terms] OR ("cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR ("economic"[All Fields] AND "evaluation"[All Fields]) OR "economic evaluation"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) AND ("acute lymphoblastic leukaemia"[All Fields] OR "precursor cell lymphoblastic leukemia-lymphoma"[MeSH Terms] OR ("precursor"[All Fields] AND "cell"[All Fields] AND "lymphoblastic"[All Fields] AND "leukemia-lymphoma"[All Fields]) OR "precursor cell lymphoblastic leukemia-lymphoma"[All Fields] OR ("acute"[All Fields] AND "lymphoblastic"[All Fields] AND "leukemia"[All Fields]) OR "acute lymphoblastic leukemia"[All Fields]) AND ("Childhood"[Journal] OR "childhood"[All Fields])

With this search strategy sixteen items were found. The third article gave the needed information about utility (Rae et al., 2014). The study found reported the utility values per treatment phase. The authors of the study used HUI questionnaires to calculate the patients' utility scores. No significant differences in the scores between patients on high-intensity and low-intensity treatments were found by Rae and others (2014). Therefore, the assumption was made that the utilities for pegaspargase and asparaginase are equal. Furthermore, it is also assumed that the utility for disease progression is equal to the utility of relapse.

Subsequently, the disutilities of adverse events were searched. It was tried to gather disutilities for all the allergic reactions from Grade 2 and higher. After an extensive search, not all disutilities were found. Consequently, based on an advice of an expert on health technology assessment, the decision was made to search for the disutility of the heaviest allergic reactions. The anaphylactic shock was examined as the most severe reaction. The disutility value (=0.08) of anaphylaxis was retrieved from the NICE clinical guideline 134 (2011) and will be included in the utilities during phases in which patients experience allergic reactions. For example, patients experience an allergic reaction with the administration of pegaspargase during delayed intensification. The utility during the delayed intensification without an allergic reaction is 0.78, so with an allergic reaction the utility is (0.78 – 0.08=) 0.70. Moreover, the probability of developing an allergic reaction and the median number of doses after which an allergic reaction arises were taken into account. For pegaspargase a probability of 0.128 with a median number of doses 2 was found for the development of allergic reactions. This means that the allergic reaction for pegaspargase will take place during the intensification phase. For asparaginase was this probability 0.4 with a median of 8 (Henriksen et al., 2015; Bauters et al., 2013; Rossey, 2013) and the allergic occurs during the induction phase. It is assumed that when patients switch to Erwinia asparaginase after having an allergic reaction that they will not experience an allergic reaction anymore. Table 4 displays the different utility values per treatment phase.

Table 4. Utilities per treatment phase

Utilities per cycle	**Utility value**
Induction phase (Ip)	0.72
Consolidation (Co)	0.90
Interim maintenance (Im)	0.85
Delayed intensification (Di)	0.78
Maintenance (M)	0.85
Off-therapy (Off)	0.92
	Disutility value
Disutility of adverse events (grade 3 and grade 4) - PEG & ASP (duAE)	**0.08**
Discrement associated with ongoing susceptibility to anaphylaxis	
Utility delayed intensification per cycle - Pegaspargase	
Delayed intensification (uDi_AE_P)	**0.70**

Utility induction phase per cycle - Asparaginase	
Induction phase (uIp_AE_A)	**0.64**
	Utility value
Disease progression (uP)	**0.72**

3.3.3 Resource use and costs

In order to determine the resource use and costs of the health states 'event-free' and 'progression' different literature sources were used. No use is made of a database like PubMed. The main sources that were used are set up by two national institutes:
www.medicijnkosten.nl (National Health Care Institute)
http://dbc-zorgproducten-tarieven.nza.nl/nzaZpTarief/Welkom.aspx (Dutch Healthcare Authority)

Other sources being used are tariff lists of health insurers and tariff lists of hospitals. The choice for using these sources is based on a recommendation of an expert in health technology assessment. The treatment program in the article of Avramis and others (2002) is maintained, in which the medication and frequency is clear. To determine the resource use of other direct medical care, two already existing cost studies are utilized (Litsenburg, De Groot, Raat, Kaspers & Gemke, 2011; Kurre et al., 2002). The frequency of this medical care is set equal per treatment program. The total costs are per treatment phase determined.

Cost in the event-free state

The 'event-free' state consists of the costs related to the treatment, concomitant medication (as mentioned in Table 3), costs related to adverse events and the costs of other direct medical care. However, it should be noted that not every treatment phase includes the same costs because these costs are dependent on the phase itself. To come to the overall costs, it is calculated what the costs are per phase per treatment (either pegaspargase or asparaginase). When considering pegaspargase, there will be a total cost for induction, consolidation, interim maintenance, delayed intensification (without adverse events), delayed intensification (with adverse events) and maintenance. In the case of asparaginase, a total for induction (without adverse events), induction (with adverse events), consolidation, interim maintenance, delayed intensification, delayed intensification with a switch to Erwinase and maintenance is calculated. The costs of the adverse events were retrieved from the webpage of the Dutch Healthcare Authority by which one can calculate the costs per Diagnosis

Treatment Combination (in Dutch: Diagnose Behandel Combinatie, DBC). The costs of the adverse events are in the same way calculated as the utility, meaning that the probability of having an allergic reaction yes or no is taken into account. The resources and costs related to other direct medical care are similar for both treatment arms. An example of the cost in the event-free state during the induction phase of the pegaspargase program is shown in Table 5. Table 6 shows the costs of the asparaginase treatment during induction in the event-free state.

The costs after treatment were also included. The treatment program of asparaginase and pegaspargase is approximately three years, but a time horizon of five years was chosen. Consequently, after the maintenance phase the costs after the treatment program are included. These costs are based on the other direct costs which were taken into account in the treatment phases. It is assumed that these costs are similar for both arms. These costs are presented in Table 7.

Cost in the progression state

The costs in state 'progression' are similar for both treatment arms. In progression, it is assumed that the resource use consists of best supportive care and other direct medical care. The specific resources and frequencies were based on information which is provided by the hospital Reinier de Graaf (Reinier de Graaf, 2016). An overview of the costs in the progression state is shown Table 8.

For all monetary values that reflect the costs of treatment were index to 2016 by the use of the Consumer Price Indexes (CPI) of the Netherlands (CBS, 2016)

Table 5. Specified costs for pegaspargase treatment – induction phase

	Cost per unit	Frequency	Amount of units per cycle	Total cost per cycle
Costs medication				
Pegaspargase per 3750 IU/m2	€ 1,249	2,500 IU/m2	0.67	€ 836.83
Total costs medication				**€ 836.83**
Concomitant medication				
Vincristine	€ 10.95	1.5 mg/m2	4	€ 43.80
Prednisone	€ 1.20	40 mg/m2	28	€ 33.60
Cytarabine	€ 1.85	50 mg	1	€ 1.85
Methotrexate	€ 0.79	10 mg	2	€ 1.58
Total costs concomitant medication				**€ 80.83**
Other direct medical costs				
Inpatient hospital day cost (based on 28 days)	€ 12,052.68	1	1	€ 12,052.68
Day care visits	€ 291.06	2	2	€ 582.12
Blood products	€ 1.45	5	5	€ 7.25
Laboratory activities	€ 7	3	3	€ 21
Bone marrow examination	€ 316.54	3	3	€ 949.62
Spinal taps	€ 47.46	3	3	€ 142.38
CT scan	€ 250	1	1	€ 250
MRI scan	€ 415	1	1	€ 415
Ultrasound	€ 84.47	1	1	€ 84.47
X-ray	€ 55.81	1	1	€ 55.81
ECG	€ 43.99	1	1	€ 43.99
Total other direct medical costs				€ 14,604.32
Total other direct medical costs corrected for 2016				**€ 14,659.88**

Table 6. Specified costs for asparaginase treatment – induction phase

	Cost per unit	Frequency	Amount of units per cycle	Total cost per cycle
Costs medication				
Asparaginase per 10000 UI/m2	€ 58	6,000 IU/m2	5.4	€ 313.20
Total cost medication without allergic reaction				**€ 313.20**
Cost medication with allergic reaction				
Asparaginase per 10000 UI/m2	€ 58	6,000 IU/m2	4.8	€ 278.40
Erwinase per 10000 UI/m2 (patients switch to Erwinase after allergic reactions to asparaginase)	€ 846	20,000 IU/m2	2	€ 1,692
Total cost medication with allergic reaction (after 8 doses of asparaginase)				**€ 1,970.40**
Concomitant medication				
Vincristine	€ 10.95	1.5 mg/m2	4	€ 43.80
Prednisone	€ 1.20	40 mg/m2	28	€ 33.60
Cytarabine	€ 1.85	50 mg	1	€ 1.85
Methotrexate	€ 0.79	10 mg	2	€ 1.58
Total cost concomitant medication				**€ 80.83**
Other direct medical costs				
Inpatient hospital day cost (based on 28 days)	€ 12,052.68	1	1	€ 12,052.68
Day care visits	€ 291.06	2	2	€ 582.12
Blood products	€ 1.45	5	5	€ 7.25
Laboratory activities	€ 7	3	3	€ 21
Bone marrow examination	€ 316.54	3	3	€ 949.62
Spinal taps	€ 47.46	3	3	€ 142.38
CT scan	€ 250	1	1	€ 250
MRI scan	€ 415	1	1	€ 415
Ultrasound	€ 84.47	1	1	€ 84.47
X-ray	€ 55.81	1	1	€ 55.81
ECG	€ 43.99	1	1	€ 43.99
Total direct medical costs				€ 14,604.32
Total direct medical costs corrected for 2016				**€ 14,659.88**

Adverse events				
Costs linked to grade 3 and grade 4 allergic reactions (zorgproductcode: 991016021)	€ 816,68	1	1	€ 816,68
Total costs adverse events				**€ 816,68**

Table 7. Cost after treatment with pegaspargase or asparaginase

	Cost per unit	**Frequency**	**Amount of units per cycle**	**Total cost per cycle**
Other direct medical cost				
Day care visits	€ 291.06	1 x every 6 months	0.17	€ 48.51
Blood products	€ 1.45	1 x every 6 months	0.17	€ 0.24
Laboratory activities	€ 7	1 x every 6 months	0.17	€ 1.17
CT scan	€ 250	1 x every 6 months	0.17	€ 41.67
MRI scan	€ 415	1 x per year	0.08	€ 31.92
Ultrasound	€ 84.47	1 x every 6 months	0.17	€ 14.08
X-ray	€ 55.81	1 x every 6 months	0.17	€ 9.30
ECG	€ 43.99	1 x every 6 months	0.17	€ 7.33
Total other direct medical cost				€ 154.22
Total other direct medical cost corrected for 2016				**€ 154.30**
Total cost event-free disease per cycle after having treatment program (dmC_afterT)	**€ 154.30**			

Table 8. Cost of disease progression

	Cost per unit	Frequency	Amount of units per cycle	Total cost per cycle
Best supportive care				
Prednisone	€ 1.20	40 mg/m2	5	€ 6
Clofarabine	€ 1,775.50	1	1	€ 1,775.50
Stem cell transplant	€ 12,794.17	1 x every 2 years	0.04	€ 492.08
Radiotherapy	€ 4,622.14	5 x per year	0.42	€ 1,925.89
Total costs of best supportive care				**€ 4,199.48**
Other direct medical cost				
Inpatient hospital day cost	€ 12,052.68	2 weeks per transplant	0.02	€ 231.78
Day care visits	€ 291.06	First three months every week, thereafter every three months	0.79	€ 230.42
Blood products	€ 1.45	First three months every week, thereafter every three months	0.79	€ 1.15
Laboratory activities	€ 7	First three months every week, thereafter every three months	0.79	€ 5.54
CT scan	€ 250	1 x in 6 months	0.17	€ 41.67
MRI scan	€ 415	1 x in 6 months	0.17	€ 69.17
Ultrasound	€ 84.47	1 x every 12 weeks	0.33	€ 28.16
X-ray	€ 55.81	1 x every 12 weeks	0.33	€ 18.60
ECG	€ 43.99	1 x every 12 weeks	0.33	€ 14.66
Total other direct medical cost				€ 641.15
Total other direct medical cost corrected for 2016				**€ 641.30**
Total cost of disease progression (dmCP)	**€ 4,840.78**			

3.3.4 Different values of parameters

The cohort in this study was modelled. Consequently, the stochastic uncertainty does not have to be addressed. Therefore, in this study the parameter uncertainty is addressed. Firstly, the analysis started with the characterization of the uncertainty of the parameter estimates. The distribution underlying the effect of the intervention is assumed to be bivariate normal. When fitting distributions for the parameters reflecting costs and utilities, some aspects should have been taken into account. Costs can never be negative, so a gamma distribution was used to represent the uncertainty in the cost parameters. Utilities, on the other hand, are bounded between infinity at the lower end and 1 at the upper end (Briggs et al., 2006). Therefore, a beta distribution was fitted around the utility parameters.

No standard errors of the parameters could be found in the literature. One reason for this is that the cost and utility parameters are compounded values. That is why the standard errors are calculated. It is assumed that 20% of the mean represents the standard error in the case of the cost parameters. This assumption can be motivated given that highly aggregated mean costs were used, consisting of several elements. This approach asks for a larger standard error to reflect the overall uncertainty. For the utility parameters, the standard error was assumed to be 5% of the mean. The disutility has another standard error, namely 20% of the mean. If 5% of the mean was chosen as standard error, then the alpha and beta show a study with many patients which would be in contrast with de utilities of the different treatment phases. When assuming 20%, the standard error of the disutility is approximately the half of the standard error of the utilities. This is more plausible. Also for the overall survival and the event-free survival, it is assumed that 10% of the mean represents the standard error. For the adverse events, also 20% of the mean is taken because there exists a significant uncertainty about this parameter. This asks for a larger standard error. In Table 9 an overview of the different parameters is given.

Table 9. Deterministic values, standard errors and distributions

Parameter name	Deterministic	Standard error	Distribution	Alpha	Beta
Pegaspargase					
Overall survival					
OS_PEG	**0.00175**	0.000175447	normal		
Event-free survival					
EFS_PEG	**0.00450**	0.000450424	normal		

Parameter name	Deterministic	Standard error	Distribution	Alpha	Beta
Asparaginase					
Overall survival					
OS_ASP	**0.00175**	0.000175447	normal		
Event-free survival					
EFS_ASP	**0.00653**	0.000652645	normal		
Costs of treatment					
dmC_i_p	**€ 15,577.54**	€ 3,115.51	gamma	€ 25	€ 623.10
dmC_c_p	**€ 826.15**	€ 165.23	gamma	€ 25	€ 33.05
dmC_im_p	**€ 857.36**	€ 171.47	gamma	€ 25	€ 34.29
dmC_di_p	**€ 7,625.72**	€ 1,525.14	gamma	€ 25	€ 305.03
dmC_di_AE_p	**€ 8,442.40**	€ 1,688.48	gamma	€ 25	€ 337.70
dmC_m_p	**€ 838.59**	€ 167.72	gamma	€ 25	€ 33.54
dmC_i_a	**€ 15,053.91**	€ 3,010.78	gamma	€ 25	€ 602.16
dmC_i_AE_a	**€ 17,527.79**	€ 3,505.56	gamma	€ 25	€ 701.11
dmC_c_a	**€ 826.15**	€ 165.23	gamma	€ 25	€ 33.05
dmC_im_a	**€ 857.36**	€ 171.47	gamma	€ 25	€ 34.29
dmC_di_a	**€ 6,788.64**	€ 1,357.73	gamma	€ 25	€ 271.55
dmC_di_Erw_a	**€ 11,864.89**	€ 2,372.98	gamma	€ 25	€ 474.60
dmC_m_a	**€ 838.59**	€ 167.72	gamma	€ 25	€ 33.54
dmC_afterT	**€ 154.30**	€ 30.86	gamma	€ 25	€ 6.17
dmCP	**€ 4,840.78**	€ 968.16	gamma	€ 25	€ 193.63
Utility of Markov States					
duAE	**0.08**	0.016	beta	22.92	263.58
uP	**0.72**	0.036	beta	111.28	43.2756
uIp	**0.72**	0.036	beta	111.28	43.2756
uCo	**0.90**	0.045	beta	39.10	4.3444
uIm	**0.85**	0.043	beta	59.15	10.4382
uDi	**0.78**	0.039	beta	87.22	24.6005

Parameter name	Deterministic	Standard error	Distribution	Alpha	Beta
uM	**0.85**	0.043	beta	59.15	10.4382
uOff	**0.92**	0.046	beta	31.08	2.7026
uIp_AE_A	**0.64**	0.032	beta	143.36	80.6400
uDi_AE_P	**0.70**	0.035	beta	119.30	51.1286
Adverse events					
no_PEG	**0.87**	0.174	beta	2.33	0.34
yes_PEG	**0.13**	0.026	beta	21.67	147.64
no_ASP	**0.60**	0.120	beta	9.40	6.27
yes_ASP	**0.40**	0.080	beta	14.60	21.90

Abbreviations:
OS_PEG = overall survival pegaspargase | **OS_ASP** = overall survival asparaginase| **EFS_PEG** = event-free survival pegaspargase | **EFS_ASP** = event-free survival asparaginase | **dmC_i_p** = direct medical cost induction pegaspargase | **dmC_c_p** = direct medical cost consolidation pegaspargase | **dmC_im_p** = direct medical cost interim maintenance pegaspargase | **dmC_di_p** = direct medical cost delayed intensification pegaspargase | **dmC_di_AE_p** = direct medical cost delayed intensification adverse events pegaspargase | **dmC_m_p** = direct medical cost maintenance pegaspargase | **dmC_i_a** = direct medical cost induction asparaginase | **dmC_i_AE_a** = direct medical cost adverse events asparaginase | **dmC_c_a** = direct medical cost consolidation asparaginase | **dmC_im_a** = direct medical cost interim maintenance asparaginase | **dmC_di_a** = direct medical cost delayed intensification asparaginase | **dmC_di_Erw_a** = direct medical cost | **dmC_m_a** = direct medical cost maintenance asparaginase | **dmC_afterT** = direct medical cost after treatment | **dmCP** = direct medical cost progression | **duAE** = disutility adverse events | **uP** = utility progression | **uIp** = utility induction phase | **uCo** = utility consolidation | **uIm** = utility interim maintenance | **uDi** = utility delayed intensification | **uM** = utility maintenance | **uOff** = utility off-therapy | **uIp_AE_A** = utility induction phase adverse events asparaginase | **uDi_AE_P** = utility delayed intensification adverse events pegaspargase | **no_PEG** = no adverse events pegaspargase | **yes_PEG** = adverse events pegaspargase | **no_ASP** = no adverse events asparaginase | **yes_ASP** = adverse events asparaginase

For each parameter presented in Table 9, 1000 random values were taking during the performance of the probabilistic sensitivity analysis. This resulted in a cost-effectiveness plane and a cost-effectiveness acceptability curve which are shown in the Chapter ‘Results’.

4 Results

The deterministic undiscounted and discounted results of the model are presented in Table 10. The value for the costs, QALYs and LYs are the total average outcome per patients over five years. In the base-case analysis, the discounted as well as the undiscounted results point out that PEGasparaginase is less expensive and more effective (although to a really small extent) than native E. coli asparaginase. The cost increment is negative, whereas the QALY increment is positive consequently leading to negative values for the ICER. A negative value of the ICER as a result of the new treatment being more effective and less costly, is a circumstance in which asparaginase is dominated by pegaspargase.

Table 10. Deterministic discounted and undiscounted results

Results (deterministic) undiscounted

Treatment	Costs	QALY	LY
Pegaspargase	€ 78,731.53	4.07	4.75
Asparaginase	€ 94,885.57	4.03	4.75
Increment	**€ 16,154.04-**	**0.04**	**0,00**
ICERs:		**Incremental costs/ QALY**	**Incremental costs/ LY**
Pegaspargase vs asparaginase		**€ 395,009.01-**	

Results (deterministic) discounted

Treatment	Costs	QALY	LY
Pegaspargase	€ 73,506.02	3.93	4.58
Asparaginase	€ 87,947.98	3.89	4.58
Increment	**€ 14,441.95-**	**0.04**	**0.00**
ICERs:		**Incremental costs/ QALY**	**Incremental costs/ LY**
Pegaspargase vs asparaginase		**€ 371,809.85-**	

QALY = Quality-Adjusted Life Year
LY = life year
ICER = incremental cost-effectiveness ratio

The ICER in which life years are included is empty, because the increment of life years is 0 (undiscounted and discounted). Consequently, it is not possible to calculate the ICER. The increment is 0, since the overall survival for pegaspargase and asparaginase is set equal.

However, in order to make a decision about reimbursement, the uncertainty of the input-parameters is of importance in addition to the base-case results. The determination of uncertainty surrounding cost-effectiveness requires the investigation of the joint distributions of costs and effects. Figure 8 shows the cost-effectiveness plane of pegaspargase compared to asparaginase. The majority of the incremental cost-effect pairs fall in the southeast quadrant of the incremental cost-effectiveness plane. This results indicates that pegaspargase is less costly and more cost-effective than asparaginase, which is in line with the results of Table 10. Nonetheless, a proportion (approx. 5%) of the points lie in the southwest quadrant and another proportion of the cost-effect pairs fall in the northwest quadrant (1%) and in the northeast quadrant (2%). When pairs lie in the southwest quadrant, it indicates that pegaspargase is less costly and less effective than pegaspargase. In the north-west quadrant, pegaspargase is less effective and costlier. The north-east quadrant implies that pegaspargase is more effective, but also costlier. These observations confirm that there is uncertainty concerning whether and at what value pegaspargase is cost-effective.

Figure 9 shows the cost-effectiveness acceptability curve (CEAC). This curve indicates the probability that an intervention is cost-effective compared with the alternative, given the observed data for a range of threshold ICERs. This is a Dutch study, therefore the Dutch threshold ICER is chosen as threshold which is € 80,000 per QALY (Zorginstituut Nederland, 2015). Thus, the CEAC in Figure 9 shows the probability that pegaspargase is cost-effective compared to asparaginase over a range of values for the maximum acceptable ceiling ratio (λ) of €80,000 per QALY. When λ was €80,000 per QALY, a proportion of the resamples falling in the other quadrants than the southeast quadrant are no longer included in the numerator. As a result, the proportion of the resamples was found to be 0.99.

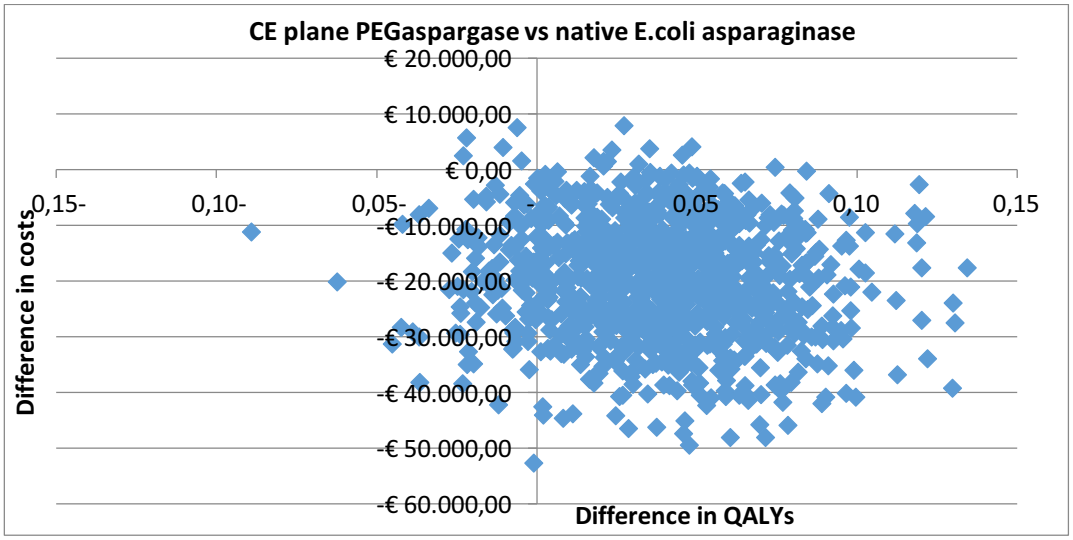

Figure 8. Scatterplot displaying uncertainty on costs and QALYs

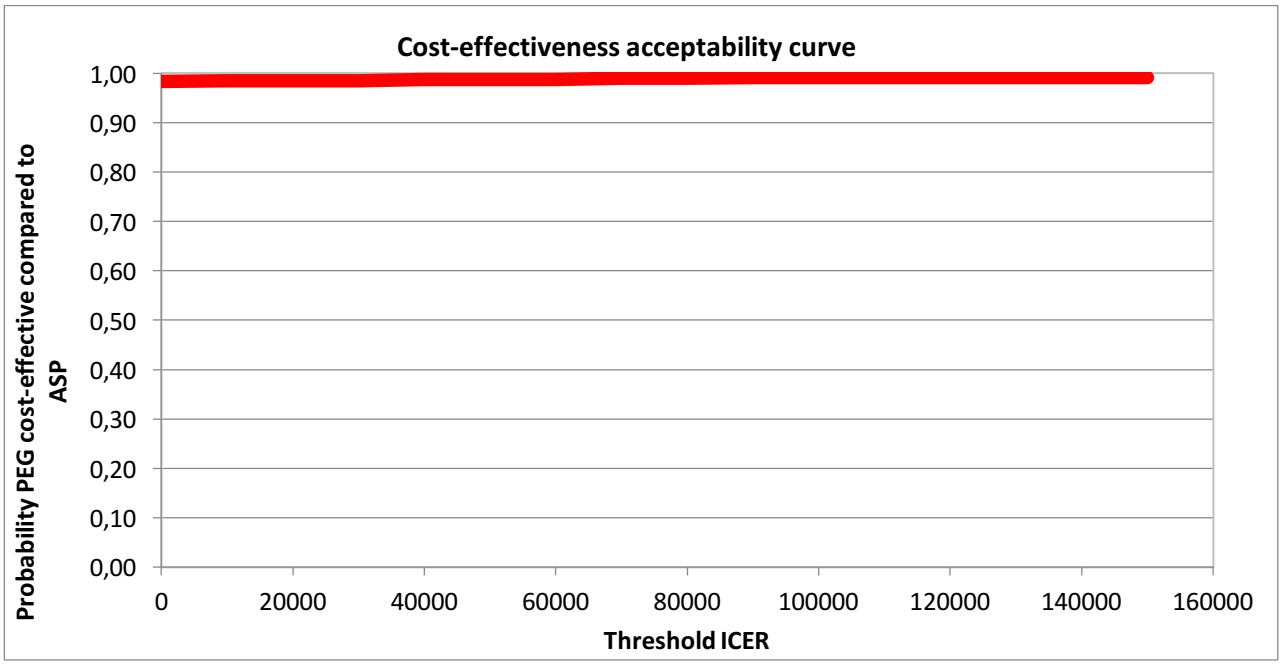

Figure 9. Cost-effectiveness acceptability curve of pegaspargase versus asparaginase

5 Conclusion and discussion

This health economic evaluation assessed the cost-effectiveness of pegaspargase compared to asparaginase in treating children who have standard-risk acute lymphoblastic leukaemia up to the age of 18. The study findings indicate that PEGasparaginase is more effective and less costly than native E.coli asparaginase, meaning that PEGasparaginase is cost-effective compared to asparaginase.

Series of decisions and assumptions were made in order to come to this result. These assumptions all have some uncertainty in them and can have an impact on the outcome of the modelling study. The importance of the assumptions, the reasons behind why the several assumptions had to be made and the possible impact of alternative assumptions will be addressed in this discussion section. Additionally, recommendations for further research will be given.

Two points are of great concern in this study. That is the study setting and the lack of expert opinion. Both aspects influenced the decisions and the assumptions to be made in the whole model. The study setting was the Netherlands. This setting was consciously chosen, because of the lack of, and thus the relevance of, a modelled cost-effectiveness study for pegaspargase compared to asparaginase in the Netherlands. However, during the literature search it was found that no Dutch RCT is available to use the clinical data. Therefore, an American RCT was used. The United States follow a different protocol than the Netherlands. The treatment scheme is linked to the protocol used. In the new protocol (ALL-11) of the Dutch Childhood Oncology Group a lower dosage (1,500 IU/m^2 instead of 2,500 IU/m^2) of pegaspargase is given. This lower dosage is linked to a lower chance of allergic reactions. Consequently, this probably will lead to a higher experienced utility and lower costs, because less disutility of adverse events is experienced and less costs have to be made. This is of great importance for the cost-effectiveness ratio and the decision on reimbursement.

Another aspect that brings even more uncertainty in the model is that different input parameters, like the overall survival curves and the median of adverse events with their frequencies, are derived from other articles in other settings. For overall survival this will not give the biggest danger, because also other articles gave more or less the same survival. The used overall survival curve is from an article in the United Kingdom (UK). The UK has approximately the same life expectancy, so that will not impact the result significantly. The frequency of hypersensitivity could not being found in the same article. This means that several articles are used with different treatment schedules that cannot being compared fully, therefore it gives actually a bias to include the values in the model.

The other great concern is the lack of an expert. Frantic efforts were made to find an expert, but this did not avail unfortunately. The opinion of the expert could raise the validity and the reliability of the model, which ultimately reduces the uncertainty. The expert could have given advice on several parameters. Concerning the costs, a close look could be taken on the treatment schedule, the different drugs and other direct medical costs during the different treatment phases. It should be checked whether it is relevant to include these different costs. Additionally, the frequency of the different costs is important and the expert can give advice on these frequencies. In this way, a more realistic view on the costs of treatment is evoked. Moreover, a better insight in allergic reactions is required. As mentioned, different articles are used for the frequency and the median onset. It is more or less required to gather data from one clinical study, because then a real comparison can be made between the two different drugs. All in all, an expert could have made a big difference. However, just one expert opinion is not enough to increase the validity and the credibility of the findings. When using expert opinion as input for the model, expert (investigator) triangulation is recommended in order to increase the validity and credibility. Fortunately, the costs in the consolidation phase, interim maintenance phase and maintenance phase are equal for both asparaginase preparations. The same is the case for the costs after treatment and costs during disease progression. Differences in costs in these phases and health states will not influence the incremental cost-effectiveness ratio.

After having discussed the biggest concerns that have influenced other choices, now the discussed assumptions and decisions will have the same order as described in the report. The study population is regarded to be homogeneous with no differences depending on age or body weight. General outcomes of the cohort treated in the trial are used, while in reality there are no ‘general patients’. Likewise, the model does not include the history of the patient. These assumptions relate to the limitations of Markov cohort modelling itself. Obviously, this has implications for the outcome of this modelling study. Subgroup analyses in an individual patient Markov model for a subgroup in boys with age of 3 with a white blood cell count of 25,000 will show a different ICER than subgroup analyses in girls with the age of 9 with a white blood cell count of 45,000. However, findings from more multiple subgroup analyses may be misleading, because the analyses are observational by nature. The more subgroup analyses are performed, the more false negative and false positive significance tests arise.

Another important assumption that should not be overlooked is the inclusion of allergic reactions. Within this study, only the grade 4 allergy is included although the recommendation of switching to Erwinia asparaginase when developing an allergic reaction. The grade 4 allergic reaction, anaphylactic shock, is probably associated with a higher disutility and higher costs than other lower graded reactions. It is assumed in the model that when an allergic reaction is experienced

it will be a grade 4 allergic reaction anyhow. There is factual chance that the experienced allergic reactions also can be of a lower gradation with a lower disutility and with lower costs to overcome them. This will of course influence the ICER eventually. Another deviation of the Dutch recommendations for hypersensitivity relates to the inclusion of silent inactivation yes or no. Not monitoring and noticing silent inactivation will lead to poorer clinical outcomes. The reason to not include silent inactivation in the model is that investigation of silent inactivation is still in its infancy. Not much is known about the frequency and the emergence of silent inactivation yet.

The decision for the health care payers' perspective although a societal perspective is advised, is a decision that should be highlighted over here. In the introduction, a little paragraph has been written about the psychosocial impact of the treatment for acute lymphoblastic leukaemia. It is cited that also the parents experience the stress due to a changing role and the caregiver burden. Despite the choice for the healthcare payers' perspective, it is still desired to have a societal perspective in this specific study (SKION, 2010). As many as 75% of cancer survivors are confronted with a wide variety of health and/or psycho-social problems which are related to disease history and/or the previous treatment. These 'late effects' become sometimes only many years after treatment obvious and are usually irreversible. The effects can lead to increased mortality compared to their peers (SKION, 2010). Early detection and treatment of these late effects are important in order to prevent increases in problems. In this way, health benefit is obtained and quality of life is obtained. This is very interesting to implement in a modelling study with the subject of paediatric cancer, because it can give higher utilities with prevented costs in the future. Next to these late effects, the financial burden for parents plays also an important role when adapting a societal perspective. Both mental stress and financial stress will be developed by the parents of children with cancer. It was investigated by Warner et al. (2014) that parents who had a child with cancer with five or more unexpected hospitalizations experienced a 24.9 point higher financial burden than those with no unexpected hospitalizations. This financial burden was rated on a visual analogue scale of 0 to 100. In addition, when a comparison was made with families without employment disruptions, the parents with a diseased child that had to quit or change their job reported 13.4 points higher on financial burden (Warner et al., 2014). This study shows clearly the impact of having a child with cancer and it shows also the relevance for choosing a societal perspective in future research.

A point that should be marked is the difference between the trial population and the hypothetical population of this modelling study. It is stated that the hypothetical population consists of children and adolescents until the age of 18 years. Nonetheless, the population that is included in the study of Avramis et al. (2002) is aged from 1 to 9. This is a clear difference and probably will have a considerable impact of the incremental cost-effectiveness ratio, because it is found that

adolescents and young adults still tend to die earlier than children for cancers like in specific acute lymphoblastic leukaemia (News Medical Life Sciences, 2016). This has an impact on the costs and ultimately on the ICER.

As probably has become evident, several assumptions are made in order to identify the cost-effectiveness of pegaspargase compared to asparaginase. Therefore, a probabilistic sensitivity analysis was performed to estimate the margins of the calculated cost-effectiveness. The cost-effectiveness plane in Figure 8 showed the results on the uncertainty in costs and effects. The location of the incremental cost-effect pairs indicated that there is little uncertainty regarding the effectiveness of pegaspargase, because all points fall on the right on the vertical axis. Nonetheless, the spread of the points in the horizontal plane indicates that some uncertainty exists regarding the magnitude of the effect (-0.09 – 0.13). Considering the costs, there is also not much uncertainty that pegaspargase is less expensive, since almost all cost-effect pairs fall below the horizontal axis. The same uncertainty about magnitude is present, also because of the wide spread (€52,711.36 - € 7.870,42). It can be checked which parameter causes this magnitude of uncertainty by the use of a univariate analysis. The uncertainty of the decision maker is summarized with the use of a cost-effectiveness acceptability curve. This curve showed clearly a dominant position for pegaspargase compared to asparaginase. When a decision maker has to decide on the reimbursement of pegaspargase, then it is advised to reimburse pegaspargase. The drug gives a small improvement in QALY, but it flourishes in the lower costs. These lower costs can be partly explained by a later onset of allergic reactions and a lower frequency.

Still, despite the attempt to make the model robust and transparent, some uncertainties have not been addressed. The biggest uncertainty in this modelling study are the allergic reactions. With other frequencies and other medians of onset, the ICER would give a total different result. This parameter is highly uncertain. Furthermore, all the standard errors were an estimation. These estimations will make the model weaker and more uncertain.

Based on the experience with this small modelling study, some recommendations can be given for further research. In the literature research, it became clear that there is lack in the literature. Due to the lack in literature, especially in the Netherlands, it is recommended to do another modelling study with the same objective. This means that the idea of this study has to be repeated, but clear clinical results on the effects with both EFS-curves and OS-curves should be presented. Additionally, little less uncertainty should exist about the allergic reactions. Data on the frequencies, the onset and the different allergic reactions should be present on beforehand. Furthermore, additional research has to

be performed to have more knowledge on the costs of care in the follow-up period and in the progression state. Besides the above-mentioned points, it is recommended to have a societal perspective. On the one hand because it is more in line with the Dutch guidelines on economic evaluations, and on the other hand because of the late effects and the related costs and disutilities to these effects. A childhood cancer like acute lymphoblastic leukaemia has considerable consequences for the future. The last recommendation, but not less important, is the use of an expert. As a layman in this field, it is really hard to find sententious information with which the cost-effectiveness model can be filled in. Without an expert, the validity, reliability and uncertainty of the model decreases significantly. Given that a model already has uncertainties and assumptions included, the lack thereto should not play the leading role.

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