

# Acute Myeloid Leukaemia treatment in Norway

*Survival and cost analysis of Acute Myeloid Leukaemia*

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Master Thesis

as part of the Master of Philosophy in Health Economics, Policy and  
Management

Department of Health Management and Health Economics  
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# Abstract

## Background

Acute myeloid leukaemia (AML) is an acute form of cancer that does not affect many individuals per year, but has a high death rate. The disease is characterized by an abnormal growth in the white blood cells in the bone marrow, which causes anaemia and infections. The incidence of AML is around 173 cases each year. Because of the disease's acute and deadly form, patients spend several months at the hospital receiving heavy chemotherapy. About one-third of the patients receive transplantation, spending from days up to months at the intensive care unit. Improving treatments strategies involves understanding the clinical pathway and identifying the associated costs.

## Aim

The aim of this study was to investigate the life expectancy and costs associated with treating AML in order to provide a representation of the Norwegian treatment regime. Additionally, we wanted to compare our results with a similar study from the UK.

## Methods

A combination of decision tree and Markov models was developed to conduct the study. The model is probabilistic with the use of Weibull regressions. By means of individual level data from OUS Rikshospitalet we were able to derive time-dependent transition probabilities. The outcome is life expectancy and costs per individual in a five-year perspective. Costs were considered from a health care provider perspective.

## Results

The result of this study shows a total cost and life expectancy of NOK 1 401 521 and 37.61 months, per patient. The result indicates a higher life expectancy and costs for young compared to elderly patients, depending on inclusion of induction treatment.

## Conclusion

AML life expectancy and costs vary according to clinical pathways and patient characteristic. When comparing our results with the UK, Norway appears to have a greater life expectancy at a higher cost.



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Additionally we would like to thank Leif Jostein Reime from the accountant department of the Haematology ward for providing us the cost data for OUS.

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Alette is glad Ludvig was able to stick out with her the last couple of months, while Beate is happy for living with the understanding roommate Marita.

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Alette Glasø Skifjeld and Beate Bjørnstad

June, 2015

**Disclaimer:** The study has used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

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# Abbreviations

ALL	Acute Lymphocytic Leukaemia
AML	Acute Myeloid Leukaemia
CE	Confidence interval
CHR	Complete hematologic remission
CPI	Consumer Price Index
DES	Discrete-event simulation
DRG	Diagnosis-related group
FLT3	Fms-related tyrosine kinase 3
GDP	Gross Domestic Product
LE	Life expectancy
MD	Medical Doctor
NHS	National Health Service
NOK	Norwegian kroner
OUS	Oslo University Hospital
PDF	Probability density function
PPP	Purchasing Power Parity
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted life years
QOL	Quality of life
SE	Standard error
UK	United Kingdom

## Data tools

Excel	Microsoft Excel 2011
Plot Digitizer	Used to digitize scanned plots of functional data
SPSS	IBM SPSS Statistics
Stata	Stata 13 (data analysis and statistical software)
TreePlan	TreePlan Software (add-in for Excel)
yEd	yEd Graph Editor





# 1 Introduction

About one third will get cancer (28.8 per cent if female and 35.9 per cent if male) at some point in life (Kreftregisteret, 2015b). This might be one of the leading factors of why we tend to focus research on this disease and its different forms. One is more likely to get cancer types such as breast cancer (if female) or prostate cancer (if male), but common for these cancer types is a high five-year relative survival. Acute myeloid leukaemia (AML) on the other hand is not frequent, but it is more difficult to treat, and the survival is poorer. Due to new and resource demanding treatment methods, the economic burden of cancer (and AML) are expected to increase in the future. Therefore, the evaluation of cancer treatment methods and monitoring of clinical courses is important (Joranger et al., 2015). This is one of the main reasons why it is interesting to look at survival and the cost for this patient group.

There is approximately 173 new cases of AML in Norway per year (Kreftregisteret, 2015a), and most patients receive treatment in specialist hospitals. OUS Rikshospitalet (OUS) treats around 40 new cases per year. This patient group is costly, especially since almost one third receives transplantation which has an estimated cost of roughly NOK 1 million per patient (in 2001) (Mishra, Vaaler, & Brinch, 2002). In addition, almost all of the patients receive chemotherapy, other medicaments and numerous amounts of blood transfusions, which together are great cost drivers.

This aim of this study is to investigate the costs and life expectancy of AML patients, in order to provide a picture of the Norwegian treatment regime. The foundation of the thesis is a similar study by Wang et al. (2014) where the cost and life expectancy in the United Kingdom (UK) was calculated. A second intention behind this thesis is to compare our results to Wang et al. (2014), and examine whether there are any differences in the amount of people treated and the survival of these. This is interesting to do especially since the UK have a relatively similar health care system to Norway (social welfare). One can learn from each other and additionally this gives a form of validation of the study (cross-validation). Analysis of the treatment strategies may be used in economic evaluation and further research.

In order to provide a picture of the cost and life expectancy of AML patients we aim at answering the following questions:

- What is the five-year survival for AML patients and what is the cost for these patients?
- Do younger patients have higher life expectancy and incur more costs than elderly patients?
- How does our findings compare to the results from the UK?

The topic opened for the possibility to use and develop more theoretical knowledge in the fields of economic evaluation, clinical pathways and modelling.

The material is based on individual data from OUS, which is a great contribution when modelling a disease, as it contains specific patient data. As far as we know, an identical study of AML treatment has not been conducted previously in Norway. In collaboration with Medical Doctor (MD) Fløisand at the Haematology ward we have identified the treatment course and the associated costs. The Cancer registry has provided register data on the number of cases in Norway, which may be used as a source of external validation.

The theoretical framework is modelling and survival analysis, as well as cost analysis. The method behind the thesis is quantitative.

Including the introduction, the thesis is divided into nine chapters. The second chapter provides information about the background of the disease and treatment strategies. The third chapter is about modelling clinical pathways and applicable theories, which is data types, disease analytic modelling, survival analysis, cost perspectives and uncertainty. The fourth chapter provides the method behind the model including our model, transitions in the model, life expectancy and costs. The fifth chapter explains different validation methods appropriate for the thesis. The sixth chapter describes the material and involves the data set, estimations and cost data. The seventh chapter provides results of the probabilistic sensitivity analysis, the comparison between Norway and the UK and validation of the study. The eight chapter contains the main findings, general discussion, strengths and weaknesses as well as future research. The ninth and final chapter presents the conclusion of the thesis.

## **1.1 Co-writing the thesis**

The thesis has been written in cooperation of two students and we were part of both the writing of the theory, methods, analysis and conclusion. The carrying-out of the project was done together. Beate Bjørnstad was mainly responsible for the analysis in Stata and Alette Glasø Skifjeld prepared the data for analysis.

Both of us have helped out each other, meaning that none of the parts was done completely individually. There have been discussions on every topic throughout the process and both have been involved in decision-making regarding what to include and how to conduct the analysis.

## 2 Background

Leukaemia is characterized by a growth of abnormal leukocytes (white blood cells) in the bone marrow. The disease may develop when an abnormal blood cell, which has the ability to self-renewal and growth advantage compared to normal cells, creates a leukemic clone. The leukemic clone may establish itself if a patient has congenital or acquired failure in the immunological monitoring. This clone does not necessarily grow more exponentially than normal cells. However, it will have a greater tendency to continue dividing itself and a less tendency to differentiate and perish. A leukemic clone will gradually differentiate and grow to the point where it has displaced other cells in the bone marrow, and the disruption further spreads to the blood system (Gedde-Dahl & Tjønnfjord, 2012).

### 2.1 Risk factors

AML is not usually related to life style. However, certain chemical exposure (such as smoking) are related to AML (American Cancer Society, 2015). Further, the American Cancer Society (2015) states that long-term exposure of high levels of benzene (used in the rubber industry, oil refineries, some glues, cleaning products and so on) can be a risk factor. The exposure of certain chemotherapies can also be a cause (and this leads to secondary cases of AML). Survivors of high-dose radiation exposure, such as atomic bomb blast or nuclear reactor accident, have a great increased risk of developing AML. Some blood diseases may also increase the risk. Lastly, some genetic syndromes and chromosome problems seems to increase the risk of AML. Family history is also a risk factor, in addition to older age and the male gender (American Cancer Society, 2015).

### 2.2 Incidence

Leukaemia is divided into acute and chronic form, where two sub groups belong to acute leukaemia; acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML). These must not be mixed up as they are different forms of cancer and have different survival and treatment regimes. Among the adult patients who get the acute form of leukaemia, 80 per cent will get AML while 20 per cent will get ALL (Gedde-Dahl & Tjønnfjord, 2012). Another significant factor regarding the disease is whether it is a primary or secondary case (Fløisand, 2015). The secondary type is a reaction of other forms of cancer and therapies.

This second type is more difficult to treat, as it tends to be more aggressive. Patients suffering from primary case of AML (meaning that that the cancer occurred unrelated to other diseases) are more likely to respond to treatment (Fløisand, 2015).

The graph (Figure 1) illustrates the cases of AML “Akutt myeloisk leukemi” and ALL “Akutt lymfatisk leukemic”, in addition to the two different forms of chronic leukaemia. The X-axis represents age, while the Y-axis is the number of cases. The graph is collected from the Store medisinskse leksikon (2015).

antall tilfeller

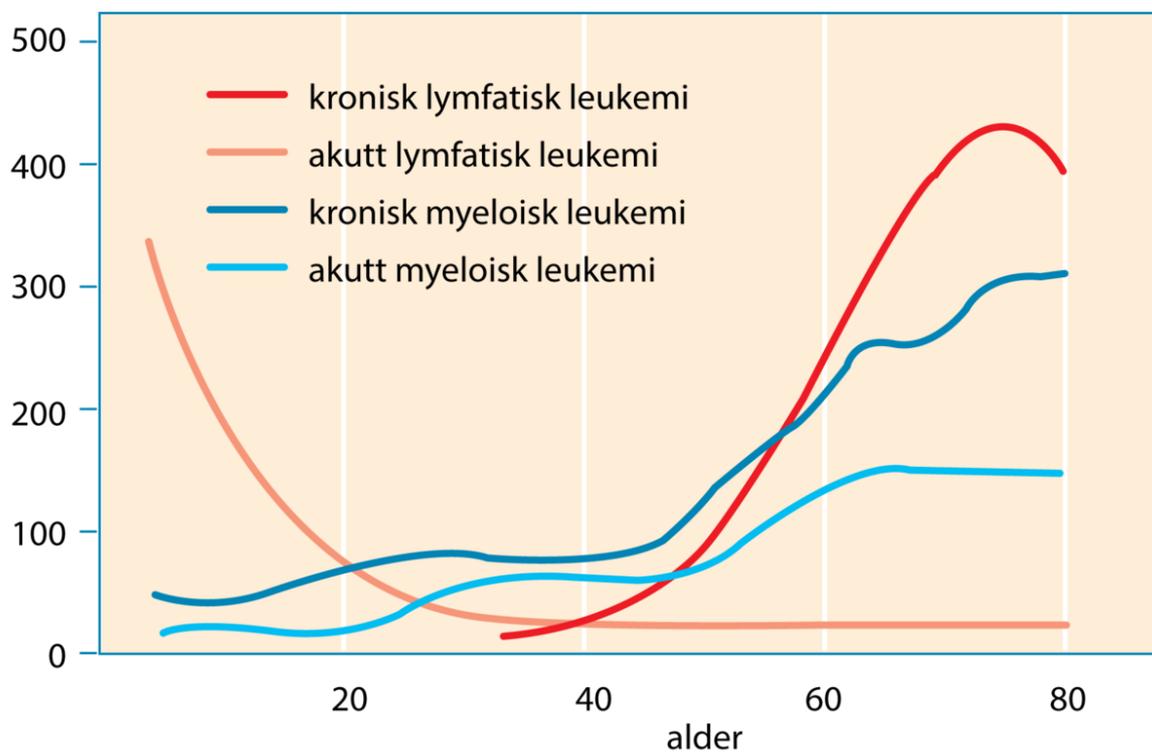


Figure 1 - Leukaemia cases in relation to age (incidence)

Incidence is defined as the proportion of people who develop a disease (or event) during a specific period of time (Hunink et al., 2001). By dividing the number of new cases on the number in the population one gets a measure of the incidence.

AML occurs at all ages but is most common in adults. The incidence has an exponential increase in individuals aged over 40 years (Pallister & Watson, 2011). This is also illustrated in Figure 2. 15 per cent of the children who suffer from leukaemia experience AML. The

disease is similar to the disease in adults; however, it can be difficult to treat (Kreftforeningen, 2015).

Table 1 - New cases (incidence) per year (average)

Number of new cases in Norway, UK and Europe	
No. of patients (%) in the population	
Norway	0.0029%
UK	0.0041%
Europe	0.0025%
<i>Average</i>	<i>0.0031%</i>

Nearly one third of the adults diagnosed with leukaemia has AML, and there are about 18 300 new cases of AML every year in Europe (Pallister & Watson, 2011). There are approximately 2600 new cases of AML in UK (NHS, 2014) and 150 new cases in Norway (Dahl, 2009). In England and Wales the incidence of AML has risen by 70 per cent since 1971 in both genders. The increase can be subject to new and improved techniques for diagnosing the disease (Dahl, 2009).

The graph on the following page (Figure 2) illustrates the number of new cases in Norway from year 2000 to 2013. The average is calculated on data from these years, and might vary if more years were included. According to Dahl (2009) the average new cases in Norway is 150, whereas the average from year 2000 to 2013 is 173 (Kreftregisteret, 2015a).

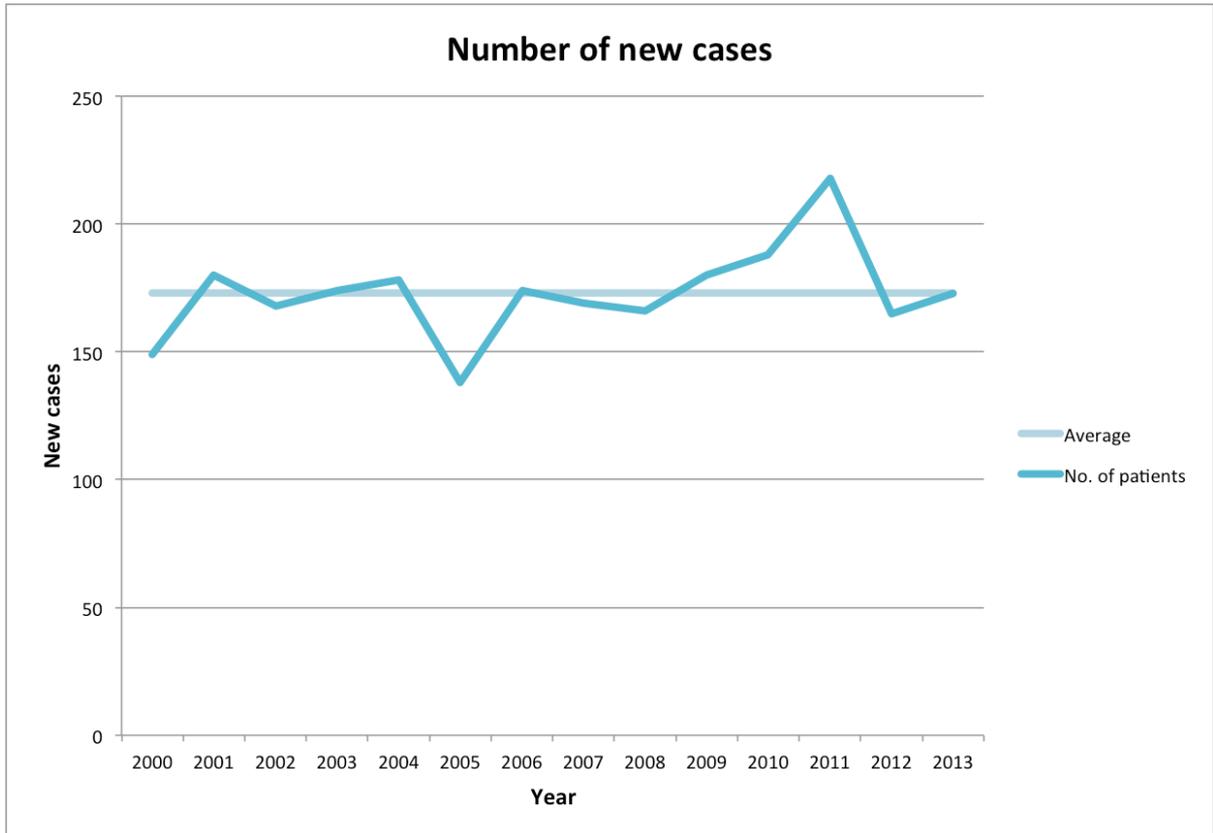


Figure 2 - New cases in Norway (Kreftregisteret, 2015a)

### 2.3 Diagnostics and symptoms

The disease typically presents itself with a short history of illness (Pallister & Watson, 2011), were the symptoms are fatigue, infections, bruising and haemorrhages, because there are no other blood cells to control the leukemic development (Blodkreftforeningen, 2015).

The Figure 3, on the following page, from Cleveland Clinic (2015) illustrates AML though (A) bone marrow aspirate and (B) bone marrow biopsy.

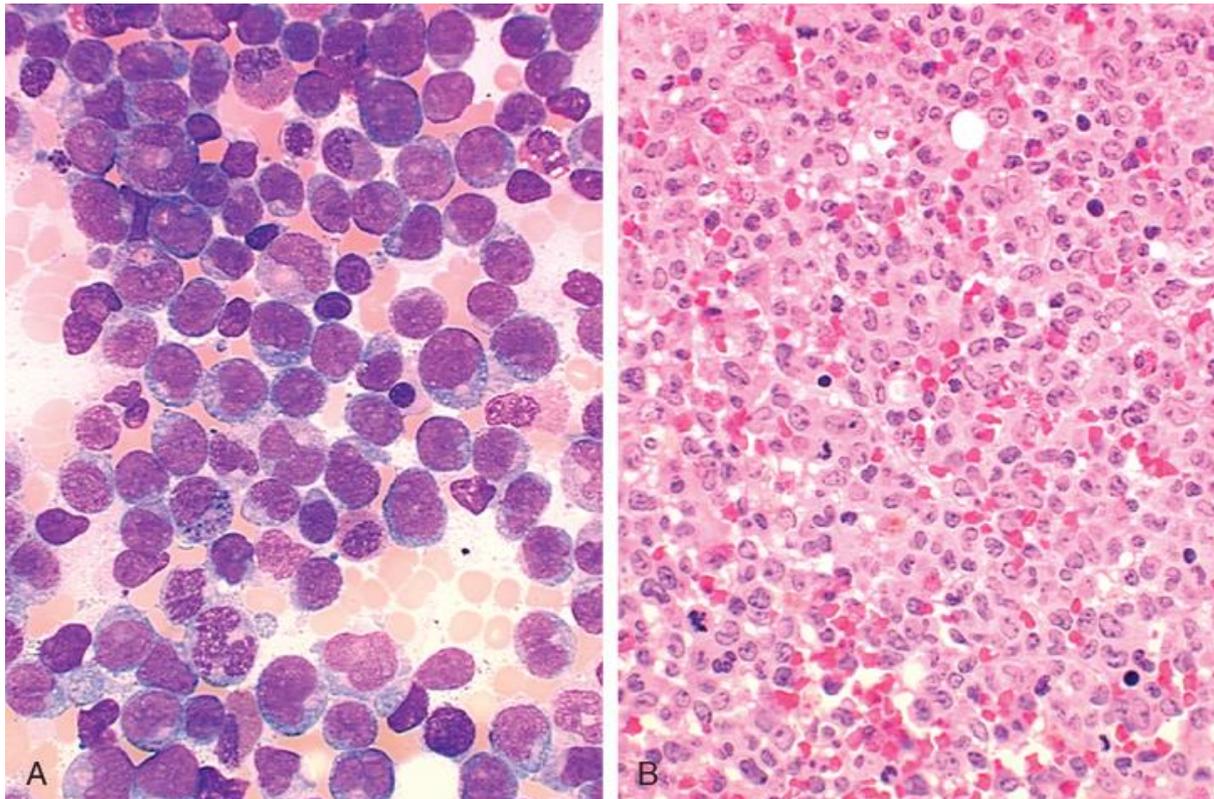


Figure 3 - Immature myeloblastic cells (microscopic) (Cleveland Clinic, 2015)

AML is a diagnosis outcome if the patient has anaemia with low haemoglobin, low number of blood platelets and too high number of white blood cells (Blodkreftforeningen, 2015). To examine whether one suffers from leukaemia one has to take blood samples as well as a bone marrow sample. The examination of the blood sample can indicate whether the patient has the disease. However, it is necessary with a test of the bone marrow in order to be certain of the diagnosis (Kreftforeningen, 2015). Nonetheless, if it is possible to see the immature myeloblastic cells under a microscope, the diagnosis is almost certain to be AML (Blodkreftforeningen, 2015). These tests are also used when undergoing treatment in order to control the effect of the treatment (Kreftforeningen, 2015).

## 2.4 Treatment

### 2.4.1 Chemotherapy and remission

The treatment is based on substantial dosages of chemotherapy and in some cases it is necessary with transplantation of hematopoietic stem cells from bone marrow or peripheral blood. The different treatments given are based on the patient's current condition. The therapies used at the Haematology ward at OUS Rikshospitalet are either a combination of

Cytarabine and Daunorubicin (Ara-C+Dauno) or Cytarabine and Idarubicin (Ara-C+Ida). These two treatments are almost identical. Some patients who have a heart condition will get other chemotherapies because Idarubicin and Daunorubicin are toxic for the heart (Fløisand, 2015).

The treatment of AML is considered potentially curative when the patient is expected to tolerate heavy chemotherapy. The treatment consists of an induction treatment followed by consolidation therapy. Stem cell transplantation is a treatment option to increase the chances of long-term survival after the patient has achieved remission (Blodkreftforeningen, 2015).

New methods are continuously being developed, and it becomes easier to treat the specific patients according to their status and molecular genetic testing.

The most important prognostic single factor for survival is whether the patients acquire complete hematologic remission (CHR). About 80 per cent of patients younger than 60 years reach remission with today's powerful cytostatic (Fløisand, 2015). The younger the patient is, the easier it is to achieve CHR. 40-50 per cent among the patients reaching remission will be alive after three years. The cytostatic treatment gives the ability to prolong a patient's life equal to the time the patient lives in CHR (Evensen & Stavem, 2008). For more than thirty years Cytarabine has been a part of almost all chemotherapy treatments in order to induce remission of AML (Dahl, 2009).

Nearly half of the patients selected by age and prognosis that enter a heavy treatment programme, are expected to have better survival, and in best case become disease free (Dahl, 2009).

After treatment, all patients who are achieving CHR will receive follow-ups in different intervals. The patients have follow-ups regularly in the first couple of months, and decreasing frequency over time. The follow-ups consist of a test to see if there are any abnormal cells in development (Fløisand, 2015).

### **2.4.2 Relapse after treatment**

The possibility of obtaining new remission with the same treatment regime after a relapse is estimated to be 30-50 per cent; with increasing results the longer the time lapsed between the start-up of new treatment and the end of first treatment. Today's recommendation is to try a new initial treatment conditioned on being over 12 months after the end of the first treatment regime. However, patients who experience relapse within the first year of treatment will rarely achieve a second remission with the initial treatment, and the prognosis is poor. If new remission is achieved, transplantation is often considered to secure remission (Kreftlex, 2015).

### **2.4.3 Side effects of treatment**

Both the use of high dosage cytostatic and stem cell transplantation induces great risk of unwanted side effects both acutely and in the long term. By unwanted effects of treatment one is referring to side effects of the disease or treatment that lasts for more than one year after the final treatment, or future health problems that probably is due to the disease or treatment (Kåresen, Wist, & Reppe, 2012).

The side effects of AML treatment are severe and may be fatal. The patient needs therefore to stay in hospital for several months under the intensive period of the treatment. Complications due to treatment can be severe and will require medications and blood transfusions.

Infections and organ failure are often seen in patients with AML. Some patients, especially elderly patients, will die of sepsis (blood poisoning) or other complications during the first months, because of the extensive chemotherapy. Medications to suppress bacteria and fungal infections given in combination with blood palates concentrates, intend to secure proper treatment (Kreftlex, 2015).

Cytostatic chemotherapy has severe side effects, since it is very difficult to tell the difference between normal and malign tissue. Additionally, the optimal dosage and individual customisation is difficult because of the pharmacokinetic variability. Some types of cytostatic drugs have effect on the DNA, and one can even become resistant against the chemotherapies used. Curative cytostatic chemotherapy is recognised by rapid treatment, high dosage intensity and often more substances combined (Kåresen et al., 2012).

Nutritional problems from the induction treatment often occur because of nausea, vomiting, sore mucosa, diarrhoea, dry mouth, constipation, and changes in smell and taste senses (Kreftlex, 2015).

Stem cell transplantation is a high-risk treatment, as 5-20 per cent of the patients die due to complications following the procedure (Fløisand, 2015). The prognosis is best for patients who suffer from chronic leukaemia (Store medisinskse leksikon, 2009).

#### **2.4.4 Palliative treatment**

Palliative care is offered to patients not responding to treatment or is unable to receive chemotherapy. Palliative care involves pain relief, psychosocial support and a closure near end of life (if possible) (Lo, Quill, & Tulsky, 1999). The patients who have terminal cancer experience many painful symptoms such as pain, anorexia, fatigue, constipation, dyspnoea and depression (Riechelmann, Krzyzanowska, O'Carroll, & Zimmermann, 2007). This gives palliative care a complex magnitude, and underlines the importance of care. The most common prescribed medications for palliative cancer treatment is opioids (such as morphine), corticosteroids (stress relief) and laxatives (increases bowel movement) (Riechelmann et al., 2007). Typically, palliative care is offered and administered in local hospitals (Fløisand, 2015).

#### **2.4.5 New methods**

All forms of cancer treatment are constantly under development, and AML is no exception. One of the most recent strategies is to investigate the impact of FLT3 (a tyrosine kinase receptor) mutations (Thiede et al., 2002). It is found to have an impact on early stem cell survival and myeloid differentiation. According to Thiede et al. (2002) the definitive goal is to be able to use this information in order to offer the more intensive treatment option, transplantation, to patients at high risk, and avoid offering this treatment to patient's with a better prognosis. AML patients displaying FLT3 aberrations are less clinically responsive. A consequence is one would want to avoid unnecessary high-risk treatment due to the possible fatale outcomes (Thiede et al., 2002).

## **2.5 Treatment facilities**

AML treatment in Norway is offered at university hospitals in each of the four Norwegian health regions, namely Oslo University Hospital, St. Olavs Hospital (Trondheim University

hospital), the University Hospital of North Norway, Haukeland University Hospital and Stavanger University Hospital (where the last two hospitals belongs to the same region). Additionally, there are some local hospitals that treat AML patients. However, these patients are old and only offered low dose chemotherapy and palliative care. Most of these patients are secondary AML cases (Fløisand, 2015).

## **2.6 Literature review**

Oria.no (The University of Oslo Library) and Google Scholar have been used to search for relevant literature. Searches were made on the topics; Acute Myeloid Leukaemia, Blood cancer, Survival analysis, Economic evaluation, Cost analysis, Decision tree, Markov models, Modelling diseases, Validation and Stem Cell Transplantation. The relevant articles found for this study is included in the thesis.

Furthermore, several books and articles on cancer treatment and blood diseases, as well as literature on economic modelling and cost analysis were found through oria.no, and creates the insight and foundation used to comprehend, analyse and model AML.

# 3 Modelling the clinical pathway

A pathway may be defined as the journey a patient follows from a given starting point, including diagnostics, treatment strategies and follow-ups, the information and staff responsibilities (Mould, Bowers, & Ghattas, 2010). An important motivation for identifying clinical pathways is to be able to estimate survival and costs for a specific disease.

There are several ways to model clinical pathways. One method is to use register data (from the Cancer Registry, Norwegian Patient Registry or other registries), while another is to use individual data, which can be found in cohorts from randomized control trials or observational studies. Registers may contain general patient data or for instance cause of death, whereas cohorts consist of specific data. Regardless of the method chosen, inclusion of both clinical outcomes and costs is possible.

This chapter includes the foundation needed in order to model clinical pathways, which comprehend register data and cohorts, decision analytic modelling (decision trees, Markov models and discrete event simulation), survival analysis and associated concepts, costs and uncertainty.

## 3.1 Register data and cohorts

The use of register data is widely recognised, but the method has both strengths and limitations. It is different from cohort studies in many ways. Firstly, register data is data from an entire population that is pre-collected and exists, and it may model both life expectancy and costs. An advantage with this type of data set is that confounders might be adjusted for the whole population. Register data could be used to model both costs and survival due to the detailed level of information, all though the data is not necessary gathered for scientific purposes. Register data has the advantage that it can be collected from different sources, which makes it heterogeneous. In essence, it is a way to refer to data that is of an unknown format and/or content. This may be an advantage in terms of selection bias and the possibility of studying rare exposure and outcome measures (Thygesen & Ersboll, 2014). A weakness of register data collected from many sources is that the researchers lack control over the data,

which it might be subject to different coding between institutions (Thygesen & Ersboll, 2014).

Potentially missing data is challenging to adjust for. Furthermore, since the data is collected on general purposes it may be difficult to make it accurate enough for specific research topics. Even though the use of register data is intensive, there are no methodological literature developed for this (Thygesen & Ersboll, 2014).

In cohort studies the researchers collect all the specifics needed, such as patient history, although these data sets might be smaller. In register data the large sample size can give great statistical power, but the size may also make register data prone to confounding. The information needed to detect this can be hidden by the fact that one is looking at variables at a point in time where the confounding variables were unimportant in regards to the question at hand (Thygesen & Ersboll, 2014).

Cohort studies monitor a group that is well defined over time in order to track the transitions going from non-cases to cases (Stata Press, 2007). This type of study can be both retrospective and prospective. If prospective, the analysis of the study is done alongside the intervention. A retrospective viewpoint will then be performed after the intervention is completed. A cohort study is relevant when assessing effects of harmful exposures. It can also be used to generalize a broader population (Sorlie & Wei, 2011). Furthermore, Sorlie and Wei (2011) claims that cohort studies can gather detailed data which reflects current clinical practices.

One may model register data or cohorts, but we will focus on modelling by the use of individual data. Decision analytic models are normally analysed with the use of cohort studies (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005).

## **3.2 Decision analytic modelling**

A model is a simplified representation of reality, which may be a great communication tool. It allows the complexity of a system to be reduced to its essential elements (Caro, Briggs, Siebert, & Kuntz, 2012). This implies that a model may present valuable information to inform decision makers on questions about medical decisions and how to allocate resources.

The appropriate way of building a model is to start by understanding the problem that is represented. It is important to understand the health care process or decision that is to be made, and conceptualize the problem at hand. The model should represent the components of the problem by using a particular analytic method (Roberts et al., 2012). This is possible through a decision tree and/or a Markov model. A model gives flexibility and can easily be modified if changes are needed, as it is future oriented and could be adapted in many ways (Briggs, Claxton, & Sculpher, 2006).

Figure 4 illustrates the components of conceptualizing a model.

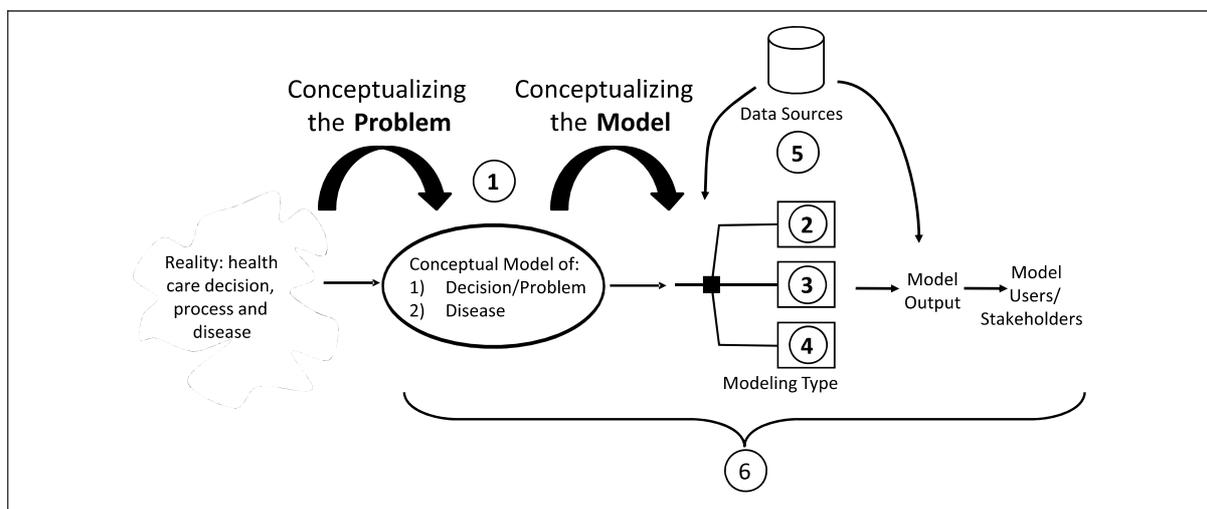


Figure 4 - Conceptualizing a model (Roberts et al., 2012)

A decision tree is used to estimate the proportion of patients from the cohort who ends up in different states (Briggs et al., 2006). Further, the objective of the Markov models is to estimate the survival and cost for the cohort depending on how the patients move between states (Briggs et al., 2006). This means that in the model the movement between states are ignored and all individuals in one state is considered homogenous (Briggs et al., 2006). The length of a cycle in a Markov model is defined by the modeller, and can be adjusted to correspond to different diseases.

### 3.2.1 Decision trees

Decision trees has gained increased popularity in economic evaluation (Drummond et al., 2005). A decision tree has the initial decision on the left side and flows to the right with chance nodes depicted in the tree. The outcomes are given of previous probabilities in the

tree (Drummond et al., 2005). The transition probabilities and the different cost for each branch can be multiplied and hence be used in evaluation. When building a decision tree one have to investigate whether the events occurs more than once and whether the probabilities are constant over time (Drummond et al., 2005). A decision tree is useful in order to provide a visual overview of the alternatives. Besides, it is used to calculate the probability of ending up in the different end points, and this probability is referred to as expected values. The pathways in the decision tree are mutually exclusive sequences of events (Briggs et al., 2006). Accounting for time is not possible with decision trees. This may lead to difficulties when implementing models that are time dependent and models that are observing longer time periods. A decision tree that contains many branches can become complex. Hence, it may be difficult to model complicated long-term diseases, especially chronic diseases, since decision trees does not take adverse events into consideration, as one can only move in one direction in the three (Drummond et al., 2005).

### **3.2.2 Markov models**

Markov models are a form of a recurring decision tree. It is possible to combine Markov models and decision trees in certain evaluations (Briggs et al., 2006). Markov models are based on a series of “states” that a patient can move to at a particular point in time. The cost for each cycle can be calculated and incorporated in the model. The probability of moving to another state is independent of earlier transitions (Drummond et al., 2005). State independency may be difficult to come around when you have previous states that might determine the probability of future outcome, and the model can become too simplified. To avoid this oversimplification of the model it is possible to add additional states to the model that may take this into consideration (Drummond et al., 2005).

The Markov model is entirely defined by the probability distribution between the states and the individual probabilities (Sonnenberg & Beck, 1993). The probability can change over time as the patient gets older or as the risk of disease is transformed. In Markov models one can have absorbing states, defined by the fact that a patient cannot leave that state. In modelling diseases, death is an example of an absorbing health state since it is only possible to enter, and not leave, this state (Sonnenberg & Beck, 1993). Muenning (2008) argues that when modelling cancer patients, the use of Markov models can incorporate the changes in

health states over time such as patient recovery or relapse. Further, he says that there is a risk that these patients can remain sick over a longer time period.

Figure 5 illustrates how a cohort is transitioning between states, from the initial state to the final absorbing state (Sonnenberg & Beck, 1993).

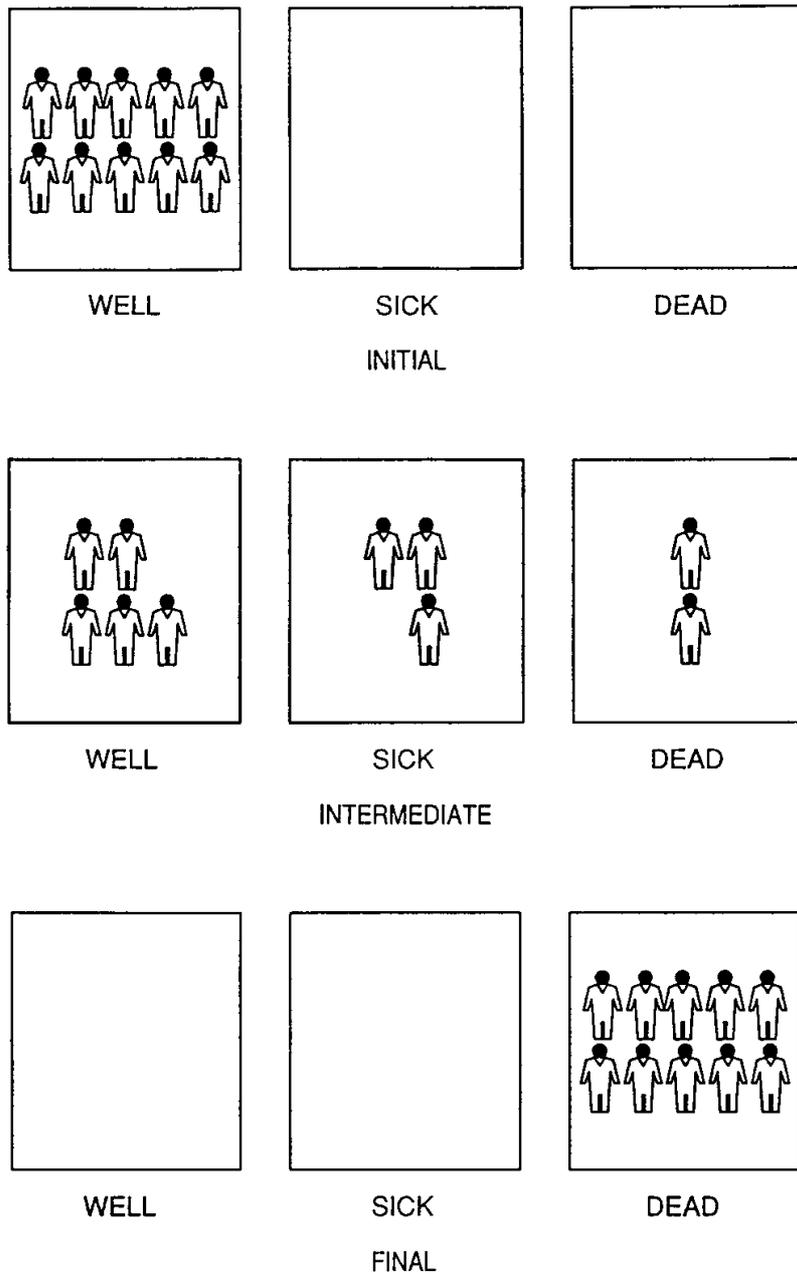


Figure 5 - Transitions in a Markov model (Sonnenberg & Beck, 1993)

In a Markov model one assumes there is no memory of where an individual was before it moved to a particular state. This is called “The Markov Assumption” (Briggs et al., 2006).

The Markov assumption has three assumptions. The first assumption is population homogeneity, which means that all individuals in the study will have the same transition rates. The second assumption is called “First-order Markov”, meaning that regardless of past history, individuals in the model have the same transition probability. The last assumption is that transition rates remains constant over time (Shorrocks, 1976). Increasing the number of states and decreasing the cycle length may account for the Markov assumption. When creating a Markov model, adjusting the number of cycles is possible to fit the development of the disease. A cycle length can vary between everything from days to years (Muennig, 2007).

In order to include time-dependency in the model, different transition probabilities are assigned to the different cycles. This means the transition probability will vary as the cohort ages (Briggs et al., 2006). Time-dependency means that the time spent in a particular cycle is important for the transition from that state. In cancer treatment, a patient in remission may have a higher probability of remaining in remission over time; hence the transition probability out of that state may decrease over time. This concept is known as tunnel states (Briggs et al., 2006).

Half-cycle correction is integrated in Markov models in order to adjust for the fact that individuals can experience the event at different times in each cycle (within the individual cycle). A half-cycle correction may be conducted in order to smoothen out the area under the curve that reflects the expected survival. An uncorrected Markov model can either lead to over- or underestimation. Under-estimation means that one are counting the cohorts membership at the end of each cycle, while over-estimation means that one are counting the membership at the beginning of each cycle. A half-cycle correction will therefore count the cohort at the middle of each cycle (Sonnenberg & Beck, 1993).

### **3.2.3 Discrete-event simulation**

Discrete-event simulation (DES) is an alternative model to the Markov model. The difference is that DES is designed to investigate how long an individual will stay in a state, rather than how this individual will move to another state (Briggs et al., 2006). In a DES model, individuals experience an event at any discrete point in time after the previous event. In contrast to the analysis of a Markov model, the analysis of a DES model is generated by the occurrence of an event, where the model explores at what and when the next event for an

individual occur (Karnon, 2003). Contradictory to Markov models and decision trees, where these models assume independence between individuals, DES will account for interactions between individuals (Barton, Bryan, & Robinson, 2004). Both Markov models and DES models are a way of simulation, where DES allows for more complicated models. Despite the flexibility of a DES model, it is more comprehensive to perform because of the requirement of more specific model characteristics (Karnon, 2003).

Disease analytic models are possible to use when analysing survival. However, it is important to choose one method that corresponds well with the data set.

### **3.3 Survival analysis**

Survival analysis attempts to answer how many individuals in a population will survival past a certain time. This is useful when modelling diseases and investigating the time perspective of a disease course.

Today, survival analysis is widely used in several aspects of society. It is used by scientists to analyse time until onset of disease, time until stock market crash, time until failure of equipment, time until an earthquake and so on. In the field of medicine it is commonly used to analyse disease, recovery, relapse and death (Singh & Mukhopadhyay, 2011). Events such as these are often referred to as failures (Cleves, Gould, Gutierrez, & Marchenko, 2008). Examples of failure are time to a heart attack for a specific patient group, time to remission for a particular cancer patient group, and time to death from a heart transplant. This makes survival analysis a useful tool in clinical research to provide valuable information about an intervention (Singh & Mukhopadhyay, 2011).

Survival analysis is typically used when we have some sort of longitudinal study, e.g. a trial or cohort study, which records the time to event for each patient. This can be analysed through the relationship between a transition probability and time, which may be explicitly estimated from patient-level data (Briggs et al., 2006).

The understanding between rates and probabilities is particularly important because survival models employ hazard rates, while Markov models employ probabilities (Briggs et al., 2006).

### **3.3.1 Spell data**

Spell data is survival data representing a fixed period that contains an onset time, failure and censoring time, as well as an end time in addition to other measurements taken during that specific period (Stata Press, 2007). The concept of censoring will be discussed in the next section (3.3.3 Censoring).

In these types of data set one has calendar dates for all events. In order to transform the calendar dates to duration (time in remission, time in relapse, time in transplantation etcetera) one has to start with the first calendar date (January) and set this to zero. February will be one, March three, and so on. When all dates are transformed into duration, it is possible to analyse time to failure, which is referred to as “time-variables”.

### **3.3.2 Censoring**

The key feature of survival analysis is the handling of censoring that often occurs in follow-up studies. When an individual is censored it means that it is not observed for the whole analysis period (Cleves et al., 2008). This means that if an individual was diagnosed in 2011, within a five-year perspective, and there are no observations on failure, such as transplantation, relapse or death, it should be censored because we do not have enough observations on this individual. In essence, when an individual enters late in the chosen time-span, and it is impossible to observe any events, the individual must be censored. There are several types of censoring whereas right censoring is more common. Right censoring implies that the failure events has not yet occurred by the end of the chosen perspective, or some might have been lost to follow-up (Cleves et al., 2008).

In Figure 6, the concept of right censoring is visualised. The time period is five years, from 2000 to 2004. Five individuals enter the observational period at different times within a time period of five years. Individual 1 enters at time zero and has an event at year five. This means that this individual has an observed event during the observational period. Similarly, individual 3 has an event between 2001 and 2002, and is recorded as a failure. Individual 2 enter at time zero and have an observed event past year 2004, which is beyond the time period. Event though individual 2 has an event; it will be accounted for as survived. Individual 4 is censored, due to short observational time, and no events are observed. Individual 5 has no observed events though out the time period and is recorded as survived.

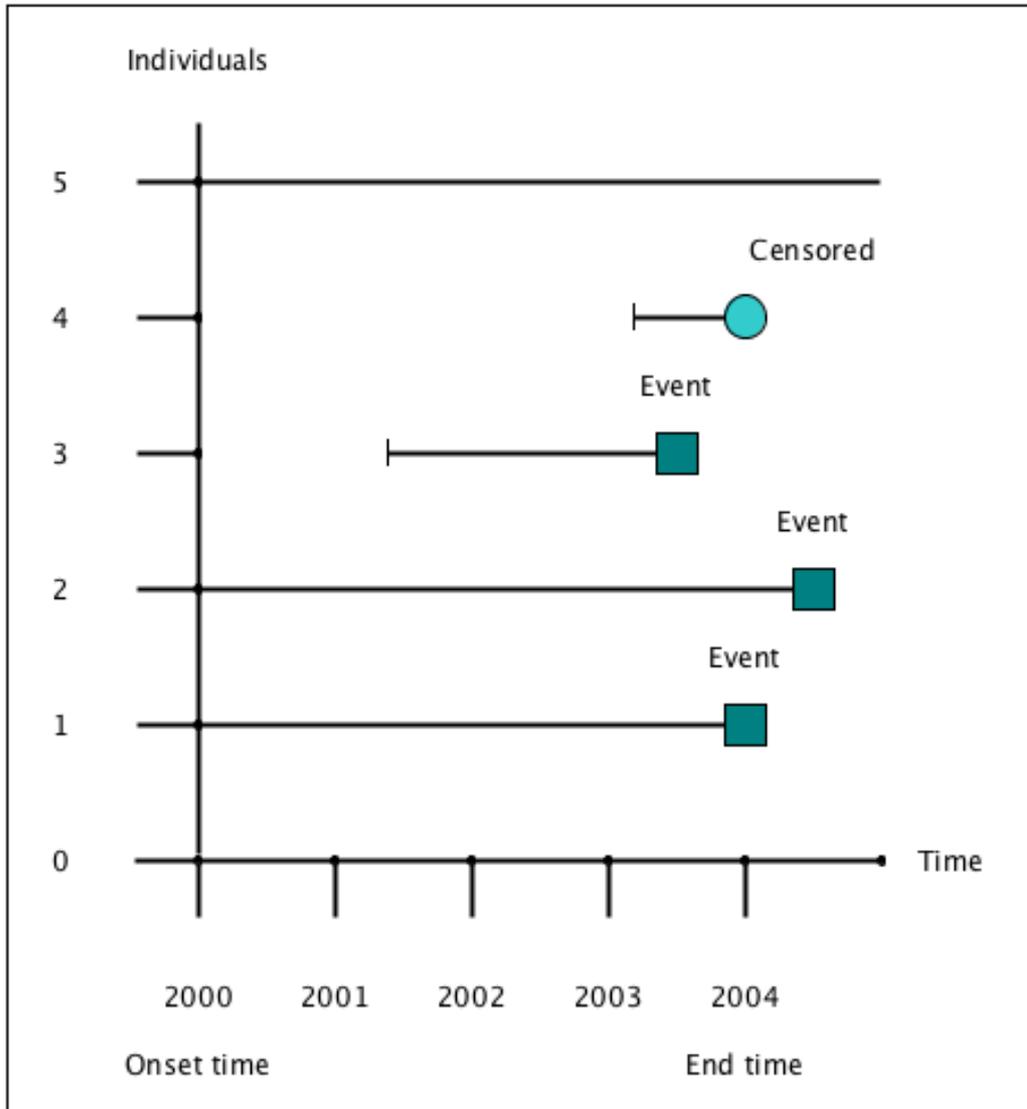


Figure 6 - Right censoring

### 3.3.3 Important concepts of survival analysis

To be able to derive transition probabilities in a survival analysis, it is important to know the concepts around survival analysis. The probability density function (pdf) for survival data,  $f(t)$ , with an associated cumulative density function, gives the cumulative probability of failure up to time  $t$  (Briggs et al., 2006):

$$F(t) = P(T \leq t) \quad [1]$$

The survival function can be rewritten as the complement of the pdf-function (Briggs et al., 2006):

$$S(t) = P(T > t) = 1 - F(t) \quad [2]$$

Equation [2] defines the proportion alive at time  $t$ , where  $P$  is the probability of surviving for a period of time greater than  $t$ . From equation [2] we can relate  $F(t)$  to  $S(t)$  (Briggs et al., 2006):

$$f(t) = \frac{dF(t)}{dt} = \frac{d(1 - S(t))}{dt} = -S'(t) \quad [3]$$

From equation [3] we can derive the hazard function, which is the instantaneous rate of failure at time  $t$ , conditional on having survived up to time  $t$  (Briggs et al., 2006):

$$h(t) = \frac{f(t)}{S(t)} \quad [4]$$

The cumulative hazard function is defined as (Briggs et al., 2006):

$$H(t) = \int_0^t \frac{f(u)}{S(u)} du \quad [5]$$

It is important to note that the probability of failure up to time  $t$ , which is given by  $F(t)$ , is not the same as the cumulative hazard up to time  $t$ . By using the results of equation [3] and the standard rule of calculus, it could be written as the survival function in terms of the cumulative hazard (Briggs et al., 2006):

$$S(t) = \exp\{-H(t)\} \quad [6]$$

Equation [6] is central to deriving transition probabilities for Markov models.

### 3.3.4 Different regression models

There are several ways of estimating survival. The Kaplan-Meier estimator is a nonparametric estimator of the survival function  $S(t)$ , which estimates censoring and failures in the data set (Cleves et al., 2008). When estimating survival, The Cox proportional model, the Weibull model and the Exponential model are all popular methods. The Cox proportional

hazard model is a regression method that provides an estimate of the hazard ratio and its confidence interval. It is considered “semi parametric” because it does not require a specification of the baseline hazard function. The model assumes that the hazard ratio of two individuals is time-independent, and it is only valid for time-independent covariates. This means that if an individual has twice the risk of death, compared to another individual, the risk of death over time remains twice as high (Singh & Mukhopadhyay, 2011).

Parametric regression, such as the Weibull model, is able to handle problems of time-varying covariates, delayed entries, gaps and right censoring. Parametric estimation is appropriate when you have an idea of how the baseline hazard looks like. The Weibull model allows the hazard to grow (or decrease), and it also gives better estimates when the estimated cumulative hazard is increasing at an increasing rate (Cleves et al., 2008).

The Exponential model is the simplest model to use because of the assumption of a constant baseline hazard (Cleves et al., 2008). Exponential models are useful when solving problems involving population changes. When a change in a quantity over a period of time occurs at a pace that is proportional to the quantity size, the exponential model is useful in looking at growth or degeneration (Newbold, Carlson, & Thorne, 2013).

### **Strengths and limitations**

Because of the constant baseline hazard in the exponential model, the model lack memory of the failure process. In other words, the failure rate is independent of time (Cleves et al., 2008) The limitation of the Cox proportional hazard model is that it does not specify how the risk of an event will change over time (the hazard function). Hence, it is not useful when looking at time-dependency in a Markov model (Briggs et al., 2006). However, in the Cox model the magnitude of the time variables does not matter, rather, the purpose of the model is to determine who is to be compared to whom (Cleves et al., 2008).

The Weibull model is advantageous when modelling time dependency (Briggs et al., 2006), and has the ability to provide reasonably precise failure analysis with extremely small samples (Abernethy, 2006). In modelling cancer treatment, it is common to use the Weibull model (Nadler & Zurbenko, 2013). Since time plays an important role in Weibull, adding risk to the time variables will change the accumulated risk (Cleves et al., 2008).

### 3.3.5 Parametric regression using Weibull

Formula of the Weibull distribution and the corresponding hazard function and survival function are as follows (Briggs et al., 2006):

$$f(t) = \lambda p t^{p-1} \exp\{-\lambda t^p\} \quad [7]$$

$$h(t) = \lambda p t^{p-1} \quad [8]$$

$$S(t) = \exp\{-\lambda t^p\} \quad [9]$$

The shape parameter  $p$  (Gamma) is the parameter estimated from the data, which determines the shape of the hazard function, while the scale parameter  $\lambda$  (Lambda) gives the scale of the distribution. The hazard rate will fall over time when the shape parameter  $p$  is between 0 and 1. The distribution of this model is able to provide a variety of monotonically increasing or decreasing shapes of the hazard function, and their shape is determined by  $p$ . When  $p = 1$ , the hazard is constant (horizontal line) so the model reduces to the Exponential model (Cleves et al., 2008).

Figure 7 illustrates the different shapes the time-dependent hazard rates can yield. This figure is drawn based on fig. 3.2 (p.54) in Briggs et al. (2006)

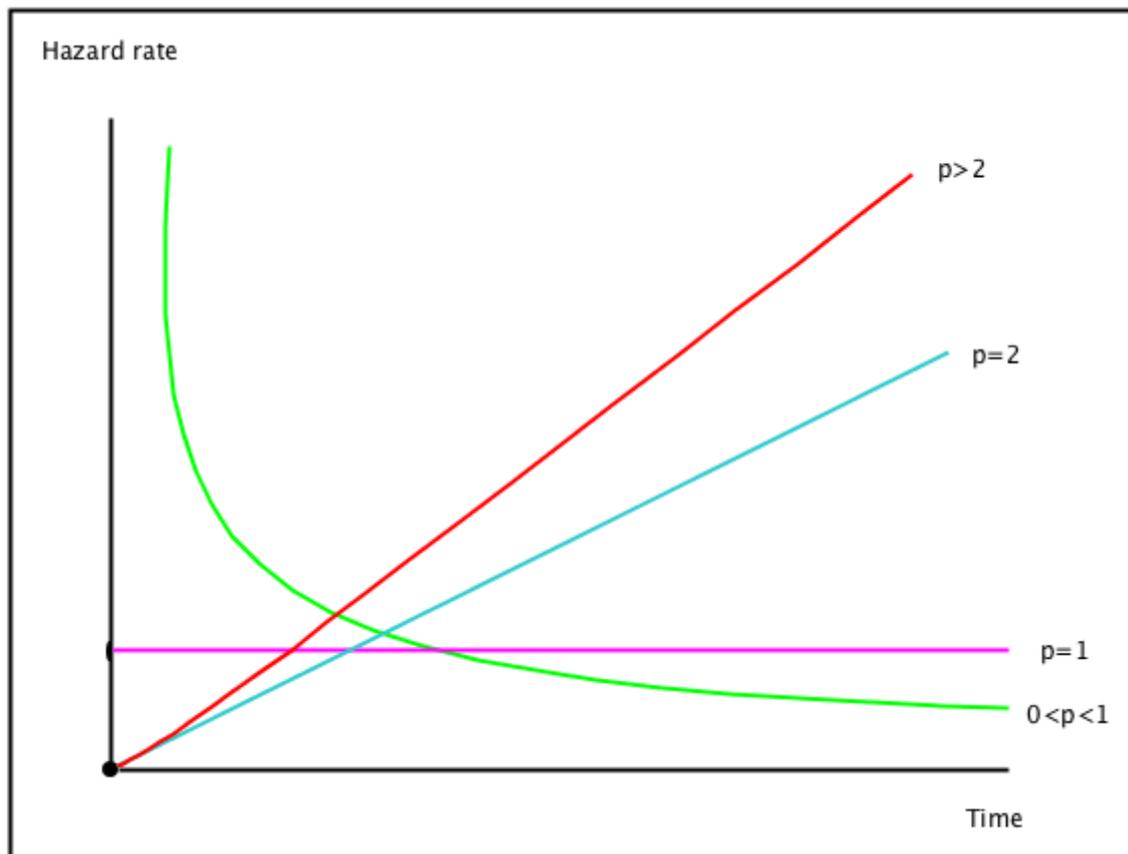


Figure 7 - Different shapes of hazard rates

### 3.3.6 Survival analysis in Stata

We used the statistical program Stata to calculate the transition probabilities, incorporation of correlations between parameters, and correlations between estimates, in order to analyse survival.

To perform survival analysis in Stata one has to use the *stset* command. This command declares the data to be *st* data, which informs Stata of the key variables and what role they play in the survival analysis (Stata Press, 2007). The purpose of this is to make Stata describe when an observation is included and excluded and what defines the start of risk and failure (Cleves et al., 2008). The entry and exit time indicate when a subject is first and last under observation (Stata Press, 2007). The entry and exit time is recorded in time units. If there are only one record per individual, the case of failure or no failure, the data is a single-record data. Stata is detecting who is censored when we declare which variable is the time-variable and which variable is the failure/no-failure variable (Stata Press, 2007).

When the data is *stset*, Stata creates three new “response” variables corresponding to the data set. These new variables are *t<sub>0</sub>*, *t*, *d*. *t<sub>0</sub>* marks the beginning of the time span, *t* marks the end of the time span and *d* indicates failure (denoted as 1), censoring and no failure (denoted as 0). These variables are based on the information in the data set and generate an indicator variable (*\_st*) that records whether the observations are relevant to the analysis. This means that by executing the command *stset* we are ensured that the data we are analysing use the same response variables. All other *st* commands, such as regression, that are performed after *stset* work with the variables Stata generated, rather than the original variables in the data set (Cleves et al., 2008).

When the data is declared as survival-data, the command *streg* can be used to look at the likelihood estimation for parametric regression survival-time. (Stata Press, 2007).

Using the command *streg*, with different options for which model you want to use, fits parametric models. In Stata *ln\_p*, *p* and *1/p* are three parameterizations of *p*. The first parameterization represents the metric in which the model is actually fit. When estimating in this metric, we are assured of obtaining an estimate of *p* that is positive, and the estimation of *p* is obtained by transforming *ln(p)* post estimation. The third parameterization is given so that one may compare these results with those of other researchers who commonly choose to parameterize the shape in this manner (Cleves et al., 2008)

*stcurve* can be used after fitting a Weibull model. We use this command to plot the fitted survival, hazard and the cumulative hazard functions. *stcurve* evaluates the fitted model at each time in the data, both censored and uncensored, and computes the means of the covariates. This means that the resulted curve is the experienced survival of a subject with a covariate pattern equal to that of the average covariate pattern in the study (Stata Press, 2007).

The command *matrix list e(b)* will give us the coefficients from the regression analysis, while *matrix list e(V)* gives us the covariance matrix. This is used to calculate the hazard functions in Excel (Cleves et al., 2008).

See the complete do-file from Stata in Appendix N.

### 3.4 Cost

According to Drummond et al. (2005), economic evaluation is a comparative tool when looking at alternative courses in terms of their costs and consequences.

in economic evaluation it is common to use either the health care provider or the societal perspective (Frick, 2009). Undertaking the social perspective would need all costs including transport, involvement of family members, sick leave and so on (Drummond et al., 2005). From the perspective of the health care provider one only need the cost associated with the treatment strategies. Most evaluations has a narrow perspective and the focus is on the relevant costs based on the background of the study (Drummond, Weatherly, & Ferguson, 2008)

Identification, quantification and valuation of costs are an important aspect of economic evaluation. Identifying costs means that one has to define the target population in order to detect the appropriate resource use. The clinical pathway of the population can be used in order to obtain this information of resource use. Quantification of costs relates to the amount of resources used by the target population, which may be acquired by specialists (expert opinion), registries and guidelines. Valuation refers to the collection of price weights from the target population experiences, which is multiplied by the resource use. One way to assess price weights is by using administrative data, such as billing records (Glick, 2007).

Cost analysis may be used to compare the cost of relative effectiveness between different strategies. As found in an article by Lawson, Drummond, and Bishop (1981), the most cost-effective methods for the given health care provider might depend on the already existing facilities. If one conduct a cost analysis one must decide on how precise the cost estimates shall be. At a micro-costing level one are including the cost for the doctors and nurses, as well as operating costs, equipment, blood products and pharmaceuticals. At a case-mix level one looks at the cost for each hospital patient and takes length of stay into account. A micro-costing level and a case-mix level are most precise in estimating costs. The detail level of each case is determining the level of precision. If one uses the disease-specific per diem or average per diem level one only looks at averages. These are the least precise cost estimates (Drummond et al., 2005).

### 3.4.1 Net health-care costs

Based on Weinstein and Stason (1977) the following expression can be used to calculate the net health-care costs of a clinical pathway:

$$C = \sum_{k=1}^h q_k c_k \quad [10]$$

$C$  = Total health-care costs

$h$  = Health care service

$k$  = Health care service  $k$ , where  $k=1, \dots, h$

$c_k$  = Includes all direct medical and health-care cost (hospitalization, physician, medication, laboratory, counseling and other ancillary services) and all health-care costs associated with the adverse side effects of treatment,  $k$ .

$q_k$  = Refers to the quantity of resources used in relation to treatment,  $k$ .

## 3.5 Uncertainty

Uncertainty as a concept is important in evaluation, because uncertainty is usually in all ways of modelling and in the input parameters. It is therefore important to understand how to deal with uncertainty (Briggs et al., 2006).

According to Briggs et al. (2006) there are four key concepts in understanding uncertainty and heterogeneity in decision modelling. These can be divided into variability, parameter uncertainty, decision uncertainty and heterogeneity.

Variability refers to the difference between patients, which, for instance, can be differences in experienced clinical event, response rate or treatment strategies. According to Briggs et al. (2006) this variability cannot be adjusted for through the collection of additional data. This will not be discussed further. Parameter uncertainty refers to the precision of the estimation of an input parameter, for instance, a probability or a mean cost that is entered into a model.

In principle, this uncertainty can be reduced through collecting additional evidence. Decision uncertainty refers to the uncertainty when making a decision about your findings. Since parameters can be uncertain, one should take precautions when making a decision based on your findings. Heterogeneity refers to a form of variability, where patient characteristics may differ (Briggs et al., 2006).

By applying a probabilistic or deterministic sensitivity analysis we can deal with parameter uncertainty (Briggs et al., 2006). Examples of deterministic sensitivity analysis are one-way and multiway sensitivity analysis. In a one-way sensitivity analysis the estimates for each parameter are varied one at a time to see how this will change the results, for instance expected values. In a multiway sensitivity analysis, the estimate for more than one parameter varies within a specific range. In a probabilistic sensitivity analysis (PSA), distributions are added to the probability parameters. The uncertainty in the probability parameters would be characterized by the distributions. A second stage of PSA is to undertake a Monte Carlo simulation. Monte Carlo simulations calculate expected values a multiple number of times, where each simulation is drawing from a random draw from each of the input parameter distributions. The outcome is a large set of expected costs and effects that reflect the combined parameter uncertainty in the model (Drummond et al., 2005)

In a decision tree with two options, a beta distribution will be appropriate for reducing the uncertainty because it bounds between zero and one, while a decision tree with three or more branches would need a Dirichlet distribution (Drummond et al., 2005). When estimating uncertainty in costs a gamma distribution is appropriate, since it is constrained on the interval between zero and positive infinity (Briggs et al., 2006).

### **3.5.1 Cholesky decomposition**

Once regression is estimated, the calculation of the transition probability as a function of the patient characteristics is possible. By doing this, we are assured an adjustment for uncertainty. The reason for using the Cholesky decomposition is that it is a way of controlling for uncertainty in the covariates between estimates, where the covariate is a variable that can affect the relationship between an independent and dependent variable. Estimating the variance of the linear predictor from the covariance matrix directly is also possible. However, it is important to note that this approach is not appropriate for survival

models with more than one parameter. When incorporating the Cholesky decomposition we ensure that the  $\lambda$  (lambda) and  $p$  (gamma) parameters are appropriately correlated on the log scale. This will reduce the uncertainty in the estimated transition probabilities (Briggs et al., 2006).

The Cholesky decomposition is a lower triangular matrix of the variance-covariance matrix (where all cells above the leading diagonal are zero). This variance-covariance matrix is easily obtained from a standard regression model. One can call the variance-covariance matrix  $\mathbf{V}$  and the Cholesky decomposition matrix  $\mathbf{T}$ , such that  $\mathbf{T}$  multiplied by its transpose gives the matrix  $\mathbf{V}$ . In this way, we can regard the matrix  $\mathbf{T}$  as the square root of matrix  $\mathbf{V}$  (Briggs et al., 2006). Constructing the correlation matrix is important because even though some parameters do not have a strong relationship there might be strong relationships within the set of parameters, especially between the regression constant and the other parameters (Briggs et al., 2006).

From the variance-covariance matrix we can calculate a vector of correlated variables, vector  $\mathbf{x}$ . To start, we generate a vector ( $\mathbf{z}$ ) of independent standard normal variates and apply the formula:  $\mathbf{x} = \mathbf{y} + \mathbf{Tz}$ , where  $\mathbf{y}$  is the vector of parameter mean values. If we have two correlating variables, the starting point is to write down the general form for a Cholesky matrix,  $\mathbf{T}$ , and multiply this matrix by its transpose to get a  $2 \times 2$  matrix. Further, this matrix can be set equal to the variance-covariance matrix (Briggs et al., 2006):

$$\begin{pmatrix} a & 0 \\ b & c \end{pmatrix} \begin{pmatrix} a & b \\ 0 & c \end{pmatrix} = \begin{pmatrix} a^2 & ab \\ ab & b^2 + c^2 \end{pmatrix} = \begin{pmatrix} \text{var}(x_1) & \text{cov}(x_1, x_2) \\ \rho \text{se}(x_1) \text{se}(x_2) & \text{var}(x_2) \end{pmatrix} \quad [11]$$

When we have a known variance-covariance matrix it is easy to solve the unknown  $a$ ,  $b$  and  $c$  components of the Cholesky decomposition matrix for the known variance and covariance (Cholesky) (Briggs et al., 2006):

$$\begin{aligned} \begin{pmatrix} a & 0 \\ b & c \end{pmatrix} &= \begin{pmatrix} \sqrt{\text{var}(x_1)} & 0 \\ \frac{\text{cov}(x_1, x_2)}{a} & \sqrt{\text{var}(x_2) - b^2} \end{pmatrix} \\ &= \begin{pmatrix} \text{se}(x_1) & 0 \\ \rho \cdot \text{se}(x_1) & \sqrt{1 - \rho^2} \cdot \text{se}(x_2) \end{pmatrix} \end{aligned} \quad [12]$$

To generate correlated random variables we need to use the original Cholesky expression;  $\mathbf{x} = \mathbf{y} + \mathbf{Tz}$  (Briggs et al., 2006):

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} a & 0 \\ b & c \end{pmatrix} \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} \quad [13]$$

where  $\mu$  is the expected value,  $x$  are the correlated variables, the matrix  $a$ ,  $b$ ,  $c$  and  $0$  is the Cholesky decomposition matrix and  $z$  is the vector of independent standard normal variates. Multiplying this equation out gives the adjusted coefficients (Briggs et al., 2006):

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu_1 + a \cdot z_1 \\ \mu_2 + b \cdot z_1 + c \cdot z_2 \end{pmatrix} \quad [14]$$

Then we can substitute  $a$ ,  $b$ , and  $c$  for what we defined previously (Briggs et al., 2006):

$$\begin{pmatrix} x_1 \\ x_2 \end{pmatrix} = \begin{pmatrix} \mu_1 + se(x_1) \cdot z_1 \\ \mu_2 + \rho \cdot se(x_2) \cdot z_1 + \sqrt{1 - \rho^2} \cdot se(x_2) \cdot z_2 \end{pmatrix} \quad [15]$$

The first random variable will require the mean and standard error. The second random variable will require mean and standard error given by the associated parameter's mean and standard error. Through the shared component of variance  $z_1$ , the correlation is introduced in proportion to the overall correlation (Briggs et al., 2006).

Having executing these steps, we can insert a distribution and a random variable to make the transition probabilities probabilistic. This creates vectors of standard normal variates ( $\mathbf{z}$ ). The next step is to enter the solutions from the Cholesky decomposition matrix and multiply this by the vector of standard normal variates ( $\mathbf{Tz}$ ). Further; we need to add the estimated mean values from the regression to  $\mathbf{Tz}$ . This will create a vector of multivariate normal parameters that are correlated according to the estimated covariance matrix,  $\mathbf{mu} + \mathbf{Tz}$ . The  $\mathbf{mu} + \mathbf{Tz}$  make up the coefficient in the survival analysis for baseline hazard. The  $\mathbf{mu}$  is extracted from the regression coefficients (Briggs et al., 2006).

# 4 Method

## 4.1 The model

### 4.1.1 Overview

For the AML patients the clinical pathway involves longer periods at the hospital due to intensive chemotherapy treatment and a high infection rate. The patients do not necessarily respond equally and a complete standardisation of the model could be difficult. Almost all patients receive an induction treatment. The decision tree and the Markov models in this thesis can be looked at as the clinical strategy for this patient group. The reason for combining a decision tree and Markov models is because of the clinical picture. The decision tree is structured to simulate the short-term survival and costs until response (remission) was achieved, while the Markov models are investigating the long-term effects. The time horizon is five years, while the cycle length is one month.

In this chapter we will explain the structure of the model, and the details of calculating transition probabilities and costs.

Figure 8 is a visual illustration of the movements along the branches of the decision tree (induction treatment), and how the patients are moved over in the Markov models. Further, it visualizes the movement in and between the Markov models. A complete view of our decision tree can be found in Appendix L, and additionally screen-prints of the Markov models Transplant, Palliative and A1 (young) are found in Appendix A, B and C. The patients move from the tree to the respective Markov models according to their response on induction treatment. The decision tree and the Markov models will be presented separately, as they represent two different ways of modelling. In our Markov models the cycle length is one month because this is the most suitable time interval for AML.

The sections describing the induction treatment and the further transactions (Markov models) below are referring to the different labels and text in Figure 8.

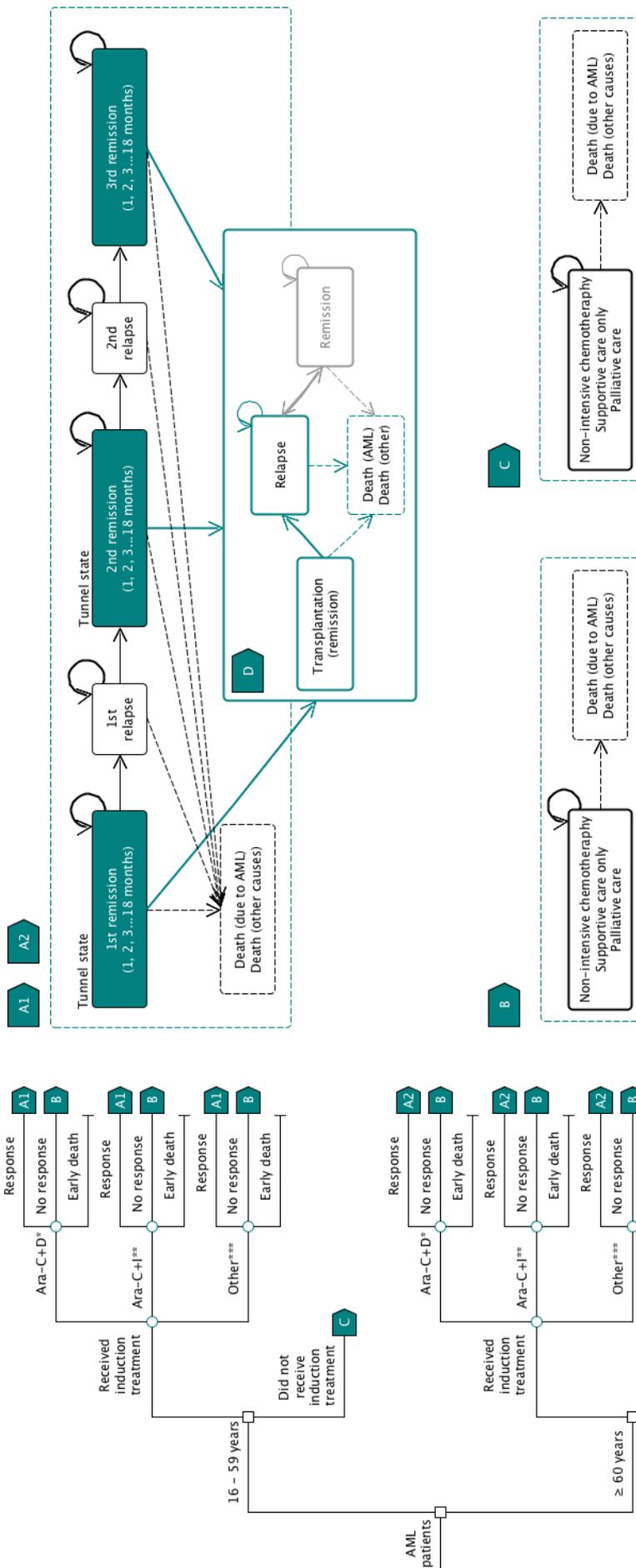


Figure 8 - Decision tree and Markov models

### **4.1.2 Induction treatment (decision tree)**

The model is based on a decision tree that estimates the probabilities of having response, no response, no induction treatment and early death. The beginning of the tree is made out of branches and different nodes. In the model the entire group of AML patients start at the same point, a starting point that is recognized by a squared box. The squared box indicates that there are two alternative options (Briggs et al., 2006). In the model this is where the patients are divided into groups according to age. The age groups are 16-59 years and 60 years and older. The second point in the tree is also a squared node and this defines those who receive induction treatment and those who receives palliative care only. This is similar for both of the age groups.

The branch for those who does not receive treatment has no more options, and a box “C” illustrates the end point. The box “C” is used to indicate which Markov model the patients who did not receive treatment are entering. Among those who receive induction treatment there are three new branches and the chance node is circular. This circle is used to indicate when there are more than two options, and where the probability of receiving a specific treatment is uncertain for the individual patients (Briggs et al., 2006).

For both of the patient groups “Ara-C+D”, “Ara-C+I” and “Other” indicate the three branches that follow the circular node. All of these treatments are different forms of chemotherapy. Ara-C+D and Ara-C+I are treatment options representing today’s practice, and are very alike. The third option “Other” is a less heavy form of chemotherapy which is given to patients with for example heart conditions. All of these branches end up in a new circular node where the three new branches are “Response”, “No response” and “Early death”. These three options are also similar for all of the treatment branches. For the young patient group the end point of “Response” is shown as a box “A1” and “No response” is shown as “B”. “Response” in the older patient group is shown as a box “A2” and “No response” is shown as a box “B”. Response is equal to achieving remission.

The branch “Early death” is a terminal state and ends in the tree. This means that the patient’s whom ends up there do not continue over in on of the Markov models. These endpoints are the same for both groups.

In the case of AML, independent of age group, the patients either ends up in the branches “Response” (Markov model A1 young and Markov model A2 elderly), “No response” (Markov model B for both age groups), “Did not receive (Markov model C for both age groups)” or “Early death”.

### **4.1.3 Treatment after induction (Markov models)**

To know which patients who enter the Markov models, and where they enter the models, the expected values of the decision tree are used. If the patient’s belongs to “A1” or “A2” they will enter the Markov model A1/A2 (young/elderly) in the box called “1<sup>st</sup> remission”. This state has several possible transitions, which is indicated by the arrows in the model. The arrow that loops the different states indicates that it is possible to remain in the state (tunnel state).

From “1<sup>st</sup> remission” it is possible to move to the states “1<sup>st</sup> relapse”, “Death” and to a new health state, transplant “Markov model D” which is a model capturing patients receiving transplantation. From relapse the patients can either stay, move to remission or die. Second and third remission has the same structure as first remission, in terms of possible pathways. Patient who ends up in “No response”, or “Did not receive induction treatment” from the decision tree enters the respective Markov models “B” or “C” (palliative care). In these models patients can either remain in the state or die.

The Markov model “D” (transplantation) capture, as already mentioned, the patients who receives transplantation. Patients can only receive transplantation if the patients are in remission and hence the arrows that point to this model comes from “1<sup>st</sup> remission”, “2<sup>nd</sup> remission” and “3<sup>rd</sup> remission”, in Markov models A1/A2. From the state “Transplantation” you can either stay, which is the opted alternative, or move to “Relapse or “Death”. The patient is not moving to any state called remission, rather it is recovering from the transplantation and remains in remission. The state identified as “Remission”, which is coloured in grey, is not included in our analysis. This is because we do not have any patients who achieve remission after relapse in our data set. However, it is technically possible to move to this state. If we had any patients in this state they could either stay in that state or move to “Relapse” or “Death”. This means that similar to the A1/A2 model, the patients can move from a remission to a relapse and in to a new remission state.

Patients cannot move in other directions than the arrows indicate, and they cannot move between the different Markov models, except to the model D, transplantation. The Markov models are based on monthly cycles and all states are mutually exclusive.

## 4.2 Transitions in the model

There are five separate Markov models in this study and there are calculated transition probabilities for every possible event and cycle. The probabilities are time-dependent, which means that they change for every cycle.

### 4.2.1 Transitions in tunnels

Tunnel states in a Markov model enable integration of health experiences from the previous cycles (Sato & Zouain, 2010). Incorporating heterogeneity and simultaneously estimating survival and cost according to age groups, is possible by using tunnels (Joranger et al., 2015). The word “tunnel” indicates that the patients can only move in a pre-determined order (Sato & Zouain, 2010).

Based on the structure of Joranger et al. (2014), the transition probabilities are defined as:

$$tp_{t,a}^{f,s} = tp_{\text{time in tunnel}, \text{age}}^{\text{from}, \text{to}} \quad [16]$$

f = the health state from which the patient was moving

s = the health state to which the patient was moving

t = number of months (time) the patient has been in the tunnel

t = 1, 2...60

t = 0, the patient had not entered a tunnel, but was in one of the treatment states

a = the age of the patient leaving a health state

For the purpose of transparency Table 2, 3, 4, and 5 shows a small extraction of Markov model A1 (young, first remission), A1 (young, first relapse and second remission), D (transplant), and C (palliative care) as performed in Excel. All remission states in all models are tunnel states, in addition to the non-curative care in model B and C, meaning they are time-dependent. The tunnels states are extracted for 18 months, from cycle zero to cycle 18. Cycle 19 to cycle 60 were given a mean transition probability for every tenth cycle. It was

assumed that individuals could transition to transplantation in all cycles in all remission states. The transition probabilities in all models are calculated by employing Equation [16].

Table 2 - Transitions in Markov model A1 (young) – first remission

Cycle	First remission (Months)			
	0	1	2	3
0	$tp_{0,0}^{Response, Rem}$			
1		$tp_{0,1}^{Rem, Rem}$ $-tp_{0,1}^{Rem, Rel}$ $-tp_{0,1}^{Rem, Trans}$ $-tp_{0,1}^{Rem, Death}$		
2			$tp_{1,2}^{Rem, Rem}$ $-tp_{1,2}^{Rem, Rel}$ $-tp_{1,2}^{Rem, Trans}$ $-tp_{1,2}^{Rem, Death}$	
3				$tp_{2,3}^{Rem, Rem}$ $-tp_{2,3}^{Rem, Rel}$ $-tp_{2,3}^{Rem, Trans}$ $-tp_{2,3}^{Rem, Death}$

Cycle 0 in Table 2 picks up the patients who ended up in the branches labelled “A1” (young) in the decision tree. In cycle 1 the cell picks up the information from cycle 0 and the amount of people who leaves remission during the first cycle. The probability of leaving first remission in cycle 0 or any other cycle is calculated by those who stay in remission subtracted by the sum of those who leave from remission to relapse, transplantation and death. The probability of staying and leaving remission is calculated similarly for all cycles in first remission, except that the probabilities take account of the time in first remission, meaning they are time-dependent.

Table 3 - Transition probabilities in Markov model A1 (young) - relapse

Cycle	First relapse	Second remission (Months)		
		0	1	2
<b>0</b>				
<b>1</b>	$tp^{Rel, Rel}_{0,1}$			
<b>2</b>	$tp^{Rel, Rel}_{1,2}$ $+tp^{Rem, Rel}_{1,2}$ $-tp^{Rel, Death}_{1,2}$	$tp^{Rel, 2Rem}_{1,2}$		
<b>3</b>	$tp^{Rel, Rel}_{2,3}$ $+tp^{Rem, Rel}_{2,3}$ $-tp^{Rel, Death}_{2,3}$	$tp^{Rel, 2Rem}_{2,3}$	$tp^{2Rem, 2Rem}_{2,3}$ $-tp^{2Rem, 2Rel}_{2,3}$ $-tp^{2Rem, Trans}_{2,3}$ $-tp^{2Rem, Death}_{2,3}$	

Table 3 shows both the first relapse and the beginning of the second remission. In cycle 0 there are no patients because it is impossible to both enter the model in cycle 0 in first remission and at the same time enter relapse. The patients, who enter relapse, enter in cycle 1 from first remission. In cycle 2 the patients who stay in relapse are added from the previous cycle with those who left the first remission, and the patients who leave relapse to death is subtracted from the previous cycle. In next column, denoted as 1, the patients enter second remission in cycle 2. Patients who enter cycle 2 are those who enter second remission from first relapse. In our data set it is calculated as one minus those who stay in relapse. Cycle 3 in second remission add those who stay in second remission from previous cycle, and subtract it with those who leave second remission to second relapse, transplantation and death in previous cycle. The cycles in second remission are tunnel stats that are extracted for 18 months.

Second relapse is calculated in the same way as first relapse. However, we had to use the same transition probabilities as first relapse, because we did not have enough data to calculate the estimates. We also had to make simplifications for the transition probabilities in third

remission for the same reason as in second relapse. We assumed that the transition probabilities for second remission were the same as in third remission. Nevertheless, there are not many patients who experience a third remission; therefore the probabilities will have little impact on the results.

The last state is death. This adds the probability of dying in each cycle in all states. It is made cumulative by adding those who died in previous state.

Model A2 (elderly) is calculated by using the same method as in A1 (young), described above. However, those entering model A2 are entering from response in the decision tree, for the older patient group. The transition probabilities in this model are adjusted for age by using the mean age of the older patients. See Appendix H and Appendix I for precise calculations.

Table 4 - Transitions in Markov model D - Transplantation

Cycle	Transplantation/remission (Months)			
	0	1	2	3
0				
1	$tp^{1Rem,Trans}_{0,1}$			
2	$tp^{1Rem,Trans}_{1,2}$	$tp^{Trans,Trans}_{1,2}$ $-tp^{Trans,Rel}_{1,2}$ $-tp^{Trans,Death}_{1,2}$		
3	$tp^{1Rem,Trans}_{2,3}$ $+tp^{2Rem,Trans}_{2,3}$	$tp^{Trans,Trans}_{2,3}$ $-tp^{Trans,Rel}_{2,3}$ $-tp^{Trans,Death}_{2,3}$	$tp^{Trans,Trans}_{2,3}$ $-tp^{Trans,Rel}_{2,3}$ $-tp^{Trans,Death}_{2,3}$	

Table 4 shows the model D (transplantation). It displays those in the cohort who enter from first, second and third remission in model A1 and A2. In cycle 0 there are no patients due to the fact that they do not enter this model until cycle 1. Those who leave second remission

from cycle 2 enter model D (transplantation) in cycle 3, while those who leave third remission from cycle 3 to transplantation enter in cycle 4.

In cycle 2, patients who stay in transplantation (remission) are added from the previous cycle (1) and subtracted with those who leave to relapse and death from transplantation (remission). This formula is consequent throughout the model and similar to the other models, the transition probabilities are in relation to the respective cycles. If one enters relapse in this model you can either stay in this state or die. The state “death” is calculated by adding those who dies in transplantation/remission and relapse. Transplantation/remission is a tunnel state that is extracted for 18 months.

Table 5 - Transitions in Markov model C – Did not receive induction treatment

Cycle	No induction treatment (Months)			
	0	1	2	3
0	$tp^{No\ treatment, Palli}$ 0,0			
1		$tp^{Palli, Palli}$ 0,1 $-tp^{Palli, Death}$ 0,1		
2			$tp^{Palli, Palli}$ 1,2 $-tp^{Palli, Death}$ 1,2	
3				$tp^{Palli, Palli}$ 2,3 $-tp^{Palli, Death}$ 2,3

Table 5 shows those who did not receive any treatment in the decision tree (“no induction treatment”). We assumed that the patients enter the Markov model C (“Palliative care”) directly. The first cycle is referring to those who enter from the decision tree, both young and elderly patients. In this model there are only two options: stay in palliative care or death. Therefore, cycle 1 is those who enter the model in previous cycle subtracted by those who leave palliative care, meaning death.

Model B “No response” has the exact same construction as model C “Palliative” (no induction treatment). However, the transition probabilities are different, and the first cycle imports the individuals from the “No response” branch in the decision tree. For both model B and C the transition probabilities are time-dependent and tunnel states, and extracted for 18 months.

#### 4.2.2 Time-independent transition probabilities

For all cohorts that are not sufficiently large, time-dependent transition probabilities are difficult to calculate. Instead one may use time-independent transition probabilities. Moving from a one-year to a one-month cycle length involves more than dividing the transition probability by 12 (Briggs et al., 2006). The formula for calculating an instantaneous event rate, if we assume 100 patients are followed up for five years, where 20 of those patients had a particular event, will be (Briggs et al., 2006):

$$Rate = - \frac{[\ln(1 - 0,2)]}{5} \quad [17]$$

The one-month probability of the event is (Briggs et al., 2006):

$$= 1 - \exp(-rate * (1/12)) \quad [18]$$

where the rate is referring to the instantaneous event rate found in Equation [17].

### 4.3 Life expectancy

Calculating life expectancy will illustrate how long an average patient live after the date of the AML diagnosis. It is also possible to estimate the life expectancy according to age group and for the different Markov models. To calculate this, we added the proportion alive in each cycle, across all cycles, and over all models (Briggs et al., 2006). This was done for all Markov models, separately. We also looked at the total life expectancy for all models (decision tree and Markov models) combined.

## 4.4 Cost

The respective costs are multiplied by the respective cycle probability for each model. This gives us an average cost per patient. Costs are added up in each model and discounted with a discount rate of 3.5 per cent. The costs reflect the resource use for the patient group at OUS. We have included both fixed costs and variable costs for medications.

Based on Drummond et al. (2005) the discount factor is:

$$c/(1 + r)^n \quad [19]$$

where  $n$  is the year of discount,  $r$  is the discount rate and  $c$  is the cost we want to discount.

### 4.4.1 Costs in the decision tree

When implementing costs in a decision tree one uses a combination of the expected values and the calculated cost for each branch. This means that the expected costs are based on the sum of the pathway cost multiplied with the pathway probabilities (Briggs et al., 2006). The costs that incur in the tree are cost of diagnosis and induction treatment (including length of stay and medicaments), and in some cases intensive care.

### 4.4.2 Costs in the Markov models

To implement costs in a Markov model one multiplies the monthly or annually cost (depending on the cycle length) associated with the different states with the probability of being in each state. In other words, one adds the cost of each state weighed by the proportion in the state and then adds across cycles (Briggs et al., 2006). If one conducts this in Excel, a column can be made in the end of the Markov model where one adds up each of the cycle probabilities multiplied with each associated cost across the rows. The overall expected cost can be found by adding the expected cost of every cycle (Drummond et al., 2005). In the Markov models the costs that are included is chemotherapy, consolidation therapy, transplantation, palliative care and follow-up, each according to the model the individuals belong to. Patients can also receive treatment at the intensive care unit.

The costs are included at a case-mix costing level which means that we have data on the mean quantity of resources and the cost of these (Frick, 2009). The hospital cost are in direct

allocation with the Haematology ward and do not include interaction with other wards, with exception of the intensive care ward and palliative care treatment.

## **4.5 Important simplifications of the model**

All models are a simplification of the real picture (Drummond et al., 2005). In order to make the model as accurate as possible one must make some decisions on what to include and not according to what is appropriate. Table 6 is a summary of the features of the model.

We will discuss the simplifications of this model in the Discussion chapter, but a short summarization of what factors is omitted is given below:

- Only patients from one hospital
- The patients are divided into two groups which means that it is not completely age specific
- The time frame is five years, which means that patients who has more than two relapses falls out of the model
- The probability from second remission to second relapse and second remission to death in model A1(young) and A2 (elderly), and relapse to death in transplant is simplified
- QALY is not included
- Molecular genetic testing is not included all though it can be used in order to avoid unnecessary transplantations
- The interval for follow-ups is average estimates
- The amount of patients and costs of those who receives treatment at the intensive care ward is based on expert opinion. The estimate is five per cent of the patients
- The amount of people who achieve remission after relapse in the transplantation model is not included

Table 6 - Overview of the model features

Features of the model	
Main issues	Description
Objective	To estimate five-year survival and expected costs for AML patients
Type of model	Combined decision tree and Markov models
Type of evaluation	Survival and cost analysis
Perspective	Health care provider
Patient group	AML patients aged 16 years and older at OUS
Time horizon	5 years
Outcome	5-year survival and treatment costs
Unit costs	Costs from the Haematology ward, costs from the Blood bank, estimates and wage rates
VAT	Not included
Year of costs	2014
Discount rate (costs)	3.5%
Sensitivity analysis	PSA

# 5 Validation

Validation is an important part of doing research. One has to investigate how reliable the research actually is. Validity is the power of an instrument to measure what it is supposed to predict (Kumar, 2011). The information can be used to support decision makers when determining the applicability of the results (Eddy et al., 2012).

Validation cannot be a general specification for all models. Rather, it has to be conducted according to particular applications, since models can have different levels of validity for different uses. For instance, when examining how an intervention will increase or decrease its costs, the need for accuracy is less important. To answer specific questions on how much an intervention will cost, accuracy is highly important (Eddy et al., 2012).

## 5.1 Internal validation

Internal validation is testing the model (Steyerberg, 2009). The method controls that the model has been applied correctly and that the mathematical calculations and the coding is correct (Eddy et al., 2012). A way to control the research's internal validation is by explaining the code to others and search for mistakes. Further Eddy et al. (2012) suggests sensitivity analysis, trace analysis and extreme value analysis to control for errors.

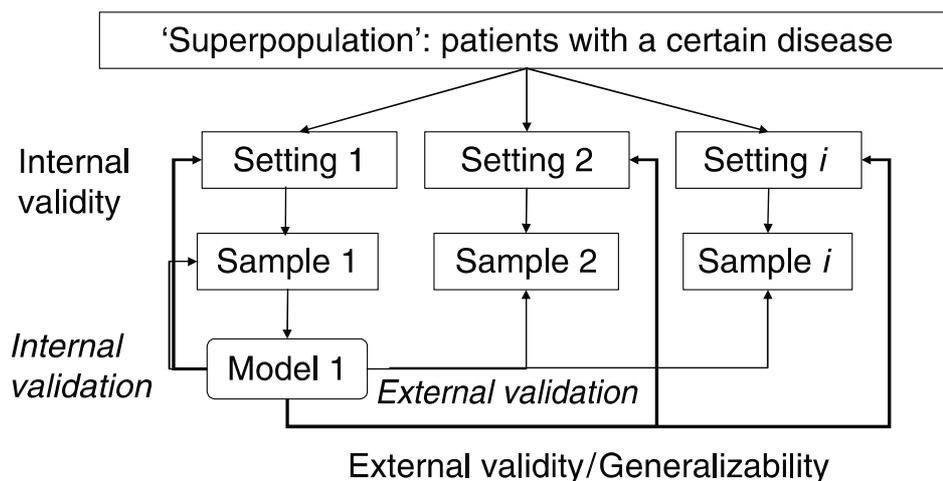


Figure 9 - Internal and external validation (Steyerberg, 2009)

Figure 9 illustrates both internal and external validation.

## **5.2 External validation**

External validation simulates events that have occurred (e.g. clinical trials) and examine how well the results correspond to real data (Eddy et al., 2012). This type of validation can be used to measure several outcomes including disease incidence and progression. The three main steps of conducting an external validation is; 1. Identifying the data sources, 2. Do the simulation, and 3. Compare the results. This type of validation tests the model's capacity to calculate actual results, and should be used in parts of the study that is covered by data sources. It can be difficult to assess external validation for costs and resource use, as cost units can vary greatly across settings (Eddy et al., 2012).

## **5.3 Face validation**

A criterion for face validation is that people who have expertise in the field judge the model. Further, the researchers must provide supporting evidence and information about the model (Eddy et al., 2012). The role of the expert is to ensure that that the results make sense (Weinstein et al., 2003). A strength of face validation is that it helps to ensure that the researchers have followed the current medical practises and the best available support material (Eddy et al., 2012). Eddy et al. (2012) also identify three limitations of face validity; firstly, it is unrealistic that patients move between states at fixed time intervals. Second, the medical evidence can be out-dated or misinterpreted and finally, the results can be manipulated to fit the wanted outcome if there are biased stakeholders.

## **5.4 Cross-validation**

When comparing a study to similar studies and looking for similar results one is doing a cross-validation. Comparing across models and controlling that the results are similar, increases the confidence of the results (Eddy et al., 2012). If there is a high degree of dependency between the models the cross-validation becomes less valuable (Eddy et al., 2012).

## **5.5 Transparency**

The purpose of transparency is to make it easier for the reader to understand the non-quantitative description of the model. Transparency gives a better foundation for readers who

want to evaluate the study at a higher level of both in mathematical and programming detail (Eddy et al., 2012).

## **5.6 Predictive forecast**

The role of predictive forecast as a form of validation is not as important as the other forms previously mentioned. Nevertheless, this validation type controls the models ability of making accurate predictions of future outcome (Weinstein et al., 2003). Eventually one compares the predicted outcomes with the actual outcome (Eddy et al., 2012).

# 6 Material

## 6.1 Ethical issues

Ethical issues in medical research involve protecting human property. In a article by Rafiquddin (2006) it is stated that: “All research involving human subjects should be conducted in accordance with three basic principles (a) Respect to persons (b) Beneficence (c) Justice”. This refers to respect to autonomy and persons with reduced autonomy, to maximize benefits and minimize harms and lastly, to treat people according to what is morally right. In this thesis we have been concerned with anonymization of the data and using only data needed in order to construct the models. This does not involve any harm or moral issues in regards to the patients. We have been in contact with the Section of Information Safety and Privacy at OUS and followed the guidelines regarding anonymization and de-identification.

## 6.2 Data set

Below is a flow chart (Figure 10) to illustrate the processes behind the data set application. It is made in order for the reader to easily follow the steps behind data set process.

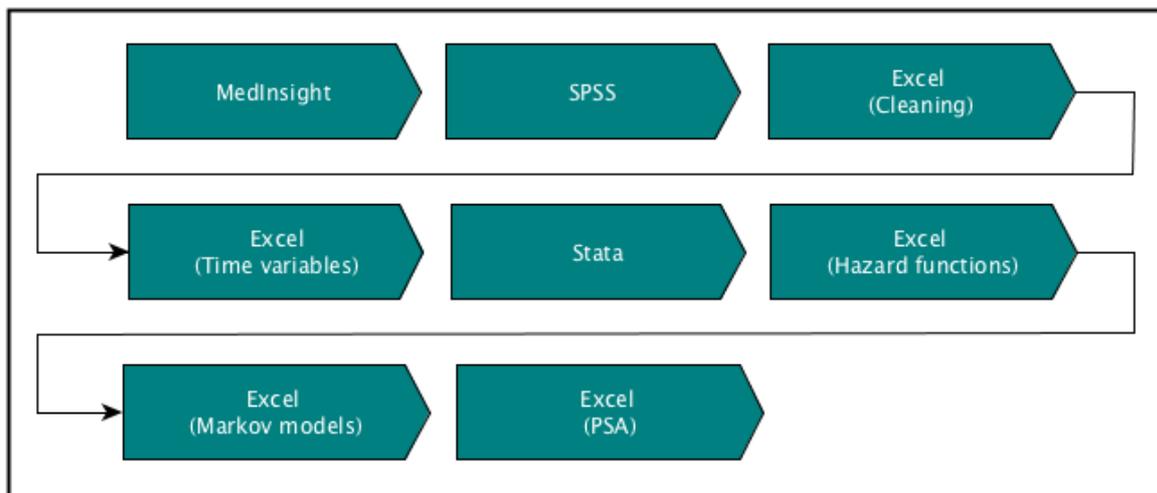


Figure 10 - Flow chart (data set)

MD Fløisand at OUS subtracted the data set from MedInsight and sensitive patient information was removed. The data was delivered in a SPSS file enabling us to read the different value labels (see Appendix G for a detailed view). The data was “cleaned” in Excel

by which we mean that unnecessary information (in terms of what we did not need in the analysis) was removed. For example, both patients with ALL and AML was received in the original SPSS file, whereas we only needed AML data. The original SPSS data set contained information from year 2000 to 2015. A few patients from 2015 were omitted based on the fact that there were so new that no remission, relapse or transplantation was registered on them. When removing patients who were diagnosed in 2015 and those suffering from ALL, we were left with a total of 307 patients in the data set. After the “cleaning of the data” we sorted the data in the order we preferred. MedInsight generates a patient number, which enabled to keep control of the patient’s events when pasting the SPSS information into new Excel sheets, before importing the data into Stata.

The variables we used from the MedInsight extraction can be seen in Table 7 on the following page.

Table 7 - Data set variables from SPSS

Variables from the MedInsight extraction		
Variables	(In english)	Definition
Patientid	(patient ID)	A number generated by MedInsight when the data was extracted and is not the true patient ID
Date_of_birth	(date of birth)	All dates that refer to the date the patient entered the described states and the values are listed as day, month and year (MM.DD.YYYY)
Dato_diagnose	(date of diagnosis)	
Dato_for_evt._komplett_remisjon	(date of first complete remission)	
Dato_for_transplantasjon	(date of transplantation)	
Residiv_dato	(date of first relapse)	
Ny_remisjon_dato	(date of second remission)	
Death_date	(date of death)	
Diagnose	(diagnosis)	Refers to whether it is AML (valued as 1) or ALL (valued as 2). All of the patients who had ALL were deleted from the data set in Excel.
Primær_sekundaer_leukemi	(primary or secondary case of AML)	Has a value between 1 and 5 where all values between 2 and 5 is secondary cases
Induksjonstype_for_AML	(induction type for AML)	Has 3 values where 1 is "Ara-C+Daunorubicin", 2 is "Ara-C+Idarubicin" and 3 is "Other cytostatic regimes". The two first treatments are almost the same, and the last one is a milder form which is given to patients who has for example a heart condition.
Ble_KR_totalt_sett_oppnaadd	(was complete remission reached)	Is either yes (value 1 and 2) or no (value 3)
Allogen_beinmargstransplantasjon	(allogeneic bone marrow transplantation)	Has only a yes (valued 1) and a no (valued 2) option. This refers to whether the patient receives transplantation from others or their own stem cells
Transplantasjon_utfoert	(transplantation performed)	Refers to if the patients has full conditioning (value 1) or reduced conditioning (value 2).
Sykdomsstadium_transplantasjonstidspunkt	(state of the disease when transplanted)	Says which state the patient is in when the transplantation is conducted. This can be either first remission (valued 1), early in relapse (valued 2), second remission (valued 3) or in a later remission (valued 4)
Residiv	(relapse)	Tells if you have a relapse or not and is valued between 1 and 3 where 1 is yes and 2 and 3 are no
Ny_remisjon	(new remission)	Refers to if the patient has a second remission and this is either yes (valued 1) or no (valued 2)
Ny_residiv	(new relapse)	Refers to if the patients has a second relapse
Status	(status)	Refers to the current status of the patients and is valued between 1 and 13. Number 1 to 5 and number 12 says which state the patient died in, and number 6 to 10 and 13 says in which state the patients lives in. The value 11 indicates that the follow-up is missing
Female_male	(gender)	This variable is used to define the gender of the patients where 0 is female and 1 is male

All variables containing dates were separated and each information day, month, and year were saved in new cells of their own. This was done to make it easier to create the time variables, discussed in section 6.3.1 "Time variables". We also defined a variable "Gruppe +/-60" in order to split the group into two, according to their age (under or above 60 years).

Table 8 provides an overview of the variables created manually by the use of the information in the data set from SPSS.

Table 8 - Data set variables (manually calculated)

Manually generated variables		
Variables	(In english)	Definition
Age	(age)	The age of the patient when diagnosed
Gruppe +/-60	(group +/-60)	The cohort was divided into groups according to their age (0 = 16-59 and 1 = ≥ 60 years)
mnd Diagnose	(diagnosis month)	The month they got their diagnosis
mnd remisjon	(remission month)	The month they got the first remission
mnd Trans	(transplantation month)	The month they got transplantation
mnd Residiv	(relapse month)	The month they got the first relapse
mnd rem2	(2nd remission month)	The month they got the second remission
2 rel mnd	(2nd relapse month)	The month they got the second relapse
mnd Death	(diagnosis month)	The month they died

The date of birth is needed to calculate the age of the patients. Likewise, the dates of the different events were necessary to be able to trace the patient's movements between states. This information is used to create time variables (explained in the section "Time variables").

### 6.2.1 Data set characteristics

In this section we will provide a brief description of the data characteristics. This includes the mean age of the patients, and how many who receives induction treatment, transplantation and dies. The data set was divided by age (young and elderly), in order to see the difference of the age impact.

The age distribution according to gender in the groups is shown in Table 9 below.

Table 9 - Age of the patients in the data set

Mean and median age of the patients				
	Age 16-59		Age ≥ 60	
	Mean	Median	Mean	Median
All cases	38.5	39.0	70.2	68.5
Female	41.3	42.0	69.6	68.5
Male	37.3	40.5	68.7	66.5

The oldest patient in the data set is aged 86, while the youngest is aged 16, on the date of diagnosis. Table 9 shows the mean age in both groups, among the genders. Females seem to be slightly older when receiving the diagnosis.

A quick overview of the patients and the amount of people who receive treatment, transplantation and dies within a five-year perspective is shown in Table 10 below.

Table 10 - Overview of induction treatment, transplantation and death (by group)

Actual number of patients from the data set who receive treatment, transplantation and dies (5-yr perspective)		
Actual no. of patients (%)	All cases (222)	
	Age 16-59 (176)	Age ≥ 60 (46)
Induction treatment	98 %	57 %
Transplantation	36 %	11 %
Death	65 %	91 %

In order to be eligible for transplantation the patient must reach complete remission. In the data set remissions is categorized either to be “full conditioning” or “reduced conditioning”. In Group 0 (< 60 years) 95 patients obtained “full conditioning” and the mean age is 42, ranging from 21 years to 59 years. Five patients had “reduced conditioning”. The age of these patients ranged from 24 years to 59 years.

In Group 1 (≥ 60 years) five patients gained “full conditioning” and their age was between 60 and 63, with a mean age of 61 year. In the same group eight patients had “reduced conditioning” and their age was between 60 and 68, while the mean age was 63 years.

Table 11 - Transplantation in different remission states

Transplantation in different states		
	Number of patients	
	16-59 yrs (99)	≥ 60 yrs (11)
1st remission	70	9
2nd remission	27	2
3rd remission	2	-

In total, 110 patients in the data set received transplantation. This is about one third (36.8 per cent) of the entire cohort.

## Death

The cause of death and time of death varies in this data set. There are 6 different values for death in the data set given. They are as follows: “Early death (<30 days after diagnosis)”, “Death without reaching remission”, “Death in first remission”, “Death in first relapse”, “Death in a later relapse” and “Death in a later remission”. This information is useful to calculate the amount of people in the decision tree that died or did not respond to the treatment. Death in all other states is based on transition probabilities.

## 6.3 Expected values and outcome in the decision tree

The input in the decision tree is given from the probability distributions and can be found in Table 12. These distributions are also used in the PSA. In order to be able to establish *Alpha* and *Beta*, the actual number of events in the data set was used. These probabilities are deterministic but in the model they are assigned probabilistic. The probabilistic approach will account for uncertainty in the parameters.

Table 12 - Deterministic transition probabilities (decision tree)

Non-time-dependent transition probabilities (deterministic) and mean costs for individuals during induction (decision tree) conditioned on “received induction treatment” and being aged 16 to 59 years or 60 years or older (in parentheses).							
Induction phase (nodes and pathways in the decision tree)	Transition probability				Distribution		
	Per month	<i>Alpha</i>	<i>Beta</i>				
16-59 y	0.7850 (0.2150)	241 (66)	66 (241)		Beta		
Received induction treatment on 16-59 y (≥60 y)	0.9876 (0.6970)	238 (46)	3 (20)		Beta		
Did not receive induction treatment 16-59 y (≥60)	0.0124 (0.3030)	3 (20)	238 (46)		Beta		
AraC+Dauno	0.7227 (0.5000)	172 (23)	66 (23)		Dirichlet		
AraC+Ida	0.1891 (0.3913)	45 (18)	193 (28)		Dirichlet		
Other Chemo	0.0882 (0.1087)	21 (5)	217 (40)		Dirichlet		
AraC+Dauno and early death	0.0465 (0.0435)	8 (1)	164 (22)		Dirichlet		
AraC+Dauno and response	0.8314 (0.6522)	143 (15)	29 (8)		Dirichlet		
AraC+Dauno and no response	0.1221 (0.3043)	21 (7)	151 (16)		Dirichlet		
AraC+Ida and early death	0.0667 (0.0000)	3 (0)	42 (18)		Dirichlet		
AraC+Ida and response	0.8222 (0.9444)	37 (17)	8 (1)		Dirichlet		
AraC+Ida and no response	0.1111 (0.0556)	5 (1)	40 (17)		Dirichlet		
Other Chemo and early death	0.9048 (0.2000)	1 (1)	20 (4)		Dirichlet		
Other Chemo and response	0.4286 (0.6000)	19 (3)	2 (2)		Dirichlet		
Other Chemo and no response	0.0476 (0.2000)	1 (1)	20 (4)		Dirichlet		



### 6.3.1 Time variables

In order to implement time-dependency in the Markov models one has to create time variables. When time in remission is less than the time-span (five years) and no events have occurred, we allow censoring of the subjects. Ignoring censoring may lead to over-estimation of the hazard. The disease course determines what is considered a failure when coding the variables. The concept of failure is referring to whether an individual is experiencing an event during the chosen time-span. The time variables are given in months, therefore, January 2000 is zero, February is one, and March is two, and so forth. This led us to 179 months, where December 2014 is month 179. The recoding was necessary to perform the survival analysis.

	mnd Diagn	mnd remi	0_mnd re	tid i rem	0_mnd Tr	0_Mnd Re	0_Mnd De	Failure	Fail death	Fail relaps	Fail
0	0	1	0	60				0	0	0	0
0	3	4	3	3	6			1	0	0	0
0	4	5	4	60				0	0	0	0
0	6	8	7	7		14	21	1	0	0	1
0	Indicates the length in remission.	8	7	18	35	25	37	1	n	0	1
0		10	9	4	13		148	1	Failure variable	0	0
0	9	10	9	60				0	0	0	0
0	9	10	9	6	15			1	0	0	0
0	12	13	12	9		21	23	1	0	0	1
0	13	15	14	20		34	37	1	0	0	1
0	14	15	14	60				0	0	0	0
0	14	15	14	56	73	70	82	1	0	0	0

Figure 12 - Excel extraction of time variables

The extraction above (Figure 12) illustrates how “time in first remission” is calculated and coded. A bigger screenshot is available in Appendix E, in addition to a detailed description of how the time variables are calculated. The length of stay in first remission is equal to the time the first possible failure occurs subtracted by the time the patient achieved remission. The red circle illustrates a patient that has no failure, hence the time in remission is 60 months (five years) and the failure variable is coded as 0. In our data set we had right censoring. If an individual had less than 60 months left in the five-year perspective, it would be censored.

## 6.4 Estimation

Estimates were carried out in Stata. We started out by importing the time variable sheet from Excel into Stata. When the regressions were completed, we noticed that there were a lot of non-significant variables. Probably, this occurred since there are fewer observed events as we went from regressing those who leave from first remission to those who leave from first relapse. Table 13, 14 and 15 shows the Weibull regression output for model A1 (young), A2

(elderly), B (no response), C (palliative) and D (transplantation), with hazard ratios, standard errors, p-values, gamma ( $\beta$ ) and 95 per cent confidence intervals.

The regression output is significant if the p-value is below 0.05. Further, a hazard ratio above 1 implies that the hazard increases with time, and opposite it decreases with time. If the confidence interval (of 95 per cent) contains 0, the null-hypothesis cannot be rejected, hence there are no statistical effects in the estimates.

Table 13 - Regression output for model A1 (young) and A2 (elderly)

Regression output for Markov model A1 (<60 yrs) and A2 (≥60 yrs)					
Variables	Haz. ratio	Str. Err.	P-value	95 % CI	
				Lower	Upper
<b>1st remission (TTRL)</b>					
lnAge	2.7372	1.1073	0.0130	1.2386	6.0487
_cons	0.0004	0.0007	0.0001	0.0001	0.0103
ln_p	-0.0256	0.0902	0.7770	-0.2023	0.1512
p	0.9748	0.0879		0.8169	1.1632
<b>1st remission (TTTR)</b>					
lnAge	2.6154	1.0139	0.0130	1.2234	5.5913
_cons	0.0020	0.0031	0.0001	0.0001	0.0402
ln_p	-0.5316	0.0943	0.0001	-0.7165	-0.3467
p	0.5877	0.0554		0.4885	0.7070
<b>1st remission (Death)</b>					
lnAge	19.166	35.907	0.1150	0.4874	753.72
_cons	0.0001	0.0001	0.0300	0.0001	0.1963
ln_p	-0.5039	0.2935	0.0860	-1.0792	0.0715
p	0.6042	0.1774		0.3399	1.0741
<b>1st relapse (LIR)</b>					
lnAge	0.3743	0.1462	0.0120	0.1741	0.8047
_cons	9.5900	14.009	0.1220	0.5475	167.97
ln_p	0.1077	0.0808	0.1820	-0.0506	0.2660
p	1.1137	0.0899		0.9507	1.3047
<b>1st relapse (Death)</b>					
lnAge	0.5294	0.3144	0.2840	0.1653	1.6953
_cons	1.0817	2.4237	0.9720	0.0134	87.363
ln_p	0.2145	0.1025	0.0360	0.0137	0.4153
p	1.2392	0.1269		1.0138	1.5148
<b>2nd remission (TTTR)</b>					
lnAge	0.1001	0.0826	0.0050	0.0198	0.5049
_cons	913.44	2699.0	0.0210	2.7897	299086.8
ln_p	-0.2719	0.1606	0.0900	-0.5866	0.0428
p	0.7620	0.1223		0.5562	1.0438

TTRL = Time to relapse, TTTR = Time to transplant, LIR = Leave in relapse

Table 13 displays the regression output from Stata for the different states.

When looking at the probability of going from first remission to relapse (TTRL) and transplant (TTTR), a one unit change in lnAge nearly three doubles the hazard of failure, whereas a one unit change in lnAge in first relapse (LIR), first relapse (Death) and second remission (TTTR) cuts the hazard with one-third, half, and one-tenth, respectively. In first remission (Death) a one-unit increase in lnAge will double by 19. This means that when a patient's age increases, the hazard of failure will increase by 19. The p-value of first remission (Death) is non-significant ( $p = 0.1150$ ), which means that the effect of age is non-significant for dying in first remission. We can also see that the 95 per cent confidence interval is too large for this to cause an effect. The p-values for first remission (TTRL), first remission (TTTR), first relapse (LIR) and second remission (TTTR) are all significant. This means that all these transitions are affected by age. First relapse (Death) and, as mentioned, first remission (Death), with a p-value of 0.248 and 0.1150 respectively, is not affected by age. In first remission (TTRL), first remission (TTTR), first remission (Death) and second remission (TTTR) all hazards are decreasing. We can see this by looking at  $p$ , where all these transitions are below zero. In first relapse (LIR) and first relapse (Death)  $p$  is equal to 1.1137 and 1.2392 respectively. This means that the hazard is growing over time.  $\ln_p$  is just the natural logarithm of  $p$ , and hence they reflect the same.

Table 14, on the following page, shows regression output for model B (no response) and model C (palliative care).

The hazard ratio in model B (no response), Table 14, is approximately one-third (0.3886), which means that a one-unit change in age will cut the hazard of failure by one-third. We can also see that the p-value is non-significant (0.2300), hence, age has no effect on dying. The  $p$  is above one, which means that the hazard is growing over time. In model C (palliative), a one-unit change in age will increase the hazard of failure by 1.1452. Here, the p-value is non-significant (0.9220); and we may deduct that age has no effect of dying in palliative care.  $p$  is almost one (0.9686), therefore the hazard is decreasing over time but are close to being exponentially distributed.

Table 14 - Regression output for model B (No response) and C (Palliative)

Regression output for Markov model B (No response) and C (Palliative)					
Variables	Haz. ratio	Str. Err.	P-value	95 % CI	
				Lower	Upper
<b>No response (Death)</b>					
lnAge	0.3886	0.3062	0.2300	0.0829	1.8205
_cons	3.1427	9.4927	0.7050	0.0084	1170.6
ln_p	0.2909	0.1350	0.0310	0.0264	0.5555
p	1.3377	0.1806		1.0267	1.7428
<b>Palliative (Death)</b>					
lnAge	1.1452	1.5901	0.9220	0.0753	17.408
_cons	0.0898	0.5208	0.6780	0.0001	7748.6
ln_p	-0.0319	0.2140	0.8820	-0.4514	0.3876
p	0.9686	0.2073		0.6368	1.4735

Table 15 - Regression output for model D (Transplantation)

Regression output for Markov model D (Transplantation)					
Variables	Haz. ratio	Str. Err.	P-value	95 % CI	
				Lower	Upper
<b>Remission (TTRL)</b>					
lnAge	0.4968	0.4800	0.4690	0.0748	3.3002
_cons	0.0200	0.0758	0.3020	0.0001	33.475
ln_p	0.3259	0.2103	0.1210	-0.0862	0.7381
p	1.3853	0.2913		0.9174	2.0919
<b>Transplant (Death)</b>					
lnAge	1.2349	0.9575	0.7860	0.2701	5.6449
_cons	0.0050	0.0153	0.0810	-0.3246	0.2916
ln_p	-0.0165	0.1572	0.9160	-0.3246	0.2916
p	0.9836	0.1546		0.7228	1.3386

TTRL = Time to relapse

In Table 15 we can see that the hazard ratio of remission (TTRL) is approximately cutting the hazard of failure by a half. The p-value is non-significant (0.4690), which means that the effect of age in remission (TTRL) is not significant. Since  $p$  is 1.3853, the hazard of failure is increasing over time. From transplant/remission to death, the hazard ratio is 1.2349. This means that a one-unit increase in age will increase the hazard of failure. The p-value is non-

significant (0.7860), showing that age has no effect on dying in transplantation/remission.  $p$  is close to one, which makes the hazard of failure decreasing, but it is close to being exponentially distributed.

### Probabilistic transition probabilities

In Table 16 one can see an extraction of the transition probabilities estimated above and by use of the Cholesky decomposition, which is used in the Markov models (A1, A2, B, C and D). The first four cycles and every tenth cycle from ten to 60 are included. This is done to draw a picture of how the transition probabilities change over time. In the Excel model all cycles are included with different probabilities for each cycle (see Appendix I). It is important to note that these transition probabilities are made probabilistic in our analysis, and because Excel conducts draws whenever something is copied and pasted, these probabilities are not from the same draw.

Table 16 - Transition probabilities (Markov models)

Time-dependent transition probabilities for individuals in post-induction phases conditioned on being aged 16 to 59 years and 60 years or older in all Markov models											
Transition probabilities in each model	Cycles 0 - 60										Distribution
	0	1	2	3	10	20	30	40	50	60	
<b>Model A1 (&lt; 60 yrs)</b>											
1st remission (TTRL)	0.0149	0.0145	0.0144	0.0143	0.014	0.0139	0.0138	0.0137	0.0137	0.0136	Weibull
1st remission (TTTR)	0.0640	0.0355	0.0293	0.0259	0.0173	0.0135	0.0117	0.0105	0.0097	0.0091	Weibull
1st remission (Death)	0.0188	0.0060	0.0044	0.0036	0.0018	0.0012	0.0010	0.0008	0.0007	0.0006	Weibull
1st relapse (SIR)	0.7731	0.7452	0.7336	0.7258	0.6994	0.6823	0.6719	0.6643	0.6583	0.6533	Weibull
1st relapse (Death)	0.1641	0.1919	0.2038	0.2120	0.2403	0.2590	0.2707	0.2793	0.2861	0.2918	Weibull
2nd remission (TTTR)	0.1664	0.0908	0.0744	0.0654	0.0429	0.0331	0.0284	0.0254	0.0233	0.0218	Weibull
<b>Model A2 (≥ 60 yrs)</b>											
1st remission (TTRL)	0.0226	0.0239	0.0244	0.0247	0.0258	0.0265	0.0269	0.0272	0.0274	0.0276	Weibull
1st remission (TTTR)	0.0861	0.0459	0.0374	0.0328	0.0213	0.0164	0.0141	0.0126	0.0115	0.0108	Weibull
1st remission (Death)	0.0300	0.0146	0.0116	0.0100	0.0062	0.0047	0.0039	0.0035	0.0032	0.0029	Weibull
1st relapse (SIR)	0.8842	0.8576	0.8455	0.8372	0.8073	0.7868	0.7738	0.7641	0.7564	0.7499	Weibull
1st relapse (Death)	0.0545	0.0857	0.1033	0.1165	0.1713	0.2150	0.2453	0.2689	0.2886	0.3055	Weibull
2nd remission (TTTR)	0.0337	0.0261	0.0238	0.0224	0.0185	0.0165	0.0154	0.0147	0.0141	0.0137	Weibull
<b>Model B (no response)</b>											
No response (Death)	0.0858	0.1171	0.1325	0.1436	0.1856	0.2162	0.2364	0.2517	0.2641	0.2747	Weibull
<b>Model C (palliative)</b>											
Palliative (Death)	0.1600	0.1955	0.2115	0.2224	0.2613	0.2876	0.3041	0.3164	0.3261	0.3343	Weibull
<b>Model D (transplant)</b>											
Remission (TTRL)	0.0176	0.0092	0.0074	0.0065	0.0042	0.0032	0.0027	0.0025	0.0022	0.0021	Weibull
Transplant (Death)	0.0334	0.0179	0.0147	0.0129	0.0084	0.0065	0.0056	0.0050	0.0046	0.0043	Weibull

TTRL = Time to relapse, TTTR = Time to transplant, SIR = Stay in relapse

The transition probability in first remission, model A1 (young) for time to relapse, decreases over time. This means the longer you stay in remission the more likely you are to avoid relapse. This is similar for time to transplant and death in remission due to the same causes.

In Model B (no response) and C (palliative), the transition probabilities increase over time. This is due to the fact that the patients only receive palliative care and death is the only state they can transit to. As already described in the Background chapter, untreated AML is deadly and the life expectancy is short.

For patients who receive transplantation, the probability of having a relapse and dying is decreasing over time. This can be explained by the fact that the post-transplantation phase is similar to being in remission, however transplanted patients have a higher risk of dying during the near future after transplantation.

### **Graphs of the probabilistic transition probabilities**

We added the probabilistic transition probabilities in several Figures (Figure 13, 14, 15, and 16) to capture the difference in leaving the different states among young and elderly.

Additionally, we wanted to compare palliative care against “no response” to see if there are any differences, since they receive the same treatment in Markov model B and C.

Transplantation is also explored to illustrate that patients in early stage of transplantation has a higher probability of relapse or death. All figures are shown in an 18 months perspective.

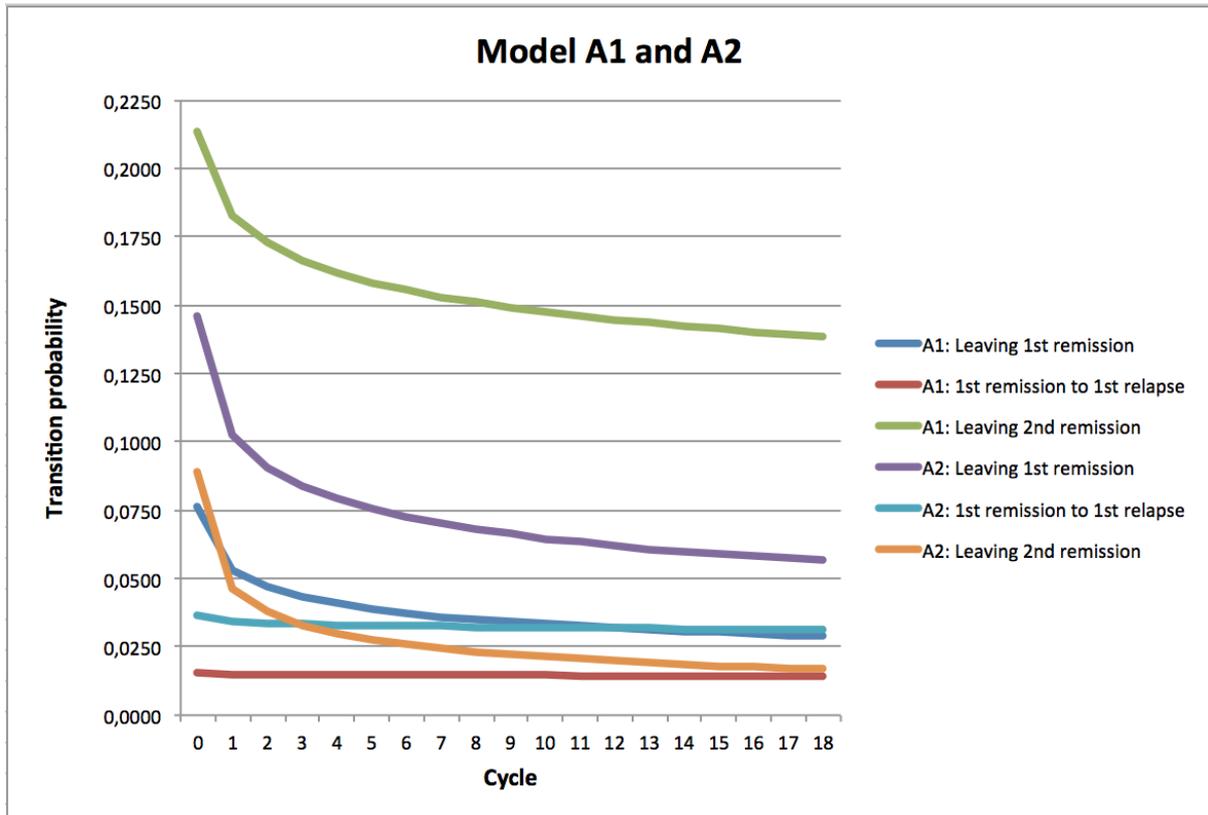


Figure 13 - Transition probabilities in model A1 (young) and A2 (elderly)

Figure 13 illustrates the probabilistic transition probabilities for “leaving 1<sup>st</sup> remission” in A1, “1<sup>st</sup> remission to 1<sup>st</sup> relapse” in A1, “leaving 2<sup>nd</sup> remission” in A1, and similar for A2. We can see that the probability of leaving second remission in model A1 is much higher than in A2. A reason may be that younger patients will receive transplantation more often than elderly patients. The probability of experiencing a relapse is lower in younger patients than elderly. This is reasonable since younger patients often have a better prognosis than elderly. We can also see that the probability of leaving first remission is lower in young patients than the elderly.

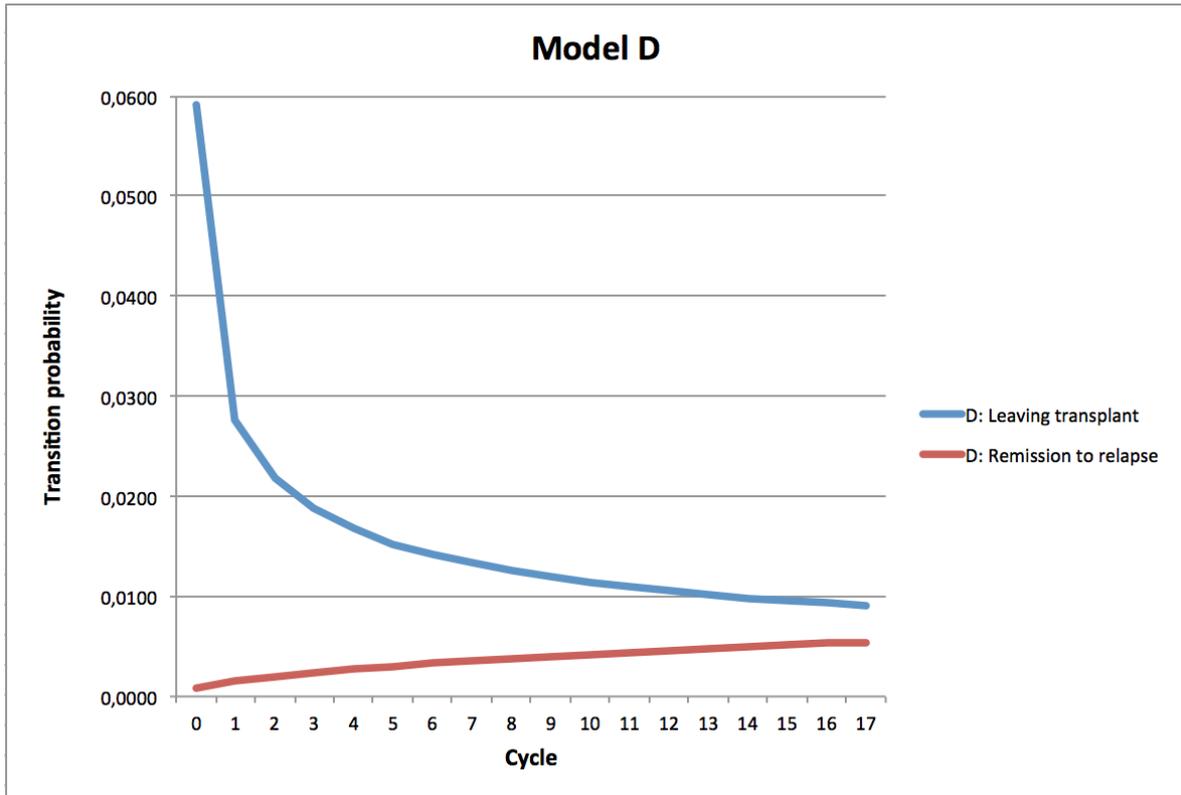


Figure 14 - Transition probabilities in Transplantation

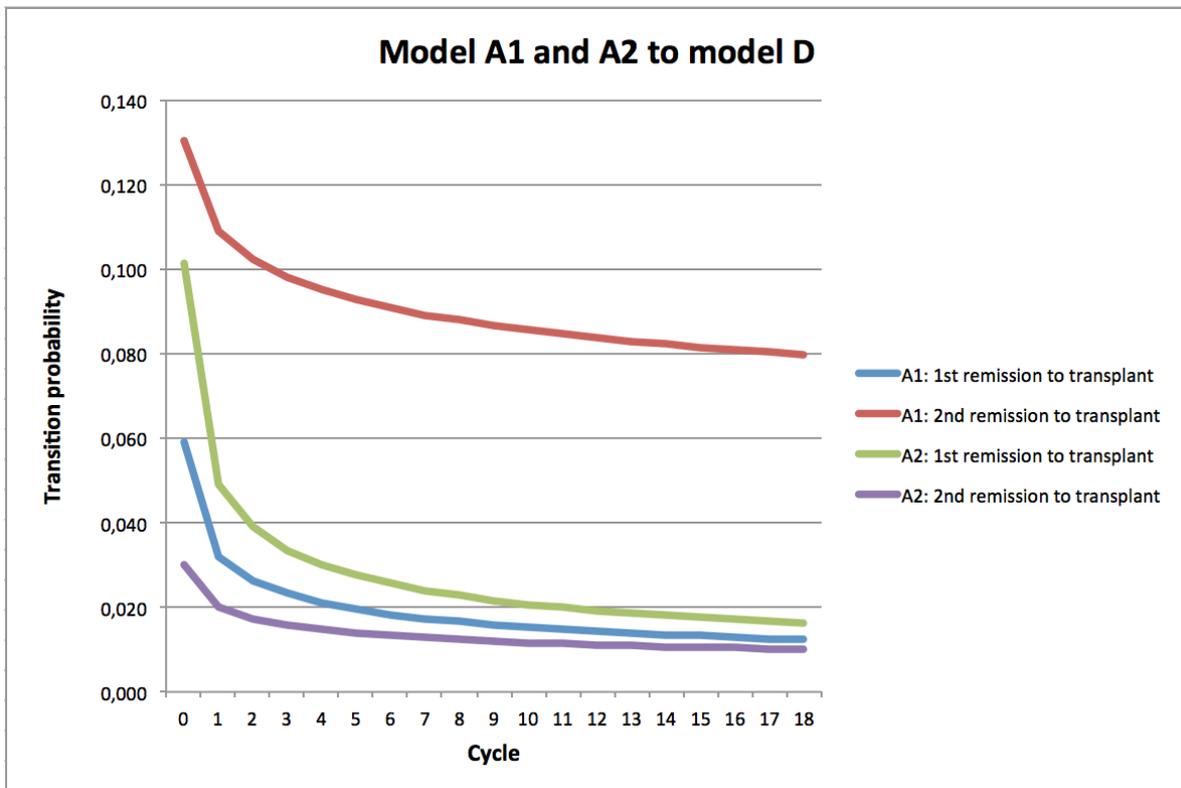


Figure 15 - Transitions probabilities in model A1 (young) and A2 (elderly) to Transplantation

Figure 14 shows that in the first couple of months after transplantation, there is a great probability of leaving this state to either relapse or death. This probability is smoothing out and decreasing after a while. Remission to relapse is very low and has a slight increase over time.

Figure 15 shows the transitions to transplant from model A1 and A2. In model A1 and A2 the probability of going from remission to transplant is higher in second remission than in first remission. Model A2 has an overall lower probability of going from remission to transplant. The probability of leaving to transplant decreases over time.

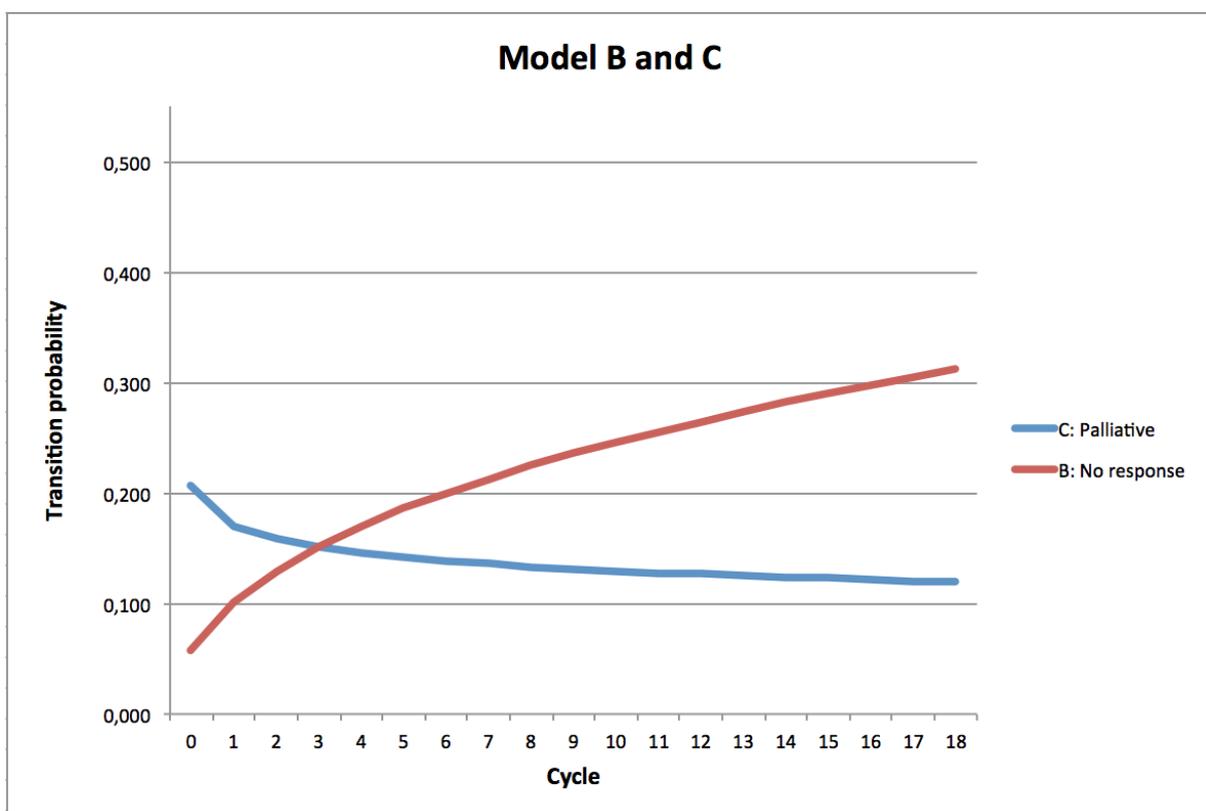


Figure 16 - Transition probabilities in Palliative care and No response

In Figure, 16 No response and palliative care, illustrates the transition from treatment to death. We can see that “No response” has an increasing curve as time goes by, while “palliative care” is slightly decreasing.

### 6.4.1 Time-independent probabilities

To compensate for too few patients in the long run and to calculate precise transitions probabilities for each cycle, we had to make some simplifications. The transition from second

remission to second relapse, from second remission to death and the probability of leaving relapse in transplant to death, was calculated by using the instantaneous event rate explained in the Method chapter. Table 17 shows these probabilities.

Table 17 - Time-independent probabilities (Markov models)

Time-independent probabilities for individuals in postremission (unconditional on age) in Markov models A1, A2 and D	
Time-independent probabilities	Per month
<b>Model A1 and A2</b>	
2nd remission (TTRL)	0.0010
2nd remission (Death)	0.0005
<b>Model D (Transplant)</b>	
Relapse (Death)	0.0140

TTRL = Time to relapse (second)

Second remission to relapse (TTRL) is used to indicate those who leave from second remission to second relapse. Further, it is used in second relapse to indicate those who enter this state from second remission. Second remission to death is used as a constant probability of dying in second and third remission. Relapse in transplant to death is used as a constant probability of dying in transplant/remission and relapse.

## 6.5 Costs

### 6.5.1 Overview

Figure 17 is a flow chart describing the different cost input sources and which costs we had to process in order to make them accurate for our purpose.

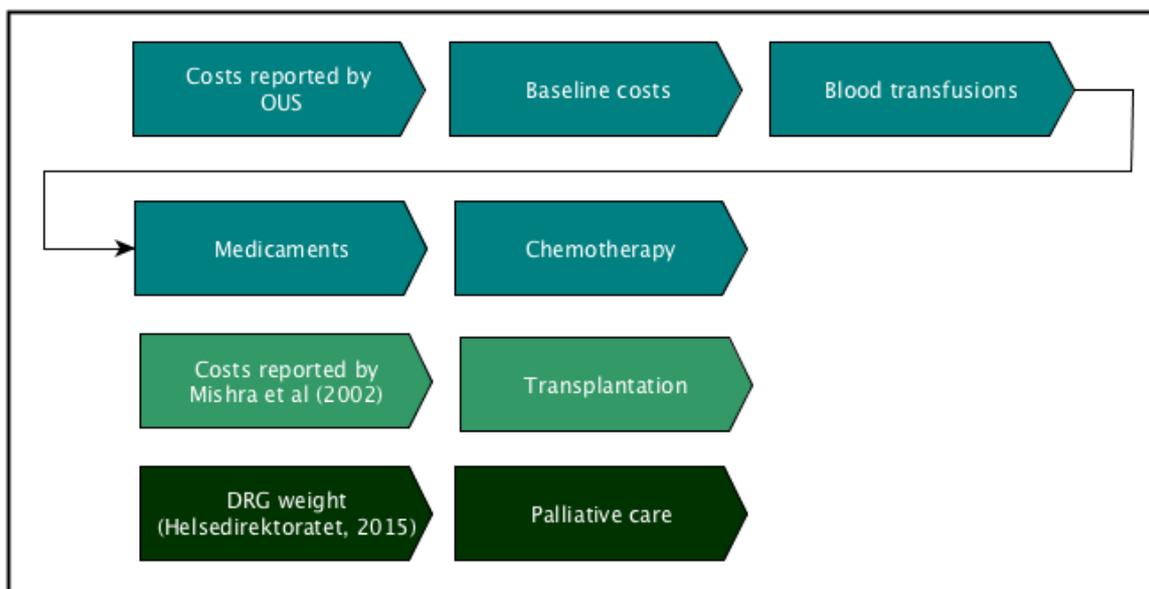


Figure 17 - Flow chart (costs)

In order to calculate the costs of treatment in the decision tree, each form of chemotherapy, including the price of the subsequent hospital stay, type and price of medications and the price of diagnosis had to be identified. For the Markov models the cost of being in remission, which is the price of follow-up, price of consolidating chemotherapy, and the cost of new treatment in relapse had to be identified. Similar, the cost of transplantation and the subsequent follow-up had to be identified. For the patients who only received palliative care the price of this had to be calculated. All of the costs mentioned above is defined as resource use and were tracked with help from the accounts department of the Haematology ward, in addition to costs reported directly from the ward staff (expert opinion). The cost of transplantation is found in a article by Mishra et al. (2002) where they identified the cost for this in Norway. The cost of palliative care, offered at local hospitals, is found by the DRG-price for palliative care. All of these costs are a part of the treatment course and important for the overall picture of AML.

The costs are estimated from the health care provider’s perspective. Throughout the analysis, we chose to use costs in 2014 NOK, because these were the year of fixed cost given to us by OUS. However, the cost of chemotherapy, blood and medications was given in 2015 NOK, and were adjusted (by using a CPI calculator). All costs are given a gamma distribution with a standard error of 20 per cent.

There are two bar charts (Figure 18 and 19) following the costs related to induction and further treatment, respectively. These are only meant to give a visual picture of the resource allocation, and are based on Table 21 and 22.

### 6.5.2 Fixed costs

The cost variables we received from the Haematology ward contains a post named “Raw materials” and this includes different equipment such as needles, patches and sterilisation material. The post named “Revenue” is including courses and lectures held by the ward, employee leasing programs and positions partly waged by the University of Oslo. Table 18 shows the total cost at the Haematology ward (excluded medicaments):

Table 18 - Haematology ward costs (2014)

Costs at the Haematology ward 2014	
Description	Total (NOK)
Revenue	kr -440 702
Material (equipment)	kr 5 532 212
Salary	kr 61 959 916
Operating expences	kr 751 427
Other operating expences	kr 89 899
Financial costs	kr 1 573
Internal transactions (blood costs)	kr 1 102 444
<b>Total</b>	<b>kr 68 996 768</b>
<i>Cost per day</i>	<i>kr 8 894</i>

To make the cost more accurate for the AML patients, we removed the cost for the average blood transfusions at the Haematology ward and created a new variable with the actual

average cost for AML patients. The cost of length of stay is NOK 7634 per day without blood transfusions. This is calculated by using the total cost found in Table 18 (excluding the internal transactions) and dividing it by the number of inpatient days at the Haematology ward which was 8 894 in 2014 (see Appendix K for details).

### Blood transfusions

To be able to calculate the cost of transfusions, we need a representative picture of the average amount of transfusions for patients treated. The average figures were produced by MD Fløisand. Next we added the price for the different blood products, and multiplied with the average amount of transfusions for each chemotherapy treatment. This is illustrated in Table 19:

Table 19 - Blood prices and quantity (OUS)

Transfusion - units and cost per treatment								
	ml	NOK	Induction treatment				Consolidation therapy	
			1st chemotherapy		2nd chemotherapy		3rd chemotherapy	
			Units	Cost	Units	Cost	Units	Cost
Thrombocytes	380	3945	9.5	kr 37 537	4.5	kr 17 633	0.2	kr 598
Erythrocytes	250	1450	8.8	kr 12 698	3.7	kr 5 405	0.4	kr 527
<b>Total</b>			<b>18.3</b>	<b>kr 50 236</b>	<b>8.2</b>	<b>kr 23 038</b>	<b>0.5</b>	<b>kr 1 125</b>

The variables for thrombocytes and erythrocytes were added directly in each model. The cost for blood transfusions is given by the Blood bank at OUS Ullevål.

### Estimated medical costs

MD Fløisand identified all of the medications involved in the different treatment strategies, while the accountant department gave the price for each medication. The list of medicaments from MD Fløisand consisted of 17 different medicaments; antibiotics, penicillin, medications against fungal infections, nausea reducing drugs, liquid transfusions such as nutrition and sodium chloride, diuretics, pain relievers and sleep medicine. The calculated average of these medications are implemented in the induction treatment. The chemotherapy is not included here (see section “Induction treatment costs” and “Further treatment costs”).

Some medications, such as medications against fungal infections are very expensive, and there is approximately one in twelve patients receiving this. MD Fløisand estimated an average dosage per patient. Table 20 shows the different medications given with associated costs per patient. See Appendix F for full price list from OUS and explanation of the calculation behind the average costs per patient.

Table 20 - Medications used in induction treatment (OUS)

List of medications used in association with AML		
Medications	Costs per induction	Description
Afipran Inj 5mg/ml	kr 106	Antiemetic
Allopur SA tab 300mg	kr 31	Inhibitor of uric acid production
AmBisome Inf subst 50mg	kr 7 816	Antimycotics
Benzylpeni pan inf/inj su 3g	kr 0.52	Pencillin
Ceftazidim fres inf/inj sub 2g	kr 0.52	Antibiotic
Fluconazole teva inf 2mg/ml	kr 3 696	Antimycotics
Furix tab 20mg	kr 5	Diuretic
Gensumycin inj 40mg/ml	kr 15	Antibiotic
Imovane tab 7,5mg	kr 32	Hypnotic
Ketorax inj 5mg/ml	kr 86	Analgesic by severe pain
Meropenem hos inj/inf subst 1 g	kr 0.03	Antibiotic
Mycamine inf subst 100mg	kr 7 847	Antimycotics
Nexium enterotab 20mg	kr 33	Proton pump inhibitors
Ondansetron fresen inj 2mg/ml	kr 231	Antiemetic
Kabiven 1026ml	kr 1 046	Nutrition
Natriumklorid 9mg/ml	kr 262	Sodium
Vancomycin hosp inf su 500mg	kr 536	Antibiotic
Mean cost per induction	kr 21 742	

Antiemetic is a drug that reduces nausea, antimycotics is a drug against fungal infections, hypnotic is a drug that helps the patient sleep, analgesic is used against severe pain, and proton pump inhibitor is used to drain out the leukemic cells after chemotherapy. Antibiotics are given to almost all patients because of the high risk of infection (Fløisand, 2015).

### 6.5.3 Induction treatment cost

The costs associated with induction treatment in the decision tree are shown in the Table 21, on the following page. The costs that incur in the decision tree are the first and second

chemotherapy, length of stay, blood transfusions, diagnosis, intensive care unit, and total average of the medication cost.

Table 21 - Unit cost and cost per patient (decision tree)

Cost associated with the decision tree conditional of treatment					
Cost variables	Unit cost (NOK)	Unit	Cost per patient (NOK)	± SE	Source
Diagnosis	kr 10 000	1 visit	kr 10 000	kr 2 000	OUS (Fløisand)
Length of stay	kr 7 634	40 days *2	kr 305 360	kr 61 072	OUS (Reime)
Intensive care unit	kr 55 000	7 days (5 %)	kr 19 250	kr 3 850	OUS (Fløisand)
Trombocytes *1	kr 3 945	14 units	kr 55 174	kr 11 035	OUS (Blood bank)
Erythrocytes *1	kr 1 450	12.5 units	kr 18 102	kr 3 620	OUS (Blood bank)
Medications *1	-	-	kr 21 742	kr 4 348	OUS (Reime)
<b>1st chemo</b>					
Cytarabine *1	kr 634	7 days	kr 4 435	kr 887	OUS (Reime)
Cytarabine (maintenance)*1	kr 6 336	3 days	kr 19 008	kr 3 802	OUS (Reime)
Idarubicin *1	kr 4 679	3 days	kr 14 037	kr 2 807	OUS (Reime)
Daunorubicin *1	kr 13 005	3 days	kr 39 015	kr 7 803	OUS (Reime)
<b>2nd chemo</b>					
Cytarabine *1	kr 6 336	6 days	kr 38 016	kr 7 603	OUS (Reime)
Amsakrin	kr 48	3 days	kr 143	kr 29	OUS (Reime)
<b>Other cytostatic</b>	-	-	kr 49 969	kr 9 994	OUS (Reime)
*1 Adjusted to 2014 NOK	*2 The average is 30 days, but is set to be 40 days to capture the cost of patients who stays longer				

MD Fløisand counted the length of stay for the different chemotherapies. The length of stay is 40 days in Table 21, to capture the cost of the patients who stays at hospital during induction treatment for more than 30 days. It is based on the average of the patients from 2014 and ensured to be representative for the entire data set. The dosages of medications are given in milligrams and multiplied with the average body surface of the patients from 2014. The average body surface of these patients is 1,92 m<sup>2</sup> (Fløisand, 2015). The patients receive chemotherapy over a period of time. Cytarabine is given each day for seven days, while Daunorubicin, Idarubicin and Amsakrin are given each day for three days. Ara-C+I is a combination of Cytarabine, Cytarabine maintenance, and Idarubicin, which has a total cost per patient of NOK 37 180. Ara-C+D is a combination of Cytarabine, Cytarabine maintenance and Daunorubicin, which has a total cost per patient of NOK 67 458. Those patients receiving a third option of chemotherapy (Other cytostatic) is estimated as a mean of Ara-C+I and Ara-C+D. Cost per patients shows the pathway cost per individual when

receiving the diagnosis and treatment. The costs that are conditional on treatment are chemotherapies and blood transfusions.

The cost of diagnosis is based on expert opinion from the Haematology ward. It includes doctor hours spent, equipment used, and laboratory testing. In the cost calculation no use of nurses is included, nor are fixed cost.

The intensive care unit reported (expert opinion) the cost for a hospital stay to be approximately NOK 55 000 per day. Around five per cent of the total number of AML patients receives intensive care at the intensive care unit. This percentage is added in to the chemotherapy treatments.

Figure 18 below shows the costs in the decision tree and one can easily tell that length of stay is the greatest cost driver.

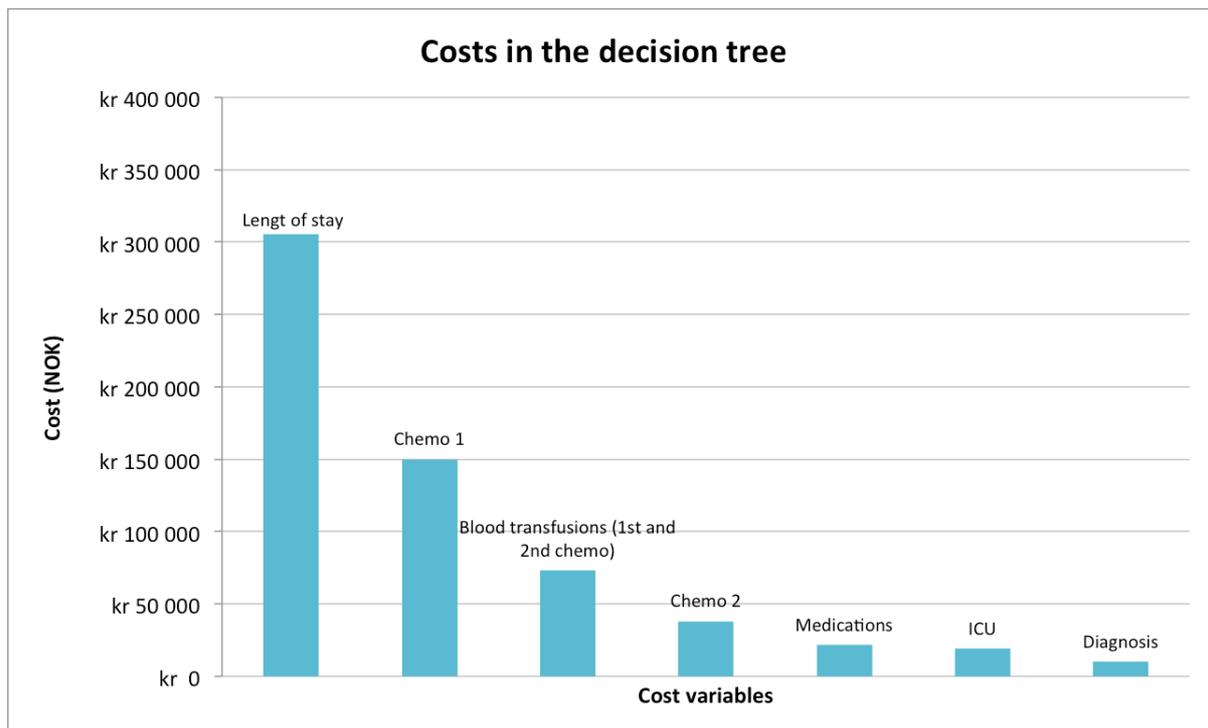


Figure 18 - Bar chart of costs related to induction treatment.

#### 6.5.4 Further treatment (Markov models)

Further treatment costs involves Markov model A1, A2, B, C, and D. The costs identified in the Markov models can be seen in Table 22.

Table 22 - Unit cost and cost per patient (Markov models)

Total cost in Markov models A1, A2, B, C and D					
Cost variables	Unit cost (NOK)	Unit	Cost per cycle (NOK)	± SE	Source
<b>Markov model A1 and A2</b>					
Length of stay	kr 7 634	30 days	kr 229 020	kr 45 804	OUS (Reime)
Intensive care unit	kr 55 000	7 days (5 %)	kr 19 250	kr 3 850	OUS (Fløisand)
Other cytostatic*	-	-	kr 49 969	kr 9 994	Estimation
Follow up	-	-	kr 1 343	kr 269	OUS (Fløisand/Reime)
Thrombocytes*	kr 3 945	0,15 units	kr 598	kr 120	OUS (Blood bank)
Erythrocytes*	kr 1 450	0,36 units	kr 527	kr 105	OUS (Blood bank)
Medications*	-	-	kr 21 742	kr 4 348	OUS (Reime)
<i>3rd chemo*</i>					
Mitoxantron	kr 2 188	5 days	kr 10 939	kr 2 188	OUS (Reime)
Etoposide	kr 131	5 days	kr 653	kr 131	OUS (Reime)
<i>Chemo in relapse*</i>					
Mitoxantron	kr 2 188	5 days	kr 10 939	kr 2 188	OUS (Reime)
Amsakrin	kr 48	3 days	kr 143	kr 29	OUS (Reime)
Cytarabine	kr 6 336	7 days	kr 44 352	kr 8 870	OUS (Reime)
<b>Markov model D (Transplant)*</b>					
Pre transplantation	-	-	kr 120 773	kr 24 155	Mishra et al. (2002)
Transplantation	-	-	kr 801 972	kr 160 394	Mishra et al. (2002)
Post transplantation	kr 145 534	0,083 month	kr 12 128	kr 2 426	Mishra et al. (2002)
<b>Markov model B and C (No response and palliative)</b>					
DRG	kr 5 382	10 days	kr 53 820	kr 10 764	The Directorate of Health
Thrombocytes*	kr 3 945	8 units	kr 31 560	kr 6 312	OUS (Blood bank)
Erythrocytes*	kr 1 450	8 units	kr 11 600	kr 2 320	OUS (Blood bank)

\* Adjusted to 2014 NOK

As mentioned before, patients who enter the Markov models are those who come from the decision tree. Patients that do not receive transplantation, go to relapse or die, will receive a third chemotherapy (see the HOVON map in Appendix J). The cost of the third chemotherapy will therefore incur in cycle one in first remission, in the Markov models A1 (young) and A2 (elderly), since those who enter the Markov model in cycle zero are those who enter directly from the decision tree. In cycle one the costs will therefore be cost of third line chemotherapy, length of stay at hospital, intensive care, blood transfusions, and medications associated with treatment. After this cycle there are only costs of follow-up that incur. For second and third remission follow-up is the single occurring cost.

Follow-up is estimated at every month for one year. The second year, they are followed up every third month for another 12 months. At year three, they are followed up once every sixths month for the rest of the observational period. Cost of follow-up is based on estimates from MD Fløisand, by using the average wage of a chief attending physician at the

Haematology ward. The equipment used and the price of laboratory testing is approximately NOK 500, and the physician hours spent is about one hour per follow-up (see Appendix N for wages of the ward). Hence the cost of follow-up per patient in Table 22 is NOK 1 343.

In relapse, a patient will receive either a combination of Mitoxantron, Cytarabine and Amsakrin (chemo in relapse), or the first chemotherapy (as in the induction treatment). 50 per cent of the patients will receive first chemotherapy, while the other 50 per cent will receive “chemo in relapse” (Fløisand, 2015). Since first chemotherapy contains three different chemotherapies, we have taken a mean of AraC+Dauno and AraC+Ida. This is a simplification, assuming that it is an equal probability of receiving either one of them. Since “other chemotherapy” is a mean of the other chemotherapies, we used this. These patients will also receive a combination of the medications connected to treatment as well as cost of blood transfusions, intensive care, and the cost of length of stay.

### **Palliative care**

The cost of receiving palliative care is found by using a general DRG (Diagnosis-related groups) for outpatient palliative care in addition to adding the cost of blood transfusions. The average outpatient visits are three times per week, while the frequency of blood transfusions is twice a week (expert opinion). DRG is a patient classification system where hospital stays (or outpatient consultation) in somatic institutions are classified in groups that are both medical and resource allocated homogeneous (Helsedirektoratet, 2015a). The DRG weight for the different diagnosis is supposed to reflect the cost of treatment.

The local hospitals administer the patients receiving palliative care. The accountant department at OUS have no data concerning costs for this group of AML patients. To be able to calculate costs for this group we chose to use the DRG price for outpatient palliative care in combination with the cost of blood transfusions. The DRG weight is 0,132 (Helsedirektoratet, 2014), and DRG price in Norway was NOK 40 772 in 2014 (Helsedirektoratet, 2015b). When multiplying this we get a cost of NOK 5 382 per day. Hence, the cost of each cycle in model B (no response) and C (palliative) is 10 (every third day) multiplied by the cost per day, which is NOK 53 820 per cycle. The cost of blood transfusions (a combination of erythrocytes and thrombocytes) is NOK 43 160 per cycle.

## Transplant

Number of days of follow-up in transplant is estimated in collaboration with MD Fløisand. When a patient has undergone transplantation, he/she is discharged at day 35, approximately. The patient is then followed up three to five days per week, in two weeks. Then for two to three days per week in four weeks, once per week in eight weeks, and lastly, once per two weeks for one year. The patients are followed up approximately two times per year. In the article by Mishra et al. (2002) it was reported that the cost of one-year follow up was \$14 553, which is NOK 145 534 in 2014. We assumed that his calculation was based on what MD Fløisand told us about how often they were followed up. Our estimation is therefore the cost of follow up divided by 1/12. This is a simplification because the intensity of follow up is higher in the first months after transplantation. After one year the patients are usually followed up at local hospitals. We used the estimated follow-up cost from remission in model A1 (young) and A2 (elderly) in the remaining cycles.

Table 23 - Transplantation costs (in US \$ and NOK) (Mishra et al., 2002)

Cost of transplantation		
	Dollar (2001)	NOK (2014)
Pre-transplantation	\$ 12 077	kr 120 773
Transplantation	\$ 80 195	kr 801 972
Post-transplantation	\$ 14 553	kr 145 534
<b>Total</b>	<b>\$ 106 825</b>	<b>kr 1 068 279</b>

The costs of transplantation reported via Mishra et al. (2002) are adjusted to represent the cost in 2014 by using the consumer price index inflation calculator from Bureau of Labor Statistics (Bureau of Labor Statistics, 2015) and then converting the US Dollar to NOK (Currency Converter, 2015). The final stage was to use the “Consumer price index” function on the Statistics Norway web page, to represent the costs in 2014 NOK (Statistics Norway, 2015).

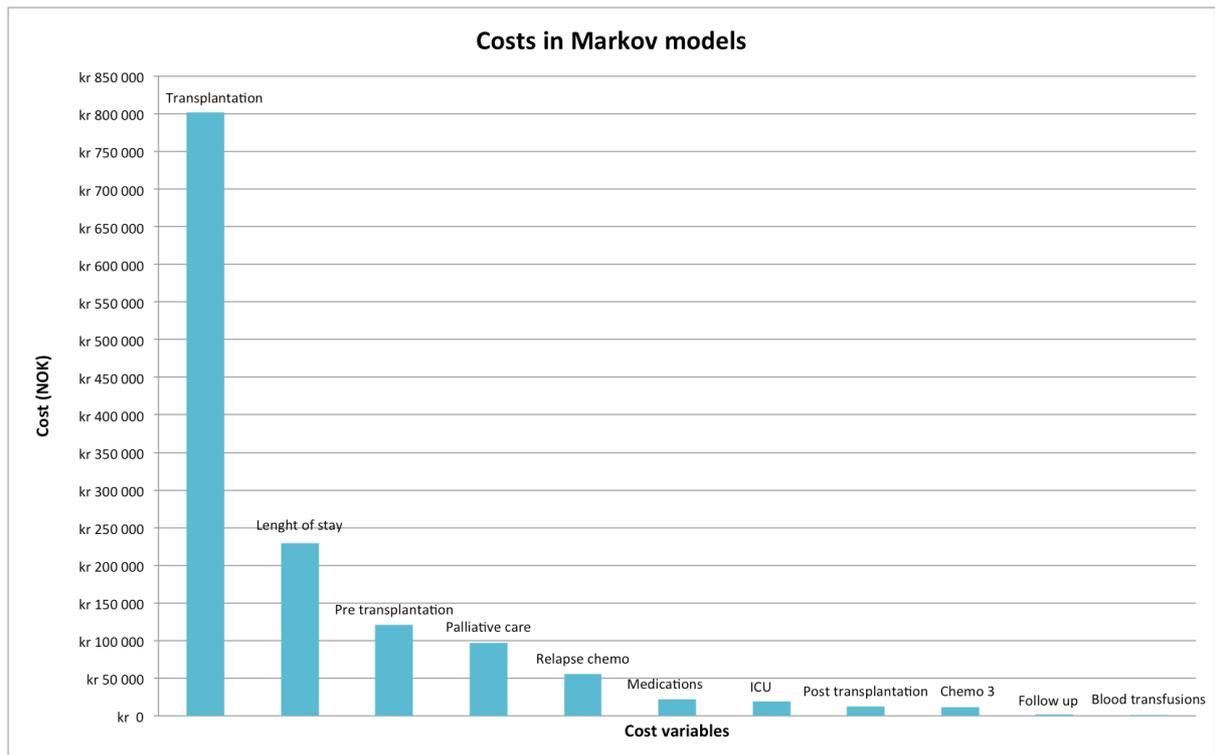


Figure 19 - Bar chart of costs related to further treatment (Markov models)

Figure 19 is a bar chart of the costs added in the Markov models. Transplantation is clearly the highest cost, but the intensive care is also a significant cost driver.

# 7 Results

The outcome of this analysis is a five-year survival of patients with AML, as well as the total cost of treatment. The model predicts the numbers of individuals who receives the different forms of treatment in addition to the price of the treatment and remission paths. All costs were discounted, except for the costs in the decision tree.

In order to conduct the PSA with 1000 iterations a Monte Carlo simulation was carried out in Excel by using Visual Basic. The expected costs and life expectancy in the models were investigated both isolated and as a total including the decision tree. The isolated analysis displays the result independent of the decision tree, which captures the total cost and life expectancy of the individual Markov models. The analysis including the decision tree takes the pathway into consideration to illustrate the total life expectancy and costs dependent of age and those responding to treatment. The PSA reflects the cost and life expectancy per individual. The results of model A1 (young) and A2 (elderly) includes transplantation, while the results reflecting the decision tree is denoted as induction treatment.

The results confirmed that AML treatment is resource demanding and there is considerable variation with respect to patient characteristic, clinical pathway and prognosis.

Table 24-29 shows the PSA result per individual in our data set. Scatter plots of cost per life expectancy resulting from the Monte Carlo simulation is shown in Figure 20-25.

## 7.1 Expected costs and survival

Table 24 refers to patients responding to treatment in the decision tree, which then goes through model A1 or A2, and receives transplantation. Palliative care includes patients who receive palliative care through either not responding to or not receiving treatment from the decision tree. Total young and elderly patients is all models combined, separated by age only. The total of the PSA results are all models combined.

Table 24 - Discounted costs per individual in all models with the decision tree

Five-year discounted costs per individual with the decision tree (PSA)								
	Total	Total Young	Total Elderly	Response Young	Response Elderly	Palliative care Y	Palliative care E	Total Palliative care
Mean	kr 1 401 521	kr 1 125 641	kr 275 880	kr 1 246 592	kr 849 935	kr 134 785	kr 404 054	kr 538 839
Min	kr 1 026 551	kr 872 552	kr 153 999	kr 944 626	kr 556 352	kr 69 093	kr 125 568	kr 194 661
Max	kr 1 792 015	kr 1 393 314	kr 398 701	kr 1 646 926	kr 1 246 656	kr 309 769	kr 1 093 547	kr 1 403 316
Std.dev	kr 120 269	kr 83 122	kr 37 147	kr 103 125	kr 111 214	kr 28 389	kr 140 025	kr 168 414
2,5th percentile	kr 1 176 269	kr 965 821	kr 210 448	kr 1 047 091	kr 642 362	kr 87 491	kr 207 806	kr 295 297
97,5th percentile	kr 1 645 234	kr 1 289 552	kr 355 682	kr 1 458 290	kr 1 065 575	kr 194 882	kr 767 374	kr 962 256

Table 24 displays the expected cost per individual. Total cost ranged from NOK 1 026 551 to NOK 1 792 015. Among the young patients, the total cost ranged from NOK 872 552 to NOK 1 393 314, while the total cost for the elderly patients ranged from NOK 153 999 to NOK 398 701. The cost of the young patients responding to treatment ranged from NOK 944 626 to NOK 1 646 926, while the cost of the elderly patient group ranged from NOK 556 352 to NOK 1 246 656. The cost of palliative care in young patients ranged from NOK 69 093 to NOK 309 769, whereas the cost of palliative care in elderly patients ranged from NOK 125 568 to NOK 1 093 547. The total cost of all models combined has a mean of NOK 1 401 521.

Table 25 - Discounted cost per individual in Markov models with the decision tree

Five-year discounted costs per individual with the decision tree (PSA)						
	Induction (Young)	Induction (Elderly)	A1 (Young)	A2 (Elderly)	No response	No induction
Mean	kr 426 648	kr 83 303	kr 639 267	kr 123 436	kr 75 737	kr 53 129
Min	kr 276 519	kr 47 487	kr 470 515	kr 75 120	kr 39 185	kr 13 302
Max	kr 653 673	kr 147 427	kr 822 701	kr 211 944	kr 169 863	kr 208 638
Std.dev	kr 54 099	kr 13 733	kr 59 016	kr 21 639	kr 16 110	kr 19 401
2,5th percentile	kr 327 568	kr 59 299	kr 523 044	kr 86 023	kr 47 254	kr 24 375
97,5th percentile	kr 541 854	kr 112 166	kr 758 752	kr 168 233	kr 110 795	kr 95 083

Table 25 shows the PSA results of the decision tree and the Markov models. The least costly treatment incur in patients who do not receives induction treatment (model C), while the highest cost incur in the model A1 for the young patients. This is NOK 53 129 and NOK 639 267, respectively. There is a substantial difference in cost between model A1 (young) and A2 (elderly), where the mean cost is NOK 639 267 in model A1 and NOK 123 436 in model A2. This is similar for induction treatment where the mean cost of young patients is NOK 426 648 and the cost of elderly patients is NOK 83 303.

Table 26 - Life expectancy per individual in all models with the decision tree

Five-year life expectancy per individual with the decision tree (PSA)								
	Total	Total Young	Total Elderly	Response Young	Response Elderly	Palliative care Y	Palliative care E	Total Palliative care
Mean	37.61	32.02	5.59	39.89	22.52	0.90	3.53	4.43
Min	26.61	23.14	3.47	29.60	13.01	0.44	0.86	1.30
Max	46.10	36.98	9.12	45.85	32.46	2.91	11.27	14.18
Std.dev	2.60	1.78	0.82	1.98	2.97	0.20	1.47	1.67
2,5th percentile	32.50	28.44	4.06	35.84	17.01	0.58	1.60	2.18
97,5th percentile	42.73	35.40	7.33	43.56	28.53	1.34	7.37	8.71

In Table 26, the total life expectancy ranged from 26.61 months to 46.10. The total life expectancy of the elderly and young patients ranged from a mean of 5.59 months to 32.02 months. Response among young patients is slightly higher than in the total for young patients, with a mean life expectancy of 39.89 month and 32.02 months respectively. The total mean life expectancy for all models combined was 37.61 months.

Table 27 - Life expectancy per individual in Markov models with the decision tree

Five-year Life expectancy per individual with the decision tree (PSA)						
	Induction Young	Induction Elderly	A1 (Young)	A2 (Elderly)	No response	No induction
Mean	0.75	0.21	30.67	4.72	0.79	0.48
Min	0.66	0.12	21.94	2.63	0.41	0.09
Max	0.84	0.30	35.65	8.45	1.74	2.22
Std.dev	0.03	0.02	1.80	0.79	0.16	0.20
2,5th percentile	0.70	0.17	27.08	3.26	0.50	0.19
97,5th percentile	0.80	0.25	34.02	6.41	1.13	0.92

In Table 27, the life expectancy in the Markov models ranged from 0.21 months for elderly patients who did not receive induction treatment to 30.67 months for model A1 (young). The survival in model A1 (young) is considerably higher than in model A2 (elderly), whereas the mean life expectancy in model A1 is 30.67 months and 4.72 months in model A2. The mean survival in the palliative treatment is 0.79 months for the patients who did not respond to treatment and 0.48 months for patients not receiving induction treatment.

The scatter plot in Figure 20 illustrates the relationship between cost per life expectancy of the young and elderly patients. Young patients has a better result in terms of life expectancy, but at a higher cost, where the average life expectancy is around 35 months and the average cost is just below NOK 1 200 000. Elderly patients shows lower costs with a poorer life expectancy compared to the young patients.

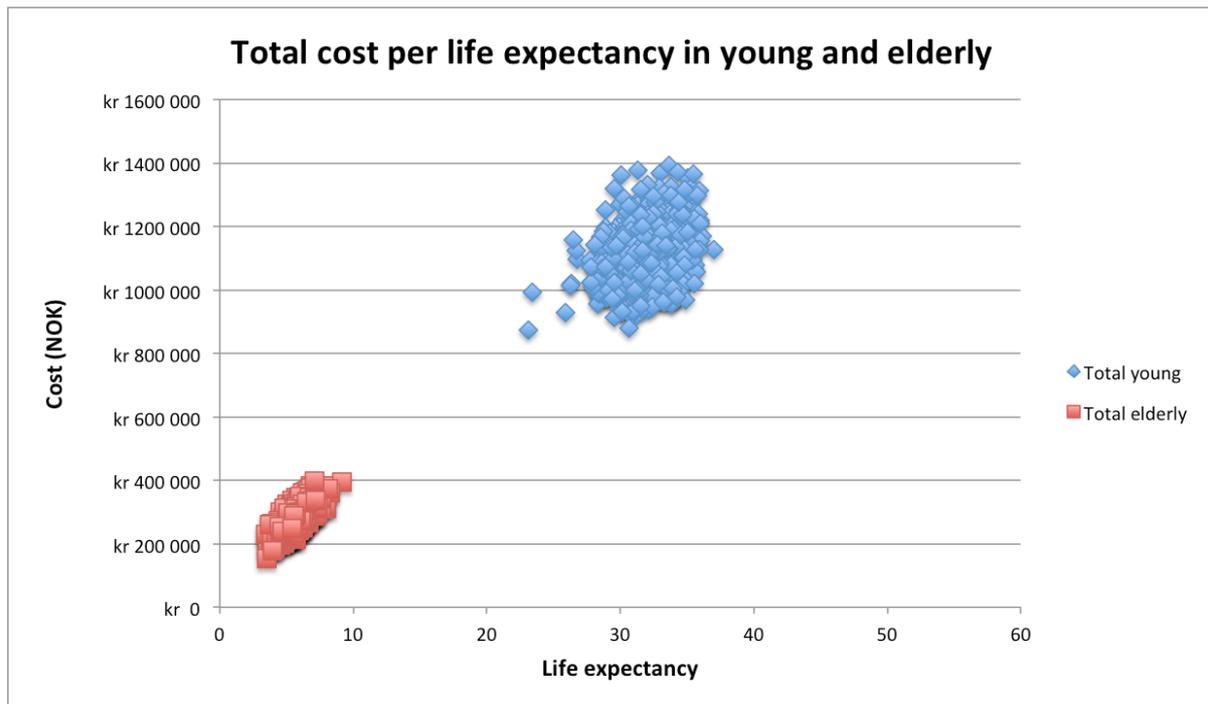


Figure 20 - Total cost per life expectancy in young and elderly

Figure 21 shows a scatter plot of patients receiving palliative care. The cost increases along with the patient's life expectancy. It is important to notice that the x-axis ends in 12 months; hence the life expectancy in palliative care is quite low. The average life expectancy is around 4 months for the elderly patients, and 1 month for the young patients. This might be due to that more elderly patients receive palliative treatment.

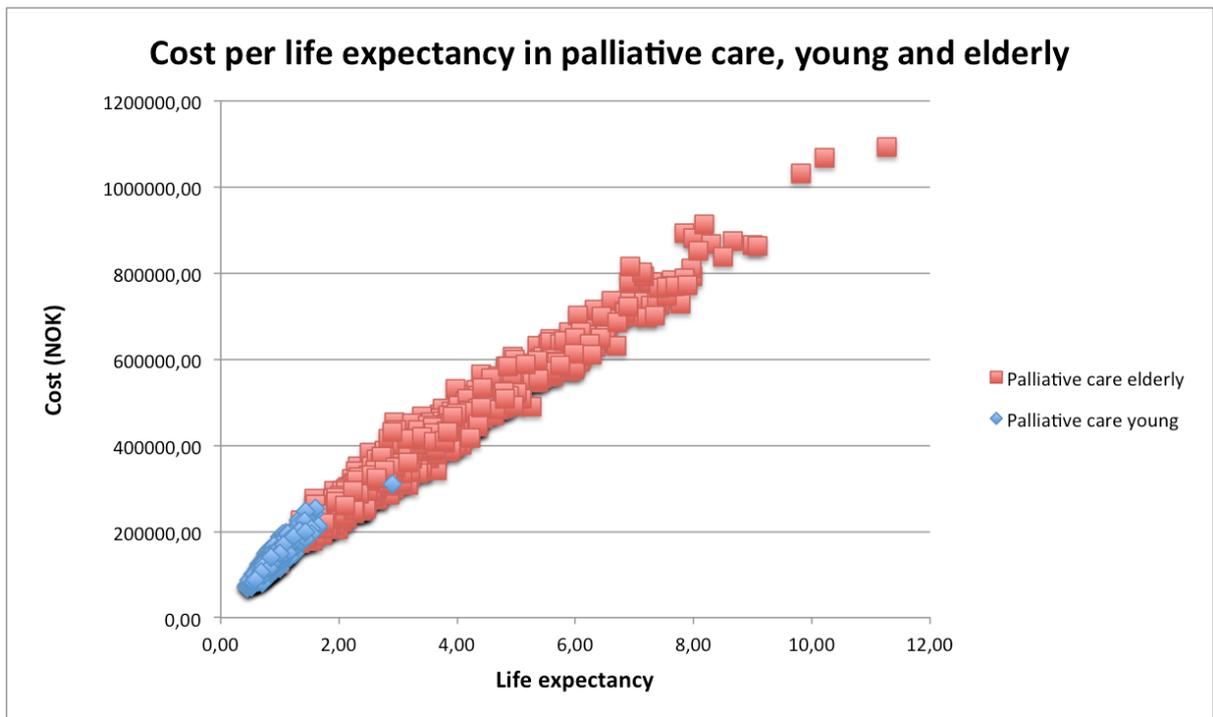


Figure 21 - Cost per life expectancy in total palliative care

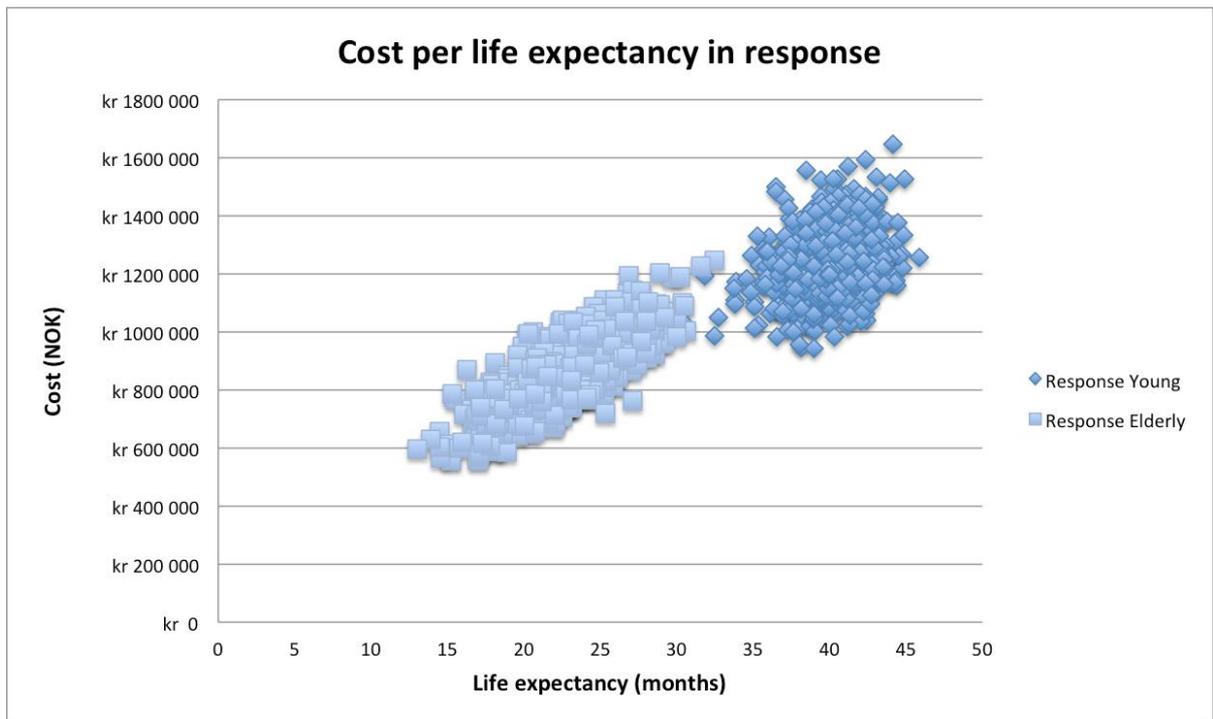


Figure 22 - Cost per life expectancy in response

Figure 22 illustrates a scatter plot of young and elderly patients who responds to treatment. The cost per life expectancy is higher in young patients than in elderly patients. For young patients, the life expectancy has an average of nearly 40 months. Elderly patients have both a shorter life expectancy, ranging between 20 and 25 months, and lower costs.

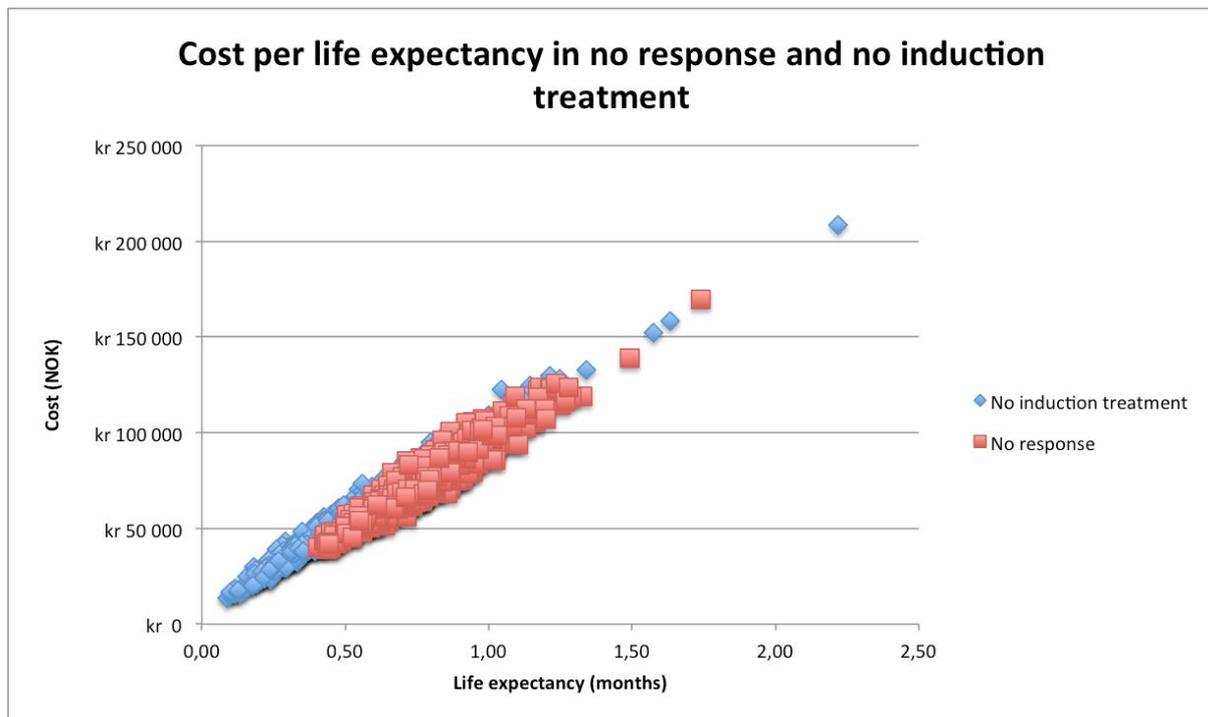


Figure 23 - Cost per life expectancy in no response and no induction treatment

In Figure 23, the cost per life expectancy is increasing for patients who did not receive any induction treatment and patients who did not respond to treatment. Patients with no induction treatment starts off with both lower costs and life expectancy than patients that did not respond to treatment. Both models have the same treatment costs. Yet, they differ slightly in cost and life expectancy, which may be due to different transition probabilities as they belong to different Markov models.

The tables below show the PSA results of receiving the specific forms of treatment. By this we mean that all Markov models are starting in one and then distributed out in the model, using the calculated transition probabilities. This is performed to express the isolated results for each model.

Table 28 - Discounted cost per individual in Markov models without the decision tree

Five-year discounted costs per individual without the decision tree (PSA)				
	A1 (Young)	A2 (Elderly)	No response	No induction
Mean	kr 917 789	kr 999 995	kr 574 975	kr 799 392
Min	kr 715 980	kr 760 365	kr 325 536	kr 117 485
Max	kr 1 167 262	kr 1 282 964	kr 954 878	kr 3 615 484
Std.dev	kr 75 241	kr 85 055	kr 91 119	kr 459 870
2,5th percentile	kr 777 748	kr 831 454	kr 408 996	kr 225 424
97,5th percentile	kr 1 068 827	kr 1 170 083	kr 765 874	kr 1 971 408

In Table 28 the mean cost of model A2 (elderly) is somewhat higher than in model A1 (young), and the result is NOK 999 995 and 917 789 respectively. Patients with no response to treatment have a mean cost of NOK 574 975, whereas patients who did not receive induction treatment have a mean cost of NOK 799 392.

Table 29 - Life expectancy per individual in Markov models without the decision tree

Five-year life expectancy per individual without the decision tree (PSA)				
	A1 (Young)	A2 (Elderly)	No response	No induction
Mean	47.27	41.11	6.15	7.54
Min	40.43	29.77	3.67	0.41
Max	52.00	48.21	9.82	37.43
Std.dev	1.88	2.85	0.90	4.88
2,5th percentile	43.23	35.06	4.61	1.5
97,5th percentile	50.57	45.93	8.06	19.90

Table 29 shows the life expectancy of all Markov models. Markov model A1 (young) has a mean life expectancy of 47.27 months, whereas Markov model A2 (elderly) has a life expectancy of 41.11 months. The model of patients with no response to treatment has a poorer life expectancy (6.15 months) than the model of patients who did not receive induction treatment (7.54 months). The difference is not substantial.

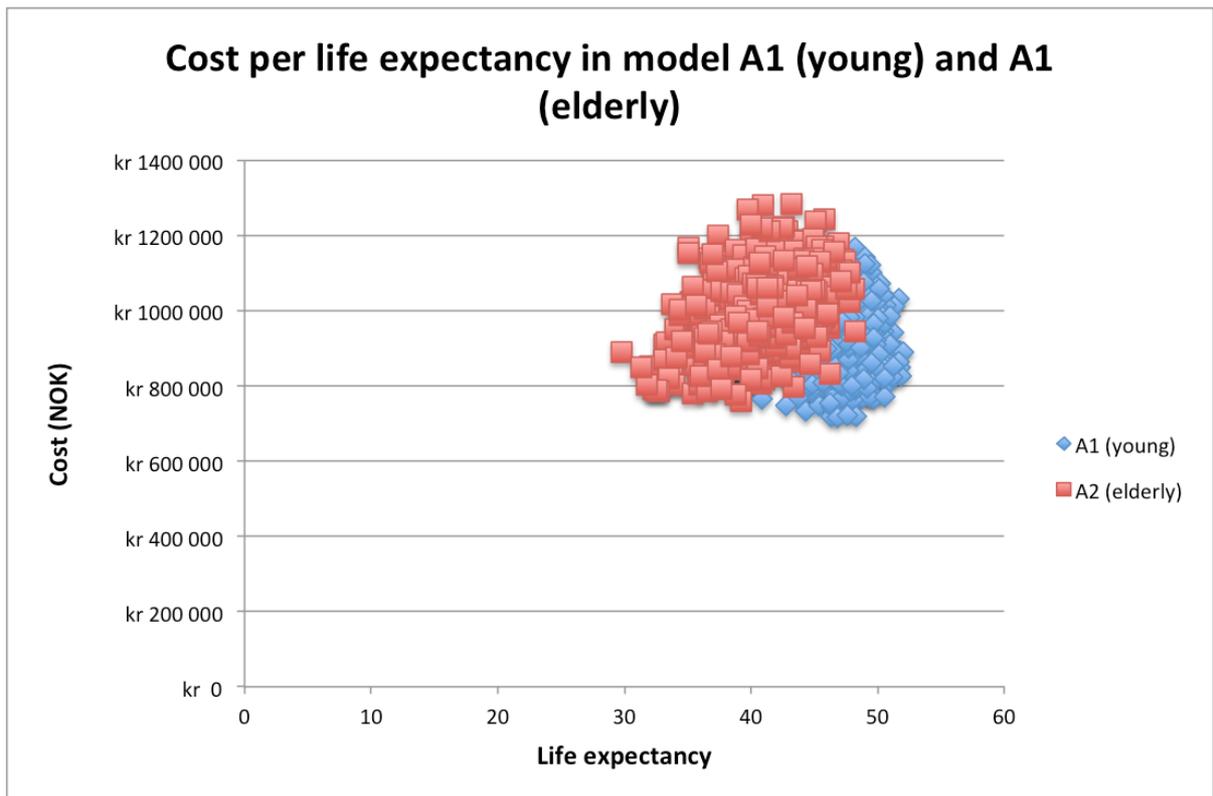


Figure 24 - Cost per life expectancy in model A1 and A2 without the decision tree

Figure 24 illustrates the relationship between cost per life expectancy in Markov model A1 (young) and A2 (elderly). Model A2 has a somewhat higher cost than model A1, but at a shorter life expectancy. Life expectancy in model A2 range from approximately 30 months to almost 50 months at cost ranging from NOK 700 000 to around NOK 1 300 000.

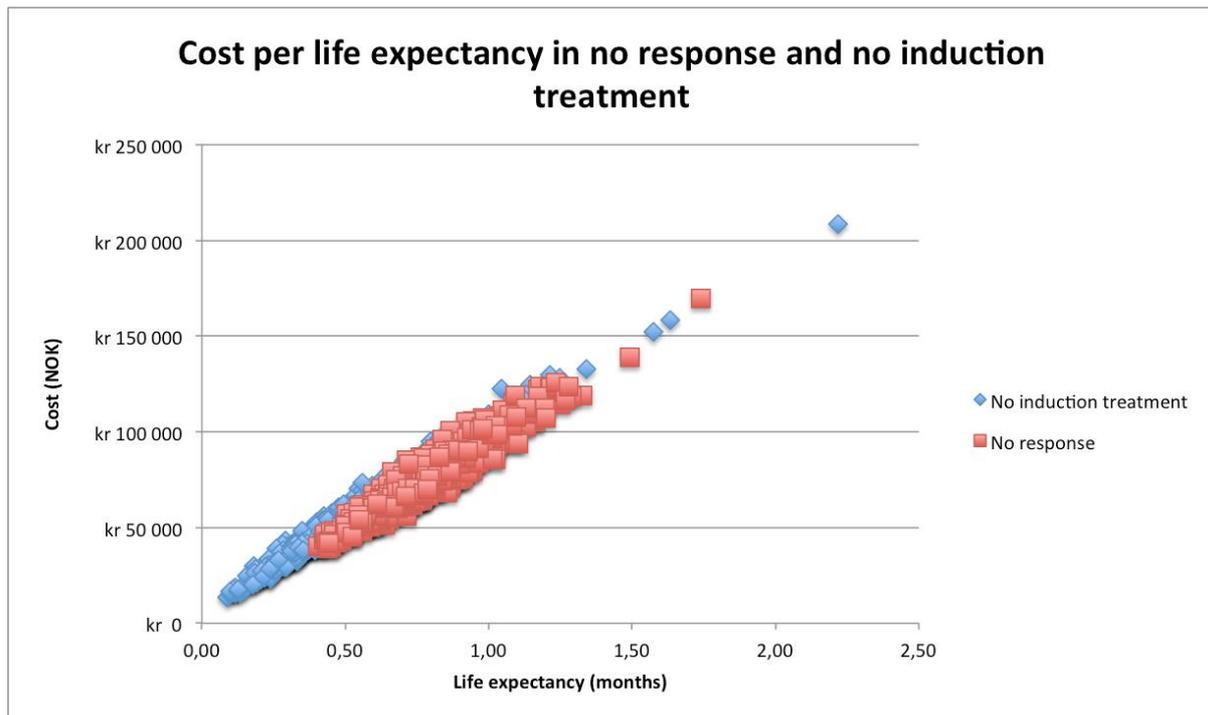


Figure 25 – Cost per life expectancy in “no response” and “no induction treatment” without the decision tree

In Figure 25, the cost and life expectancy of patients who did not receive induction treatment is visibly higher than for patients who had no response to treatment. Cost per life expectancy is increasing over time in both models.

### Cost per cycle in all Markov models

Figure 26 below shows the costs incurring from cycle zero to 18 in Markov models A1 (young), A2 (elderly) and transplantation. The costs are evidently highest during the first couple of months, with model A1 generating the highest costs. It dramatically decreases past cycle two, below the costs of transplantation. This is because the consolidation therapy (including length of stay, medications, ICU etcetera) occurs only in the first cycle in Model A1. The cost of transplantation is higher during the first months because the transplantation in itself is very costly.

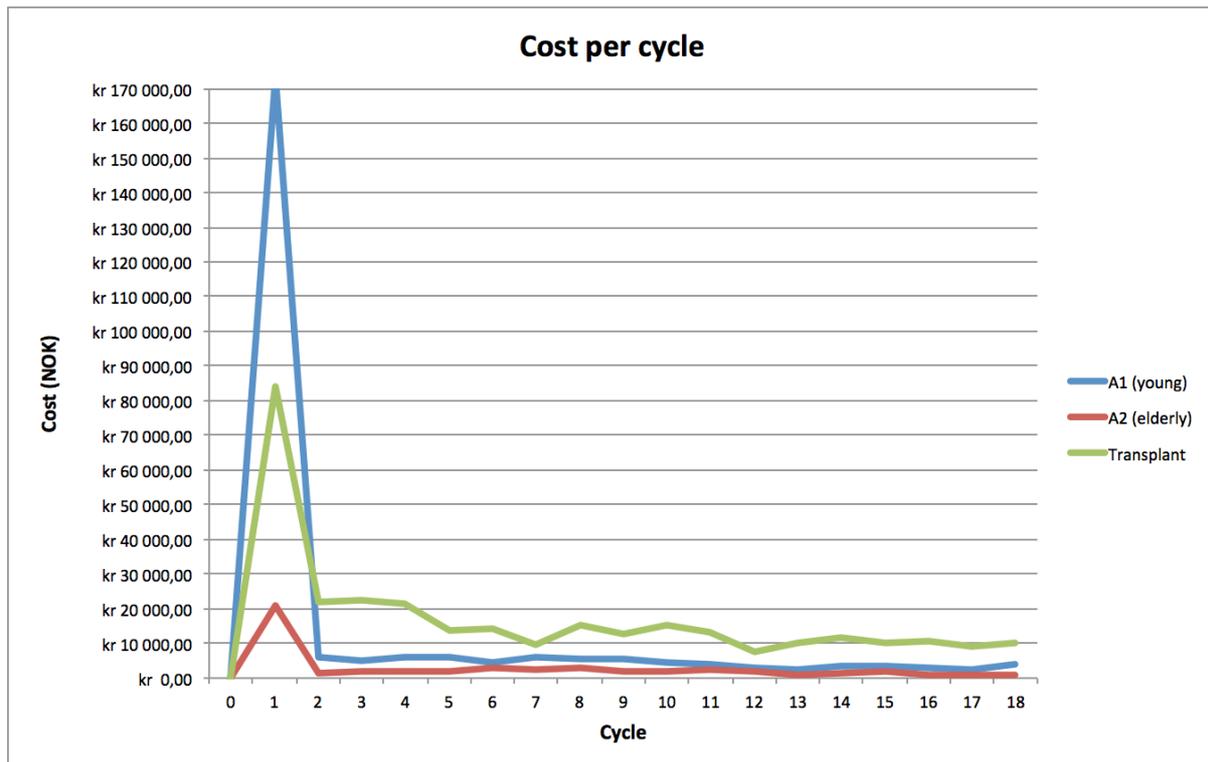


Figure 26 - Cost per cycle in cycle 0-18 for A1 (young), A2 (elderly), and transplantation

In Figure 27, on the following page, the cost per cycle is highest during the first cycles. It decreases consequently until cycle nine, where it partly flattens out, and further it is stabilizing in the later cycles. The cost per cycle is highest for patients who had no response to treatment during all cycles, except for a peak at cycle one for patients who did not receive induction treatment. Cost for patients who did not respond to treatment initiates below NOK 10 000 at cycle zero, and terminates at below NOK 1 000 in cycle 18. The cost of patients who did not receive induction treatment starts below NOK 6 000 in cycle zero, has a peak in cycle one at below NOK 8 000, and ends at zero cost in cycle 18.

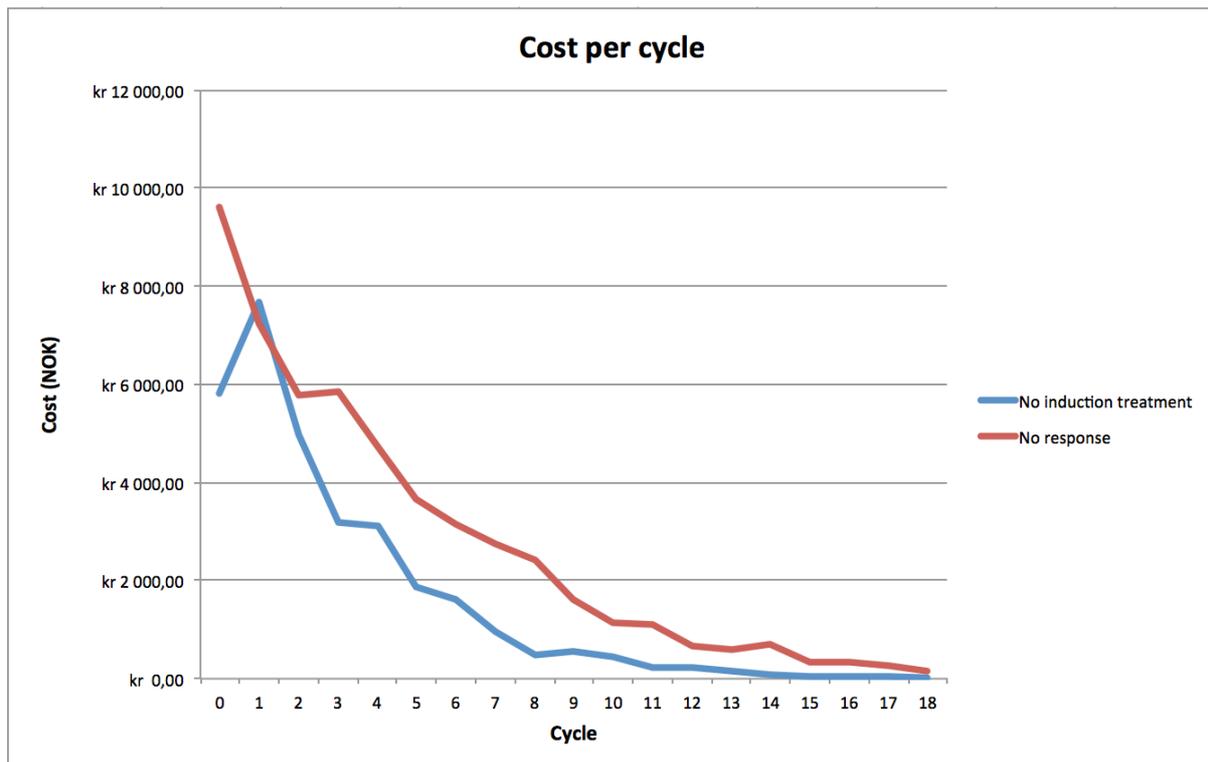


Figure 27 - Cost per cycle in “no induction treatment” and “no response” in cycle 0-18

## 7.2 Comparing results to the UK

In order to be able to compare our results to the study by Wang et al. (2014), we had to adjust the cost in terms of purchasing power. Purchasing Power Parities (PPP) are currency converters, which take account of the effects of differences in price levels between countries. PPPs make volume comparisons of Gross Domestic Product (GDP) components and comparisons of price levels. A PPP show how many units of currency A needed to be spent in country A in order to attain the same volume of a product in currency B in country B (Koechlin, Lorenzoni, & Schreyer, 2010).

In a paper by (Koechlin, Konijn, Lorenzoni, & Schreyer, 2014) we found that the hospitals price level is 207 for Norway and 119 for the UK. The EU average is 100. By dividing the price level of the UK by the price of Norway we found that UK has a purchasing power of 57.5 per cent relative to Norway.

Table 30 - Cost and life expectancy in Norway and the UK

Cost and life expectancy in Norway and UK adjusted by purchasing power*						
	Norway			UK		% cost difference
	Cost (unadjusted)	Cost (adjusted)	Life expectancy	Cost	Life expectancy	
Total	kr 1 401 521	kr 805 705	37.61	kr 593 545	16.56	-35.7 %
Young	kr 1 381 377	kr 794 125	40.79	kr 1 147 602	34.18	30.8 %
Elderly	kr 1 253 989	kr 720 892	26.05	kr 323 432	8.56	-122.9 %

\*2014 NOK

Table 29 shows the comparison of our results to the results of Wang et al. (2014), adjusted for purchasing power of 57.5 per cent for health care (Koechlin et al., 2014). From this table we can see that the total cost is higher in Norway opposed to the UK. The difference in total cost between our study and the UK is approximately 35.7 per cent, where Norway has higher costs. The cost of young patients in the UK is higher than in our study, with a difference of 30.8 per cent. For elderly patients there is a difference in costs of nearly 122.9 per cent, where Norway spends more than the UK. Overall, Norway predicts a greater life expectancy compared to the UK.

## 7.3 Validation of the research

The decision tree and the Markov model are validated according to internal validity, external validation, face validity, cross-validation and transparency.

### 7.3.1 Internal validation

This study is conducted by two persons and has therefor been controlled and discussed regularly. Additionally, our supervisor Eline Aas has controlled the formulas and the work along the way. In order to control that the Markov models are correctly built we added a “Control” column at the end of each model where one easily could tell if the entire cohort was distributed throughout the rows. There are five separate Markov models in Excel; Markov A1, Markov A2, Markov Transplant (D), Markov Palliative (C) and Markov No response (B). Together with the amount of people who dies in the decision tree all of these models should sum up to 1 for each cycle. To control for this we made a new sheet in Excel where we added each value for all of the “Control” columns of the respective models in addition to the “Early death” from the tree. (A screen shot of the Control sheet in Excel can be seen in Appendix D.) All of the rows sums up to 1, which is an internal validation of the

models. By having the control columns in each of the Markov models it was easier to debug the model since we could see which rows that did not sum up correctly.

### 7.3.2 External validation

Our output from the study can be compared to the numbers from the Cancer Registry, and if our model corresponds to the reported survival one can say that it is externally validated. If our results correspond to the anticipated results this is an important validation and strength of the model.

Figure 29 illustrates the difference of the five-year survival in our data set and our estimated model compared to the cancer registry numbers from 2004 to 2008 and 2009 to 2013.

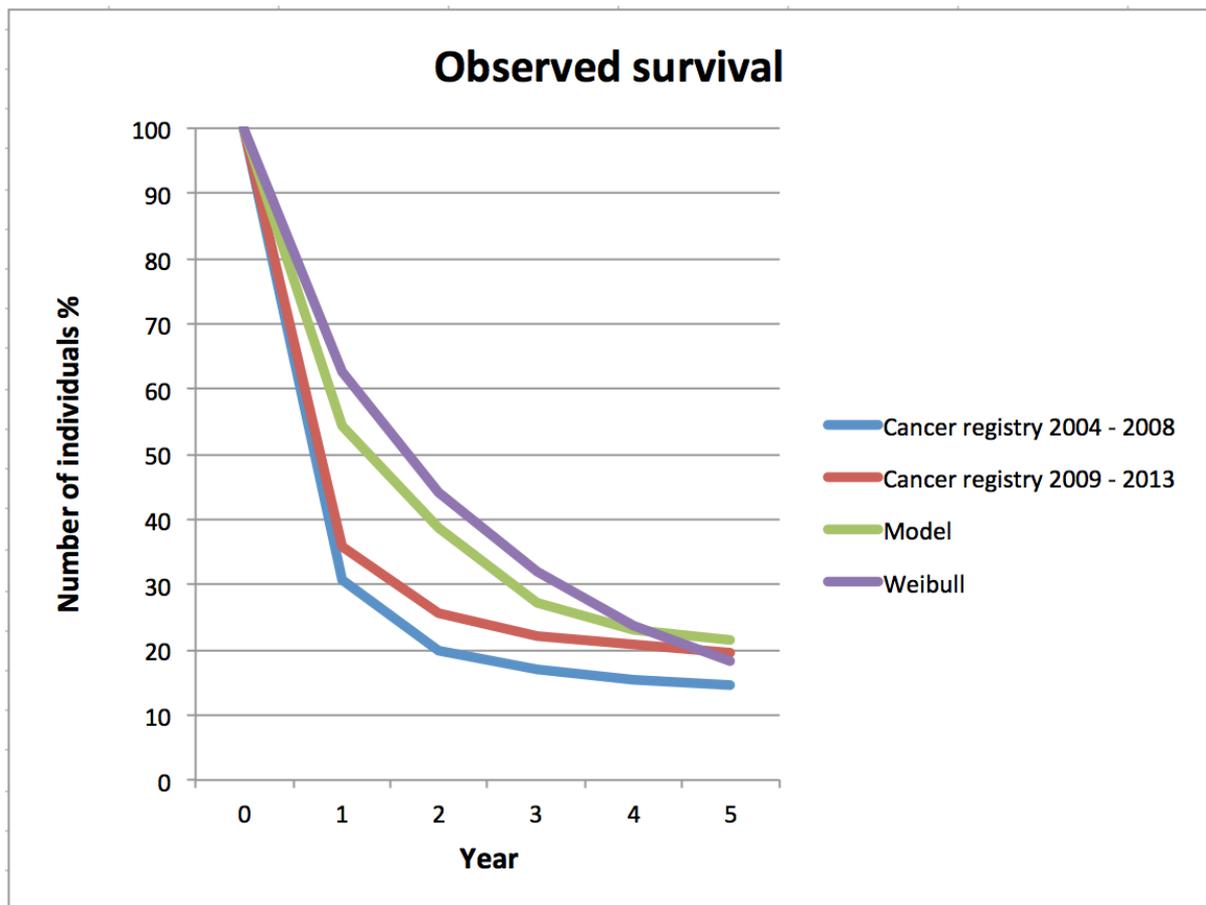


Figure 28 - Comparison of five-year survival in (external validation)

Our data set indicates a better survival than the Cancer registry data. The Weibull model is higher than all other curves in the graph, but it goes below both our data set and the Cancer registry (2009-2013) curve between years four and five. Our model did not demonstrate a

good fit compared to the empirical data. The predicted survival did not match the empirical curve, except for the first and last years of the time perspective. This might be due to a low mean age in our data set.

### **7.3.3 Face validation**

The AML study is conducted in collaboration with a specialist doctor at the Haematology ward at OUS Rikshospitalet and the model has been constantly discussed with him. This gives face validity. Since the framework for this thesis has been worked out together with MD Fløisand he has controlled that the decision tree is correct and that the use of the variables in the data set is correct. He has also ensured that the medical strategies have been interpreted correctly. To correct for the unlikelihood that patients move between states at fixed time intervals the cycle length is only one month. He also controlled that we included the correct chemotherapies, blood transfusions and other medicaments. An important factor of face validity is that the expert can recognise the actions in the model, which is confirmed by MD Fløisand. The study by Wang et al. (2014) is also a form of face validation, as the structure of our models is based on this paper. The structure of their model corresponds well with our data set.

### **7.3.4 Cross-validation**

The foundation of our AML study is based on a previous study from the UK by Wang et al. (2014), which may be considered as cross-validation, as the studies are examining the same topic. However, our results appear not completely comparable to the UK model, because the groups are not entirely corresponding, nor are the results reported identically. However, the clinical pathway is equal in both studies. The life expectancy and costs varies between Norway and the UK, but this can also be subject to different inclusion criteria's.

### **7.3.5 Transparency**

The study is transparent as all of the methods are available and explained in the Method chapter. It shall be possible to replicate this study if one is given the data. The do-file from Stata can be seen in Appendix N. We have also included several screen prints from the Markov models in Excel in the appendices (Appendix A, B and C), which mean that one ought to be able to rebuild the model based on these. The calculation of the costs has been through roughly discussed in the Material chapter and should be easy to recalculate.

### **7.3.6 Predictive forecast**

The study can be used in prediction of the outcome of treating AML patients, both in relation to survival in different states, as well as the cost for treatment in Norway, but to conduct a predictive forecast would not be possible as no time has passed, and it is impossible to control that the results are valid in the future.

# 8 Discussion

## 8.1 Main findings

Both costs and life expectancy varied according to the initial treatment and the age of diagnosis. The results of our models indicate that the total life expectancy is 37.61 months, while the expected total cost is NOK 1 401 521.

As expected, younger patients have a higher life expectancy and incur more costs than elderly patients. However, in the PSA result when not including the decision tree, the cost of model A2 (elderly) is higher than model A1 (young). This might be caused by elderly patients having a higher probability of leaving remission to relapse than young patients. In relapse, patients receive an additional chemotherapy, and since elderly patients have a higher probability of relapse, the costs will increase.

It is interesting to compare the survival and costs in Norway and the UK. In the UK more elderly patients was included, which might make a comparison unfeasible. However, since the UK study separates responding to treatment with early response and late response, the variation from our study should be interpreted with precaution. The UK study used register data from the Haematological Malignancy Research Network (Wang et al., 2014) while we used individual data. It may be an advantage of their study that specific registry data is used to model AML, whereas our study has the advantage of using individual data. On this basis, the studies appear comparable.

## 8.2 General

New and improved methods may affect the results both in relation to survival and costs. One could use the results to rank the least and most costly treatments, but this would not be a suitable foundation for economic evaluation since it involves different risk groups. Further, if one wanted to use this study as a basis for decision making one would need to apply some more details to the model, such as the utility measure “Quality Adjusted Life Year” (QALYs), and a threshold for willingness to pay. The societal perspective should be considered as well. Nevertheless, it was beyond the scope of this study to compare the economic impact of the different treatment strategies.

In the case of AML there are no pre-determined ways of treating that will be the best treatment strategy. Rather, the purpose is to treat with a curative goal for those patients that may have a possibility of handling heavy treatment. This individual customization makes it difficult for the modeller to build a model that reflects this patient group true clinical pathway. Much work has been put into making the model as accurate as possible. The validation of the model is conducted to control for this.

Weinstein and Stason (1977) discuss that the estimates of medical effectiveness and cost used in analysis ought to express and reflect explicitly the uncertainties surrounding the estimates. The sensitivity analysis is conducted to correct for the uncertainty, but some strengths and limitations will be discussed further in next sections.

We chose not to discount life expectancy because it does not make any sense that “using” less health now will give a benefit of more health in the future. It is argued that comparing the size of the health loss is easier when using undiscounted units in prioritizing health interventions (NOU 2014: 12, 2014).

## **8.3 Strengths and limitations**

### **Material**

As mentioned in the Method chapter, we had to make some simplifications along the way. This study only looks at AML as a distinct cancer form, and does not look at the difference between primary and secondary cases. We did not differentiate between primary and secondary cases due to the number of people in the cohort. If we did so the results could be misleading since there are too few individuals in the secondary group. Nevertheless, if possible, one should separate these two forms in order to get a more accurate picture of the transition probabilities and life expectancy.

The study does not look at other hospitals than OUS Rikshospitalet. Inclusion of patients from other hospitals that actively treat AML patients could have given other results. MD Fløisand suggested that there are elderly patients in local hospitals who also have the AML diagnosis, but are not actively treated for the disease. A reason for this might be comorbidity

and the fact that they would not handle the heavy chemotherapy treatment. Still, this does affect the results, as they are not accounted for.

Another factor is that the patients are divided into two groups; under 60 years or 60 years and older. This means that the model is not completely age specific. At OUS Rikshospitalet the treatment line differs between patients at the age of 65, rather than 60 years, which we have used in our model. This “manipulation” was done for two reasons; firstly, this is the subdivision used by Wang et al. (2014) in their study and what we wanted to compare our study to. Secondly, there were not many patients in the older group if we divided the group at the age of 65, and this would lead to non-significant results in the regression analysis.

Our data set consists of individual data subtracted for our specific research. This can be found as strength of the study compared to register data where one has a large data set unspecified for specific research.

### **Time frame**

The time frame of this study was set to five years. It is common to use a three or five-year perspective in cancer research, and in this relation it was natural to adopt a five-year time frame. A drawback by only following the patients for five years is that some patients experience more than two relapses, and this will not be captured in our model. On the other hand, there are not many patients who experience this; therefore it would not make any huge impact on the results.

### **Probabilities**

Due to few patients left in the cohort after the first relapse, it was not possible to calculate any transition probabilities by using Weibull regression. We had to make simplified probabilities for the states that occurred after second remission. These adjustments should not have any huge effect on the results. We assumed that the second relapse is equal to the first relapse in relation to the transition probabilities and treatment costs. There were not many patients in the data set that had a second relapse, nor third remission, and hence it was difficult to make individual calculations for these patients.

We performed many commands in Stata to get a full picture on how the data set looks like and how the regressions would compare. Many of the regressions are not significant, which

may be due to few numbers of patients in the cohort. We assumed that the size of the cohort was the main reason for the non-significant regressions; hence we chose to accept the regression output.

In our study we over-estimate survival because half-cycle correction is not been incorporated. Since we are only looking at the clinical pathway it might not be necessary to adjust for this, but in an economic evaluation study it could be important.

### **Costs**

The costs have been identified at an average level, and should reflect the average cost of an AML patient. Through the PSA we know that the results vary to some degree. This makes sense as the treatment course can involve everything from only receiving palliative care or transplantation.

Another perspective, which is not included, is the cost of patients who achieve remission, but continue their lives with complications or side effects from the treatment. These patients can still be costly if they have follow-ups exceeding the five years we investigated and if they are unable to go back to work (partly or completely).

Patient involvement is becoming a greater part of the health care, and the cost of this may be difficult to include, but from a societal perspective it plays an important role.

The interval for follow-up in the Markov models is based on an average, since it is difficult to make this completely general. Some patients have follow-ups more than weekly, while others only have follow-ups on a monthly or even more rarely interval, depending on the patients expected outcome of treatment.

The cost and the average amount of patients who receives treatment at the intensive care unit is based on expert opinion and is set to be five per cent of the patients. We have not adjusted the estimate, as our data set does not provide any information in regards to this. The average length of stay at intensive care is also based on a mean, since it was difficult for MD Fløisand to provide precise numbers. Some patients stay at the intensive care for a couple of days, while others stay for months. The reason for this is that the cause for ending up at intensive care can vary. Our average is one week, based on an expert opinion. The cost of intensive

care is an estimate by the expert, it could be higher, but adopting a higher cost could be misleading on the results. Hence, we chose to rely on the expert.

The cost of patients who receives palliative care is based on DRG-cost and expert opinion. Most patients have outpatient visits and blood transfusion two to three times per week. We have used this average in both Markov model B (no response) and model C (no induction treatment). To track the specific costs of palliative care is too comprehensive for this thesis, but one could argue that it would have given more precise cost prediction if conducted. The costs of patients in palliative care who are admitted to hospital for shorter periods due to infections are not included. Elderly patients suffering from AML who receives palliative care might be transferred or enrolled to nursing home, and this has not been included in the thesis either. Hence, our results in palliative care might underestimate the true cost of palliative care in AML patients.

The cost of palliative care could have been included in the decision tree for patients who experience an early death. Additionally, we could have included palliative care for patients dying in the Markov models. By including palliative care in these states the costs of patients would perhaps been adjusted to a higher total palliative care cost in our results.

The costs in this thesis are a combination of direct costs from the Haematology ward, and amounts of recourses manually counted by MD Fløisand, which is multiplied with the price by us. This can be a weakness of the estimation. To correct for this we used a standard error of +/- 20 per cent. We have tried to make as accurate estimates as possible, and included all aspects explained to us by MD Fløisand. Since we are not specialists in the field we had to completely rely on the doctor and literature to know what to include. This makes is difficult for us to validate the costs.

The cost of transplantation is based on an article written in 2001 (Mishra et al., 2002) and to adjust the costs we have used consumer price index calculator to adjust the costs in in 2014 NOK, which is the period all other costs are tracked from. This can lead to some misinterpretations, and one can discuss whether we should have collected the costs associated with transplantation specifically for this study. Due to the short time period of conducting our study we had to make some appraisals, and we assume that the finding by Mishra et al. (2002) is representative.

We have used costs from 2014 for the entire model, and to adjust the findings from Mishra et al. (2002) we used an American consumer price index calculator (Bureau of Labor Statistics, 2015), since the cost is denoted in US Dollars. To convert the cost given in British Pounds from Wang et al. (2014) we used an inflation calculator from the Bank of England (2015). After adjusting respectively Dollars and Pounds to current costs, we converted the values into NOK by using a currency converter (Currency Converter, 2015). Lastly, we used an index regulator from Statistics Norway (2015) to adjust the costs from 2015 NOK to 2014 NOK, since the currency converter was unable to convert the currencies to 2014 NOK. The adjustment of the costs might lead to certain skewness, but this should be taken into account by the standard error of 20 per cent and the gamma distribution in the uncertainty analysis.

Increased amounts of research on AML treatment is focused on molecular genetic testing and the usefulness of this. When being able to track the different genes that affect the outcome of treatment the pathways may be more individualised and one can avoid treating patients with a poor prognosis. For some patients, palliative care might be a better option instead of going through heavy chemotherapies that will not have any positive effect. Similar, one can offer transplantation treatment only to patients who will benefit from it. This would also impact the cost.

### **Validation**

Four types of validation are used in our study. It might be a critique that the external validation does not completely correspond to our data, but this is probably because the Cancer Registry has data from the entire country, while our study only looks at patients from OUS. Further, the curves in Figure 29 from the Cancer registry imply that survival is increasing. Additionally the cross-validation is not completely fulfilled. This might be reasoned by different age composition between our study and the UK.

In the external validation we combined four different curves in one figure. We used a plot digitizer application (Plot Digitizer) in order to extract the plot values for implementation of the Weibull curve from Stata into Excel. It might lead to some misinterpretation in the comparison between the Cancer registry and our model.

Face validation, internal validation and transparency appear to be accomplished.

### **Other issues in the model**

QALY is not included in the study because these data is not collected. Consequently, it is not possible to make any economic evaluation based on cost and utility. This can be considered a weakness of the study. If QALY was included, this could have led to a reduction in effect of certain health states, as QALYs are assigned to account for patient utility (Drummond et al., 2005).

A study conducted on experienced QOL (quality of life) of AML patients found that most patients experience distress and that this can disrupt daily activities and hence affect the QOL (Bryant, Walton, Shaw-Kokot, Mayer, & Reeve, 2015). Further, the study by Bryant et al. (2015) found that young patients have less dysfunction. All surviving patients have a fairly stable physical function and this increase over time. Additionally Bryant et al. (2015) reports that 71 per cent of the survivors returned to full-time employment. This study is conducted in USA, so it is not definite that this is completely transferable to Norway due to other social welfare systems among many factors. QALY seeks to reflect the effect of the intervention on a individuals length and quality of life (Briggs et al., 2006). Based on this it can be argued that one should have included QALY in the analysis to give a more complete picture of the treatment and effect, rather than just considering the survival and cost of the patients.

In the visualisation of the model (Figure 8), in the Markov model D (transplantation), we included a state called “remission” following relapse. This state is coloured in grey due to the fact that no individuals in our data set reached this. We still chose to include the possibility, because technically patients may achieve this. It can be considered a weakness that we were unable to track the transition probability of moving to this remission state, and this would perhaps be solved if we included more patients in the cohort.

## **8.4 Findings of similar studies**

The study by Wang et al. (2014) which investigated the survival and treatments costs in the UK, found that the life expectancy for this patient group varied from 3.03 months to 34.74 months. The medical cost was found to range between £ 8 170 and £ 81 636. This is approximately equal to NOK 94 386 and NOK 943 117 (unadjusted for inflation). The life expectancy depended on the respective treatments, and reflects the heterogeneity in AML patients. The cohort involved 352 patients aged 18 and older. Since this study has been used

as foundation of our study, some aspects of our findings is appropriate to compare with Wang et al. (2014).

In a study by Tangen et al. (2008) the four-year survival of AML patients was found to be 43 per cent. The study differentiated between the different risks groups, and the results show that patients with low-risk AML had a much greater survival than the high-risk groups. The study included patients from all the university hospitals in Norway and the cohort consisted of 253 patients aged between 15 and 61 years. This study does not look at the costs, rather only the survival of the different treatments according to risk groups. This make comparisons between our study and Tangen et al. (2008) unfeasible.

It does not seem to be as much research on AML with analysis of survival and costs. However, it appears that there is a general agreement that the survival of AML patients is poor.

## **8.5 Future research**

We have not included the variable that includes FLT3 (molecular examination) and this means that in a future evaluation study this could be implemented and new calculations can be made based on this. Additionally, QALYs have not been included and could also be done in a future research. If one wanted a more complete picture it could also be interesting to investigate the cost of sick leave due to the disease as well as how many who goes back to full-time employment. Lastly, if interested, one should include more patients by collecting data from all of the Norwegian hospitals that provides AML treatment.

## 9 Conclusion

AML life expectancy and costs vary according to the age of patients and clinical pathway. In the probabilistic sensitivity analysis, the total five-year expected cost and life expectancy was NOK 1 401 521 and 37.61 months.

When investigating the Markov models individually the highest cost of NOK 999 995 occurred in A2 (elderly patients responding to treatment), while the lowest cost of NOK 574 975 occurred for patients who had no response to treatment. Life expectancy was highest in model A1 (young patients responding to treatment) and shortest for patients who did not respond to induction treatment, with a mean of 47.27 months and 6.15 months, respectively.

Our study is to some extent comparable to the UK. The study shows a higher life expectancy with an overall higher total costs relative to the UK. It is important to notice that the study by Wang et al. (2014) model an older population than our study. This may lead to better survival at generally higher costs in our study compared to the UK study.

More effort should be put in analysing cost and survival of AML patients in order to adopt a societal perspective and by including more patients from other hospitals.

This AML model may be used to evaluate treatments and enable policy makers to initiate informed decisions. Our model constructed for AML treatment has to be further developed if applied in the future due to the constant improvement in treatment and procedures.

## References

- Abernethy, R. (2006). *The New Weibull Handbook - Reliability and Statistical Analysis for Predicting Life, Safety, Supportability, Risk, Cost and Warranty Claims* (5th ed.): Published and distributed by Robert B. Abernethy.
- American Cancer Society. (2015). What are the risk factors for acute myeloid leukemia? Retrieved 27.02.2015, from <http://www.cancer.org/cancer/leukemia-acute/myeloidaml/detailedguide/leukemia-acute-myeloid-myelogenous-risk-factors>
- Bank of England. (2015). Inflation Calculator. Retrieved 14.05.2015, from <http://www.bankofengland.co.uk/education/Pages/resources/inflationtools/calculator/index1.aspx>
- Barton, P., Bryan, S., & Robinson, S. (2004). Modelling in the economic evaluation of health care: Selecting the appropriate approach. *Journal of Health Services Research and Policy*, 9(2), 110-118. doi: 10.1258/135581904322987535
- Blodkreftforeningen. (2015). Akutt myelogen leukemi. Retrieved 04..04.2015, from <http://www.blodkreftforeningen.no/diagnoser/akutt-myelogen-leukemi/>
- Briggs, A., Claxton, K., & Sculpher, M. (2006). *Decision Modelling for Health Economic Evaluation*. Oxford: Oxford University Press.
- Bryant, A. L., Walton, A. L., Shaw-Kokot, J., Mayer, D. K., & Reeve, B. B. (2015). Patient-Reported Symptoms and Quality of Life in Adults With Acute Leukemia: A Systematic Review. *Oncol Nurs Forum*, 42(2), E91-E101. doi: 10.1188/15.ONF.E91-E101
- Bureau of Labor Statistics. (2015). CPI Inflation Calculator. Retrieved 09.05.2015, from [http://www.bls.gov/data/inflation\\_calculator.htm](http://www.bls.gov/data/inflation_calculator.htm)
- Caro, J. J., Briggs, A. H., Siebert, U., & Kuntz, K. M. (2012). Modeling Good Research Practices—Overview: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-1. *Value in Health*. doi: 10.1016/j.jval.2012.06.012
- Cleveland Clinic. (2015). Acute Myeloid Leukemia. <http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/hematology-oncology/acute-myelogenous-leukemia/Default.htm>.
- Cleves, M. A., Gould, W. W., Gutierrez, R. G., & Marchenko, Y. U. (2008). *An Introduction to survival analysis using Stata* (2nd ed. ed.). College Station, Tex: Stata Press.
- Currency Converter. (2015). Convert Currency. Retrieved 01.04.2015, from <http://www.currencyconverterx.com>
- Dahl, O. (2009). *Medikamentell kreftbehandling : Cytostatikaboken* (7. utg. ed.). Oslo: Farmakologisk institutt, Fakultetsdivisjon Rikshospitalet, Det medisinske fakultetet, Universitetet i Oslo.
- Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the economic evaluation of health care programmes* (3rd ed. ed.). Oxford: Oxford University Press.
- Drummond, M. F., Weatherly, H., & Ferguson, B. (2008). Economic evaluation of health interventions. *Br. Med. J.*, 337(7673). doi: 10.1136/bmj.a1204
- Eddy, D. M., Hollingworth, W., Caro, J., Tsevat, J., McDonald, K., & Wong, J. (2012). Model Transparency and Validation: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. *Value Health*, 15(6), 843-850. doi: 10.1016/j.jval.2012.04.012
- Evensen, S. A., & Stavem, P. (2008). *Blodsykdommer* (6. utg. ed.). Oslo: Gyldendal akademisk.

- Fløisand, Y. (2015, 25.02.2015). [Meeting with the doctor].
- Frick, K. D. (2009). Micro-Costing Quantity Data Collection Methods. *Medical care*, 47(7 Suppl 1), S76-S81. doi: 10.1097/MLR.0b013e31819bc064
- Gedde-Dahl, T., & Tjønnfjord, G. E. (2012). Leukemi. *Krefttyper*. Retrieved 10.01, 2015, from <http://oncolex.no/no/Leukemi.aspx>
- Glick, H. A. (2007). *Economic evaluation in clinical trials*. Oxford: Oxford University Press.
- Helsedirektoratet. (2014). *Innsatsstyrt finansiering 2015*. (IS-2230). Helsedirektoratet v/ Trykksaksekspedisjonen.
- Helsedirektoratet. (2015a). DRG-systemet. Retrieved 16.05.2015, from <https://helsedirektoratet.no/finansieringsordninger/innsatsstyrt-finansiering-isf-og-drg-systemet/drg-systemet>
- Helsedirektoratet. (2015b). Regelverk innsatsstyrt finansiering (ISF) for 2014. Retrieved 16.05.2015, from <https://helsedirektoratet.no/finansieringsordninger/innsatsstyrt-finansiering-isf-og-drg-systemet/regelverket-for-isf>
- Hunink, M., Glasziou, P., Siegel, J., Weeks, J., Pliskin, J., Elstein, A., & Weinstein, M. (2001). *Decision making in health and medicine : integrating evidence and values*. Cambridge: Cambridge University Press.
- Joranger, P., Nesbakken, A., Hoff, G., Sorbye, H., Oshaug, A., & Aas, E. (2014). Modeling and Validating the Cost and Clinical Pathway of Colorectal Cancer (Supplementary material). Retrieved 27.04.2015, from [http://mdm.sagepub.com/content/suppl/2014/07/29/0272989X14544749.DC1/DS\\_10.11770272989X14544749\\_Appendix1.pdf](http://mdm.sagepub.com/content/suppl/2014/07/29/0272989X14544749.DC1/DS_10.11770272989X14544749_Appendix1.pdf)
- Joranger, P., Nesbakken, A., Hoff, G., Sorbye, H., Oshaug, A., & Aas, E. (2015). Modeling and Validating the Cost and Clinical Pathway of Colorectal Cancer. *Medical Decision Making*, 35(2), 255-265. doi: 10.1177/0272989X14544749
- Karnon, J. (2003). Alternative decision modelling techniques for the evaluation of health care technologies: Markov processes versus discrete event simulation. *Health Econ.*, 12(10), 837-848. doi: 10.1002/hec.770
- Koechlin, F., Konijn, P., Lorenzoni, L., & Schreyer, P. (2014). Comparing Hospital and Health Prices and Volumes Internationally: Results of a Eurostat/OECD Project. *OECD Health Working Papers*(No. 75). doi: <http://dx.doi.org/10.1787/5jxznwrj32mp-en>
- Koechlin, F., Lorenzoni, L., & Schreyer, P. (2010). Comparing Price Levels of Hospital Services Across Countries: Results of Pilot Study. *OECD Health Working Papers*(No. 53). doi: <http://dx.doi.org/10.1787/5km91p4f3rzw-en>
- Kreftforeningen. (2015). Leukemi hos voksne. Retrieved 03.04.2015, from <https://kreftforeningen.no/om-kreft/kreftformer/blodkreft-og-leukemi-hos-voksne/>
- Kreftlex. (2015). Medisinsk behandling av akutt myelogen leukemi. Retrieved 04.04.2015, from <http://kreftlex.no/no/Leukemi/ProsedyreFolder/BEHANDLING/Cellegift/AML.aspx?lg=ks&SearchText=Akutt myelogen leukemi>
- Kreftregisteret. (2015a). *5-års relativ overlevelse (%) for personer diagnostisert med AML* [Statistics].
- Kreftregisteret. (2015b). Fakta om kreft. Retrieved 12.04.2015, from <http://www.kreftregisteret.no/no/Generelt/Fakta-om-kreft-test/>

- Kumar, R. (2011). *Research methodology : a step-by-step guide for beginners* (4th ed.). London: Sage.
- Kåresen, R., Wist, E., & Reppe, A. (2012). *Kreftsykdommer: en basisbok for helsepersonell* (4. utg. [illustrasjoner: David Keeping, Zoobotanica, Ane Reppe]. ed.). Oslo: Gyldendal akademisk.
- Lo, B., Quill, T., & Tulsky, J. (1999). Discussing palliative care with patients. *Ann. Intern. Med.*, 130(9), 744-749.
- Mishra, V., Vaaler, S., & Brinch, L. (2002). A prospective cost evaluation related to allogeneic haemopoietic stem cell transplantation including pretransplant procedures, transplantation and 1 year follow-up procedures. *Bone Marrow Transplantation*, 28(12), 1111. doi: 10.1038/sj.bmt.1703310
- Mould, G., Bowers, J., & Ghattas, M. (2010). The evolution of the pathway and its role in improving patient care. *Quality and Safety in Health Care*, 19(5), 1-6. doi: 10.1136/qshc.2009.032961
- Muennig, P. (2007). *Cost-Effectiveness Analysis in Health*: Jossey-Bass.
- Muenning, P. (2008). Decision Analytic Modeling. In H. K. Heggenhougen (Ed.), *International Encyclopedia of Public Health* (pp. 71-76). Oxford: Academic Press.
- Nadler, D. L., & Zurbenko, I. G. (2013). Developing a Weibull Model Extension to Estimate Cancer Latency. 2013. doi: 10.5402/2013/750857
- Newbold, P., Carlson, W. L., & Thorne, B. M. (2013). *Statistics for business and economics* (8th ed., Global ed. ed.). Boston, Mass: Pearson.
- NHS. (2014). Acute myeloid leukaemia Retrieved 15.01, 2015, from <http://www.nhs.uk/conditions/leukaemia-acute/pages/introduction.aspx>
- NOU 2014: 12. (2014). *Åpent og rettferdig – prioriteringer i helsetjenesten*. (NOU 2014: 12). Retrieved from <https://http://www.regjeringen.no/nb/dokumenter/NOU-2014-12/id2076730/>.
- Pallister, C., & Watson, M. (2011). *Haematology* (2nd ed. ed.). Banbury: Scion.
- Rafiquddin, A. (2006). Ethical Issues in Medical Research & Publications. *Journal of Medicine*, 7(2), 42.
- Riechelmann, R., Krzyzanowska, M., O'Carroll, A., & Zimmermann, C. (2007). Symptom and medication profiles among cancer patients attending a palliative care clinic. *Supportive Care in Cancer*, 15(12), 1407-1412. doi: 10.1007/s00520-007-0253-8
- Roberts, M., Russell, L. B., Paltiel, A. D., Chambers, M., McEwan, P., & Krahn, M. (2012). Conceptualizing a model: A report of the ISPOR-SMDM modeling good research practices task force-2. *Medical Decision Making*, 32(5), 678-689. doi: 10.1177/0272989X12454941
- Sato, R. C., & Zouain, D. M. (2010). Markov Models in health care. *Einstein*, 8(3), 376.
- Shorrocks, A. F. (1976). Income mobility and the Markov assumption. *The Economic Journal*, 566-578.
- Singh, R., & Mukhopadhyay, K. (2011). Survival analysis in clinical trials: Basics and must know areas. *Perspectives in Clinical Research*, 2(4), 145-148. doi: 10.4103/2229-3485.86872
- Sonnenberg, F. A., & Beck, Jr. (1993). MARKOV-MODELS IN MEDICAL DECISION-MAKING - A PRACTICAL GUIDE. *Med. Decis. Mak.*, 13(4), 322-338.
- Sorlie, P., & Wei, G. (2011). Population-Based Cohort Studies: Still Relevant? *J. Am. Coll. Cardiol.*, 58(19), 2010-2013. doi: 10.1016/j.jacc.2011.08.020
- Stata Press. (2007). *Stata Survival Analysis and Epidemiological Table Reference Manual* (10 ed.). College Station, Tex: Stata Press.

- Statistics Norway. (2015). Consumer price index. Retrieved 28.04.2015, from <http://www.ssb.no/en/priser-og-prisindekser/statistikker/kpi>
- Steyerberg, E. W. (2009). *Clinical Prediction Models : A Practical Approach to Development, Validation, and Updating* Statistics for Biology and Health. New York, NY: Springer-Verlag New York.
- Store medisinsk leksikon. (2009). Stamcelletransplantasjon. Retrieved 09.04.2015, from <https://sml.snl.no/stamcelletransplantasjon>
- Store medisinsk leksikon. (2015). Leukemi. from <https://sml.snl.no/leukemi>
- Tangen, J.-M., Fløisand, Y., Foss-Abrahamsen, J., Haukås, E., Næss, I. A., & Skjelbakken, T. (2008). Overlevelse hos voksne med akutt myelogen leukemi. *Survival in adults with acute myelogenous leukemia*, 128(10), 1164-1167.
- Thiede, C., Steudel, C., Mohr, B., Schaich, M., Schakel, U., Platzbecker, U., . . . Illmer, T. (2002). Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. *Blood*, 99(12), 4326-4335.
- Thygesen, L. C., & Ersboll, A. K. (2014). When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol*, 29(8), 551-558. doi: 10.1007/s10654-013-9873-0
- Wang, H. I., Aas, E., Howell, D., Roman, E., Patmore, R., Jack, A., & Smith, A. (2014). Long-term medical costs and life expectancy of acute myeloid leukemia: a probabilistic decision model. *Value Health*, 17(2), 205-214. doi: 10.1016/j.jval.2013.12.007
- Weinstein, M. C., O'Brien, B., Hornberger, J., Jackson, J., Johannesson, M., McCabe, C., & Luce, B. (2003). Principles of good practice for decision analytic modeling in health-care evaluation: Report of the ISPOR task force on good research practices-modeling studies. *Value Health*, 6(1), 9-17.
- Weinstein, M. C., & Stason, W. B. (1977). Foundations of Cost-Effectiveness Analysis for Health and Medical Practices. *New England Journal of Medicine*, 296(13), 716-721. doi: doi:10.1056/NEJM197703312961304

# Appendix A: Screen print Markov C Palliative (Excel)

L15		=K14-(K14*LeavePai19)																					
1	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	
2	Turned state 18 months																						
3	Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			
4		Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Palliative	Death	Sum
5	0	0.0749186	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0749186	
6	1	0	0.0502557	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.03586197	0.0749186	
7	2	0	0.0390566	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.04344739	0.0749186	
8	3	0	0	0.0314712	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.04903235	0.0749186	
9	4	0	0	0	0.0258862	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05332595	0.0749186	
10	5	0	0	0	0	0.0215926	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05671855	0.0749186	
11	6	0	0	0	0	0	0.0182	0	0	0	0	0	0	0	0	0	0	0	0	0	0.05945160	0.0749186	
12	7	0	0	0	0	0	0	0.015467	0	0	0	0	0	0	0	0	0	0	0	0	0.06168567	0.0749186	
13	8	0	0	0	0	0	0	0	0.0132329	0	0	0	0	0	0	0	0	0	0	0	0.06353298	0.0749186	
14	9	0	0	0	0	0	0	0	0	0.0113856	0	0	0	0	0	0	0	0	0	0	0.06507466	0.0749186	
15	10	0	0	0	0	0	0	0	0	0	0.0098437	0	0	0	0	0	0	0	0	0	0.06697192	0.0749186	
16	11	0	0	0	0	0	0	0	0	0	0	0.0085466	0	0	0	0	0	0	0	0	0.06747034	0.0749186	
17	12	0	0	0	0	0	0	0	0	0	0	0	0.0074482	0	0	0	0	0	0	0	0.06840593	0.0749186	
18	13	0	0	0	0	0	0	0	0	0	0	0	0	0.0065126	0	0	0	0	0	0	0.06920686	0.0749186	
19	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0057117	0	0	0	0	0	0.06989561	0.0749186	
20	15	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.005023	0	0	0	0	0.07049027	0.0749186	
21	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.0044283	0	0	0	0.07100556	0.0749186	
22	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.00391301	0	0	0.07145355	0.0749186	
23	18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.003465	0.07184419	0.0749186		
24																				0.00307744	0.07216748	0.0749186	
25																				0.00272511	0.07245677	0.0749186	
26																				0.0024618	0.07271565	0.0749186	
27																				0.00222029	0.0729473	0.0749186	
28																				0.0019713	0.07315459	0.0749186	
29																				0.001764	0.07334008	0.0749186	
30																				0.0015785	0.07350607	0.0749186	
31																				0.0014125	0.0736546	0.0749186	
32																				0.0011311	0.07389531	0.0749186	
33																				0.0010233	0.07408106	0.0749186	
34																				0.0009257	0.07423309	0.0749186	
35																				0.0008375	0.07439843	0.0749186	
36																				0.0007577	0.07456287	0.0749186	
37																				0.0006855	0.0747273	0.0749186	
38																				0.0006081	0.07489186	0.0749186	



# Appendix C: Screen print Markov A1 Young (Excel)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X			
1	Turntable 18 months																										
2	Months																										
3		0	Model A1 Response 60	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	1st relaps	2nd relaps	1	2	3		
4		0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	1st relaps	0	
5		0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925	0.63921925		
6		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
7		0	0	0.610159528	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
8		0	0	0	0.58631355	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
9		0	0	0	0	0	0.5544718	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
10		0	0	0	0	0	0	0.54663633	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
11		0	0	0	0	0	0	0	0.52934872	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
12		0	0	0	0	0	0	0	0	0.51303452	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
13		0	0	0	0	0	0	0	0	0	0.49283032	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
14		0	0	0	0	0	0	0	0	0	0	0.48412819	0	0	0	0	0	0	0	0	0	0	0	0	0		
15		0	0	0	0	0	0	0	0	0	0	0	0.47073343	0	0	0	0	0	0	0	0	0	0	0	0		
16		0	0	0	0	0	0	0	0	0	0	0	0	0.4582076	0	0	0	0	0	0	0	0	0	0	0		
17		0	0	0	0	0	0	0	0	0	0	0	0	0	0.4458739	0	0	0	0	0	0	0	0	0	0		
18		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.43423249	0	0	0	0	0	0	0	0	0		
19		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.42319718	0	0	0	0	0	0	0	0		
20		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4125532	0	0	0	0	0	0	0		
21		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.4023256	0	0	0	0	0	0		
22		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3924841	0	0	0	0	0		
23		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3830023	0	0	0	0		
24		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3738397	0	0	0		
25		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3649851	0	0		
26		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3564307	0		
27		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3481846		
28		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3402451	
29		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3326128
30		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3252842
31		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3182599
32		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3114366
33		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.3048133
34		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2983897
35		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2921651
36		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2861402
37		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2803149
38		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2746892
39		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2692633
40		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2640372
41		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2590109
42		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2541846
43		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2495583
44		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2451320
45		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2409057
46		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2368794
47		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2329531
48		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2291268
49		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2254005
50		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2217742
51		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2182479
52		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2148216
53		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2115053
54		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2082890
55		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.2051727

## Appendix D: Control cells all Markov models (Excel)

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
D4				=Markov A1!BHS + Markov A2!BHS + Markov Transplant!W5 + Markov palliative!V5 + Markov No response!V5 + yDeathARAD + yDeathARAI + yDeathOTHER + eDeathARAD + eDeathARAI + eDeathOTHER												
1				Control all sheets												
2																
3																
4				0	1											
5				1	1											
6				2	1											
7				3	1											
8				4	1											
9				5	1											
10				6	1											
11				7	1											
12				8	1											
13				9	1											
14				10	1											
15				11	1											
16				12	1											
17				13	1											
18				14	1											
19				15	1											
20				16	1											
21				17	1											
22				18	1											
23				19	1											
24				20	1											
25				21	1											
26				22	1											
27				23	1											
28				24	1											
29				25	1											
30				26	1											
31				27	1											
32				28	1											
33				29	1											
34				30	1											
35				31	1											
36				32	1											
37				33	1											
38				34	1											
39				35	1											
40				36	1											



We started out by looking at how many experience a failure in first remission, during the observed period. To do this, we had to define two new variables in Excel; one that specified failure and non-failure (1 and 0), and one variable where “time in first remission” was calculated. To establish the variable “time in first remission” we subtracted the first occurring failure (relapse, transplantation or death) with time in remission, and subtracted this by 1 (to “reset” the variables to account for the aging of the patients, since the first patient experiencing remission was in month one). This means that if an individual experienced relapse in month eight, and the first remission occurred in month 2, that individual had been in first remission in 5 months.

No observed failure indicates that the individual was given 60 (months) of time in remission, since this individual would then still be alive and should be included in the analysis.

Individuals observed in one of the failure states, was coded as 1, else why coded as 0.

Whenever an individual was more than 60 months in remission this was coded as 0, due to the five-year observational period, even though it could have a failure after 60 months. The cut-off point for the survival analysis was December 2014. The four individuals diagnosed in 2015 were left out, since they had not experienced a failure or been in remission long enough. Hence the cut was in December 2014. Individuals who did not have any failure, but had not survived for 5 years will be censored in Stata.

## Appendix F: Medication costs and calculation

The Table below illustrates the input list of medications given to patients at the Haematology ward. These numbers was used to calculate the mean cost per patient. Quantity indicates the amount of ampules, tablets and bottles in the respective packages of medications. Total purchase is the total amount of packages bought at the Haematology ward. All prices shown in 2015 NOK, but are adjusted in the calculations.

List of billed medications for AML patients at OUS			
Product	Quantity	Total purchase	Price per package
Afipran inj 5mg/ml	10x2	22,00	kr 61
Afipran inj 5mg/ml	5x10x2	149,80	kr 181
Allopur SA tab 300mg	50	4,38	kr 223
AmBisome inf subst 50mg	10	13,00	kr 12 682
Cytarabine pfiz inf/inj 100mg	10	138,00	kr 167
Cytarabine pfiz inf/inj 100mg	10x20	3,20	kr 2 663
Fluconazole teva inf 2mg/ml	10x100	23,00	kr 2 676
Furix tab 20mg	100	21,00	kr 73
Gensumycin inj 40mg/ml	5x2	479,00	kr 160
Imovane tab 7,5mg	10	6,00	kr 49
Imovane tab 7,5mg	30	125,00	kr 51
Imovane tab 7,5mg	100	66,00	kr 63
Ketorax inj 5mg/ml	5x1	186,00	kr 67
Ketorax inj 5mg/ml	5x5x1	483,00	kr 158
Meropenem hos inf/inj subst 1g	10	415,00	kr 410
Mycamine inf subst 100mg	1	274,00	kr 2 273
Nexium enterotab 20mg	50	86,92	kr 165
Ondansetron fresen inj 2mg/ml	5x2	831,00	kr 44
Ondansetron fresen inj 2mg/ml	5x4	107,00	kr 57
Vancomycin hosp inf su 500mg	1	240,00	kr 45
Ceftazidim fres inf/inj sub 2g	10	41,60	kr 236
Novantrone inf kons 2mg/ml	5	35,00	kr 1 155
Benzylpenicillin 0,6g	10x1	67	kr 74
Benzylpenicillin 1,2g	10x2	432	kr 89
Benzylpenicillin 3g	10x5	969	kr 112
Vepesid 100mg	10	15	kr 8 576
Vepesid 20mg/ml	5	2 844	kr 65
Amsakrin 75mg	5	40	kr 15 410
Amsakrin 75mg/1,5ml	6	1	kr 14 839
Natriumklorid 0,9%	1 L	-	kr 7
Kabiven 1475 kcal (mean)	-	-	kr 212

The OUS list of medications we received included prices of medicaments given in cost of milligrams (mg) per millilitre (ml). In order to calculate the price of the different dosages given, we had to recalculate the different mg per ml into the price per mg. For example, Afipran is an infusion that comes in 5 mg/ml. This means that for every ml of Afipran there is 5 mg of the substance. We used the cost per ml, divided it by the amount of mg, and found the price per mg by conducting the following steps: First, we found the price per package divided by the volume in each package, second, the cost found in the first step divided by the mg per unit. In the example of Afipran this will be 61,10 (price per package) / 20 (the volume in each package), and then 3,06 (the price per volume) / 5 (amount of mg per ml). This gives a price of NOK 0,611 per mg. Further; we know that the dosage of Afipran is  $10 * 4$  mg per day for 7 days. When multiplying the cost of Afipran with the dosage this gives a cost of NOK  $(10*4*7)*0,611$  which is NOK 171,08. For some of the medications we had two or three different prices listed, and this was also the case for Afipran. In order to take this into account we did the same steps as described above for all of the different versions of the substance. The second cost we calculated for Afipran was the version of the medication that contained a different combination of ampoules in the packages. The cost for this version is NOK 0,3619 per mg. To find out which price accordingly to use, we incorporated the number of packages sold of each version and calculated the distribution in per cent. Next we discovered that they had bought 87 % of the version of a mg price of 0,3619 and 13 % of the version with a mg price of 0,611. We used this fraction and multiplied it with the respective prices. A new price was then calculated based on the estimated distribution and the cost per mg were then 0,394. When multiplying this with dosage ( $10*4*7$ ) we get a new cost of Afipran of NOK 110,32. These steps were done for all medications that were used (different brands) in order to get the correct price according to the billed prices at the Haematology ward.

## Appendix G: SPSS Variables

Untitled4AML.sav [DataSet1] - IBM SPSS Statistics Data

	Name	Type	Width	Decimals	Label	Values	Missing	Columns	Align	Measure	Role
1	patientid	Numeric	10	0		None	None	10	Right	Unknown	Input
2	Diagnose	Numeric	10	0	Diagnose	{1, AML}...	None	10	Right	Unknown	Input
3	Dato_diagn...	Date	11	0	DatoDiagnose	None	None	11	Right	Unknown	Input
4	Primær_se...	Numeric	10	0	Primær_Sekun...	{1, Primær}...	None	10	Right	Unknown	Input
5	Siste_FU_dato	Date	11	0	SisteFUDato	None	None	11	Right	Unknown	Input
6	AMLFAB_kl...	Numeric	10	0	AMLFABklassif...	{1, AML 1-2...	None	10	Right	Unknown	Input
7	WHO_klassi...	Numeric	10	0	WHOklassifika...	{1, AML me...	None	10	Right	Unknown	Input
8	Cytogenetikk	Numeric	10	0	Cytogenetikk	{1, God Pro...	None	10	Right	Unknown	Input
9	Molkylaerg...	String	12	0	Molkylægeneti...	None	None	12	Left	Nominal	Input
10	Induksjonst...	Numeric	10	0	induksjonstype...	{1, ARA-c+...	None	10	Right	Unknown	Input
11	Ble_KR_tot...	Numeric	10	0	BleKRTotaltSet...	{1, Ja,alle k...	None	10	Right	Unknown	Input
12	Dato_for_e...	Date	11	0	DatoForEvtKom...	None	None	11	Right	Unknown	Input
13	Tillegg_av...	Numeric	10	0	TilleggAvCysto...	{1, Ja}...	None	10	Right	Unknown	Input
14	AML	Numeric	10	0	AML	{1, Høydose...	None	10	Right	Unknown	Input
15	Allogen_bei...	Numeric	10	0	Allogen beinm...	{1, Ja}...	None	10	Right	Unknown	Input
16	Giver	Numeric	10	0	Giver	{1, Familieg...	None	10	Right	Unknown	Input
17	Transplant...	Numeric	10	0	Transplantasjo...	{1, Full kon...	None	10	Right	Unknown	Input
18	Dato_for_tr...	Date	11	0	DatoForTransp...	None	None	11	Right	Unknown	Input
19	Sykdomssta...	Numeric	10	0	Sykdomsstadiu...	{1, Første k...	None	10	Right	Unknown	Input
20	Followup_d...	Date	11	0	Followup dato	None	None	11	Right	Unknown	Input
21	Residiv	Numeric	10	0	Residiv	{1, Ja}...	None	10	Right	Unknown	Input
22	Residiv_dato	Date	11	0	Residiv dato	None	None	11	Right	Unknown	Input
23	Ny_remisjon	Numeric	10	0	Ny remisjon	{1, Ja}...	None	10	Right	Unknown	Input
24	Status	Numeric	10	0	Status	{1, Tidlig de...	None	10	Right	Unknown	Input
25	Doedsarsak	Numeric	10	0	Dødsårsak	{1, Behandli...	None	10	Right	Unknown	Input
26	Date_of_birth	Date	11	0		None	None	11	Right	Unknown	Input
27	Death_date	Date	11	0		None	None	11	Right	Unknown	Input
28	male_female	Numeric	10	0		{0, female}...	None	10	Right	Unknown	Input

Data View Variable View

## Appendix H: Hazard function sheet (Excel)

Leave1rel12										fx = 1-EKSP((\$G\$99*H84)-(\$G\$99*H85))	
	A	B	C	D	E	F	G	H	I	J	
69	1 rem to relaps										
70	Prob from 1 rem to relaps	explanatory variables	coefficient	se	hazard ratio	InAge	3,637586				
71		Ingamma	-0,02556	0,09017	-0,02556	-4,102	0,016539				
72		cons	-7,76483	0,00069	0,00042			0,0000			
73		InAge	1,00693	1,10734	2,737176			1,0000			
74								2,1848			
75		Covariance matrix						3,4510			
76		InAge	cons	Ingamma				4,7732			
77		InAge	0,1637					6,1387			
78		Cons	-0,6451	2,6421				7,5397			
79		Ingamma	0,0055	-0,0476	0,00813			8,9708			
80								10,4284			
81		Correlation matrix						11,9095			
82		InAge	Cons	Ingamma				13,4117			
83		InAge	1					14,9332			
84		Cons	-0,981024	1				16,4724			
85		Ingamma	0,150822	-0,3246425	1			18,0282			
86								19,5992			
87		Cholesky decomposition						21,1847			
88		InAge	Cons	Ingamma				22,7837			
89		InAge	0,4046					24,3955			
90		Cons	-1,5946	0,3152				26,0194			
91		Ingamma	0,0136	-0,0822	0,0346			27,6549			
92								29,3014			
93		Random variables						30,9584			
94		z			Tz		mu + Tz	32,6256			
95		InAge	-0,5693		-0,2303		0,7766	34,3024			
96		Cons	-1,7247		0,3643		-7,4006	35,9885			
97		Ingamma	0,3347		0,1455		0,1200	37,6836			
98								39,3874			
99							0,0103	41,0996			
100							1,127483	42,8199			
101								44,5480			
102								46,2837			
103								48,0269			
104								49,7772			
105								51,5345			
106								53,2986			
107								55,0693			
108								56,8465			
109								58,6300			
110								60,4197			
111								62,2153			
112								64,0169			
113								65,8242			
114								67,6371			
115								69,4556			
116								71,2794			
117								73,1086			
118								74,9429			
119								76,7823			
120								78,6267			
121								80,4760			
122								82,3302			
123								84,1890			
124								86,0525			
									cycle	Probabilistic transition probabilities	
									0	0,0102474	
									1	0,0121293	
									2	0,0129579	
									3	0,0135269	
									4	0,0139663	
									5	0,0143267	
									6	0,0146335	
									7	0,0149012	
									8	0,0151394	
									9	0,0153541	
									10	0,0155498	
									11	0,0157299	
									12	0,0158967	
									13	0,0160523	
									14	0,0161980	
									15	0,0163353	
									16	0,0164649	
									17	0,0165879	
									18	0,0167049	
									19	0,0168164	
									20	0,0169231	
									21	0,0170253	
									22	0,0171234	
									23	0,0172178	
									24	0,0173087	
									25	0,0173964	
									26	0,0174812	
									27	0,0175632	
									28	0,0176427	
									29	0,0177197	
									30	0,0177945	
									31	0,0178672	
									32	0,0179379	
									33	0,0180067	
									34	0,0180737	
									35	0,0181391	
									36	0,0182029	
									37	0,0182651	
									38	0,0183259	
									39	0,0183854	
									40	0,0184435	
									41	0,0185005	
									42	0,0185562	
									43	0,0186108	
									44	0,0186643	
									45	0,0187167	
									46	0,0187682	
									47	0,0188187	
									48	0,0188682	
									49	0,0189169	
									50	0,0189648	
									51	0,0190118	
									52	0,0190580	

# Appendix I: Hazard function sheet (Excel)

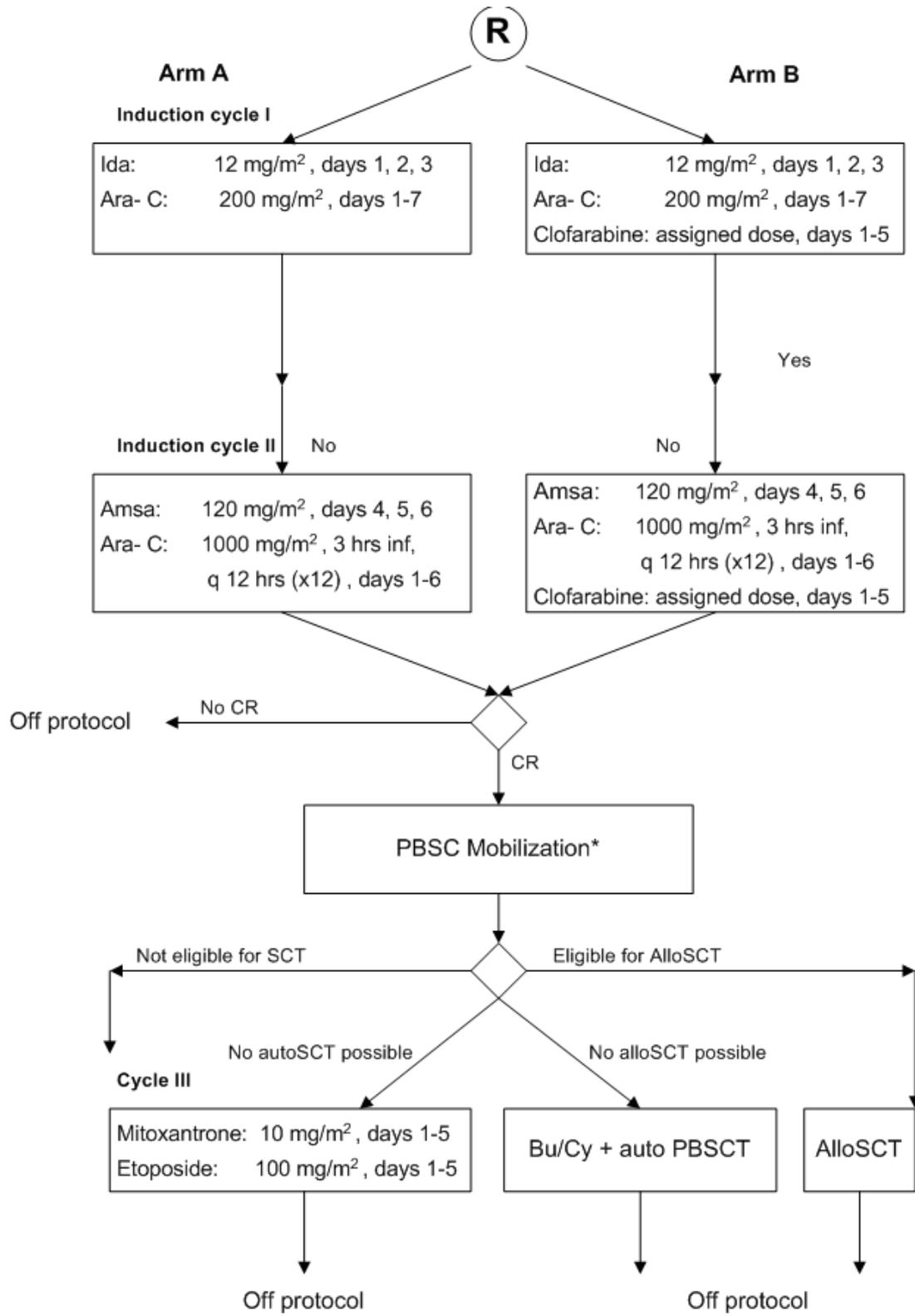
AE4    fx =LN(Age\_2)

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH
2											
3		2 rem to transplant									
4		Prob from 2 rem to trans	explanatory variables	coefficient	se	hazard ratio	lnAge	4,248495			
5			lngamma	-0,27186	0,16056	-0,27186	-2,963649	0,05163			
6			cons	6,81722	2699,01500	913,43870			0,0000	0	0,0228833
7			lnAge	-2,30220	0,08263	0,100039			1,0000	1	0,0201168
8									1,8779	2	0,0191894
9			Covariance matrix						2,7149	3	0,0186106
10			lnAge	cons	lngamma				3,5264	4	0,0181917
11			lnAge	0,6822					4,3195	5	0,0178646
12			Cons	-2,4247	8,7308				5,0982	6	0,0175971
13			lngamma	-0,0608	0,1786	0,02578			5,8651	7	0,0173712
14									6,6221	8	0,0171761
15			Correlation matrix						7,3705	9	0,0170046
16			lnAge	Cons	lngamma				8,1114	10	0,0168518
17			lnAge	1					8,8456	11	0,0167141
18			Cons	-0,99354	1				9,5737	12	0,0165888
19			lngamma	-0,458339	0,376391	1			10,2963	13	0,0164741
20									11,0139	14	0,0163682
21			Cholesky decomposition						11,7268	15	0,0162701
22			lnAge	Cons	lngamma				12,4354	16	0,0161786
23			lnAge	0,8259					13,1400	17	0,0160929
24			Cons	-2,9357	0,3353				13,8409	18	0,0160125
25			lngamma	-0,0736	-0,1118	0,0887			14,5382	19	0,0159366
26									15,2321	20	0,0158649
27			Random variables						15,9230	21	0,0157969
28			z		Tz		mu + Tz	16,6108		22	0,0157323
29			lnAge	-0,8391	-0,6930	-2,9952	17,2958			23	0,0156707
30			Cons	-0,9576	2,1422	8,9595	17,9781			24	0,0156119
31			lngamma	0,0878	0,1766	-0,0953	18,6579			25	0,0155556
32							19,3351			26	0,0155017
33							20,0100	0,023149		27	0,0154500
34							20,6826	0,909096		28	0,0154003
35							21,3531			29	0,0153525
36							22,0214			30	0,0153064
37							22,6877			31	0,0152619
38							23,3521			32	0,0152189
39							24,0146			33	0,0151774
40							24,6752			34	0,0151372
41							25,3341			35	0,0150982
42							25,9913			36	0,0150604
43							26,6469			37	0,0150237
44							27,3008			38	0,0149881
45							27,9531			39	0,0149535
46							28,6040			40	0,0149198
47							29,2533			41	0,0148870
48							29,9013			42	0,0148550
49							30,5478			43	0,0148239
50							31,1929			44	0,0147935
51							31,8368			45	0,0147639
52							32,4793			46	0,0147349
53							33,1205			47	0,0147067
54							33,7606			48	0,0146790
55							34,3994			49	0,0146520
56							35,0370			50	0,0146256
57							35,6735			51	0,0145998

LN(Age\_2) refers to the mean age of group 1 (older patients)

Control    PSA    Hazard functionsY    simplified probabilities    Hazard functions Transplant

## Appendix J: HOVON (treatment strategies)



\* unless to proceed to AlloSCT

## Appendix K: Costs at OUS Haematology ward

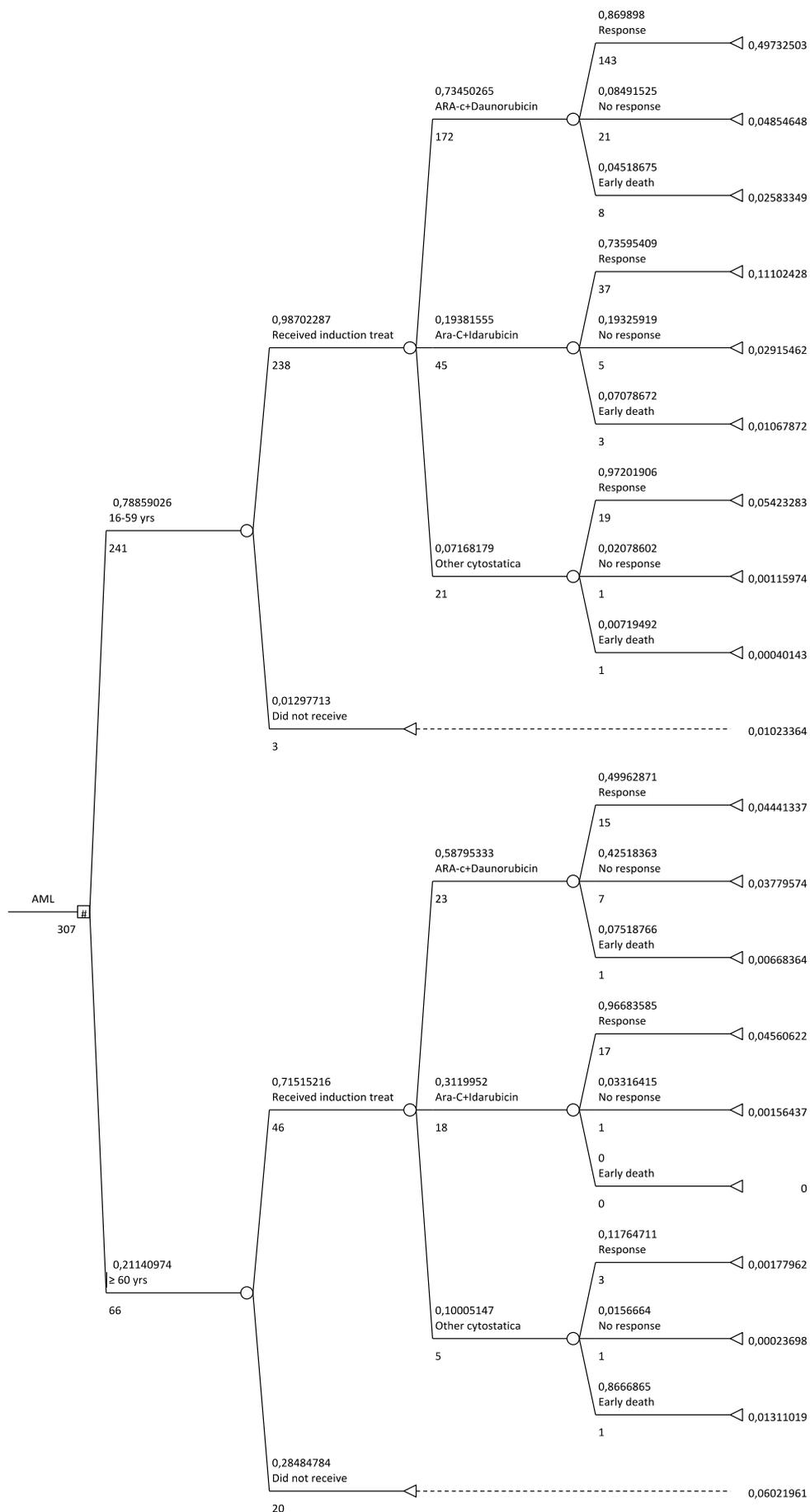
Måned innlev. År	Antall SHO avsluttet ved	Antall liggedøgn	Kostnader sengepost blodsykdommer 2014
	Døgnopph.		
jan.14	83	617	
feb.14	69	633	
mar.14	92	751	
apr.14	85	800	
mai.14	67	715	
jun.14	77	894	
jul.14	79	559	
aug.14	61	532	
sep.14	63	861	
okt.14	81	890	
nov.14	82	763	
des.14	69	879	
<b>Totalt</b>	<b>908</b>	<b>8894</b>	<b>68996768</b>

Pris per døgnopphold 75 988  
 Pris per liggedøgn 7 758

Kostnader sengepost blodsykdommer 2014		
Kontoklass	Beskrivelse	Totalt
3	Inntekter	- 440 702
4	Varekostnader	5 532 212
5	Lønn	61 959 916
6	Driftskostnader	751 427
7	Andre driftskostnader	89 899
8	Finansposter	1 573
9	Internhandel (blodkostnader)	1 102 444
<b>Totalt</b>		<b>68 996 768</b>

Pris per liggedøgn uten blodkostnader  
 7 634

# Appendix L: Decision tree (Excel)



## Appendix M: Wages at Haematology ward

Doctor's salary at the haematology ward (cost in 2014 NOK)	
Position	Salary (Mean)*
Chief attending physician	kr 1 485 151
Resident physician	kr 1 111 726
<b>Total</b>	<b>kr 2 596 877</b>
* Includes 40 % of social cost (pension, payroll tax etc)	

## Appendix N: Stata do-file

```
1 *****
2 *** Leaving 1st remission***
3 *****
4
5 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
6 25.02.15/Stata/Samlet/1Remission-failure.dta"
7
8 gen lnAge = ln(Age)
9
10 stset Timetodeaht, fail(Failure)
11
12 streg lnAge, d(weibull)
13
14 stcurve, survival
15 stcurve, hazard
16
17 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
18
19 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
20
21 ** coefficients ***
22 matrix list e(b)
23
24 ***
25 matrix list e(V)
26
27 clear
28
29 *****
30 ***1 Remission to relaps***
31 *****
32
33 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
34 25.02.15/Stata/Samlet/1Remission-failure.dta"
35
36 gen lnAge = ln(Age)
37
38 stset tidirem, fail(Failrelaps )
39
40 streg lnAge, d(weibull)
41
42 stcurve, survival
43 stcurve, hazard
44
45 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
46
47 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
48
49 ** coefficients ***
50 matrix list e(b)
51
52 ***
```

```

51 matrix list e(V)
52
53 clear
54
55 *****
56 ***1 Remission to Transplant ***
57 *****
58
59 use "/Users/Dropbox/Masteroppg/Statistikk – data/Ny data
25.02.15/Stata/Samlet/1Remission–failure.dta"
60
61 gen lnAge = ln(Age)
62
63 stset tidirem, fail(FailTransplant )
64
65 streg lnAge, d(weibull)
66
67 stcurve, survival
68 stcurve, hazard
69
70 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
71
72 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
73
74 ** coefficients ***
75 matrix list e(b)
76
77 ***
78 matrix list e(V)
79
80 clear
81
82 *****
83 *** 1 Remission to death ***
84 *****
85
86 use "/Users/Dropbox/Masteroppg/Statistikk – data/Ny data
25.02.15/Stata/Samlet/1Remission–failure.dta"
87
88 gen lnAge = ln(Age)
89
90 stset tidirem, fail(Faildeath )
91
92 streg lnAge, d(weibull)
93
94 stcurve, survival
95 stcurve, hazard
96
97 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
98
99 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
100

```

```

101  ** coefficients ***
102  matrix list e(b)
103
104  ***
105  matrix list e(V)
106
107  clear
108
109  ****
110  ***1relaps ***
111  ****
112
113  use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
25.02.15/Stata/Samlet/1relaps-failure.dta"
114
115  gen lnAge = ln(Age)
116
117  stset Tidires, fail(Failure )
118
119  streg lnAge, d(weibull)
120
121  stcurve, survival
122  stcurve, hazard
123
124  stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
125
126  stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
127
128  ** coefficients ***
129  matrix list e(b)
130
131  ***
132  matrix list e(V)
133
134  clear
135
136  ****
137  *** 1relaps to death ***
138  ****
139
140  use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
25.02.15/Stata/Samlet/1relaps-failure.dta"
141
142  gen lnAge = ln(Age)
143
144  stset Tidires, fail(FailDeath )
145
146  streg lnAge, d(weibull)
147
148  stcurve, survival
149  stcurve, hazard
150

```

```

151 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
152
153 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
154
155 ** coefficients ***
156 matrix list e(b)
157
158 ***
159 matrix list e(V)
160
161 clear
162
163 *****
164 *** 2remission to transplant ***
165 *****
166
167 use "/Users/Dropbox/Masteroppg/Statistikk – data/Ny data
25.02.15/Stata/Samlet/2remission-failures.dta"
168
169 gen lnAge = ln(Age)
170
171 stset tidi2rem, fail(FailTransplant )
172
173 streg lnAge, d(weibull)
174
175 stcurve, survival
176 stcurve, hazard
177
178 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
179
180 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
181
182 ** coefficients ***
183 matrix list e(b)
184
185 ***
186 matrix list e(V)
187
188 clear
189
190 *****
191 *** Transplant ***
192 *****
193
194 use "/Users/Dropbox/Masteroppg/Statistikk – data/Ny data
25.02.15/Stata/Samlet/Transplant.dta"
195
196 gen lnAge = ln(Age)
197
198 stset Tidrem1Trans, fail(Failure )
199
200 streg lnAge, d(weibull)

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201
202 stcurve, survival
203 stcurve, hazard
204
205 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
206
207 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
208
209 ** coefficients ***
210 matrix list e(b)
211
212 ***
213 matrix list e(V)
214
215 clear
216
217 *****
218 *** Transplant to relaps ***
219 *****
220
221 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
222 25.02.15/Stata/Samlet/Transplant.dta"
223
224 gen lnAge = ln(Age)
225
226 stset Tidrem1Trans, fail(Failrelaps)
227
228 streg lnAge, d(weibull)
229
230 stcurve, survival
231 stcurve, hazard
232
233 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
234
235 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
236
237 ** coefficients ***
238 matrix list e(b)
239
240 ***
241 matrix list e(V)
242
243 clear
244
245 *****
246 *** Transplant to death ***
247 *****
248
249 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
250 25.02.15/Stata/Samlet/Transplant.dta"
251
252 gen lnAge = ln(Age)

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251
252 stset Tidrem1Trans, fail(Faildeath)
253
254 streg lnAge, d(weibull)
255
256 stcurve, survival
257 stcurve, hazard
258
259 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
260
261 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
262
263 ** coefficients ***
264 matrix list e(b)
265
266 ***
267 matrix list e(V)
268
269 clear
270
271 *****
272 *** No response ***
273 *****
274
275 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
25.02.15/Stata/Samlet/NoResponse.dta"
276
277 gen lnAge = ln(Age)
278
279 stset Tidnoresponse, fail(Failure )
280
281 streg lnAge, d(weibull)
282
283 stcurve, survival
284 stcurve, hazard
285
286 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
287
288 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
289
290 ** coefficients ***
291 matrix list e(b)
292
293 ***
294 matrix list e(V)
295
296 clear
297
298 *****
299 *** Palliativ ***
300 *****
301

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302 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
25.02.15/Stata/Samlet/Model c palliative.dta"
303
304 gen lnAge = ln(Age)
305
306 stset Tidipalli, fail(Failure )
307
308 streg lnAge, d(weibull)
309
310 stcurve, survival
311 stcurve, hazard
312
313 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
314
315 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
316
317 ** coefficients ***
318 matrix list e(b)
319
320 ***
321 matrix list e(V)
322
323 clear
324
325 *****
326 *** Total Survival ***
327 *****
328
329 use "/Users/Dropbox/Masteroppg/Statistikk - data/Ny data
25.02.15/Stata/Samlet/Totalsurvival.dta"
330
331 gen lnAge = ln(Age)
332
333 stset Timetodeath, fail(Failure )
334
335 streg lnAge, d(weibull)
336
337 stcurve, survival
338 stcurve, hazard
339
340 stcurve, survival at1(lnAge=3.63758616) at2(lnAge=4.248495242)
341
342 stcurve, hazard at1(lnAge=3.63758616) at2(lnAge=4.248495242)
343
344 ** coefficients ***
345 matrix list e(b)
346
347 ***
348 matrix list e(V)
349
350 clear
351

```