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**Economic evaluation of immediate administration of
tranexamic acid after aneurysmal subarachnoid
hemorrhage.**

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1. Key words (for indexing)	2
2. Abbreviations	2
3. Abstract:	3
3.1 Purpose:	3
3.2 Setting:	3
3.3 Methods:	3
3.4 Results:	3
4. Introduction	4
4.1 Medical Background	4
4.2 On the theoretical background of evaluation of health technology	5
4.3 Data and Methods	7
4.4 Morbidity and mortality	7
4.5 Costs	9
4.5.1 Medical and non-medical resources	9
4.5.2 Patient time, productivity changes and time of informal caregivers and other costs	11
4.6 Cost-Utility Analysis.	14
4.7 Discounting	16
4.8 Cost-benefit analysis and willingness to pay.	18
5. Results	21
6. Discussion	21
7. Acknowledgements	25
8. References	26
Appendix:	28
How the GOS scores were converted into the EuroQol descriptive system	28
Legend to the figures:	30

1. Key words (for indexing)

- intracranial aneurysm
- subarachnoid hemorrhage
- antifibrinolytic therapy
- rebleeding
- cost-utility (C/U)
- willingness to pay (WTP)
- societal perspective

2. Abbreviations

- AF: Antifibrinolytica. Medicine that decreases the risk of rebleeding.
- C/B: Cost Benefit.) The sum of the society's willingness to pay for a medical treatment minus direct and indirect cost associated with the treatment. If the net result is positive, the treatment is *cost-effective*.
- C/E: Cost Effectiveness. The incremental costs divided by a single output measure. E.g. Life saved, life-year saved or number of successful operations.
- C/U: Cost Utility. The incremental costs divided by the quality adjusted life-years saved.
- CG: Control group. Patients that are included in the study for observation but do not receive the treatment.
- CPI: Consumer Price Index. A weighted index of the price increase of essential good.
- GOS: Glasgow Outcome Scale. A method for describing the medical condition of patients that suffered neurological traumas.
- MAHSCS. Multi-Attribute Health Status Classification System.
- QALYs: Quality adjusted life years. A patients remaining expected life-years adjusted by their quality of life.
- QOL: Quality Of Life. How "well" a person is from a medical point of view.
- SAH: Sub-Arachnoid Hemorrhage. Bleeding in the brain.
- SEK: Swedish Crowns
- SMR: Standardized Mortality Ratio. A standardized mortality ratio of two means that the patients fares twice the risk of dying than an average person of that age.

3. Abstract:

3.1 Purpose:

A recent randomised medical study by Hillman et al (97) has proved that an immediate administration of tranexamic acid reduced the incidence of early rebleeding after aneurismal subarachnoid haemorrhage. The cost of the tranexamic acid is negligible and has few side effects but the reduced incidence rate may have far-reaching effects on the societal and clinical treatment costs, therefore justifying an economic analysis.

Our *primary objective* is to make a retrospective study of the incremental cost-utility ratios, from the treatment clinic and societal perspective, incorporating direct and indirect costs, for short-term application of the antifibrinolytica Cyklokapron with a do-nothing alternative as comparator. The do-nothing alternative is the standard treatment of patients with diagnosed aneurismal subarachnoid haemorrhage. We will also try to estimate societal willingness-to-pay. Since the available data is limited, our *secondary objective* is to try illuminate the need for further research and methods for future economic evaluation.

3.2 Setting:

Three neurological centers in Sweden serving a population of 4.6 million people.

3.3 Methods:

254 randomised patients suffering SAH verified on computerized tomography scans were immediately given tranexamic acid every 6 hours. The treatment was terminated at point of occlusion of the aneurysm, or after 72 hours. Outcome was assessed at 6 months post-SAH by using the Glasgow Outcome Scale. The GOS scores were converted into the EuroQOL EQ-5D score, and CU ratios were calculated from a county council- and societal perspective. The CU ratio was compared with an elicited WTP per QALY value.

3.4 Results:

The incremental cost-utility ratio from the county council perspective was 6356 SEK/QALY, range -12775 SEK/QALY to 10704 SEK/QALY. This is much less than relevant benchmark figures for the limit of cost-effectiveness. The incremental cost-utility ratio from the societal perspective was 117 050 SEK/QALY, range -22 113 SEK/QALY to 154 894 SEK/QALY. The expected societal impact per year was 497 079 SEK for the Swedish County Councils as whole and 9 104 44 SEK for the Swedish society.

4. Introduction

4.1 Medical Background

Rehaemorrhage is a major cause of incidences of mortality and morbidity in treatment for ruptured intracranial aneurysms. The recent practice of early aneurysm surgery has contributed significantly to the protection of patients from rebleeding. By operation early, in-hospital rebleeds occurring later than 24 hours after referral can be virtually eliminated. Several studies has clarified that the risk of rebleeding is at its peak during the first 24 hours after first occurrence of SAH. As many as 15% of the patients suffer from very early rebleeding. Even the most ambitious practice for initial diagnosis and referral to neurosurgical centres is therefore not enough for patients that suffer rebleeding before any therapeutic intervention is possible. In theory, the only viable option for softening the devastation of such ultraearly rebleeds is treatment with drugs immediately after the diagnosis of subarachnoid haemorrhage. Short-term antifibrinolytic treatment with tranexamic acid reduced the rebleeding rate from 10.8% to 2.4%.¹ In other words, the additional treatment with Cyklokapron reduces the number of deaths and the risk of disability caused by rebleeding in the brain. With 400 patients every year suffering SAH, 14 lives could be saved, and the favourable general outcome could increase. The short-term administration of Cyklokapron is therefore from a medical perspective an effective improvement of the standard treatment of bleeding in the brain.

Our *primary objective* is to make a retrospective study of the incremental cost-utility ratios, from the treatment clinic and societal perspective, incorporating direct and indirect costs, for short-term application of the antifibrinolytica Cyklokapron with a do-nothing alternative as comparator. The do-nothing alternative is the standard treatment of patients with diagnosed aneurismal subarachnoid haemorrhage. We will also try to estimate societal willingness-to-pay. Since the available data is limited, our *secondary objective* is to try illuminate the need for further research and methods for future economic evaluation.

¹ Hillman et al. (2002) Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurismal subarachnoid haemorrhage: a prospective randomised study. Journal of Neurosurgery : 771-778.

4.2 On the theoretical background of evaluation of health technology

The purpose of an economic evaluation is to trace all costs and benefits that are born by the institution that dictates the perspective.² This could e.g. mean an analysis from a societal or health care sector. Most economic evaluations published during the recent years take a health care sector perspective. Only costs that arose in hospitals and nursing homes were taken into account, despite the fact that the decisions made by politicians, doctors and hospital managements could have great effects on the rest of society. Reasons mentioned were the lack of relevance for their decision-making process, lack of data or ethical grounds.

The first purpose of an economic evaluation from a societal perspective is to compute all costs and consequences that are caused by the implementation of a particular health technology and to try to describe these in quantitative terms. The second purpose is to compare these costs and consequences with other alternatives according to one set of criteria that might influence the decision process.³ If the taxpayers' money is to be spent where the greatest benefit is to be found, then information on the benefits associated with different alternatives is required. We then need to decide on a) how to define benefits, b) how to measure costs. In choosing a method we make a normative statement, therefore it is essential to be as explicit as possible as to the reasons for choosing a particular model, and how this choice affects the results. The foundation of economics is the belief that every decision implies a trade-off. In making a choice, something else is forsaken

In a utopian society with infinite resources there would be no need for an economic analysis and the only relevant criteria for the evaluation of health technology would be its clinical efficacy. But with today's aging population, an increased number of available treatments and escalating costs in the health care sector have further increased the need for rational calculation of the value-for-money. Objections may be raised against economic evaluations of health care are that any attempt to compare saved lives and money is morally

² Some confusion exists as to the definition of the most common output methods in health economic evaluation. My definitions are:

- *Cost-Effectiveness Analysis*. (C/E analysis). The incremental costs divided by a single output measure. E.g. Life saved, life-year saved or number of successful operations.
- *Cost-Utility Analysis*. (C/U analysis) The incremental costs divided by the quality adjusted life-years saved.
- *Cost-Benefit Analysis*. (C/B analysis) The sum of the society's willingness to pay for a medical treatment minus direct and indirect cost associated with the treatment. If the net result is positive, the treatment is *cost-effective*.

³ Drummond et al. (2001) *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press. I will rely quite heavily on two books in health economics written by Drummond et al. (See references). Drummond is a well-known name in Health Economics and these two books provide an attractive source since they cover both the practical and theoretical aspects of health economic evaluation.

wrong. If the value of a person is not enough to cover for his or hers costs, does economic evaluation imply that it's justified to terminate that existence? No. Firstly, it's important to note the morally relevant difference between letting nature running its course (not treating for SAH) or actively taking a persons life. Secondly, the economic calculations are not of the value of an individual's life, but the cost of further reducing the risk for death or injuries. Also, money spent on the introduction of a new treatment on one part of the population means lower health for another group of patients since less money will be available for their treatment. Motivating the cost therefore becomes essential. Also, without some attempt at measurement, the uncertainty surrounding orders of magnitude can be critical.⁴

Evaluations of health technology have their theoretical foundation in the theory of welfare economics. Individuals derive utility from both physical goods and abstract goods like health. An example; the individual is the best judge of the value of spending 5 years in good health in comparison with spending with 10 years in bad health. A change in health economic policy can only be deemed worthwhile when no one becomes worse off than before.⁵ This would in our case translate into a both gained life years and lesser costs for all parties involved. These are very conservative criteria since there is almost always someone who loses. Therefore the concept of hypothetical compensation was introduced.⁶ If the gainers can fully compensate the losers and still be better off, the policy is deemed worthwhile. It would practically unfeasible to find and motivate all affected individuals to honestly reveal their preferences. Therefore, the rule-of-thumb is to derive the average preferences from a sample of the general population and for a independent researcher to estimate the money value of the gains and losses and see if the net effect is positive. We will therefore perform an incremental cost-benefit analysis.

The societal impact may not affect the decision making process as much as the cost and effects on the county council level. Still, the hospital perspective may be too narrow, hiding costs or benefits. If the new treatment increases the costs for the health care sector, but reduces costs borne by the rest of the Swedish society, redistribution of resources may be in order. Also, the societal perspective is more in line with the orthodox economic theory.

⁴ Zweifel, Peter; Breyer, Friedrich. (1997) Health Economics. Oxford University Press.

⁵ Pareto improvement

⁶ Hicks- Kaldor criteria. See e.g. Hurley, Jeremiah. "An overview of the normative economics of the health sector" Handbook of Health Economic, Volume 1

4.3 Data and Methods

In lack of Swedish health economic guidelines⁷, we will follow the Norwegian and Danish informal guidelines.⁸ Both Norwegian and Danish guidelines suggest taking a societal perspective, and Norwegian guidelines state that indirect costs should be reported separately. The only stochastic data directly related to this study was the mortality and morbidity outcome 6 months post-operation, and all other data were collected from an overview of other relevant studies. No financial resources were available for any random collection of data, other than the one available from the clinical study. We will not discuss alternative treatments in this study other than the status quo. This is referred to as the “do-nothing alternative”. This does not mean that the alternative to treatment with Cyklokapron is no treatment at all. All patients were treated according to the standard practise for intervention in case of bleeding in the brain. The difference was the *additional* treatment with antifibrinolytica. Costs (and partly the effects) will be measured in SEK, and costs will be adjusted for inflation to the CPI for 2003, when possible.⁹

Every type of economic study involves some kind of guess making. When forced to make assumptions, we will choose the ones that are to the detriment of the AF treatment. It is better to underestimate the positive effects than to overestimate them.

4.4 Morbidity and mortality

The medical study was undertaken for a 30-month period from September 1997 to March 2000 at the neurosurgical departments at the university hospitals in Linköping, Lund and Gothenburg. 596 patients suffering CT-verified SAH within 48 hours prior to the first hospital admission were included in this open, randomised trial. Pregnant patients, patients under 15 years, and patients with a history of thromboembolic disease were excluded. For 91 patients included in the study no aneurysm was demonstrated, and these patients were excluded. After fulfilling the entry criteria the patients were randomised to receive the drug received 1 g of tranexamic acid (Cyklokapron) intravenously before being transported to the regional neurosurgical centre. Another dose was given after 2 hours, followed by 1 g every six hours until the aneurysm was occluded or 72 hours after the treatment for SAH.

Only objectively documented cases of rebleeding were included in the statistics. The outcome was assessed six months after SAH according to the Glasgow Outcome Scale

⁷ Drummond, Michael; Jönsson, Bengt; Rutten, Frans. (1997) The Role of Economic Evaluation in the Pricing and Reimbursement of Medicines. *Health Policy* 40; 205.

⁸ Hjelmgren J, Berggren F, Andersson F. (2001) Health economic guidelines – similarities, differences and some implications. : *Value in Health* vol: 4:225-250

⁹ Privata Affärer. <http://www.privataaffarer.se/>

(GOS), which is a 5-grade post-recovery outcome scale. GOS levels are death, persistent vegetative state, severe disability, moderate disability and good recovery.¹⁰ No patients were lost in the follow-up. The overall outcome among the patients in the group receiving antifibrinolytics was better, but the increase in favourable outcomes was not statistically significant. This may be due to the slightly skewed distribution of patients of different pre-bleed grade between the two groups. A statistically significant reduction in the number of rebleeds, and a significant difference in the GOS distribution between rebleeders and monobleeders were found. In other words, we cannot prove that the AF had a direct effect on the morbidity of the surviving monobleeders in the AF group. What we can prove is that the AF decreased the number of rebleeders, and that you fare a lower risk of brain damage if you do not rebleed. This means we can compute a positive effect on the overall outcome in the AF group, despite the lack of evidence of a direct effect from the drug on the morbidity and mortality. (See fig 1)

The long-term mortality after treated SAH were calculated with Finnish standardized mortality rates for GOS 2-5 patients and GOS 5 patients¹¹ and Swedish average length of life.¹² We postulate that the true excess mortality rate is constant. We also assume that the excess mortality for the Finnish GOS 2-5 group corresponds to the long-term mortality for the GOS 2-3 patients in the Hillman et al study, and that the mortality rate of Finnish patients with good recovery corresponds to the mortality rate of the GOS 4-5 group in our study. We will therefore likely overestimate the life expectancy for the GOS 2-3 patients. The number of men and women that participated in Hillman study was not stated so we have to assume that the distribution over the age groups is equal to the distribution in the general population.

¹⁰

1. *Death.*

2. *Persistent vegetative state.*

3. *Severe disability.* (Conscious but disabled). "Patients who are dependent for daily support by reason of mental or physical disability. Many will in institutions, but this should not be a criterion because exceptional family efforts may enable such to be looked after at home."

4. *Moderate disability.* (Disabled but independent.) "...independent in so far as daily life is concerned... ...may produce considerable family disruption."

5. *Good recovery.* "This implies resumption of normal life even though there may be minor neurological and psychological deficits. Return to work is regarded as an unrealistic index of recovery, because it may lead to false impressions in either direction." See: Jennet, Bryan; Bond, Michael. Assessment of outcome after severe brain damage. - A practical scale. The Lancet 1:480-484, 1975

¹¹ Ronkainen, Anti et al. (2001) Evidence for Excess Long-Term Mortality After Treated Subarachnoid Hemorrhage. Stroke.32: 2850-2853.

¹² Swedish Statistical Board. Återstående medellivslängd för åren 1751-2001. www.scb.se

4.5 Costs

An economist's definition of a cost is the value of best alternative use of the scarce resources spent. In a market with very high levels of competition, and when the customers are fully informed of the advantages and disadvantages of the products offered and when no one has to bear the costs of another person's actions, the market price is equal to the alternative cost. Since the health care market is as far from this hypothetical state as possible, this presents a serious problem in estimating costs. For the cost of the AF drug, there exist a market price. We have to assume that it does not differ all too much from their alternative cost. For other costs, like hospital administration costs or the cost of patient/family leisure time there isn't a clear market price. We are forced to make pseudoprices, and opinions differ how these should be approximated.

The purpose of the study is to assess the *additional effect* of treatment with antifibrinolytika, not to justify the general treatment of aneurismal subarachnoid haemorrhage. If costs or effects are believed to be the same for both study arms we can exclude them since they'll not affect the decision making process. Although, the extra time spent on tracking down costs that would sum out might be worthwhile if we were to conduct a broader study on other treatment options at a later stage. Unfortunately, the available cost data isn't solid enough for us to include more than what we assume to be an absolute minimum. Categories of resource used are¹³:

4.5.1 Medical and non-medical resources

Unfortunately there were no available data on the individual patient's costs, only aggregated costs from the annual reimbursement scheme. We are therefore forced to make an educated guess as to the costs of treating patients with or without the help of Cyklokapron. We can statistically ascertain the risk of rebleeding for both study arms, but not the direct effect of AF on the patients' health status. In making the assumptions necessary for the analysis, we choose the alternatives to detriment of the AF treatment. We therefore assume that AF has no positive effect on the outcome of the patients that do not rebleed. Cyklokapron only affects the distribution of rebleeders and monobleeders, and only the actual rebleeding affects the health of the patients. We are therefore interested in the costs for the rebleeders and

¹³ Brouwer, Werner; Rutten, Frans; Koopmanschap, Marc. (2001) Costing in economic evaluations. Economic evaluation in health care. Ed: Drummond, McGuire. Oxford University Press

monobleeders and how the AF-treatment affects the number of, presumably, more expensive cases of rebleeders. According to the medical staff, the Swedish County Councils reimburse the hospitals with a standard fee of 190 000 SEK per patient, regardless of the initial diagnosis. If a case is complicated, and the costs exceeds the limit, the hospital is reimbursed with 330 000 SEK.¹⁴ In discussion with the medical staff, we find that approx 1/3 of the patients are reimbursed with 330 000 SEK and 2/3 with 190 000 SEK. The rebleeding cases that survive the first days are with few exception always complicated, and therefore reimbursed with 330 000 SEK. These costs are administratively set, and may not correspond to the true costs, but since the number of cases of subarachnoid hemorrhage is relatively few, the absolute size of the costing error is small. We assume that most fatal cases occur within 48 hours, since most cases of rebleeding occur within 24 hours. We calculate a cost of approx. 100 000 SEJ for patients that die at the hospital. (65 000 SEK for the fist operation and 32 000 for two days at intensive care since plus other expenses.¹⁵) The cheap patients group therefore consists of patients that die early and patients that survive. Therefore:

$$190\ 000 = Z * 100\ 000 + (1-Z) * W$$

Z is the share of patients that are diagnosed with GOS 1, and W is the cost of a cheap, surviving patient. W is therefore approximately 205 450 SEK. The cost of an average rebleeder is calculated as following:

$$C(\text{rebleeder}) = 330\ 000 * P(\text{GOS 2-5} \mid \text{rebleeding}) + 100\ 000 * P(\text{GOS1} \mid \text{rebleeding})$$

$P(\text{GOS 2-5} \mid \text{rebleeding})$ is the probability of surviving a rebleeding. This was calculated as the number of surviving rebleeders for both study arms, divided by the number of rebleeders for both study arms. (18/33. See fig 1). $P(\text{GOS1} \mid \text{rebleeding})$ is the risk of dying, given that you rebleed. This was calculated as the number of rebleeders that died for both study arms, divided by the number of rebleeders for both study arms. (15/33, which are rather grim odds. Even a small reduction in the number of rebleeders can therefore have a profound effect on the overall outcome. See fig 1). As you can see, we use compounded averages for the probabilities above, since no statistically significant difference in the outcome classified according to the GOS could be detected between the two test groups. Since the patients that do not rebleed consists of cheap and expensive cases, the cost for an average monobleeder is somewhat more ambiguous. The cost can be approximated as the sum of the weighted costs

¹⁴ I haven't been able to find figures that confirm or dispute this claim.

¹⁵ Figures elicited from *Jeppsson, Bengt. Somatisk Sjukvård Universitetssjukhuset i Lund. 2001* and in discussion with medical staff at the neurological centre of Lidköping University Hospital.

for the cheap and expensive surviving monobleeders and the weighted costs for the patients that didn't neither survive nor rebleed.

$$C(\text{monobleeder}) = X * 205\,450 * P(\text{GOS 2-5} \mid \text{no rebleeding}) + (1-X) * 330\,000 * P(\text{GOS 2-5} \mid \text{no rebleeding}) + 100\,000 * P(\text{GOS 1} \mid \text{no rebleeding})$$

Since a third of the patients belong to the expensive category, and only 7% of the patients in the study rebleeded, some of the monobleeders must have belong to the expensive category. X is the share of the surviving monobleeders that were cheap to treat.

We approximate X as;

$$(1-X) = 33\% - (\text{the number of surviving patients that rebleeded}) / (\text{total number of patients in the study})$$

We know how Cyklokapron affects the rate of rebleeding, and we know how rebleeding affects the outcome. The costs are the cost for rebleeders and monobleeders that are given placebo minus the costs for the monobleeders and rebleeders that are given AF.

$$\Delta C = C_{\text{rebleeder}} * P(\text{rebleeding} \mid \text{AF}) + C_{\text{monobleeder}} * P(\text{no rebleeding} \mid \text{AF}) - C_{\text{rebleeder}} * P(\text{rebleeding} \mid \text{placebo}) - C_{\text{monobleeder}} * P(\text{no rebleeding} \mid \text{placebo})$$

We rearrange this as:

$$\Delta C = C_{\text{rebleeder}} * [P(\text{rebleeding} \mid \text{AF}) - P(\text{rebleeding} \mid \text{placebo})] - C_{\text{monobleeder}} * [P(\text{no rebleeding} \mid \text{AF}) - P(\text{no rebleeding} \mid \text{placebo})]$$

According to the medical staff, the actual cost of the AF was 300 SEK per dozes or 1320 SEK per patient.

4.5.2 Patient time, productivity changes and time of informal caregivers and other costs

Including indirect costs, such as the change in the patients' production and consumption is the most important difference in taking a societal perspective than from a health care sector perspective. Changes in the patient's working capacity affects both his or hers time spent on leisure and working, and therefore his level of consumption. Also healthier patients mean a

larger tax base, and therefore the possibility of spending more on health care. Unfortunately there is limited agreement on the methods for and validity of measuring the patient's productivity. There is no clear market value of the time spent in recuperation or the informal caregiver's time. If the patient recovers 2 weeks earlier, does that mean that society gained 2 weeks of his potential production? We divide the time costs into¹⁶:

Time spent on paid work. The employer has to buy the employee's leisure time at the market wage as a compensation for his work. According to the human capital method, the wage rate is seen as a relevant opportunity cost of time absent from paid work. If the responsibility of caring for the patient is left to informal caregivers like family and friends, Brouwer et al recommends that their lost work time should be measured the same way. The definition of "good recovery" according to GOS does not imply that the person is able to return to work. Neither does it imply that the patient is unable to return to work. As stated before, when we are in doubt, we will choose the assumption that is to the detriment of the treatment. We will therefore make the assumption that none of the patients are able to return to work. This is not so farfetched, considering the average age (55 years) and the situation on the Swedish labour market¹⁷. We can therefore exclude the cost of the patients lost production, since the lost production is not an additional effect of the AF treatment.

Time spent on unpaid work. Both people that have paid jobs and those who are unemployed spend time on unpaid household chores like cooking, cleaning or caring for children. The Washington Panel recommends that "when a person is of working age, but does not work for pay... option is to use the hourly wage rate of individuals with the similar characteristics.. who do work for pay" (Brouwer et al) The wage rate should then correspond to the true opportunity cost of lost household production. Brouwer et al raises several objections against this method. If it were a simple trade-off between the value of home production and the value of a regular job, then high wage earners wouldn't perform any home production. An extra hour at work would buy more goods than what you could produce at home. You derive an indirect utility from the household production itself, which adds to the gain of the household chores. Also, your regular wage might not respond to your productivity in the household. A manager might earn five times more than a kindergarten teacher, but that does not make him five times more productive in e.g. baking bread. Brouwer et al

¹⁶ Brouwer, Werner; Rutten, Frans; Koopmanschap, Marc. (2001) Costing in economic evaluations. Economic evaluation in health care. Ed: Drummond, McGuire. Oxford University Press

¹⁷ I haven't been able to find any hard figures on the probability of returning to work for these patients, but we do not find this unreasonable considering the severity of the disease. According to the Swedish Statistical Board, 54% of all persons receiving supplementary disability pension in Sweden are 55-65 years old. (SCB "OHÄLSODATA 1999-12-31 - Befolkningen 16-64 år. Antal personer med status som förtidspensionerade.")

recommends taking the wage rate of a professional housekeeper as an estimation of the monetary value of household production. The utility reduction of “being less able or unable to engage in home production activities that contribute positively to one’s quality of life” should be captured in the QALYs. If the responsibility of caring for the patient is left to informal caregivers like family and friends, Bouwer et al recommends that the cost of lost household production should be measured in the same way. In accordance with the definition of the GOS, we assume that the GOS 2-3 patients need full assistance with their household production and self-care. The societal cost for these patients are the future stream of consumption of normal goods and health care¹⁸ plus the cost of informal care. We assume that standard gross wage rate for a personal assistant best correspond to the true social cost of the work done by the informal caregiver. We thus ignore market imperfections like oligopoly power and effect of taxation on the demand and supply. The gross wage rate for 2002, excluding overtime pay, is 511 crowns¹⁹. The average OECD citizen spends 1357 hours per year on household production.²⁰ The monetary value of one year of informal care therefore sums up to about 700 000 crowns. We consider this an upper limit to the true social cost, since we ignore economies of scale in the additional household production provided by the informal caregiver.

Leisure time. Using wage forgone as a measurement of the value of lost leisure time may, as in the case of time spent on unpaid work, not include the full opportunity cost of time. If the value of our leisure time would be equal or less than the value of our time spent on work, then it would be more profitable to work during our leisure time. We will not assign a monetary value to leisure time lost due to illness, since this is already captured in the quality-for-life value. The value of household production consists of its production value, which is mentioned in the paragraphs above, and the pleasure we receive from the actual process of household production. I will assume that this is captured in the quality-of-life value.

Time of unemployed, the elderly and disabled persons. How much is a non-working persons time worth? How much leisure does that person have, and what is the marginal utility of that time? The considerations are similar as earlier. Brouwer et al recommends that loss of time spent on leisure should be measured as a cost to the quality-of-life and that the price of time spent on household production should be measured as wage rate of a professional housekeeper.

¹⁸ Ekman et al: (2002) Kostnadseffektivt att behandla kronisk hjärtsvikt med bisoprolol. *Läkartidningen* 99: 647-650,

¹⁹ Calculated from the wage rate suggested by www.kommunal.se, the SWEDISH MUNICIPAL WORKERS' UNION. General payroll tax included.

²⁰ Ironmonger, Duncan: (1996) Counting Outputs, Capital Inputs and Caring Labor: Estimating Gross Household Production. *Feminist Economics* 2(3), 37-64

Future medical costs as a cause of the intervention. The direct medical costs are the future costs that can be attributed to the medical treatment. We have no data on the difference in future demand for neurological care among the two study arms, and have to assume that the patients do not consume more health care than the average person of the same age. This unavoidable assumption will probably cause us to underestimate future indirect medical costs. The indirect medical costs are the changes in the consumption of health care, as the patients grow older. The consumption of health care among individuals at the age of 50+ grows significantly in Sweden until the time of death.²¹ Consistency requires us to make all implicit trade-offs to be made explicit.²² Therefore, the change in consumption of geriatric health care related to the change in mortality within the timeframe of the study must be included. The aggregated consumption of health care is included in our data on general consumption.

The monetary social costs. We define the average social cost for a patient in the three cost groups as following (excluding hospital costs):

$C_{GOS\ 1} = 0$ since the “future” consumption – minus production is zero. (Se fig 1)

$C_{GOS\ 2-3}$ = The discounted sum of costs for future informal and formal care plus the discounted sum of future consumption of an person of that age.

$C_{GOS\ 4-5}$ = The discounted sum of future consumption of an person of that age.

The incremental change in the social costs for unpaid work per patient is the incremental change in the probability of each outcome times the average social cost as defined above. If we rearrange this, we get;

$$\Delta C = C_{GOS\ 1} * [P(\text{rebleeding} \mid \text{AF}) - P(\text{rebleeding} \mid \text{placebo})] * [P(\text{GOS } 1 \mid \text{rebleeding}) - P(\text{GOS } 1 \mid \text{no rebleeding})] + C_{GOS\ 2-3} * [P(\text{rebleeding} \mid \text{AF}) - P(\text{rebleeding} \mid \text{placebo})] * [P(\text{GOS } 2-3 \mid \text{rebleeding}) - P(\text{GOS } 2-3 \mid \text{no rebleeding})] + C_{GOS\ 4-5} * [P(\text{rebleeding} \mid \text{AF}) - P(\text{rebleeding} \mid \text{placebo})] * [P(\text{GOS } 4-5 \mid \text{rebleeding}) - P(\text{GOS } 4-5 \mid \text{no rebleeding})]$$

4.6 Cost-Utility Analysis.

The medical study has shown that the administration of AF increases the chances of survival. But are the patients better off? Respondents in quality-of-life studies have shown that some

²¹ Ekman et al: (2002) Kostnadseffektivt att behandla kronisk hjärtsvikt med bisoprolol. Läkartidningen 99: 647-650,

²² Dolan, Paul. (2001) Output measures and valuation in health. Economic evaluation in health care. Ed: Drummond, McGuire. Oxford University Press

health states are worse off than death, making a medical intervention both expensive and unwanted. The purpose of cost-utility and cost-effectiveness studies is to aid the decision making process in the health care sector. With the purpose of providing as high health as feasible to its clients, the health care sector needs to weight different treatments against each other. Cost-effectiveness ratios (e.g. cost per saved life) can't be compared with benchmarks for treatments that increase health, but do not save lives. With cost-utility analysis we can compare this treatment with a wide range different treatments.

The principle of cost-utility analysis is simple. The incremental cost per patient of the treatment is compared to incremental utility the average patient derives from the treatment. The theory of utility is several centuries old, and the meaning is ambivalent. The definition of utility used for cost-utility analysis is that some health states are better than others. E.g. having limited eyesight is better than being blind. (Ordinal preferences) The patients are also able to express the strength of their preferences towards these health states in a non-random way. E.g. if having perfect eye-sight is equal to 1.0 and being blind is equal to 0, then the patient is able to assign a number in between for certain levels of sight. (Cardinal preferences). By eliciting the preferences from the patients in question or the general public we can assign subjective values to objective outcomes.

Since aneurismal subarachnoid haemorrhage can result in both physical and psychological disabilities we need a multi-attribute health status classification system. Making new measurement of the preferences and health status of the patients is not possible. A attractive, and widely used solution is using an existing MAHSCS. Three examples of systems available are; Quality of Wellbeing, Health Utility Index and EuroQol. The EuroQol Group is a consortium of investigators in the European Union. We will choose the EuroQol classification system since it's one of the more widely used.²³ The EuroQol classification system is non-disease specific and based on the patient's health and ability to function in the daily life. The patient is classified in 3 levels according to mobility, self-care, usual activities, pain/discomfort and anxiety/depression. (See appendix) The patient's health profile is then weighted, where death is equal to 0, negative values to health states worse than death and 1 to a state of perfect health. The growing use of the EQ-5D system makes comparison with other studies easier.

The GOS is an outcome scale designed for assessment of neurological damage, and not fully non-disease specific. For us to use available quality of life-tariffs, we must convert the GOS to some other scale. The ideal solution for converting the Glasgow outcome scale to the EQ-5D scale would be to let the patients state their health status, and how they

²³ Rabin, Rosalind; de Charro, Frank. EQ-5D: a measure of health status from the EuroQol Group.

value it in relation to a state of perfect health. Since this option was unavailable to us, and since we couldn't find any study that had converted the GOS into QALYs, the health professionals at the neurosurgical department of the University Hospital Linköping that undertook the postoperation outcome assessment were asked to hypothesize the relation between GOS state 1-5 and the EQ-5D outcome scale. This is of course a far from ideal solution, since we assume that the doctors can correctly assess and summarize all the patients health states. We risk under- or overestimating the gains. The effects will be controlled for in the sensitivity analysis. The different outcome possibilities were then weighted with the UK EuroQOL tariffs.²⁴ Since the conversion method being non-random, computation of a statistical interval would be incorrect. Instead we use the average, the maximum and minimum QOL value for the computation of the C/E ratios²⁵. The rebleeders for both study arms were grouped together into GOS1, GOS 2-3, and GOS 4-5 groups. To estimate the QOL score for group GOS 2-3 and GOS 4-5 we weighted the scores according to their frequency, and not as a simple average.²⁶

4.7 Discounting

Individuals have shown to exhibit positive time preferences. It means that individuals value today's costs and benefits higher than those of tomorrow. There are three arguments for this. First diminishing marginal utility of consumption over time. The more we consume the less additional utility do we get from the additional consumption. Secondly, the risk of death or disability decreases the chance of further consumption. Finally, if people can choose to consume a good today or in the future, people will choose today.

This year's value of future costs due to the implementation of the AF-treatment is calculated. Therefore the choice of discount rate may have a profound on the relative cost-effectiveness of different interventions. Time preferences and discounting has long been a topic of research in the field of economics. Unfortunately, lack of agreement over standard

²⁴ The preferences were elicited from a random sample of approximately 3000 members of the adult population of the United Kingdom using the time trade off method. There are several methods for measuring peoples' preferences, but the time trade off method has proven itself in comparative studies such as *Torrance, George W. (1976) Social Preferences for Health States: An Empirical Evaluation of Three Measurement Techniques. Socio-Economic Planning Sciences. (10):129-136.* Danish informal guidelines suggest the TTO, Rating Scale or the SG methods.

²⁵ We calculate the ratio as the societal cost divided by the number of discounted qalys saved per patient. A negative result means either that the average outcome is worse than death or that society saves resources for each patient that receives the treatment.

²⁶ E.g. $QOL[GOS\ 2-3] = \frac{QOL[GOS\ 2] * n[GOS\ 2]}{n[GOS\ 2] + n[GOS\ 3]} + \frac{QOL[GOS\ 3] * n[GOS\ 3]}{n[GOS\ 2] + n[GOS\ 3]}$.

[n(GOS 2) is the number of all the patients diagnosed as GOS 2 and QOL[GOS 2] is the quality-of-life-score for being in the state GOS(2).]

discounting practice, and dissimilar empirical findings make it hard to pick a certain discount rate²⁷. Discount rates elicited from the general public in economic surveys have varied strikingly, and tended to be quite high. Three types of preferences concerning discounting can be discerned;

Intertemporal social preferences concern society's preferences for costs and benefits in one time period compared with another. *Individuals' preferences for private intertemporal choices* are factors influencing our private savings and consumption.

Interpersonal social preferences concern society's preferences for costs and benefits accruing to another group of individuals in the future other than the people asked. (Intertemporal equity) Using private discount rates, elicited from individuals, for decisions concerning the public sector is problematic when the health insurance system is financed as pay-as-you-go. The private discount rate may not necessarily correspond to the interpersonal discount rate. A high discount rate implies that the individual is willing to postpone paying for the costs. If you include productivity costs and health care costs due to a longer lifespan, and use a higher discount rate than the true interpersonal discount rate you will underestimate costs borne by future generations. An external effect will be imposed on future generations. Our approach to this analysis was to make assumption to the detriment of the AF-treatment in case of doubt. But setting a high discount rate will decrease the cost-utility ratio, since the GOS 2-3 patients contribute much to the costs, but little to the aggregated quality of life as defined by the QALY approach and have a short expected life-span. We will therefore choose a more conservative discount rate, in order not to underestimate future costs.

Should all costs and benefits be discounted? We have among others productivity costs, medical costs, out-of-pocket expenses and health benefits. Although there is a strong tradition in health economics to include individual preferences, we are in doubt whether those are applicable for all costs in this evaluation. Current practise and most guidelines recommend that future health benefits should be discounted at the same rate as future costs. A relevant argument mentioned is the risk of eternal delay^{28 29}. If health benefits were discounted at a lower rate than costs, it would be attractive to delay the project. This is not a very strong argument since the treatment is already implemented in Swedish health care. It is also seldom a question of when to implement a given policy, but rather which of several projects to implement at the moment. Another and more important argument is of consistency. The value

²⁷ Cairns, John. (2001) Discounting in Economic Evaluation. . Economic evaluation in health care. 237-255. Ed: Drummond, McGuire. Oxford University Press

²⁸ Cairns, John. (2001) Discounting in Economic Evaluation. . Economic evaluation in health care. 237-255. Ed: Drummond, McGuire. Oxford University Press

²⁹ Drummond et al. (2001) Methods for the Economic Evaluation of Health Care Programmes. 107-109 Oxford University Press.

of health versus money should remain the same in the present as in the future, and treating health projects different from other government projects would lead to inconsistencies in the allocation of resources. Also, people trade health through time. E.g. by consuming harmful substances, you trade your future health for the pleasure of consuming that good today.

Danish informal guidelines suggest that both costs and consequences should be discounted and Norwegian informal guidelines suggest discount rates of 2.5% to 10%. We will therefore use a discount rate of 3%³⁰, which corresponds to the current interest rate the Swedish state pays on the open market.

4.8 Cost-benefit analysis and willingness to pay.

The cost per quality adjusted life-years ratio gives us a measure of the effect of the treatment but not if it's profitable from the tax-payers point of view. The definition of societal cost effectiveness is if all the people that gain from the treatment are willing to cover for the all costs.³¹ In this case it would be the willingness to pay for the reduced risk of patients rebleeding. We have to estimate the willingness to pay for the use of Cyklokapron. A method available is looking at real market situations where people pay for more for decreasing the risk of death and injuries (revealed preferences). Another is interviewing test subjects (stated preferences). One example of a revealed preferences approach is comparing the market price for airbags in cars with their benefits. An airbag reduces the total risk of dying in a traffic accident with a probability of just a few in a thousand. Dividing the price with the reduced risk of dying, we get the value of a statistical life. Comparing this with e.g. risk premiums for oilrig workers, we get widely dissimilar results. A stated preferences approach is more common, since its easier to control for unknown variables, although stated preferences studies that used similar methods for calculating the willingness to pay for decreasing risk have shown widely different results.³² Eliciting WTP in a health care setting is still a field of intensive debate.

The large differences in definitions of WTP, methods used, culture and income of the test subjects, the respondents ability to comprehend the questions asked, and ethical objections to the framework of the surveys, are some of the reasons that different studies have found widely dissimilar results. One problem is that people have large difficulties imagining

³⁰ The average interest rate that the Swedish state had to pay on the open mark during 2001-2003 was 3.1%. (www.csn.se)

³¹This includes the WTP of persons affected and the altruistic WTP by individuals not affected.

³² De Blaeij, Arianne et al. (2003) The Value of Statistical Life in Road Safety: A Meta Analysis. Accident Analysis and Prevention. 35-6:973-986.

risks larger than 90% and smaller than 10%.³³ E. g, if the respondents are indifferent between .01% and 0.1% risks, the bias in WTP elicited may be tens of millions SEK.

Unfortunately, we could not find any relevant studies that directly estimated the willingness to pay for avoiding the risk of disability that comes with rebleeding. One elegant solution is to convert QALYs to WTP. We will utilize data a recent study on the willingness to pay for improving your health measured in QALY steps³⁴. A discrete-choice model was used to collect the respondents' preferences. The respondents were randomly presented with two different chronic health states, qualified with the EuroQoL EQ5D method, and were asked to point out the worst. Then they were offered a treatment at a fixed price that would improve their health to the point of the better alternative. The estimated WTP per QALY was 88000 DKK (110000 SEK). To utilize Gyrd-Hansens findings we are forced to make a group of assumptions. Since Cyklokapron is a prophylactic medicine, any study of the WTP for the treatment must be formulated as an *ex ante* question. This means that the respondents are asked to state their willingness to pay for insuring themselves against rebleeding *before* they rebleed. The Gyrd-Hansen study was formulated as an *ex post* question, meaning people were asked to imagine that they already were experiencing the health state, and how much they were willing to pay for alleviating their suffering.

In comparing the WTP per QALY of Gyrd-Hansens study with our average incremental cost per QALY won we assume that the patients are a) *risk neutral* and b) *fully aware of the magnitude of the risk*. Risk neutrality means that you value e.g. a bird in your hand the same as a 50% chance of getting two in the woods. In most situations people are *not* risk neutral, otherwise there wouldn't be a market for insurances. Gyrd-Hansen's study didn't deal with risk, thus eliminating the problem of risk perception. Even if individuals are risk neutral, a sufficiently large society could be assumed to be risk neutral, and if decisions are based on statistics and not on individual perception, then risks are not overestimated or underestimated. If we assume risk neutrality in the decision making process, we diverge from the welfarist's believe that the individual is the best judge of his or hers utility.

Since it's assumed that the QALY tariffs are influenced by the individual's income loss (lost wage minus sickness benefits, disability pension etc), in using the Danes' WTP we should have used Danish QALY tariffs as compensation for differences in the social benefit systems of Sweden and Denmark. Unfortunately, they were not available for free. Since the patients were asked to consider themselves in the state of ill health, altruistic WTP

³³ Torrance, George W. (1986) Measurement of Health State Utilities for Economic Appraisal: A Review. *Journal of Health Economics* ;5:21

³⁴ Gyrd-Hansen, Dorte. (2003) Willingness to pay for a QALY. *Health Economics*. 12:12. 1049-1060,

can be assumed not to have influenced the level of WTP per QALY. We will therefore likely underestimate the true societal WTP in our study.

Another solution for finding WTP for the QALY gain is to convert the value of a statistical life used for road safety economics in Sweden into WTP for a QALY as done in a recent paper.³⁵ With up-to-date figures, the WTP for a QALY would amount to 650 000 SEK, with a recommended interval of 400 000 SEK to 1 200 000 SEK.³⁶

³⁵ Ekman et al (2002): Kostnadseffektivt att behandla kronisk hjärtsvikt med bisoprolol. Läkartidningen 99: 649

³⁶ Johansson, Joakim. (2002) Trafiksäkerhet. Översyn av samhällsekonomiska metoder och kalkylvärden på transportområdet. SIKÅ (The Swedish Institute For Transport and Communications Analysis) Rapport 4. Chap 6;89-96

5. Results

Figure 1 presents the decision tree, and the societal and county council costs associated with each node. Table 1 presents the conversion of the GOS classification system into the EuroQoL descriptive system, using UK EuroQoL scoring system. Table 2 presents how the utility scores for each GOS state was weighed in the calculation of the GOS 2-3 and GOS 4-5 utility scores. Table 3 presents the change in risks associated with the treatment. Table 4 presents the result of the economic evaluation including the sensitivity analysis and societal impact.³⁷

6. Discussion

The Hillman et al study, like most medical studies (and hence most health economic evaluations), was of *efficacy*. The question posed was if the treatment or service has a positive effect on people who fully comply with the treatment plan. In real life, people often do not. More desirable for economic evaluations from a societal perspective is to measure the *efficiency*, i.e. if a treatment or service does more good than harm to people in need.³⁸ It's easier to control for unwanted, random influences on the test results if the study is undertaken in clinical settings. Unfortunately with efficacy studies you risk getting a biased test population. The persons undertaken the study are not representative of the general population and do not behave like the average. People that could have benefited from the treatment do not seek medical care, and do therefore not end up in the study.

A solution would have been treating a randomly selected population group, regardless if they sought for treatment or not. It would be ethically impossible to perform an efficiency study of the effect of AF on the incidence of rebleeding, since the side effects on healthy subjects are too large. A rule of thumb in medical statistics is to perform an efficiency study for highly common diseases, like a common cold, and efficacy studies for uncommon ailments. The efficacy approach is not a source of bias, since AF for prevention of rehemorrhage is always administered in a controlled clinical environment. This is, of course, under the assumption that the clinical practise during the trial did not differ substantially from usual clinical treatment aneurismal subarachnoid haemorrhage.

³⁷ Norwegian informal guidelines suggest that the average C/E ratio should be stated. We will not, since covering *all* the costs with the SAH treatment would be beyond the scope of this evaluation.

³⁸ Drummond et al (2001). *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press.

In using the excess mortality rate for an entire SAH patient group in calculating the expected life span for the GOS 2-3 group, and in assuming the excess mortality to be equal for GOS 4 and GOS 5 patients, we most likely overestimate the remaining no of life-years. An increase in the SMR of 20% increased the average incremental social C/U ratio increased by 5000 SEK, which is acceptable because it does not make the AF treatment dramatically less appealing.

The QOL value for the health state GOS 2-3 was rated at lower than zero. In other words, the average person would rather be dead than suffer the mental and physical disability associated with being either in a persistent vegetative state or suffer severe disability as classified by the Glasgow Outcome Scale. Although the evidence is mixed, several studies suggest that patients value their health higher than the average person not affected by the ailment.³⁹ People adapt to their disabilities. This would suggest a different cost-utility ratio, if we were to elicit the utility scores from haemorrhage patients. We test for an adaptation bias by increasing the QALY score by 0.2. This value is large enough to show any sensitivity to of adaptation bias in the results, but larger than a reasonable value. The change in average QALY won per SAH patient receiving the treatment was only half a quality-adjusted *life-week*. Unfortunately, economists disagree on whether to take an ex-ante perspective, i.e. to measure the preferences before the illness, or an ex-post perspective, i.e. after the illness. If we were to measure the WTP for avoiding rebleeding, and not the QOL associated with rebleeding-related disability, the choice between the ex-ante and ex-post perspective would be simpler. We ignore any process utility from the treatment, since we have no such data and believe this would have negligible effect on the end result.

In the “minimum life-span”- and “maximum life-span”-test we look at how choosing SMR at endpoints of the 95% confidence interval would affect the overall result. A longer life span increases the incremental cost per QALY gained, but in a marginal way. We also test the effect of the assumption that the average hospital cost for a patient that dies at hospital stays at 100 000 SEK. We substitute 100 000 for 190 000, and find that the average incremental cost per QALY becomes a incremental *gain* per QALY.

In a recent study of the C/E of Nimodipone treatment after SAH⁴⁰, 55% of the H&H I and III⁴¹ patients in the placebo group were still working after 10 years. If we assume

³⁹ Dolan, Paul. (2001) Output measures and valuation in health. Economic evaluation in health care. Ed: Drummond, McGuire. Oxford University Press

⁴⁰ Karinen, Petri et al. (1999) Cost-Effectiveness Analysis of Nimodipone Treatment after Aneurysmal Subarachnoid Hemorrhage and Surgery. Neurosurgery, 45-4.780-785.

⁴¹ Classification of patients with intracranial aneurysms according to surgical risk. Among the number of grade I and III patients that rebleeded and survived more than 6 months in Hillman et al study, most were diagnosed with GOS 4-5.

that 55% the GOS 4-5 patients manage to work until their retirement, society *saves* 22 000 SEK for each QALY gained. The treatment would increase the GNP with 2 million SEK every year. This is calculated according to the human capital method, where the wage rate is seen as a relevant opportunity cost of time absent from paid work. Arguments have been raised that the human capital method of calculating the alternative cost of lost production, may not hold from a societal viewpoint. In taking a societal viewpoint, we cannot count a change as a loss, when someone gains from it. If the patient's employment position is taken up by an unemployed, the only loss to society is the production lost during the time it takes to hire and train the replacement workforce. (The friction cost method) This holds true when the unemployment is larger than the non-inflationary rate of unemployment in the work sectors of the affected patients, and the number of patients is small enough not to affect the rate of the population that is in the workforce. Both these conditions may hold true for our evaluation subject. If we can assume a return to work, there is some claim to believe that the true C/U ratio may lie between 117 000 SEK and -22 000 SEK.⁴²

Cost-effectiveness ranking as a decision-making tool is based on the premise that projects with larger benefits per cost unit should be given priority over projects with lower benefits per cost unit. Studies have shown that people were unwilling to choose between patients on the ground of the QALY gain.⁴³ People wanted to give priority to the very ill, despite the lower expected CE ratio. Such preferences strip away the foundation of CE analysis, if we are not to incorporate such equity of health considerations into the QALY model. Unfortunately, this would be beyond the scope of this evaluation. Still, we believe that incorporating such preferences into our model would benefit the profitability of the AF-treatment. Rehemorrhage have devastating effects on the patients health, thus our patients would expect to arouse more sympathy from general public. Test subjects have also shown tendencies to discriminate in favour of the patients that have dependants. It is unclear how an incorporation of such preferences into our model would change the relative value of prevention from rebleeding. The devastation from a rebleeding will surely affect the patients family in a negative way, but the average age of the patients suggest that most rebleeders no longer have underage children to support. Some of the burden placed on the next-of-kin is incorporated into the monetary value of informal care.

We assume that the GOS 2-3 patients are only cared for at home. If we were to assume that the these patients are treated at hospital for their remaining years, the cost of

⁴² See: *Koopmanschap, Marc A. et al; "The friction Cost Method for Measuring Indirect Costs of Disease: J Health Ec: 14;171-189* or *Liljas, Bengt: "How to Calculate Indirect Costs in Economic Evaluations", Pharmoeconomics 13;1-7* for a discussion of the human capital and friction cost method.

⁴³ Dolan, Paul. (2001) Output measures and valuation in health. Economic evaluation in health care. Ed: Drummond, McGuire. Oxford University Press

formal care more than doubles.⁴⁴The average social cost per QALY gained then decreases to 31 000. We also test for a higher discount rate of 8%, but due to the low life expectancy of the patient, the higher discount rate had minimal effect on the overall outcome.

Our findings suggests that the incremental C/U ratio lies somewhere around 100 000 SEK. Is the treatment cost-effective? The theory of willingness-to-pay states that any project where the aggregated demand among the persons affected is larger than the all the costs is cost-effective, *regardless of the absolute levels of the costs*. If we are to use Gyrd-Hansens elicited WTP for a QALY, the treatment is at a risk of not being cost-effective, but if we are to use the WTP taken from the Swedish studies on the value of a statistical life, the treatment is clearly profitable. Still, hidden costs could undermine our conclusions. Our problem is that neither kind of study is appropriate for valuing parts of the Swedish health care from a societal perspective. The economic value measured in the Gyrd-Hansen study is essentially the marginal rate of substitution of wealth for non-fatal illness, and value of statistical life-studies measure the marginal rate of substitution of wealth for risk of death. Individuals WTP for a commodity includes:

- Use value. This is the value of the treatment to the patients affected. Essentially encompassed in Gyrd-Hansen study. We therefore feel that the 110000 SEK per QALY can be used as a limit for cost-effectiveness for C/U ratios calculated from an county council perspective.
- Option value. Value of having the treatment available. From a societal perspective, the sum of individuals' option value would be equal to sum of the use value, plus a risk premium. The risk premium, due to people being risk-averse, could explain the higher WTP for a QALY when using the value of a statistical life as a benchmark figure for cost-effectiveness.
- Existence value. The altruistic utility people place on having the treatment available to those in need. Not to be neglected. Especially in Sweden where people place great value of equity of access, and the institutions of the welfare state.

If there exists an existence value for treatment of SAH with AF, it will surely increase the WTP per QALY above the 110 000 SEK, as suggested in the Gyrd-Hansen study. Despite the little data we had at hand, the rather large risk of bias, and despite the many assumptions we had to make, we therefore feel confident in stating that the treatment is cost-effective. Both the C/U ratio from the county council and societal perspective according the worst-case scenarios of the sensitivity analysis, was far below the 660 000 SEK suggested by the study by Ekman et al. Also one must take our method of calculating societal cost in consideration.

⁴⁴ Jeppsson, Bengt. (2001) Somatisk Sjukvård Universitetssjukhuset i Lund.

Most cost-effectiveness studies only count medical costs, but we have taken a more modern and less frequently used approach in including as many relevant indirect costs as was possible with the available data. We have shown that minuscule hospital costs could hide substantial societal costs. If we were only to take the county-council perspective, as is usually done, the treatment would clearly be one of the most worthwhile, in comparison with other Swedish and international studies. A US benchmark for cost-effective care often cited is 375 000 SEK/QALY gained (US \$50 000).⁴⁵ If we compare the ten thousand crowns per QALY from the county council perspective we calculated with any of the benchmark figures we mentioned, it is without doubt that the treatment is worthwhile.

The lack of relevant data reveals a need for further study on economic evaluations of in the neurology field. The low impact of the short-term treatment with AF, and the relatively few numbers of patients affected, may cast some doubt on the relative cost-effectiveness on more advanced economic evaluations of the same treatment from the county council perspective. In our study, with a relatively conservative life-expectancy of the patients, the average incremental costs from the societal perspective was more than 10 times higher than average incremental hospital costs. Also, long-term studies of mortality and morbidity of SAH patients have suggested e.g. a link between SAH and excess occurrence of systemic cardiovascular disease.⁴⁶ With a larger yearly patient pool, and higher life expectancies, the magnitudes of the uncertainty concerning the societal impact are large enough to justify a costly long-term study of the medical and economic effects of neurosurgery. A multi-disease, multi-treatment study in a Swedish setting perhaps?

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⁴⁵ Coy et al. (2000) "The cost-effectiveness and cost-utility of high-dose palliative radiotherapy for advanced non-small-cell lung cancer" *Int. J. Radiation Oncology Biol. Phys.*; 48:4; 1025-1033

⁴⁶ Ronkainen, Anti et al. (2001) Evidence for Excess Long-Term Mortality After Treated Subarachnoid Hemorrhage. *Stroke*. 32: 2850-2853.

8. References

- Brouwer, Werner; Rutten, Frans; Koopmanschap, Marc. (2001) Costing in economic evaluations. *Economic evaluation in health care*. Ed: Drummond, McGuire. Oxford University Press
- Cairns, John. (2001) Discounting in Economic Evaluation. . *Economic evaluation in health care*. 237-255. Ed: Drummond, McGuire. Oxford University Press
- Coy et al. (2000) The cost-effectiveness and cost-utility of high-dose palliative radiotherapy for advanced non-small-cell lung cancer *Int. J. Radiation Oncology Biol. Phys.*; 48:4; 1025-1033
- De Blaeij, Arianne et al. (2003) The Value of Statistical Life in Road Safety: A Meta Analysis. *Accident Analysis and Prevention*. 35-6:973-986.
- Dolan, Paul. (2001) Output measures and valuation in health. *Economic evaluation in health care*. Ed: Drummond, McGuire. Oxford University Press
- Drummond et al. (2001) *Methods for the Economic Evaluation of Health Care Programmes*. Oxford University Press.
- Drummond, Michael; Jönsson, Bengt; Rutten, Frans. (1997) The Role of Economic Evaluation in the Pricing and Reimbursement of Medicines. *Health Policy* 40; 205.
- Ekman et al: (2002) Kostnadseffektivt att behandla kronisk hjärtsvikt med bisoprolol. *Läkartidningen* 99: 647-650,
- Gyrd-Hansen, Dorte. (2003) Willingness to pay for a QALY. *Health Economics*. 12:12. 1049-1060,
- Hillman et al. (2002) Immediate administration of tranexamic acid and reduced incidence of early rebleeding after aneurismal subarachnoid haemorrhage: a prospective randomised study. *Journal of Neurosurgery* : 771-778.
- Hjelmgren J, Berggren F, Andersson F. (2001) Health economic guidelines – similarities, differences and some implications. : *Value in Health* vol: 4:225-250
- Hurley, Jeremiah. An overview of the normative economics of the health sector *Handbook of Health Economic, Volume 1*
- Ironmonger, Duncan: (1996) Counting Outputs, Capital Inputs and Caring Labor: Estimating Gross Household Production. *Feminist Economics* 2(3), 37-64
- Jennet, Bryan; Bond, Michael. (1975) Assessment of outcome after severe brain damage. - A practical scale. *The Lancet* 1:480-484,
- Jeppsson, Bengt. (2001) *Somatisk Sjukvård Universitetssjukhuset i Lund*.
- Johansson, Joakim. (2002) *Trafiksäkerhet. Översyn av samhällsekonomiska metoder och kalkylvärden på transportområdet*. SIKÅ (The Swedish Institute For Transport and Communications Analysis) Rapport 4. Chap 6;89-96
- Karinen, Petri et al. (1999) Cost-Effectiveness Analysis of Nimodipone Treatment after Aneurysmal Subarachnoid Hemorrhage and Surgery. *Neurosurgery*, 45-4:780-785.
- Koopmanschap, Marc A. et al; The friction Cost Method for Measuring Indirect Costs of Disease: *J Health Ec*: 14;171-189 or Liljas, Bengt: How to Calculate Indirect Costs in Economic Evaluations, *Pharmaceutics* 13;1-7
- Privata Affärer. <http://www.privataaffarer.se/>
- Ronkainen, Anti et al. (2001) Evidence for Excess Long-Term Mortality After Treated Subarachnoid Hemorrhage. *Stroke*. 32: 2850-2853.
- SCB OHÄLSODATA 1999-12-31 - Befolkningen 16-64 år. Antal personer med status som förtidspensionerade.

- Swedish Statistical Board. Återstående medellivslängd för åren 1751-2001.
www.scb.se
- Torrance, George W. (1976) Social Preferences for Health States: An Empirical Evaluation of Three Measurement Techniques. *Socio-Economic Planning Sciences*. (10):129-136.
- Torrance, George W. (1986) Measurement of Health State Utilities for Economic Appraisal: A Review. *Journal of Health Economics* ;5:21
- Zweifel, Peter; Breyer, Friedrich. (1997) *Health Economics*. Oxford University Press.

Appendix:

How the GOS scores were converted into the EuroQol descriptive system

Delas ut till neurologer som någon gång har diagnostiserat patienter enligt Glasgow Outcome Scale. Formuläret består av 4 (A-D) huvudfrågor och tar ca 5 minuter att fylla i. Du ska föreställa dig en patient som är representativ för huvuddelen av patienter som drabbats av subarachnoid blödning orsakad av aneurysm.

A. Du har diagnostiserat en patient enligt Glasgow Outcome Scale (GOS) som kategori 2. (persistant vegetative state). Ringa in den siffra som bäst stämmer överens med patienten.

Rörlighet

1. Patienten går utan svårigheter
2. Patienten kan gå med vissa svårigheter
3. Patienten är sängliggande

Hygien

1. Patienten behöver ingen hjälp med sin dagliga hygien, mat eller påklädning
2. Patienten har vissa problem med att tvätta eller klä mig själv
3. Patienten kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter. (Tex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Patienten klarar av sin huvudsakliga sysselsättning.
2. Patienten har vissa problem med att klara av sin huvudsakliga sysselsättning
3. Patienten klarar inte av sin huvudsakliga sysselsättning

Smärtor/besvär

1. Patienten har varken smärtor eller besvär
2. Patienten har måttliga smärtor eller besvär
3. Patienten har svåra smärtor eller besvär

Rädsla/nedstämdhet

1. Patienten är inte orolig eller nedstämd
2. Patienten är orolig eller nedstämd i viss utsträckning
3. Patienten är i högsta grad orolig eller nedstämd

B. Du har diagnostiserat en patient enligt Glasgow Outcome Scale (GOS) som kategori 3. (severe disability). Ringa in de siffror som bäst stämmer överens med patienten.

Rörlighet

1. Patienten går utan svårigheter
2. Patienten kan gå med vissa svårigheter
3. Patienten är sängliggande

Hygien

1. Patienten behöver ingen hjälp med sin dagliga hygien, mat eller påklädning
2. Patienten har vissa problem med att tvätta eller klä mig själv
3. Patienten kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter. (Tex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Patienten klarar av sin huvudsakliga sysselsättning.
2. Patienten har vissa problem med att klara av sin huvudsakliga sysselsättning
3. Patienten klarar inte av sin huvudsakliga sysselsättning

Smärtor/besvär

1. Patienten har varken smärtor eller besvär
2. Patienten har måttliga smärtor eller besvär
3. Patienten har svåra smärtor eller besvär

Rädsla/nedstämdhet

1. Patienten är inte orolig eller nedstämd
2. Patienten är orolig eller nedstämd i viss utsträckning
3. Patienten är i högsta grad orolig eller nedstämd

C. Du har diagnostiserat en patient enligt Glasgow Outcome Scale (GOS) som kategori 4. (moderate disability). Ringa in de siffror som bäst stämmer överens med patienten.

Rörlighet

1. Patienten går utan svårigheter
2. Patienten kan gå med vissa svårigheter
3. Patienten är sängliggande

Hygien

1. Patienten behöver ingen hjälp med sin dagliga hygien, mat eller påklädning
2. Patienten har vissa problem med att tvätta eller klä mig själv
3. Patienten kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter. (Tex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Patienten klarar av sin huvudsakliga sysselsättning.
2. Patienten har vissa problem med att klara av sin huvudsakliga sysselsättning
3. Patienten klarar inte av sin huvudsakliga sysselsättning

Smärtor/besvär

1. Patienten har varken smärtor eller besvär
2. Patienten har måttliga smärtor eller besvär
3. Patienten har svåra smärtor eller besvär

Rädsla/nedstämdhet

1. Patienten är inte orolig eller nedstämd
2. Patienten är orolig eller nedstämd i viss utsträckning
3. Patienten är i högsta grad orolig eller nedstämd

D. Du har diagnostiserat en patient enligt Glasgow Outcome Scale (GOS) som kategori 5. (good recovery). Ringa in de siffror som bäst stämmer överens med patienten.

Rörlighet

1. Patienten går utan svårigheter
2. Patienten kan gå med vissa svårigheter
3. Patienten är sängliggande

Hygien

1. Patienten behöver ingen hjälp med sin dagliga hygien, mat eller påklädning
2. Patienten har vissa problem med att tvätta eller klä mig själv
3. Patienten kan inte tvätta eller klä mig själv

Huvudsakliga aktiviteter. (Tex arbete, studier, hushållssysslor, familje- och fritidsaktiviteter)

1. Patienten klarar av sin huvudsakliga sysselsättning.
2. Patienten har vissa problem med att klara av sin huvudsakliga sysselsättning
3. Patienten klarar inte av sin huvudsakliga sysselsättning

Smärtor/besvär

1. Patienten har varken smärtor eller besvär
2. Patienten har måttliga smärtor eller besvär
3. Patienten har svåra smärtor eller besvär

Rädsla/nedstämdhet

1. Patienten är inte orolig eller nedstämd
2. Patienten är orolig eller nedstämd i viss utsträckning
3. Patienten är i högsta grad orolig eller nedstämd

Legend to the figures:

<illustrerande noddiagram>

Fig 1: The probabilities of rebleeding for both study arms, combined with the outcome probabilities for rebleeders and monobleeders in both study arms. We combine the two probability trees to calculate the effect on overall morbidity and mortality. E.g. the probability of dying for the AF branch is the probability of rebleeding times the probability of dying after a rebleed plus the probability of dying without rebleeding times the probability of not rebleeding. Since no overall significance could be computed for the AF and the control group, the distribution according to the GOS in the rebleed and the no rebleed groups were calculated as the average of the AF and the control group.

<konvertering av gos till eq5d>

Table 1: The GOS Score was converted into EuroQOL 5D after consultation of the chief medical staff involved in the medical study.

<vägning av QALY-resultatet>

Table 2: The average QALY utility score for the GOS 2-3 and GOS 4-5 groups were composed of the individual utility scores for each GOS state, weighed with their relative occurrence.

<förändring av sannolikhet>

Table 3: The change in risk of occurrence.

<grand result>

Table 4: Scores and sensitivity analysis

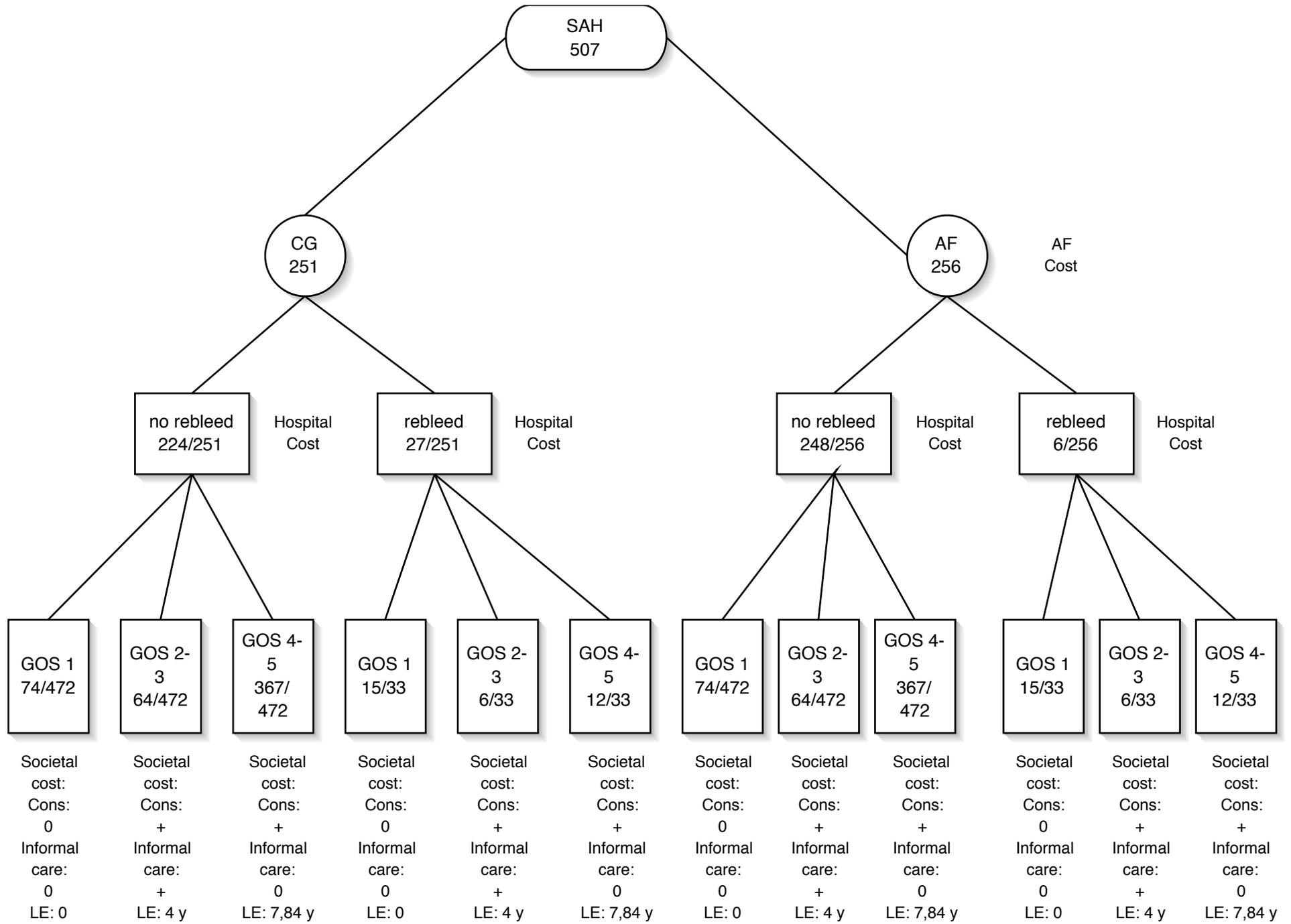


Table 1. Conversion table GOS to EQ5D and QALYs.

	<i>Mobility</i>	<i>Self-Care</i>	<i>Usual Acti</i>	<i>Pain/Disc</i>	<i>Anxiety/D</i>	<i>Medel</i>	<i>Max</i>	<i>Min</i>
gos 2	3	3	3	1	1	2,80%	2,80%	2,80%
gos 3	2	3	3	2-3	2	-5,25%	7,90%	-18,40%
gos 4	1-2	1-2	2	1-2	1-2	58,93%	81,50%	6,89%
gos 5	1	1	1-2	1	1	94,15%	100,00%	88,30%

Table 2. QALY weights for outcome groups.

Spread both study arms compounded

GOS	No Patient	Weight
1	74	100,00%
2	7	10,94%
3	57	89,06%
4	95	25,89%
5	272	74,11%
<i>sum</i>	<i>505</i>	

Table 3. The incremental probability outcome due to administration of AF to the study group.

P (rebleeding placebo)	8,39%
P (GOS 1 rebleeding)-	32,95%
P (GOS 2-3 rebleeding)	5,89%
P (GOS 4-5 rebleeding)	-38,85%

Table 4. Summary of results and the sensitivity analysis.

	3% discounting	8% discounting	0.2 adapt bias	Instit. Patients	Minimum Lifespan	Maximum Lifespan	GOS 4-5 in work	HC death = 190'
Average Remaining Life-Years								
GOS 2-5	4,03	4,03	4,03	4,03	3,35	4,86	4,03	4,03
GOS 5	7,84	7,84	7,84	7,84	5,60	10,74	7,84	7,84
Expected QALYs GOS 2-3 patients								
Maximum QALYS	0,28	0,28	1,05	1,02	0,24	0,34	0,28	0,28
Minimum QALYS	-0,62	-0,62	0,15	0,15	-0,52	-0,74	-0,62	-0,62
Average QALYS	-0,17	-0,17	0,60	0,59	-0,14	-0,20	-0,17	-0,17
Expected QALYs GOS 4-5 patients								
Maximum QALYS	6,77	5,83	7,11	7,11	4,99	8,89	6,77	6,77
Minimum QALYS	4,78	4,11	5,76	5,76	3,52	6,28	4,78	4,78
Average QALYS	6,04	5,20	6,72	6,72	4,46	7,94	6,04	6,04
Incr. C/U from county council perspective								
Minimum incr. C/U (SEK per QALY)	5 737	6 669	5 553	5 549	7 783	4 362	5 737	-12 775
Maximum incr. C/U (SEK per QALY)	7 918	9 167	6 722	6 721	10 704	6 034	7 918	-9 256
Average incr. C/U (SEK per QALY)	6 356	7 376	5 820	5 818	8 611	4 837	6 356	-10 255
Incr. C/U from societal perspective								
Minimum incr. C/U (SEK per QALY)	105 651	104 116	102 255	28 736	96 497	111 963	-27 547	120 645
Maximum incr. C/U (SEK per QALY)	145 809	143 097	123 777	34 802	132 706	154 894	-19 960	166 502
Average incr. C/U (SEK per QALY)	117 050	115 153	107 177	30 127	106 753	124 167	-22 113	133 661
Societal impact for Sweden per year								
Hospital cost	497 079	497 079	497 079	497 079	497 079	497 079	497 079	-801 987
Societal cost	9 104 444	7 710 638	9 104 444	2 524 797	6 113 434	12 710 326	-1 778 551	7 805 378