The quality of life and cost-effectiveness of treatment after a serious neurosurgical illness

Kirsi Malmivaara

Department of Neurosurgery, Helsinki University Central Hospital
Faculty of Medicine
University of Helsinki
Helsinki, Finland

The National Graduate School of Clinical Investigation

ACADEMIC DISSERTATION

To be presented,
with permission of the Faculty of Medicine of the University of Helsinki
for public examination
in the Töölö Hospital
on January 31th 2014, at 12 noon.

Helsinki 2014

Supervised by

Docent Jari Siironen
Department of Neurosurgery of
Helsinki University Central Hospital
Helsinki, Finland

and

Professor Juha Hernesniemi
Department of Neurosurgery of
Helsinki University Central Hospital
Helsinki, Finland

Reviewed by

Docent Esa Heikkinen
Department of Neurosurgery
Oulu University Central Hospital
Oulu, Finland

and

Docent Antti Malmivaara
National Institute for Health and Welfare
University of Oulu
Oulu, Finland

Official opponent

Professor (emer.) Martti Kekomäki
Helsinki University Central Hospital
University of Helsinki
Helsinki, Finland

ISBN 978-952-10-9688-4 (paperback)
ISBN 978-952-10-9689-1 (PDF)
http://ethesis.helsinki.fi
Unigrafia Oy
Helsinki 2014

CONTENTS

ORIGINAL ARTICLES

I

Malmivaara K, Hernesniemi J, Salmenperä R, Öhman J, Roine RP, Siironen J. Survival and outcome of neurosurgical patients requiring ventilatory support after intensive care unit stay. *Neurosurgery* 2009; **65**: 530-537.

II

Malmivaara K, Öhman J, Kivisaari R, Hernesniemi J, Siironen J. Cost-effectiveness of decompressive craniectomy in non-traumatic neurological emergencies. *European Journal of Neurology* 2011; **18**: 402-409.

III

Malmivaara K, Kivisaari R, Hernesniemi J, Siironen J. Cost-effectiveness of decompressive craniectomy in traumatic brain injuries. *European Journal of Neurology* 2011; **18**: 656-662.

IV

Malmivaara K, Juvela S, Hernesniemi J, Siironen J. Health-related quality of life and cost-effectiveness of treatment in subarachnoid haemorrhage. *European Journal of Neurology* 2012; **19**:1455-61.

ABBREVIATIONS AND DEFINITIONS

€	Euro
15D	15D HRQoL instrument
ACA	Anterior cerebral artery
ACoA	Anterior communicating artery
AVM	Arteriovenous malformation
CBA	Cost-benefit analysis
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CER	Comparative effectiveness research
CMA	Cost-minimization analysis
CUA	Cost-utility analysis
CT	Computed tomography
DALY	Disability adjusted life year
DC	Decompressive craniectomy
DRG	Diagnosis-Related Group
EBM	Evidence-based medicine
EDH	Epidural haemorrhage
EEG	Electroencephalography
EQ-5D	EuroQol HRQoL instrument with 5-dimensions
Fisher	Classifies the subarachnoid haemorrhage on a CT scan
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
HRQoL	Health-related Quality of Life
HUI	Health Utility Index
ICA	Internal carotid arteries
ICH	Intracerebral haemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IQR	Interquartile range
IVH	Intraventricular haemorrhage
Le	Life expectancy
MCA	Middle carotid artery
MRI	Magnetic resonance imaging
NHP	Nottingham Health Profile
NICE	National Institute of Clinical Excellence (UK)
NICU	Neurointensive care unit
Q1	25th percentile
Q3	75th percentile
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomized controlled trial

SAH	Subarachnoid haemorrhage
SD	Standard deviation
SDH	Subdural haemorrhage
SF-36	Short-Form item survey
TBI	Traumatic brain injury
TTO	Time trade-off
VAS	Visual analogue scale
WFNS	Grading scale of the World Federation of Neurological Surgeons
WHOQOL	World Health Organization Quality of life
WPT	Willingness to pay

ABSTRACT

Aims: The overall purpose of this study was to evaluate the health-related quality of life (HRQoL) and cost-effectiveness of the treatment of severely, acutely ill neurosurgical patients. The majority of the study illnesses and conditions are known to have a relatively high mortality or an otherwise poor outcome but, they are also known to be highly resource-demanding. Since the economics of health care is attracting more and more interest, it will become more important to evaluate the cost-effectiveness of treatment so that it can be demonstrated that the resource allocation is justified.

Methods: The patients (n=620) for these four separate studies were treated in the Department of Neurosurgery of Helsinki University Central Hospital between 1998 and 2006. The first of these four studies was a ***Step-Down Unit study*** in which we evaluated a group of patients (n=346) who underwent a major neurosurgical operation and were treated in the neurosurgical intensive care unit (NICU) and, due to a poor prognosis, were then discharged from the NICU to the step-down unit, still depending on life support devices. The following two studies evaluated patients who underwent a decompressive craniectomy (DC) for intractable intracranial pressure. The first of these, the ***DC after SAH study***, concerned patients (n=42) with subarachnoid haemorrhage (SAH) or other neurological emergencies, and the second one, the ***DC after TBI study***, evaluated patients (n=54) with traumatic brain injury (TBI). The fourth study, the ***SAH study*** (n=178), evaluated the long-term outcome, HRQoL and cost-effectiveness of the treatment of the SAH patients.

Results: The mortality in the Step-Down Unit study and both of the DC studies was high and moderate in the SAH study, 59%, 53%, 41%, and 24% respectively. The median follow-up times were 5, 3, 5.6 and 10.8 years. The health-related quality of life was assessed with the EuroQol EQ5D instrument and the median HRQoL index was compared to the median index of the Finnish reference population (0.85). The indices were 0.71, 0.41, 0.85 and 1.00. The outcome was also evaluated on the Glasgow outcome scale (GOS), and 49%, 25%, 69% and 75% of the patients achieved a good outcome (GOS 1-2). An important measure of well-being is the ability to live at home, and 49%, 50%, 78% and 88% of the study patients were able to live at home. The direct costs of the neurosurgical treatment per quality adjusted life year (QALY) were 2521€, 5000€, 2400€ and 1700€.

Conclusions: For the total of 620 severely ill neurosurgical patients treated in the Helsinki Department of Neurosurgery between 1998 and 2006, we found the treatment to be cost-effective, and it resulted in health-related quality of life that

varied from acceptable to good when compared to the reference population. We found no evidence of unnecessary prolongation of human suffering when death was inevitable. The worst state of health-related quality of life did not occur among the survivors. In summary, these studies indicate that current healthcare resources are utilized cost-effectively to achieve a life that is meaningful. Allocation of healthcare resources to the severely ill neurosurgical patients seems to be justified.

TIIVISTELMÄ

Tavoite: Tämän tutkimuksen tarkoituksena oli arvioida akuutisti ja vakavasti sairaiden, neurokirurgisten potilaiden terveyteen liittyvää elämänlaatua (HRQoL) ja hoidon kustannusvaikuttavuutta. Tutkimuksessa potilailla olleisiin sairauksiin tiedetään liittyvän suhteellisen korkeaa kuolleisuutta tai muutoin huonoa lopputulosta, ja sen lisäksi nämä sairaudet ovat myös hoidollisesti paljon resursseja vaativia. Koska terveydenhuollon taloudellinen arviointi kiinnostaa yhä enemmän ja enemmän, on tärkeää, että hoitojen kustannusvaikuttavuutta arvioidaan niin, että voitaisiin osoittaa, että resurssien suuntaaminen on perusteltua.

Menetelmät: Näiden neljän erillisen tutkimuksen potilaat (n = 620) hoidettiin Helsingin yliopistollisen keskussairaalan Neurokirurgian klinikassa vuosina 1998-2006. Ensimmäinen tutkimus, ***Tarkkailupotilas-tutkimus*** (n=346) arvioi potilasryhmää, joille oli tehty merkittävä neurokirurginen leikkaus, joita hoidettiin neurokirurgisella teho-osastolla (NICU), mutta huonon ennusteen vuoksi siirrettiin teholta pois, vaikka potilaat olivat kuitenkin edelleen hengityskoneessa. Seuraavat kaksi tutkimusta käsittelivät potilaita, joille tehtiin dekompressiivinen kraniektomia (DK) hallitsemattoman kallonsisäisen paineen vuoksi. Ensimmäisessä, ***DK SAV:n jälkeen -tutkimuksessa*** potilailla (n=42) oli subaraknoidaalinen verenvuoto (SAV) tai jokin muu neurologinen hätätilanne ja toisen ***DK trauman jälkeen -tutkimuksen*** potilaat (n=54) olivat saaneet traumaattisen aivovamman. Neljännessä, ***SAV-tutkimuksessa*** (n=178) arvioitiin SAV-potilaiden pitkän aikavälin tuloksia, elämänlaatua ja kustannustehokkuutta.

Tulokset: Kuolleisuus Tarkkailupotilas- ja DK-tutkimuksissa oli korkea ja SAV-tutkimuksessa kohtalainen (59%, 53%, 41% ja 24%). Seuranta-ajan mediaani oli 5, 3, 5.6 and 10.8 vuotta. Terveyteen liittyvä elämänlaatu arvioitiin EuroQol EQ5D – instrumentilla, josta laskettiin indeksi elämänlaadulle. Tätä verrattiin suomalaisen normaaliväestön indeksiin (0,85). Indeksit olivat 0,71, 0,41, 0,85 ja 1,00. Lopputulokset arvioitiin myös Glasgow Outcome -asteikolla (GOS) ja 49%, 25%, 69% ja 75% potilaista saavutti hyvän lopputuloksen (GOS 1-2). Yksi hyvinvoinnin tärkeä indikaattori on mahdollisuus asua omassa kodissa ja 49%, 50%, 78% ja 88% tutkimuksen potilaista pystyivät asumaan kotona. Neurokirurgisen hoidon suorat kustannukset laatupainoitettua elinvuotta (QALY) kohti on olivat 2521€, 5000€, 2400€ ja 1700€.

Johtopäätökset: Näiden 620 vaikeasti sairaan neurokirurgisen potilaan, jotka hoidettiin neurokirurgian klinikassa vuosina 1998-2006, hoidon arvioitiin olevan kustannusvaikuttavaa ja heidän terveyteen liittyvä elämänlaatunsa vaihteli hyväksyttävästä hyvään verrattuna normaaliväestöön. Emme löytäneet todisteita

tarpeettomasta inhimillisten kärsimyksien pitkittämisestä silloin, kun kuolema oli väistämätön. Myöskään tutkimuksessa kenelläkään eloonjääneistä ei ollut huonointa mahdollista terveyteen liittyvää elämänlaatua. Terveydenhuollon resurssien kohdentaminen akuutisti ja vakavasti sairaille neurokirurgisille potilaille näyttää olevan perusteltua.

INTRODUCTION

The basic question in an economic evaluation of health services is whether the accomplishment achieved by medical intervention is worth the money spent on it. This question can be further divided into two parts: Is the medical intervention effective in ordinary circumstances working, and at what costs? The requirement for evaluation rises from the fact that resources are limited also in the field of medicine. Economic evaluation is becoming more and more important because several factors contribute to the increasing costs of health care. The population is aging and the number of people with chronic diseases is increasing. The development of technology and the pharmaceutical industry provides increasingly more possible treatments but also raises the costs of health care. Medicalization, in which human conditions or problems are defined and treated as medical conditions, also raises the costs.

Evaluation is required from health care administrators as well as from anyone who plans, provides or pays for health care. The question is not only whether to offer a particular treatment or not, but extensive consideration is needed on how to allocate the limited resources in a way that the largest amount of health is achieved.

The next question is: When should evaluation be executed? On rare occasions, there is a need to evaluate existing treatments that have proved their efficacy and effectiveness over the years. The demand for evaluation rises when new treatments or drugs are considered. Also objectives, benefits, costs, and potential adverse effects of population screening programs should be subject for evaluation. Further, a difference between two or more treatments could be a target of evaluation. The uttermost case of an evaluation is whether to treat or not, which arises when treating the most severely ill patients and when the prognosis of the treatment is unclear.

This area of research is continuously gaining more interest; the number of studies is exponentially rising. Studies are conducted by clinicians, medical researchers, economists, etc. How can effectiveness be measured in medicine? Traditionally medical studies often deal with measurable quantities such as survival, disease-free time or laboratory results. In health economic evaluation, both quantity and quality of life is assessed and compared to the costs. For this purpose, the concept of health-related quality of life was developed and several different approaches have been developed to convert it to a numerical value. The concept of a quality-adjusted life year (QALY) is a numerical value which includes both the estimation of "how good" and "how long". When medical costs of an intervention in question are estimated, the cost of a QALY can be calculated. By using a numeric value for

intervention, interventions and health services may become comparable with each other and forward information to resource allocation.

Neurosurgery is a highly resource-demanding field of medicine. Treatment is performed by highly specialized professionals, which refers not only to the surgeons but the entire treatment team. A lot of high technology and equipment is utilized, and neurosurgical intensive care is among the most expensive treatment units. Severely ill patients may need prolonged ventilator support and hospital periods are longer compared to many other diseases. Recovery time is also in many cases prolonged, and many neurosurgical illnesses, even when treated, lead to severe morbidity, loss of capability to work and independency.

Increasingly greater numbers of economic evaluation studies of neurosurgical illnesses have been published, but the majority of such publications concern elective surgery, such as spinal surgery. Many studies compare different treatment techniques or screening methods of certain diseases. However, the quality of life or cost-effectiveness of the treatment for acutely and severely ill neurosurgical patients is an almost unexamined field. When treating these patients, it may not be easy to determine whether the patients will benefit from the resource-demanding treatment and there may be a fear that the treatment will lead to an unwanted outcome, such as death or an unacceptably poor quality of life. Therefore, the aim of this study was to perform a long-term evaluation of the health-related quality of life of acutely and severely ill neurosurgical patients and calculate the cost-effectiveness of the treatment.

REVIEW OF THE LITERATURE

ECONOMIC EVALUATION

The basic economic problem has been sometimes summarized into one sentence: How to best satisfy unlimited wants with limited resources (Mike Moffatt, a Canadian economist). The most quoted definition of an economic evaluation is: 'the comparative analysis of alternative courses of action in terms of both their costs and consequences' by Drummond [Drummond 2005]. The objective of a health economist is to evaluate, measure, and compare the costs and consequences of a particular medical intervention.

The evaluation is needed in order to show that what we do is not only subjectively important, but it "is working" and it "is worth it". In medicine, different groups of patients compete on resources, and in the larger view, the whole health care system competes on resources with other areas such as education or national defence. Evaluation is even more important in cases where what we do is "not working" and is "not worth it". The lost resources are also lost benefits of another program which could have been cost-effective [Cunningham 2001].

The number of conducted cost-effectiveness analyses is constantly increasing (Figure 1.). While in the 1970s and 1980s the economics of health care was an almost unexamined field, in the 1990s the subject started to gain interest. In the 2000s, economic evaluation became more of a requirement than an object of interest. The evaluation of health care programs can be subdivided into different types of analysis: Cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis (Table 1.).

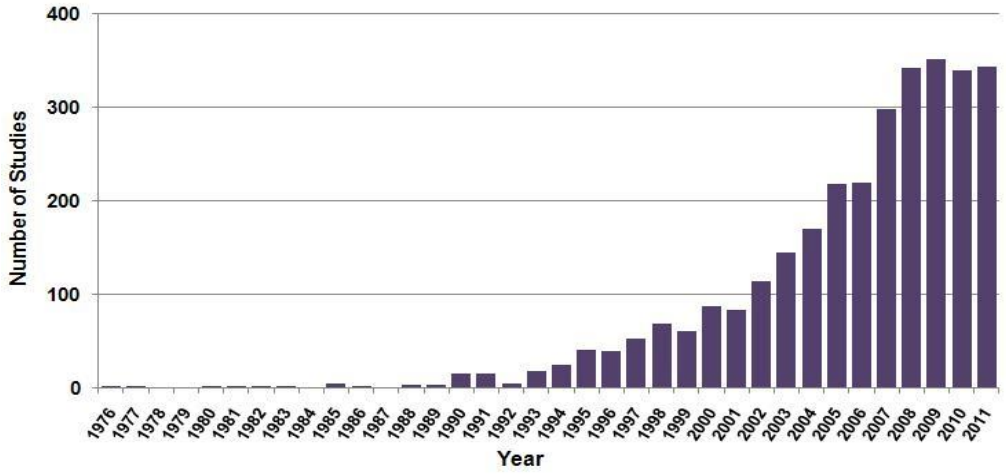

Figure 1. Number of cost-effectiveness publications per year. (Source: Center for the Evaluation of Value and Risk in Health. The Cost-Effectiveness Analysis Registry [www.cearegistry.org], reprinted with permission)

Table 1. Types of economic evaluation

Analysis	Cost-minimization analysis	Cost-effectiveness analysis	Cost-utility analysis	Cost-benefit analysis
Abbreviation	CMA	CEA	CUA	CBA
Method of analysis	Analysis in which two or more interventions of the same effectiveness are compared in net costs.	Analysis in which costs and benefits of intervention are assessed in monetary and non-monetary units	Subdivision of CEA, in which costs are assessed in monetary units and the benefits are measured as QALYs	Measures all the positive (beneficial) and negative (costly) consequences of an intervention or program in monetary terms.
Question	Which is the cheapest intervention?	What is gained or what is avoided by an intervention and at what costs?	What is the price of a QALY gained?	What is the cost intervention in relation to monetary savings?
Answer	An intervention	Cost and benefits	Costs per QALY	Total costs of a program?
Unit of outcome	Monetary	Monetary and non-monetary	Monetary and non-monetary	Monetary

COST-MINIMIZATION ANALYSIS

Cost-minimization (CMA) analysis is an economic comparison of two or more medical interventions in order to find the least expensive. This type of analysis expects that the interventions as well as the outcome are clinically equivalent and the research is aimed at solely the costs. Although on the surface CMA appears to be the most straightforward of the four common types of economic analysis, careful consideration must be given to the first critical steps of determining the therapeutic equivalence of the interventions. Publications that use CMA are less common than other three types of economic studies. One theory for the small number of CMA publications is that the researchers are reluctant to claim that a new intervention is no better than the existing option [Newby 2003].

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis (CEA) is a form of full economic evaluation where both the costs and the consequences are examined. The main ideology of CEA is not to identify programs that will save money for a system or a provider, although this may be the ultimate result, but its aim is to get the most benefits from each additional health care euro or dollar expended. Though the basic idea of CEA is valid, the limits are the underlying measures of cost and outcomes. The methods in use vary considerably while making these assessments. There are standards for cost-effectiveness study methods, but at times the standards are quite difficult to meet, although the compromises may be scientifically entirely legitimate [Gold 1996].

COST-UTILITY ANALYSIS

Cost-utility analysis (CUA) follows the same principle as CEA, in fact, it could be considered a form of CEA [Drummond 2005]. In CUA analyses as well, the costs and outcomes and the cost evaluation follow the same principle as in CEA. The outcome measure is more structured in CUA. The term "Quality adjusted life year" (QALY) is presented here and the concept enables arithmetic processing of the outcome. QALY takes into account both the quality and quantity of life. Therefore much of the appeal of CUA must be attributed to the fact that it uses QALY [Richardson 1990]. Quality of life is indisputably relevant to the allocation of

resources. The final product of CUA is monetary value, a cost of one QALY achieved by an intervention. The concept of CUA enables a comparison of the cost-effectiveness of the different diseases, treatments or different groups of patients. Again, the reliability of the results lies beneath the execution of the cost and outcome analysis.

COST-BENEFIT ANALYSIS

The cost-benefit analysis (CBA) is, in theory, the most powerful method of economic evaluation [Drummond 2005]. CBA quantifies benefits and indirect costs strictly in monetary terms. CBA evaluates whether the benefits of the intervention exceed the costs for the society. CBA has significant value in welfare economics. The Hicks-Kaldor criterion designates that the gainers from the intervention could, in principle, compensate the losers [Gafni 2006]. Further, this concept of net benefit is applicable for intersectoral comparisons (e.g. education, social services, national defence).

QUALITY-ADJUSTED LIFE YEAR

The concept of "quality-adjusted life year" (QALY) was originally presented in 1976 by Zeckhauser and Shepard, as they included both the quality and duration of life in health outcome measurements [Sassi 2006]. The underlying concept of QALY was developed in the late 1960s by economists, operation researchers and psychologists, primarily for use in cost-utility analysis (CUA) [Gold 2002]. The concept was adopted and advocated by many health economists [Williams 1996]. The basic idea of QALY is to take the health-related quality of life (HRQoL) as a parameter with which the duration of life is weighted. Perfect health equals 1 and death equals 0. The basic equation is

$$\boldsymbol{QALY = HRQoL * Le}$$

in which **Le** is life expectancy. The equation shows that the year of perfect health equals to 1 QALY and a year in which HRQoL is reduced to half equals to 0.5 QALY. Some health statuses may be considered to be worse than death and therefore HRQoL may have negative scores [Marcan 2001].

EVALUATING HEALTH-RELATED QUALITY OF LIFE

Though the basic equation of QALY is quite simple itself, the evaluation of HRQoL and also life expectancy (Le) is more challenging. Several methods have been developed to evaluate the HRQoL [Gold 2002].

WEIGHTING

Weighting, sometimes referred to as direct elicitation, means that respondents are asked to assess a numerical value for their HRQoL between 0 and 1. There are several ways to lay out the question.

1.) In the Time-trade-off (TTO) method, the respondents are asked to choose between a longer time in compromised health to a shorter time in perfect health.

2.) In the Standard Gamble (SG) method, respondents are asked to choose between remaining in a state of ill health for a period of time or choosing a medical intervention which has a chance of either restoring them to perfect health or killing them. The TTO and SG methods are preferred by many economists.

3.) The Visual analogue scale (VAS) has, for instance, a thermometer-looking scale in which respondents are asked to mark a point which represents their health-related quality of life. This method has been considered to be theoretically inferior to SG and TTO because it is a rating task instead of a choosing task [Wein 2009]. The method has the advantage of being the easiest to ask, but has been considered to be the most subjective. On the other hand, also advocates exist [Parkin 2006].

HEALTH UTILITY INSTRUMENTS

Another way to describe HRQoL is to use health utility instruments. These multiattribute instruments can be, for example, a disease-specific evaluating effect of a particular disease and thus an important tool for evaluating the effectiveness of a particular treatment. More commonly, however, instruments are generic

multipurpose instruments which can evaluate HRQoL independently of a disease, disability or treatment. These scales are used to determine HRQoL in terms of their levels of several attributes. The number of attributes and levels describing the status of each attribute vary among the instruments. The underlying theory behind the scales varies. The scales have commonly been calibrated by fitting them to preference values obtained from a standard population. These reference values have been elicited by using one of the weighing methods mentioned before [Hammitt 2002].

There are several instruments from which the most suitable one can be selected. There is no consensus on which instrument is preferable. The main purpose of the instrument is to produce a single index value for QALY calculations. The most utilized instruments are EQ-5D [Brooks 1996], SF-36 (RAND-36), NHP, WHOQoL-BREF, HUI, and 15D.

- The Medical Outcomes Study Short-Form item survey (SF-36) is a widely used, multi-purpose health survey with 36 questions, which yields an 8-scale profile of HRQoL [Ware 1992]. It is suitable for any age, disease, or treatment group. The RAND-36 is based on SF-36. The measured health dimensions are: Physical functioning, daily routines (physical limitations), social functioning, daily routines (emotional limitations), general mental health, vitality, pain, and perception of general health. The score range varies from 0 to 100. First publications which utilized SF-36 were published in 1988. The Finnish version is "RAND SF-36" [Aalto 1995].

- Nottingham Health Profile (NHP) was developed in 1980 [Hunt 1980]. The two-part survey measures subjective physical, emotional, and social aspects of health. Part 1 contains 38 questions in six dimensions of health, including physical mobility, pain, social isolation, emotional reactions, energy, and sleep. Part 2 consists of seven yes/no statements about seven areas of life that most reflect the health status. The scoring range is from 0 to 100.

- The World Health Organization Quality of Life (WHOQOL) project was initiated in 1991, targeting to develop an international cross-culturally comparable quality of life assessment instrument. The WHOQOL-BREF is a shorter version of the original instrument and it contains 26 questions which measure the physical health, psychological health, social relationships, and the environment. The WHOQOL-BREF is sometimes considered to be more convenient in large research studies or clinical trials [Murphy 2000].

- The Health Utilities Index (HUI) is a family of generic preference-based systems, with the instruments HUI, HUI mark2, and HUI mark3. The

health dimensions include vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion and cognition. Each dimension has 3-6 levels. HUI systems describe almost a million unique health states.

- 15-D is a Finnish questionnaire which consists of 15 questions. The development of the 15-D started in the late 1970s and it was originally published in a 12-question form [Sintonen 1981]. In 1986, the first 15-question version was released [Sintonen 1992]. The examined health areas are: mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. There are 5 ordinal levels on each dimension. 15-D enables to evaluate the results either in profile mode or it can convert answers to a preference-based single index value for HRQoL on a 0-1 scale. 15-D is the most widely used instrument in Finland, but the questionnaire is also available in 20 languages.

EQ-5D

The EuroQol organization started developing a non-disease-specific multipurpose instrument in 1987. EQ-5D was initially developed simultaneously in Dutch, English, Finnish, Norwegian and Swedish. The questionnaire is currently being translated into 102 languages. It consists of five questions evaluating five dimensions of health: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (Figure 2.). In the 3-L version, each question can be answered by one of the three following responses: no problems (1), some or moderate problems (2), and extreme problems (3). Euroqol has recently also released EQ-5D-5L, which consists of 5 available levels. In 3the L-version, the answers of five questions form a sequence of five numbers (e.g. 11212, Table 2.), which can then be converted into the HRQoL index by a EuroQol algorithm which uses reference values obtained from the standard population by a weighing method. The reference value is elicited with either the TTO or VAS method, and the TTO method based references are preferred to use when an economic evaluation is concluded in the research. In the EQ-5D system, the HRQoL index value can have negative values, as some states of health can be considered worse than death [Marcan 2001].

The HRQoL index value can be compared to the values of the reference population. The median HRQoL of the reference population is presented in Figure 3. The value is based on questionnaires of 2411 Finnish residents [Ohinmaa 1996].

Mobility
I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care
I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

Figure 2. EQ-5D questions

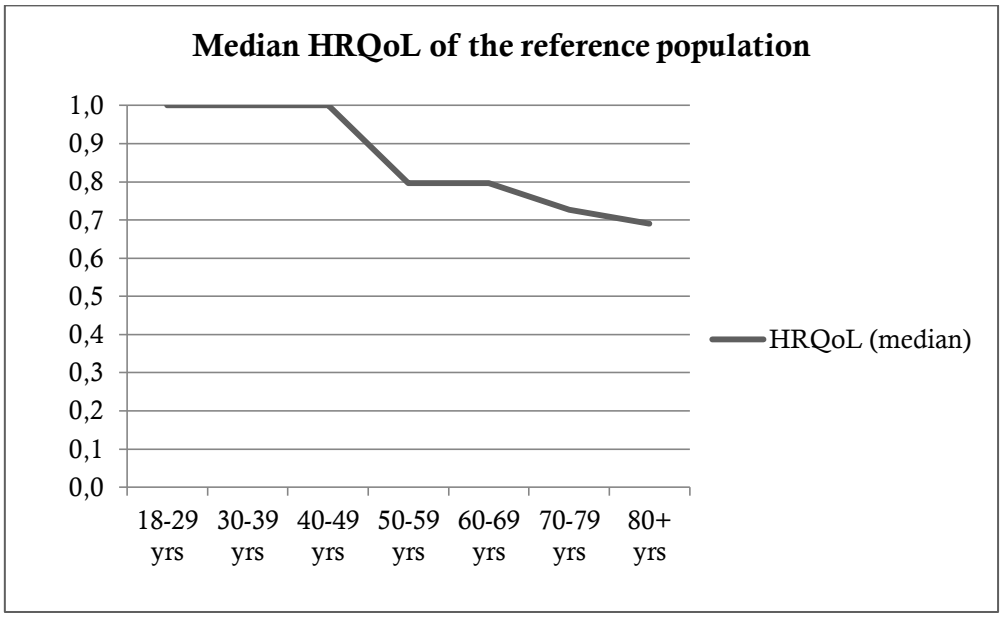

Figure 3. EQ-5D median reference values of HRQoL based on questionnaires of 2411 Finnish residents.

Table 2. Examples of EQ-5D health state valuations

Health state	Description	HRQoL index value
11111	no problems walking about no problems with self-care no problems with usual activities no pain not anxious or depressed	1,00
12211	no problems walking about some problems with self-care some problems with usual activities no pain not anxious or depressed	0,78
22222	some problems walking about some problems with self-care some problems with usual activities some pain some anxious or depressed	0,52
33333	confined to bed unable to take care of self unable to perform usual activities extreme pain extreme anxious or depressed	-0,59

COSTS ANALYSIS

Evaluating the costs of the intervention is the other central feature of the economic evaluation [Drummond 2005]. There have been critical reviews that cost analysis had received relatively little attention compared to the evaluation of the benefits. It is clear that the economic evaluation consists of two equal components and the adequate cost analysis may not be underestimated. Fundamentally, all relevant costs should be determined and included in the analysis, but in practice this might be challenging.

In literature, the concept of "direct costs" in this context comprises all medical costs of the intervention including treatments, operations, rehabilitation, special equipment, in-patient days, and also non-medical costs such as travel expenses, the costs of social services, etc. "Indirect costs" arise from an illness but are not medically based. They can be costs because of morbidity or premature death, such

as loss of productivity. The calculation of the direct costs could be challenging. Some aspects should be considered, such as how long the cost should be taken into account and what costs should be included in the health care perspective. How should capital costs (e.g. hospital buildings, equipment) and overhead costs (e.g. laundry, medical records, cleaning) be handled? The indirect costs can be monetary and possible to evaluate, such as loss of productivity, or they can be non-monetary, such as loss of family leisure time, and therefore the monetary value is harder to assess. As a conclusion, the area of the cost analysis is incoherent and demands for a more unambiguous and transparent analysis exist, since no amount of statistical analysis can compensate for poor quality cost data [Graves 2002].

DIAGNOSIS-RELATED GROUPS

The costs analysis is a critical step in economic evaluation and unfortunately it is also one of the most challenging steps to evaluate precisely. Many attempts have been made to elucidate this field, and at present time a system called Diagnosis-Related Group (DRG) has been utilized widely. It is a statistical classification system for hospital cost evaluation. The system estimates costs by dividing patients into groups according to their diagnosis. This system was originally developed by scientists in Yale University and it was first implemented in New Jersey by a small group of hospitals [Fetter 1980]. The DRG system is mainly based upon the patient's principal diagnosis, which originally was divided into 467 groups, but also other diagnoses, gender, age, sex, treatment procedure, discharge status, and the presence of complications or comorbidities are taken into account. The national program of implementing DRG in Finnish health care was conducted between 2008 and 2011. As a result, the DRG system is now been utilized in the majority of the hospital districts and the new health care law aims at comprehensive national usage of the DRG system.

EVALUATION OF THE EFFECTIVENESS OF AN INTERVENTION

The QALY calculation and the resulting answer depends on the type of intervention in question. QALYs can be calculated for one or several treatments. QALYs can be compared as a function of time, and a single patient or patients with and without intervention can be compared (incremental QALYs). For a particular intervention, QALYs can be calculated by first assessing the QALY amount without intervention and then after an intervention. The first QALY amount

depends on the health-related quality of life (HRQoL) and the life expectancy / Le) before and after.

QALY(before)=HRQoL(before)*Le(before)

QALY(after)=HRQoL(after)*Le(after)

The gained number of QALYs = QALY(after) – QALY(before).

The same way the incremental value of two different treatments can be calculated, the acquired QALYs with separate groups of patients are calculated and compared with each other. For example, treatment A costs 1500€ and outcomes 3.6 QALYs, and treatment B costs 1000€ and outcomes 1 QALY, the incremental cost is 500€ and incremental QALYs are 2.6, which results in 192.31€ per QALY gained.

These first two measurements are particularly suitable for an evaluation of an elective intervention in which patients can be contacted and interviewed beforehand. Evaluation of acute illnesses differs from this scenario, as there is no way of anticipating these events. HRQoL and Le can be approximated retrospectively. For example, QALYs can be used to compare a treatment that has a substantial impact on health quality and no effect on life expectancy with a different treatment that results in no change in health quality but a longer life expectancy (Figures 4. and 5.).

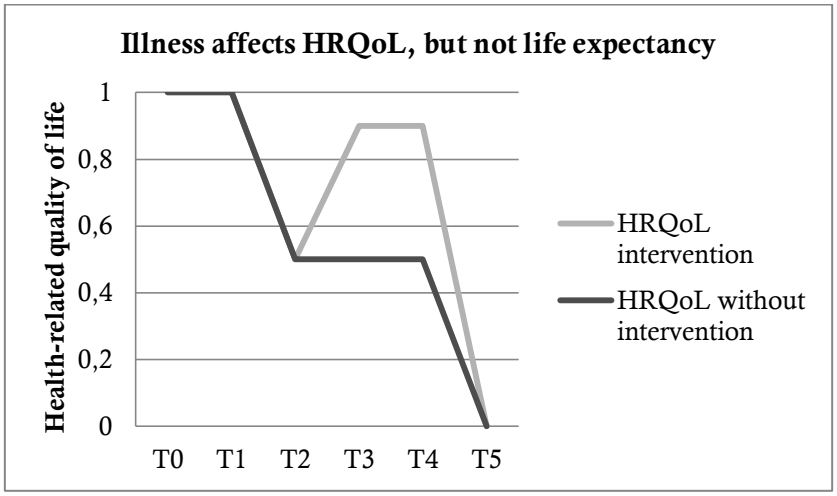

Figure 4. Example case of HRQoL. The X-axis presents time points: T0 is the date of birth. T1 is the date of getting ill; the illness affects HRQoL, but not life expectancy. The T2 intervention starts. The T3 intervention restores HRQoL partially, without intervention HRQoL stays on a lower level. Life continues to point T4 with the same level of HRQoL. T5 is the date of death, not related to a particular illness.

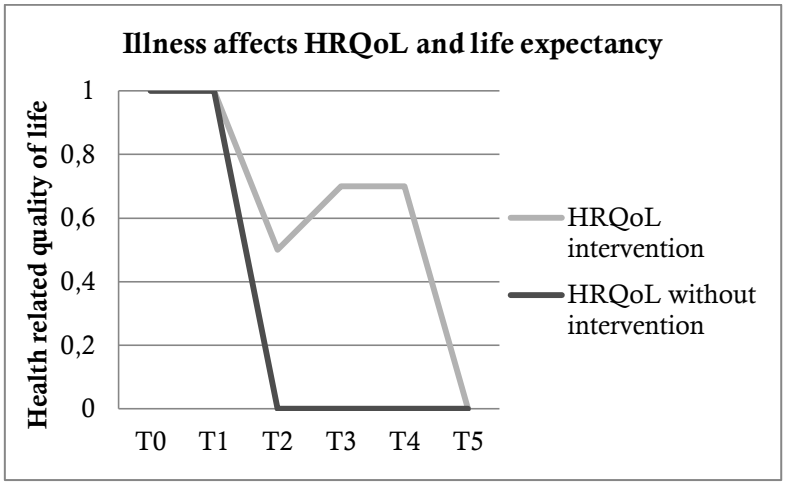

Figure 5. Example case of HRQoL. The X-axis presents time points: T0 is the date of birth. T1 is the date of getting ill, a serious illness affects HRQoL and life expectancy. The T2 intervention starts. The T3 intervention restores HRQoL partially and enhances life expectancy; without intervention patient dies. Life continues to point T4 with the same level of HRQoL. T5 is the date of death, could be related to a particular illness.

COST-EFFECTIVENESS THRESHOLD

The next step of the evaluation process is a calculation of the cost of one QALY achieved by intervention. Once we have an explicit number of QALYs and the total sum of costs to produce these QALYs, we can calculate the cost per QALY by dividing costs by QALYs. This monetary value of QALY can then be used in several ways. The costs can be compared with each other regardless of the heterogeneity of the patients, illnesses, treatment, or medical programs.

In order to determine whether the intervention is cost-effective, there has to be an established threshold with which a value can be compared. This value is a price of how much society should be prepared to pay for a QALY. There is no exact consensus on the price, but a commonly cited number is US is $50 000. According to Grosse [Grosse 2008], there was over 500 CEA studies published and in half of them the threshold of the cost of one QALY was set to $50 000. Although there are no theoretical bases for that specific figure, it has been widely referred in publications as ‘generally accepted’, ‘commonly cited’ or ‘an established practice’. The history of the $50 000 threshold is not well established, but it first appeared in the late 1980s in studies of end stage renal failure and it was associated with CE evaluations of dialysis. Since the 1990s it has been adopted as a main figure of CEA

studies. This figure has also raised criticism due to the lack of theoretical or empirical justification, and it has also been considered to be outdated. The criticism is well founded, as the same figure has been referred to already in the 1940s. The usual range of the CEA threshold is from $20 000 to $100 000 [Kaplan 1982, Laupacis 1992]. In the UK, the National Institute for Clinical Excellence (NICE) does not present strict decision rules, the cost of a QALY being acceptable when ranging between £20,000-30,000 [Rawlins 2004].

The uttermost question is where these figures eventually originate from. Willingness to pay (WTP) for one QALY is the cardinal utility measure. In the end, people are in charge of which costs are covered by common funds. However, the WTP for QALY is not simple to define. There is a lack of evidence of a constant value of WTP for a QALY. In particular, there is evidence that the average individual WTP for QALY is lower when it results from improvements in health status from relatively minor conditions than the WTP for QALYs gained from life-saving interventions [Gyrd-Hansen 2003].

One adverse aspect of the widespread use of CE thresholds, such as $50,000/QALY in the USA or £30,000/QALY in the UK, is that it might also contribute to the rise of healthcare costs by encouraging the coverage of costly new therapies, especially pharmaceuticals [Gafni 2006]. Thresholds and especially the upper boundaries of the CE range might work as a target toward which the costs of new treatments are customized.

COMPARATIVE EFFECTIVENESS RESEARCH

The concept of "Comparative effectiveness research" was defined by the US Committee on Comparative Effectiveness Research Prioritization of the Institute of Medicine in 2009 [Committee 2009]. The term Comparative effectiveness research (CER) gathers the methods and technologies of the economic evaluation, health-related quality of life and effectiveness of the treatment under one field of research. The Institute of Medicine's committee has defined CER as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels" [Committee 2009].

While the numbers of economic evaluations and CER studies are constantly increasing in other fields of medicine, in neurosurgery the use of CER methodology and economic evaluation overall remains in its infancy [Marko 2012]. The American Association of Neurological Surgeons, AANS/CNS Guidelines Committee has expressed concern about the lack of CER studies in neurosurgery [Zusman 2010]. The reluctance of the neurosurgical community to conduct CER studies is not well understood, since neurosurgery could be considered an optimal field for CER [Stein 2012]. The volume of the patients is relatively small, but the neurosurgical treatment is highly resource-demanding. There are many existing treatments with unanswered questions, but on the other hand there are relatively few randomized controlled trials (RCT), since they are difficult to fund, recruit, conduct and justify, and this is even more difficult when dealing with acute neurosurgical emergency. Partly due to the difficulties in executing traditional evidence-based medicine (EBM) with RCTs, there are more and more advocates for CER studies. In 2012, an expert panel in TBI pointed out that randomized controlled trials have not led to any identifiable major advances. The rigorous protocols and tightly selected populations of the RCT studies make the results difficult to generalize, and therefore the panel suggested that future research could concentrate on comparative effectiveness studies [Maas 2012].

COST-EFFECTIVENESS STUDIES OF ACUTE NEUROSURGICAL ILLNESSES

NEUROSURGICAL INTENSIVE CARE UNIT

Over the past decades, intensive care units have specialized to focus on care for e.g. trauma, cardiac and post-surgical care as well as stroke units and neonatal and neurosurgical care. Care in these specialized units is often provided by physicians within those specialties and dedicated nurses who have additional training in those areas [Diringer 2001]. Neurosurgical ICU is highly specialized in monitoring and treating intracranial pressure. Though the field is less studied, there is evidence that the outcome of neurosurgical patients treated in the NICU have a better outcome and lower mortality than patients treated in the general ICU [Mirski 2001, Diringer 2001]. The treatment in any ICU is expensive, but treatment in these specialized

ICUs is even more resource-demanding. In order to be cost-effective, the NICU treatment has to target the resources correctly, which basically means selecting the patients correctly.

A proper patient policy includes selecting patients on admission, according to who will most likely benefit from the treatment, and on the other hand withdrawal of the treatment when the patient is not considered to benefit from the treatment any longer. The difficulty is to identify these patients at the earliest opportunity. When the clinical condition of the patient is taking a course towards a hopeless situation, the decision of the withdrawal of the treatment should be done. Futile treatment periods should be limited to the minimum in order to retain the cost-effectiveness of the ICU treatment and to ensure a consensus on the willingness to pay for extended treatments in the ICU. The literature search on NICU patients' QoL or the cost-effectiveness of the treatment yielded no published studies.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a common cause of death and disability and it often involves young persons. The prevalence of TBI in Finland in 1990-2000 was 1/1000, which means approximately 15 000 to 20 000 new TBIs each year [Käypä hoito -suositus, Aivovammat]. Half of the TBIs occur in the age group of 15 to 34 years, and when it leads to permanent disability of a young person, the economic burden is enormous. Worldwide, TBIs cause the largest number of disability-adjusted life years lost, which includes both years lost to death and to varying degrees of disability [Ghajar 2000]. The majority of TBIs arise from motor vehicle accidents, falls, violence and a large portion of injuries in Finland is associated with alcohol abuse.

TBIs are graded as mild, moderate and severe injuries, and the evaluation of the severity of the injury is often conducted by using the Glasgow coma scale: mild GCS 13-15, moderate GCS 9-12 and severe GCS 3-8 [Ghajar 2000]. TBIs are usually divided into primary and secondary injuries. A primary injury is caused by the original insult and it may be a penetrating or closed injury. It may cause a fracture of the skull, a concussion, a cerebral laceration or contusion, haemorrhages (subarachnoid, subdural, epidural or unspecified intracranial haemorrhage) or nerve damage (diffuse axonal injury). The first insult leads to secondary brain damage, which is damage that evolves over time after the trauma, and may include: brain oedema and lead to increased intracranial pressure. Other common consequences are: Epilepsy, intracranial infection, abnormalities of the cerebrospinal fluid cycle,

haemodynamical instabilities, other infections (also treatment related), abnormal blood coagulation, metabolic, hormonal and nutritional disorders.

The diagnostics of the injury may begin at the injury site by an evaluation of the GCS and may include, for instance, computerized tomography (CT), CT angiography, magnetic resonance imaging (MRI), electro-encephalogram (EEG), and measurement of intracranial pressure. The treatment of severe TBI usually is, and should be, centralized in specialized units. Treatment consists of pre-hospital care, operational treatment (e.g. hematoma evacuation, repairing skull fractures, decompressive craniectomy), medical treatment (anaesthesia, seizure prevention, metabolic and cardiovascular stabilizing drugs) physiological and psychological rehabilitation. The treatment is highly resource-demanding and specialists of multiple fields are required; neurosurgeons, neuroanaesthesiologists, specially trained nursing staff for treatment and rehabilitation and various therapists (speech, physical, occupational).

Even though TBIs are common, they usually affect young and "profitable" citizens, and the economic burden is enormous (including expensive treatments and loss of QALYs), the actual QALY studies of TBI are quite rare. The literature search from PubMed with the combination of "Traumatic brain injury" and "QALY" returned a total of 19 published studies. Of these 19 papers, two are partial works of the present research (DC after SAH study and DC after TBI study). Despite the keywords, the QALYs and cost-effectiveness were calculated only in a few of these studies. The first published studies estimated the methods of assessing the quality of life of neurological and TBI patients [Riemsma 2001, von Steinbuechel 2005]. A few publications study the economic burden of neurological diseases. Olesen et al. studied the economic burden in Europe [Olesen 2003], Haagsma et al. estimated the burden of non-fatal injuries by calculating disability-adjusted life years. They concluded that the burden of years lived with disability with TBI patients is underestimated by ignoring temporary health consequences [Haagsma 2008]. Levi et al. studied the burden of occupational injuries in Italy [Levi 2011]. Norum el al. estimated non-proven intensive treatments and rehabilitation of the TBI in Norway and calculated QALYs, and they found that the cost of a QALY was unacceptably high in these experimental treatments and TBI treatment should use evidence-based methods [Norum 2012]. Tilford et al. studied paediatric TBI and the cost-effectiveness of treatment and technology [Tilford 2007(7) and 2007 (12)]. A few studies dealt with diagnostic strategies and their cost-effectiveness [Stein 2006, Dunham 2011, Holmes 2012]. Ryynänen et al. also included severe TBI patients in their literature review of the level of pre-hospital care. They also compared the advanced and basic level of pre-hospital care in terms of quality of life and cost-effectiveness, but the comparison turned out to be challenging. The pre-hospital care given by emergency medicine experts might be good, but given by paramedics it might even be harmful (e.g. intubation without anaesthesia) [Ryynänen 2010].

Galvagno et al. also conducted a literature review of pre-hospital care and helicopter use in trauma and also in severe TBI. However, no studies were found to evaluate the secondary outcome of morbidity as assessed by QALYs and DALYs [Galvagno 2013]. Cotton et al. performed a cost-utility analysis of levetiracetam and phenytoin for posttraumatic seizure prophylaxis, which revealed the superiority of phenytoin [Cotton 2011]. Three studies of TBI and decompressive craniectomy have been published [Ho 2011, Whitmore 2012 and Honeybul 2012]. These are discussed further in the next section.

DECOMPRESSIVE CRANIECTOMY

Decompressive craniectomy (DC) is an extreme treatment for a malignant increase of the intracranial pressure (ICP). In DC, a large piece of the skull is removed in order to enlarge the space for oedematous brain and therefore lower the ICP. Brain oedema is usually due to a primary insult, in which underlying causes might be traumatic brain injury (TBI), ischemic strokes, intracerebral haemorrhage, infection, tumour, a demyelinating process or a systemic condition (e.g. electrolyte imbalance, diabetic ketoacidosis). The conservative treatment methods include, for example, administration of hypertonic fluids, mannitol infusions, mild hyperventilation, sedation and hypothermia [Sahuquillo 2006]. When ICP is not responding to either maximum conservative treatment or drainage of cerebrospinal fluid via a ventriculostomy, there is no other treatment than enlarge the space to lower ICP.

The concept of DC is, in fact, over a hundred years old [Kakar 2009] and in 1902 Emil Kocher, the first Swiss neurosurgeon stated that "if there is no CSF pressure, but brain pressure exists, then a pressure relief must be achieved by opening the skull" [Hutchinsson 2011]. The DC procedure gained success in the early 1970s, until publications showed a poor outcome of DC patients and DC was abandoned until the 1990s [Tagliaferri 2012]. In 1999, Guerra et al. published the results of a 20-year period of utilizing DC. His good results lead to the rediscovery of DC in intractable ICP management [Guerra 1999]. Since 2000, DC has been gaining popularity and the number of publications is increasing steadily.

DC is a perfect example of such neurosurgical treatment referred in previous paragraph. It has been utilized for a long time, but no RCTs have been conducted until 2010. Case studies and retrospective series of DC patients were published, presenting various conclusions. The immediate effect of a craniectomy in lowering the intracranial pressure is well recognized [Daboussi 2009, Timofeev 2008], but the effect on the patient's long-term outcome has been controversial. A number of

publications have cautiously taken a stand in either direction, on behalf of DC or against it. The most common conclusion has been that there is a need for randomized studies [Hutchinsson 2007, Kakar 2009, Sahaquillo 2006, Morgalla 2008, Daboussi 2009, Danish 2009, Lemcke 2010, Howard 2008]. DC is utilized the most after TBI. It has been shown that children benefit from DC after TBI [Appelboom 2011], and for adults many reports have been very encouraging [Sahaquillo 2006]. Reports of small series or case reports also exist on DC as being useful with a malignant MCA infarction with restriction [Arac 2009, Vahedi 2007]. DC has also been found to be useful and resulting in a good outcome in some neurological emergencies with intractable ICP, such as encephalitis [Adamo 2008, Pérez-Bovet 2012], toxoplasmosis [Agrawal 2005], sinus thrombosis [Ferro 2011], SAH [Gueresir 2009, Schirmer 2009] and demyelinating disease [Ahmed 2010, Nilsson 2009].

There are some studies on the long-term outcome of DC after TBI [Timofeev 2008, Danish 2009, Morgalla 2008, Lemcke 2010, Howard 2008, Meier 2000, Pompucci 2007, Harrison-Felix 2009], but only few have evaluated the health-related quality of life. Until 2010, not a single DC study has been published evaluating the cost-effectiveness of the treatment.

The first randomized multicentre DC study, DECRA, was highly expected. The study group published their results in NEJM in April 2011 and the conclusion was: "In adults with severe diffuse traumatic brain injury and refractory intracranial hypertension, early bifrontotemporoparietal decompressive craniectomy decreased intracranial pressure and the length of stay in the ICU but was associated with more unfavourable outcomes" [Cooper 2011]. Instead of offering clarifying aspects of the outcome and indications of DC, the results of DECRA have been rather confusing. The study setup has raised a lot of criticism and the generalization of the results is not evident [Hutchinson 2011, Torres 2012]. This might have affected the statement of the TBI panel to favour CER studies over the RCTs.

The literature search from PubMed with a combination of "Decompressive craniectomy" and "QALY" returned a total of 5 published studies. Of these 5 papers, two are partial works of the present research. In 2011, Ho el al. published a study of 168 Australian TBI patients who underwent DC. In their study, the average cost per QALY was high (US$682,000), and therefore they concluded that DC was not cost-effective for patients with extremely severe TBI [Ho 2011]. Whitmore et al. presented opposite conclusions in their study in 2012. They found that when all the costs of severe TBI are considered, aggressive treatment (meaning invasive ICP measuring and DC) is a cost-effective option, even for older patients [Whitmore 2012]. Honeybul et al. considered an important ethical aspect of DC in their study in 2012. They concluded that DC would appear to have a medical indication for carefully selected patients, but they presented the need to develop

reliable outcome prediction models for patient selection which would provide an objective assessment of the most likely outcome for those patients who require decompression [Honeybul 2012].

The latest review of DC was published by Kolias et al. in June 2013 [Kolias 2013]. They reviewed the evidence and presented considerations regarding the surgical technique, ethics and the cost-effectiveness of DC. As a conclusion, they presented that DC can reduce ICP acutely and decrease the risk of herniation, and most of the available evidence for DC comes from studies in TBI and ischemic stroke. As the DECRA study failed to provide evidence of the superiority of early (so-called "prophylactic") DC, the ongoing trial (RESCUEicp) is investigating the effectiveness of DC as a last tier therapy.

ANEURYSMAL SUBARACHNOID HAEMORRHAGE

Aneurysmal subarachnoid haemorrhage (SAH) is a neurological emergency and often a severely disabling disease [Nieuwkamp 2009]. Aneurysmal SAH is the most common cause of nontraumatic SAH, which accounts for about 80% of cases. The remaining 20% of nontraumatic cases are nonaneurysmal, including perimesencephalic subarachnoid haemorrhage, and are associated with a good prognosis [Suarez 2006].

The incidence of SAH varies widely throughout the world. The worldwide incidence is estimated to be 9.1. Finland has a high incidence of SAH, 22.7 per 100 000 [Steiner 2013]. The incidence increases linearly with patient age and the median age of onset of the first SAH is 50–60 years. The overall mortality is estimated to be 50-60%. It has been estimated that 10-15% of the patients die before ever reaching the hospital and that out of all concerned, 25% die within 24 hours from the insult with or without medical treatment. Of the hospitalized patients, 40% die within a month, and within 6 months the total mortality of all patients rises to over 50% and approximately one third of the survivors need lifelong care [Suarez 2006]. Even if a patient is still alive one year after SAH, it has been demonstrated that survivors have excess mortality, which is attributed to an exceptional risk of deadly cerebrovascular events [Korja 2013].

In aneurysmal SAH, three variables are the most closely related to the outcome: the neurological condition of the patient on admission, age, and the amount of extravasated blood seen on CT scans [Steiner 2013]. The other prognostic factors are occurrence of rebleeding, appearance of cerebral vasospasm, co-morbidities, a history of smoking and the location of the aneurysm [Rosengart 2007]. The

diagnostics of the SAH includes a CT scan, in which SAH is almost always detectable one day after SAH. CT angiography or digital subtraction angiography (DSA) are used to locate the aneurysm. MRI can detect SAH weeks after the original bleed, and normal cerebrospinal fluid excludes SAH within the last 2–3 weeks [Steiner 2012].

The treatment protocol usually involves early occlusion of the aneurysm by surgical clipping or endovascular coiling [Withfield 2001]. This reduces the risk of rebleed, which is associated with high mortality and morbidity. After that, the treatment is targeted to prevent and/or treat the complications. Other than rebleeding, cerebral vasospasm is the leading cause of morbidity and mortality following aneurysmal SAH. While angiographic vasospasm, typically observed between 5 and 14 days, may occur in up to 70% of patients, symptomatic vasospasm may only occur in about 30% of patients [Velat 2011]. Spasm is generally treated by so-called triple-H therapy (hypervolemia, hypertension, haemodilution) and a calcium antagonist. Other complications, such as hydrocephalus and seizures, may require treatment [Bederson 2000]. Hydrocephalus occurs in approximately 20% of patients during the acute phase and in about 10% during the chronic phase after SAH [Steiner 2012]. Acute phase treatment is a complex combination of surgical, intensive care and medical treatment.

The recovery may be slow and require extensive rehabilitation. The long-term recovery and prognosis depend on the severity of the initial haemorrhage and the number and severity of the complications. A high proportion of long-term survivors of SAH experience ongoing deficits in high level (neuropsychological) functioning. These deficits result in impairment in social roles [Hackett 2000].

The importance of assessing the health-related quality of life (HRQoL) has also yielded studies of SAH patients' HRQoL within the last few years [Ronne-Engström 2011, Leach 2011, Wong 2011, Meyer 2010, Al-Khindi 2010]. The literature search from PubMed with the combination of "Subarachnoid haemorrhage" and "QALY" returned a total of 20 published studies in English. Of these 20 papers, two are partial works of the present research. The cost-effectiveness of the diagnostic strategies was evaluated in five publications [Jethwa 2013, Ward 2012, Sanelli 2009, Kallmes 1997, Tolias 1996]. Eight of these publications evaluated the cost-effectiveness of screening and treating asymptomatic aneurysms [Bor 2010, Wermer 2008, Takao 2008, Wermer 2004, Brown 2004, Johnson 1999, King 1995, Gaetani 1998]. Bardach el al. studied the cost-effectiveness regionalization of SAH treatment [Bardach 2004]. Koffijberg et al. performed a cost-utility analysis of aneurysm occlusion in elderly patients [Koffijberg 2011]. D'Ambrosio et al. evaluated the clinical outcome and quality of life of patients with decompressive hemicraniectomy for poor-grade aneurysmal SAH [D'Ambrosio 2005] Comparative studies of treatments of surgical clipping or endovascular

coiling of aneurysm have been published [Zubair 2009, Takao 2008]. The economic burden of SAH in the UK has been evaluated [Rivero-Arias 2010]. Predictors of a good or poor outcome have been determined [Hütter 2000].

OTHER ACUTE ILLNESSES AND COST-EFFECTIVENESS

Altogether, there are very few published studies of the HRQoL, QALY or cost-effectiveness of the treatment of acute neurosurgical illnesses. A literature search in PubMed with "QALY" and "epidural or subdural hematoma" yielded no results. "Intracerebral haemorrhage" and "QALY" yielded 8 publications and half of them estimated anticoagulation drugs. The most recent publication on the cost-effectiveness of surgical decompression for space-occupying hemispheric infarction by Hofmeijer et al. was published in *Stroke* in August 2013 [Hofmeijer 2013]. They randomized 39 patients with middle cerebral artery infarction into two groups; surgical compression and medical treatment groups. After 3 years, 24% of the surgical patients and 78% the medical patients had died. They found that the surgical group had more QALYs but at high costs.

AIMS OF THE PRESENT STUDY

The overall purpose of this study was to evaluate the health-related quality of life and the cost-effectiveness and cost-utility of the treatment of severely, acutely ill neurosurgical patients. The majority of the study illnesses and conditions are known to have relatively high mortality or have an otherwise poor outcome, but on the other hand they are also known to be highly resource-demanding. While the economics of the health care is gaining more and more interest, there is a demand to evaluate the cost-effectiveness of the treatment and a further need to demonstrate that the resource allocation is justified.

1. One of the main challenges of a neurosurgical intensive care unit (NICU) is the end-of-life decision making and restriction of the treatment. When the patient is not considered to benefit from NICU treatment because of a poor prognosis, one way to manage it, is to disconnect patients from life-supporting devices. Previously, the policy in the Department of Neurosurgery in Helsinki was to remove patients from the highly resource-demanding NICU to the common hospital wards with respirators. Therefore, despite the poor prognosis, they were given more time for the recovery. The purpose of the Step-Down Unit study was to evaluate the outcome of this seriously ill group of patients. Was the previous policy just extension of humane suffering or was the treatment clinically justified? Further, the cost-effectiveness (CE) of the treatment was evaluated.

2. Decompressive craniectomy (DC) is one of the most extreme treatments in medicine. When all conservative means to handle intracranial pressure fail, a large piece of bone is removed from the skull in order to expand the space for injured or affected brain, as the oedema of the brain is elevating the intracranial pressure and threatens to damage the brain permanently. The purpose of the DC after SAH study was to evaluate the outcome and the health-related quality of life (HRQoL) of the patients who underwent DC because of SAH or other neurological emergency. The purpose was also to conduct the first cost-effectiveness evaluation of the DC treatment.

3. The purpose of the DC after TBI study was to evaluate the poor grade TBI patients who underwent DC. The study group consisted of patients who suffered severe TBI with hematoma, contusion or diffuse brain injury. The trauma led to elevated intracranial pressure, which was untreatable despite the maximum conservative treatment in the NICU. As a last possible treatment, a surgical enlargement of the space for swollen brains was conducted. As the previous literature on the advantages of DC remains contradictory, our aim was

to study the outcome of this group of patients, and the main goal was to execute the first cost-effectiveness study of DC after TBI.

4. The subarachnoid haemorrhage (SAH) is one of the most dramatic and devastating acute conditions. It is associated with high mortality and morbidity. Although an increasing number of HRQoL studies of SAH patients are being published, long-term studies do not exist. SAH is fairly common in Finland and the long-term outcome of the patients is a subject of special interest. Our previous studies implicated that the recovery of neurosurgical patients took a lot longer than generally was expected in the literature; therefore our purpose was to examine the outcome of SAH patients after ten years from the original bleeding.

MATERIALS AND METHODS

Patients for these four studies were treated in the Department of Neurosurgery of Helsinki University Central Hospital, which is the only neurosurgical unit in Southern Finland and serves a population of almost 2 million. More than 3100 operations are performed each year. All of these studies were approved by the ethics committee of the Helsinki and Uusimaa Hospital District.

PATIENT SELECTION FOR THE STEP-DOWN UNIT STUDY

The Quality of Life after Neurosurgical Disease and Treatment study began on April 1, 2000 at our institution. Every patient admitted to the neurosurgical clinic between May 2000 and January 2003 was asked by a study nurse to participate in this study. Only those admitted for spinal surgery were excluded. During this 33-month study period, 6959 patients were admitted to our institution and a total of 3637 (52%) patients entered the program. Consent for study participation came either from the patient or from next-of-kin. Of the total of 6959 patients, 5367 were at some point treated in the intensive care unit (ICU) (Figure 6.). For the Step-Down Unit study, the patients were selected by the following criteria: 1) Patients were first treated in the ICU. 2) The treatment period in the ICU of patients in poor condition was prolonged 3) A multidisciplinary assessment evaluated that there is no improvement in the prospect in ICU care despite the need for ventilator support. 4) Patients were transferred to a step-down unit. Of the ICU patients, 478 met the enrolment criteria. Consent was available from 346 patients, who then joined this study. The underlying diagnosis of the patients of the Step-Down Unit study were SAH (21%), intracerebral haemorrhage (ICH,16%), acute or chronic subdural hematoma (SDH, 25%), TBI or epidural hematoma (25%), and primary intracranial tumour (benign, malignant)(5%).

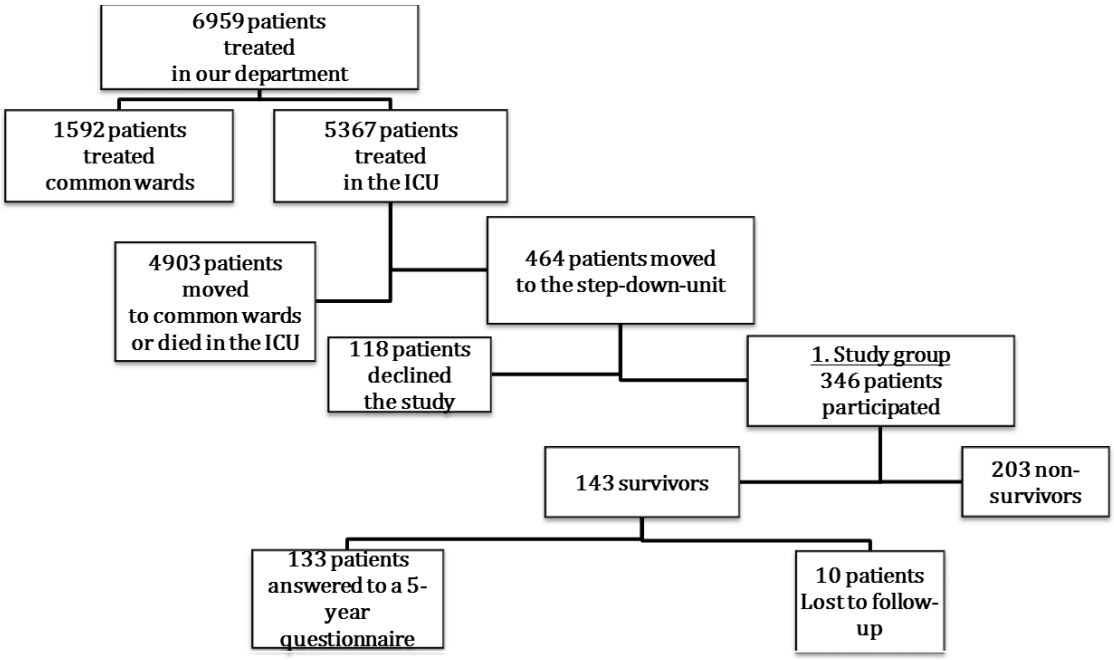

Figure 6. Patient selection for the Step-Down Unit study.

PATIENT SELECTION FOR THE DC STUDIES

The DC after SAH and DC after TBI studies involved an evaluation of the outcome and cost-effectiveness of decompressive craniectomy. The patients for these two studies were treated in our institute in 2000 - 2006. After the DC was performed, all the bone autografts removed were stored in the same freezer at -70 degrees, with patient identification data stored in the same room. Among all these data, we selected all 102 surgeries performed to lower intractable intracranial pressure between 2000 and 2006. For the first DC study (DC after SAH study), we excluded the standard indications of DC, such as TBI and malignant media infarction, leaving a study group of 42 patients: 29 SAH patients and 13 patients with other indications, including 2 each of unruptured aneurysm, arteriovenous malformation (AVM), fulminant demyelinating disease, virus encephalitis, and intracerebral haemorrhage, and one each of esthesioneuroblastoma and sinus thrombosis.

For the other DC study (DC after TBI), we found in total 56 cases of DC having been performed to lower intractable ICP after TBI. We excluded 2 children under age of 10, and therefore our study group consisted of 54 patients (Figure 7.).

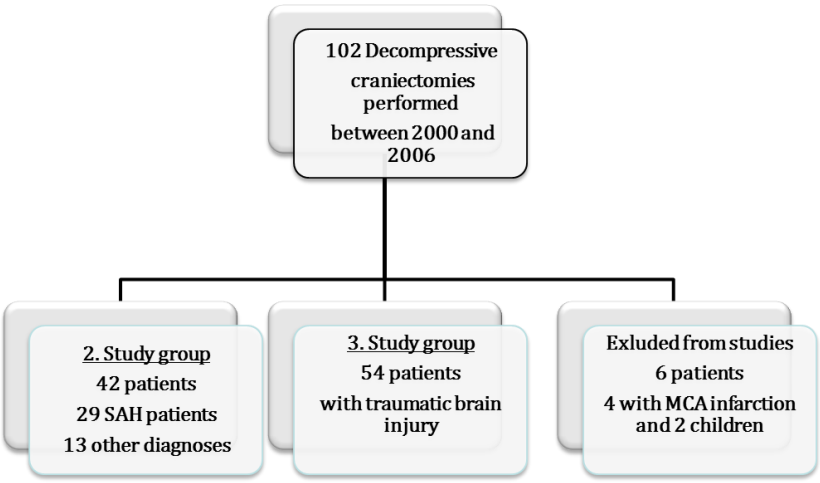

Figure 7. Patient selection for the DC studies.

PATIENT SELECTION FOR THE SAH STUDY

For the SAH study, patients were originally selected prospectively for a randomized, placebo-controlled study of the effectiveness of enoxaparin treatment of SAH patients. The original study showed no effect on the outcome, infarction or blood clotting status between the two original study groups [Siironen 2003]. The patients were selected among 546 aneurysmal SAH patients treated during the study period between February 1998 and March 2001 in our institution. The general inclusion criterion for the original study was radiologically verified aneurysmal SAH. The exclusion criteria concerned study drug administration: 1) hospital administration occurred later than 72 hours from SAH; 2) age over 75 years; 3) post-operative ICH larger than 20mm; 4) any pre-existing bleeding disorder; 5) severe hypertension (>200/110 mmHg), renal of liver failure or pre-existing neurological illness; 6) pregnancy or allergy to study drug; 7) post-operative anaemia or coagulopathy. Of the 546 SAH patients, 178 fulfilled the enrolment criteria and were accepted to the study. All patients or their closest relatives gave written consent for participation before entry into the study.

DATA COLLECTION AND FOLLOW-UP METHODS

The medical records of all the patients (620) in all four studies were examined and the baseline and treatment data was gathered. From medical records, all the

recorded information of the patient's previous condition, the current illness, the first aid and paramedics' information, condition on admission, treatments, operational treatments, laboratory results, and CT scan results were studied, and if there were data from further care, those were studied as well. At the beginning of our study, the patient status, date of death for those deceased and the recorded addresses for survivors were established from the Central Population Registry by phone inquiry.

In the Step-Down Unit study, the survivors received 6-month, 1-year and 2-year questionnaires, and their answers were recorded in the database. The 5-year inquiry was performed by interviewing the patients over the phone (126 patients or patients' caregivers). The 7 patients without a known telephone number received questionnaires. Of the 143 patients, 10 were lost to follow-up. The response rate was 93%. The first three questionnaires contained 15D questionnaires, which were compounded by additional questions about the type of residence, continuance of treatment, and management of daily living, and was meant for evaluating the outcome. In the 5-year inquiry, the 15D form was replaced by the EuroQol EQ-5D questionnaire.

For the DC studies and the SAH study, patients were sent somewhat similar questionnaires as in the first study about their outcome, including EQ-5D questions. For these three studies, we also asked about the patient's ability to work after the illness. In the DC after SAH study, each patient answered a written questionnaire, and in the DC after TBI study, the patients were interviewed over the phone. In both studies the response rate was 100%. For the SAH study, a written questionnaire was mailed to the survivors and the response rate was 95%.

COSTS

All the costs of the neurosurgical treatment period of each patient of these 4 studies were obtained from the Ecomed PP database (Datawell Ltd., Espoo, Finland), where all cost data concerning the treatment of individual patients in the hospital is routinely stored. The hospital stay costs included all expenses of a treatment period; inpatient days, medical treatments, laboratory and radiological investigations, and outpatient visits. Data on other costs such as treatment in any other establishment or any rehabilitation were not available, and thus were not included in the cost-effectiveness calculations of the direct neurosurgical treatment. The data was gathered from the "Musti" program by entering the patients' social security numbers and then searching for costs from the department of neurosurgery during the time period of the illness and treatment.

In the DC studies, we conducted a more precise evaluation of the total costs. The estimations of the total treatment costs were based on the data received from the patients. Patients were asked what kind of further treatment they received, where and how long. Medical records were also checked for further treatment data when available. The cost estimations were calculated according to the detailed healthcare cost data from the National Research and Development Centre for Welfare and Health publications [Hujanen 2008]. The calculations also included estimations of the future costs of all survivors, based on their reply, how they live (home, nursing home, hospital) and whether their treatment continues in some way (doctor visits, physiotherapy, etc.) (Figure 8.). The estimation also included the costs of the non-survivors before they deceased, assuming they spent their last days in hospital. The sum of the total costs was achieved by adding the costs of treatment in our department, costs of further treatment for the eventual non-survivors, costs of the further treatment for survivors and estimation of the future treatment for the survivors. It was assumed that eventual non-survivors were hospitalized until the end of life.

In the SAH study, we gathered only the direct neurosurgical costs and the total costs were approximated using the results of previous studies, in which we concluded the total cost to be seven times the acute cost. Because the treatment period occurred over 10 years ago, the figures were corrected by annual average inflation rates, which were obtained from the Statistics Finland website.

CALCULATION OF QALYS AND COSTS

The QALYs were calculated by evaluating the HRQoL index and life expectancy. The HRQoL index was evaluated by a EQ-5D questionnaire. The answers yielded a 5-digit sequence, which was converted into a weighted health state index by applying scores from EQ-5D "value sets," achieved from general population samples. We used value sets which were derived by a choice-based method (Time Trade-Off, TTO). The HRQoL index was derived for each patient individually according to their answers. Then the life expectancy was derived also individually for each patient. The tables of life expectancy and death risk by age and sex for the Finnish population came from Statistics Finland. Life expectancies were corrected based on the patients' diagnoses. The effect of each diagnosis on life expectancy was studied based on the literature. We had no control group to compare the results with. The QALY calculations were based on one group of patients in each study. We calculated the number of gained QALYs by subtracting the number of QALYs after an intervention with the number of QALYs before the intervention. The

HRQoL index was assumed to be 1 (best possible) before illness, but the life expectancy was assumed to be equal to zero (i.e. dead) without intervention, and therefore QALYs before the intervention were equal to zero. The non-existing life expectancy without intervention was supported by the extremely poor condition of the study patient. No one in the first three studies was assumed to survive without treatment. After QALYs for each patient were calculated, the QALYs were added up to achieve the total number of the QALYs of the survivors. Then to calculate a cost per one QALY, all the costs (as explained previously) were added together and this amount was divided by the total number of QALYs.

Direct neurosurgical costs, retrieved from the database			**47 200 €**
Further care	cost per day	number of days	costs
Secondary care unit	300 €	21	6 300 €
Primary care unit	141 €	20	2 820 €
Rehabilitation center	300 €	14	4 200 €
Nursing home	83 €	0	0 €
			13 320 €
Outpatient services	cost per visit	number of visits	
Doctor appointments	82 €	10	820 €
Physiotherapist	41 €	200	8 200 €
Speech therapist	72 €	30	2 160 €
Occupational therapist	54 €	30	1 620 €
			12 800 €
Approximated future costs			
Patient visits the doctor once a year, has physiotherapy once a week and visits Rehabilitation centre once a year for two weeks. Life expectancy 14 years			
	Cost per day/visit	Costs per year	Costs for life
Doctor appointments	82 €	82 €	1 148 €
Physiotherapist	41 €	2 050 €	28 700 €
Rehabilitation center	300 €	4 200 €	58 800 €
			88 648 €
Direct neurosurgical costs			47 200 €
Further care costs			13 320 €
Outpatient costs			12 800 €
Approximated future costs			88 648 €
TOTAL			**161 968 €**

Figure 8. Example of one patient in studies 2 and 3 to illustrate the calculation of the costs.

Statistical analysis was performed with the Windows software PASW Statistics 18, 2009. The EQ-5D HRQoL indices were calculated with the PASW syntax from the EuroQol Group. The normality of the data was tested (Kolmogorov-Smirnov test). The results were given as mean ± standard deviation (SD) or as median and percentiles (25th and 75th). The significance of the difference was estimated either with the Student t-test (Gaussian) or the unpaired Mann-Whitney U-test (non-Gaussian) and the correlation of variables was evaluated by calculating the non-parametric Spearman correlation coefficient (ρ); $p \leq 0.05$ was considered to be statistically significant.

A total of 620 patients took part in the four studies (Figure 9.). The median age of the patients in studies 1 to 4 was 58, 48, 37 and 50 years respectively.

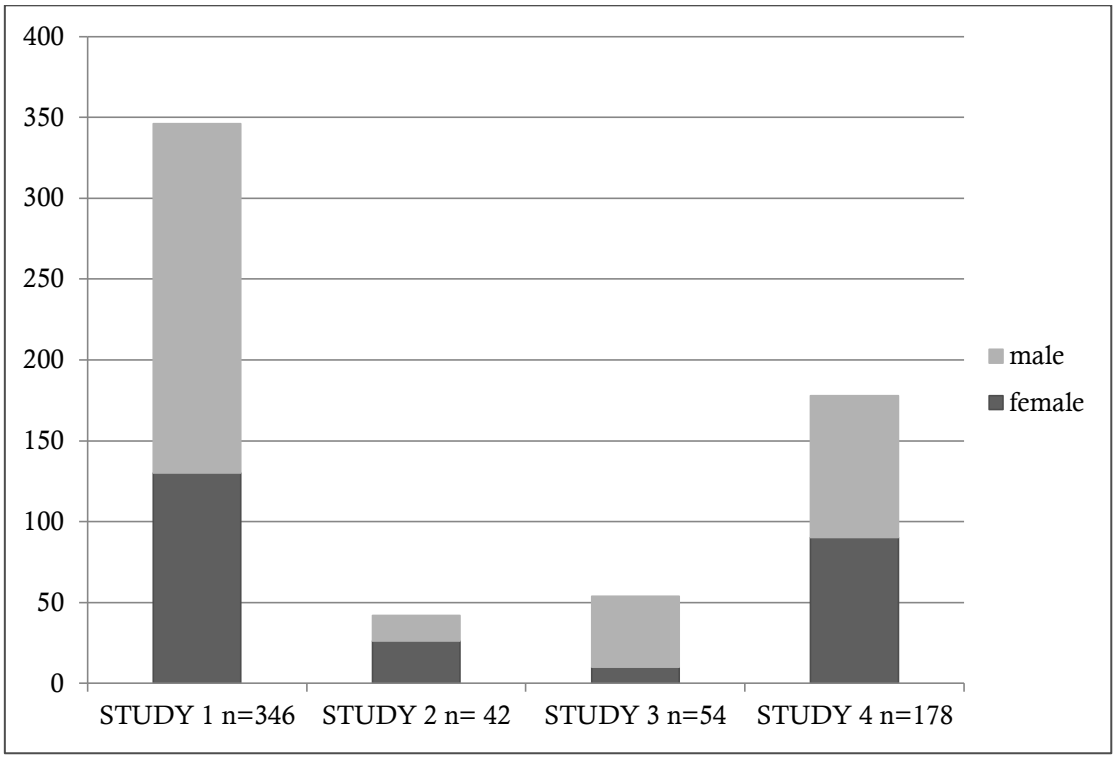

Figure 9. Number of study patients and gender distribution.

The distribution of the clinical condition of the patients on admission was assessed (Table 3.). The DC after TBI study had the most severely ill patients: 64% of the patients were considered to have a GCS value of less than 7. On the other hand, the SAH study patients had the best clinical condition on admission: 54% had WFNS I, which is comparable to GCS 15.

Table 3. Clinical condition of the patients on admission to the hospital.

GCS score	*Step-down unit study*	*DC after SAH study*	*DC after TBI study*	WFNS score	*SAH study*
15	16%	38%	5%	I	54%
13-14	9%	10%	13%	II - III	25%
7-12	23%	14%	18%	IV	16%
<7	52%	38%	64%	V	5%

MORTALITY AND OUTCOME

The total mortalities of the studies were 59%, 53%, 41%, and 24%. Besides the total mortality, we were also interested when death had occurred. The cumulative survival is presented in Figure 10. It shows that in studies 1-3 the mortality was the highest soon after the first insult. Of the non-survivors, 50% died within one month and 70-80% within 6 months.

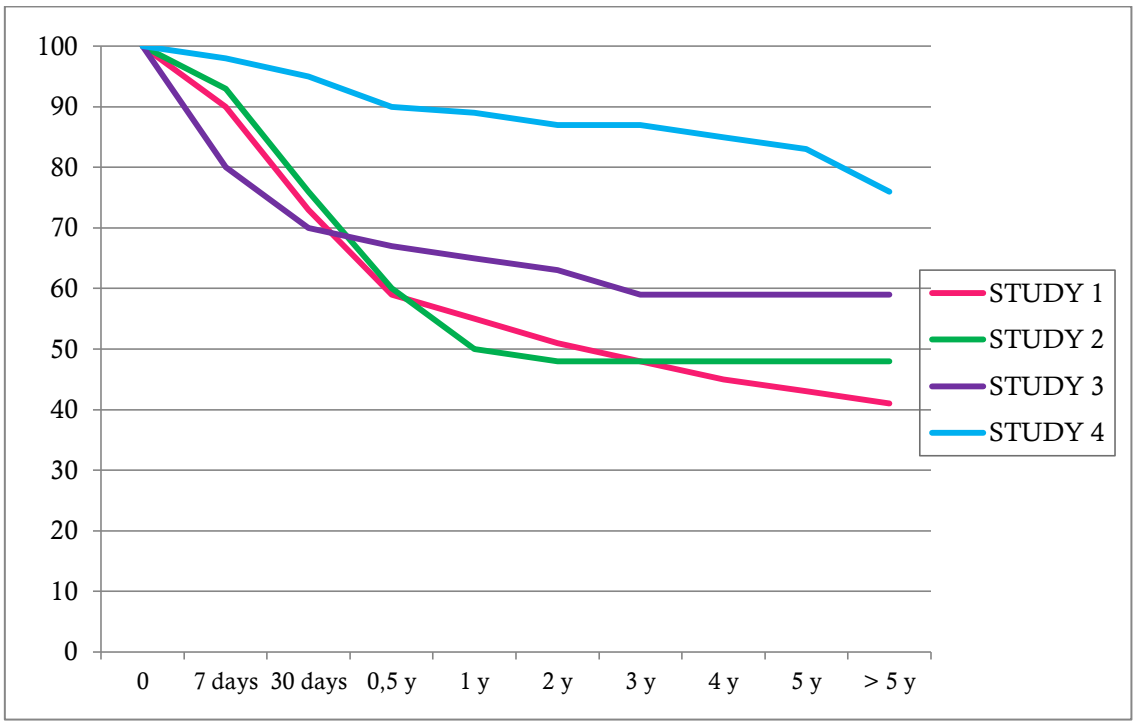

Figure 10. Cumulative survival of the patients in all four studies.

In the Step-Down Unit study, the mortality was the highest among patients suffering from a malignant primary brain tumour (88%), ICH (78%) or subdural hematoma (60%). The outcome on the Glasgow Outcome Scale (GOS) and the type of residence in all four studies are presented in Tables 4-7.

Table 4. Outcome of the 143 survivors in the Step-Down Unit study.

		Survivors
Outcome	Good (GOS 1-2)	70/143 (49%)
	Moderate (GOS 3)	63/143 (44%)
	Poor (GOS 4)	0/143 (0%)
	Lost to follow-up	10/143 (7%)
Type of residence	Home	70/143 (49%)
	Home assisted	28/143 (20%)
	Nursing home	32/143 (22%)
	Hospital	3/143 (2%)
	Lost to follow-up	10/143 (7%)

Table 5. Outcome of the 20 surgery survivors in the DC after SAH study.

		Survivors
Outcome	Good (GOS 1-2)	5/20 (25%)
	Moderate (GOS 3)	14/20 (70%)
	Poor (GOS 4)	1/20 (5%)
Type of residence	Home	10/20 (50%)
	Home assisted	6/20 (30%)
	Nursing home	3/20 (15%)
	Hospital	1/20 (5%)

Table 6. Outcome of the 32 survivors in the DC after TBI study.

		Survivors
Outcome	Good (GOS 1-2)	22/32 (69%)
	Moderate (GOS 3)	8/32 (25%)
	Poor (GOS 4)	2/32 (6%)
Type of residence	Home	25/32 (78%)
	Home assisted	1/32 (3%)
	Nursing home	5/32 (16%)
	Hospital	1/32 (3%)

Table 7. Outcome of the 135 survivors in the SAH study.

		Survivors
Outcome	Good (GOS 1-2)	101/135 (75%)
	Moderate (GOS 3)	27/135 (20%)
	Poor (GOS 4)	0/135 (0%)
	Lost to follow-up	7/135 (5%)
Type of residence	Home	119/135 (88%)
	Home assisted	4/135 (3%)
	Nursing home	5/135 (4%)
	Hospital	0/135 (0%)
	Lost to follow-up	7/135(5%)

HEALTH-RELATED QUALITY OF LIFE, QALYS AND COSTS

The health-related quality of life was assessed as a median EQ5D index (Table 8.). The DC after SAH study patients had the lowest EQ-5D index, 0.41. Particularly the SAH group in study 2 had poor HRQoL with the median index 0.15. The Step-Down Unit study patients had an almost surprisingly good EQ-5D index, 0.71, considering the basis of the study. The index of the DC after TBI study patients reached the level of the standard population (0.85) and the index of the SAH study patients even exceeded it (Figure 11.). Figure 12 shows the EQ-5D health states of all 4 studies. The poor outcome of the study 2 group is also evident in the figure, since the majority of the patients reported having either moderate or extreme problems in mobility, self-care or usual activities. What is reassuring is that a minority of the patients reported having anxiety or depression and none reported pain or discomfort. The health states of the patients in studies 3 and 4 were good, which is evident by the good index number.

The total costs of the treatments in studies 1 to 4 were 6.00 million €, 1.66 million €, 2.01 million €, and 1.75 million €. The median number of QALYs, costs per patient, the neurosurgical costs and the total costs for a QALY are presented in Table 8.

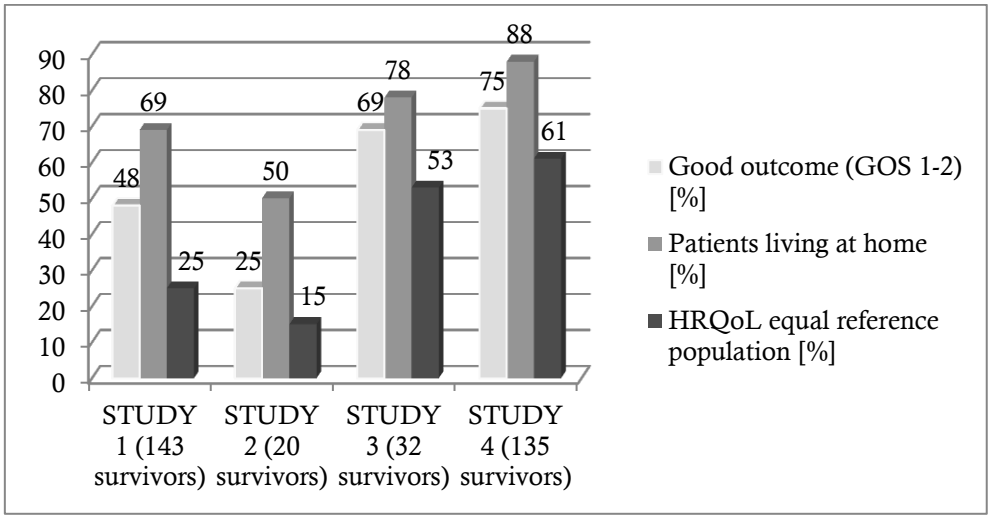

Figure 11. Percentages of good outcome, living at home and HRQoL being equal or higher compared to the reference population.

Table 8. Treatment costs and costs per QALY.

	Step-down unit study	DC after SAH study	DC after TBI study	SAH study
Median EQ-5D index (25th and 75th percentile)	0.71 (0.38, 0.85)	0.41 (0.02, 0.7)	0.85 (0.56, 1.00)	1.00 (0.80, 1.00)
Total number of QALYs achieved	2392	333	865	1036
Mean/median QALYs per patients (±SD/25th and 75th percentile)	17 ±13	16 (1, 30)	35 (17, 41)	23 (16, 31)
Total costs of all patients	6 000 000€	1 660 000€	2 010 000€	1 750 000€
Median cost of the treatment per patient (25th and 75th percentile)	15 000€ (10 000-22 000€)	38 000 € (27 000, 50 000€)	40 000€ (22 000, 48 000€)	9 000€ (7 200, 11 500€)
Neurosurgical costs per QALY	**2 521€**	**5 000€**	**2 400€**	**1 700€**
Estimated total costs per QALY	29 000€	58 000€	17 900€	12 000€

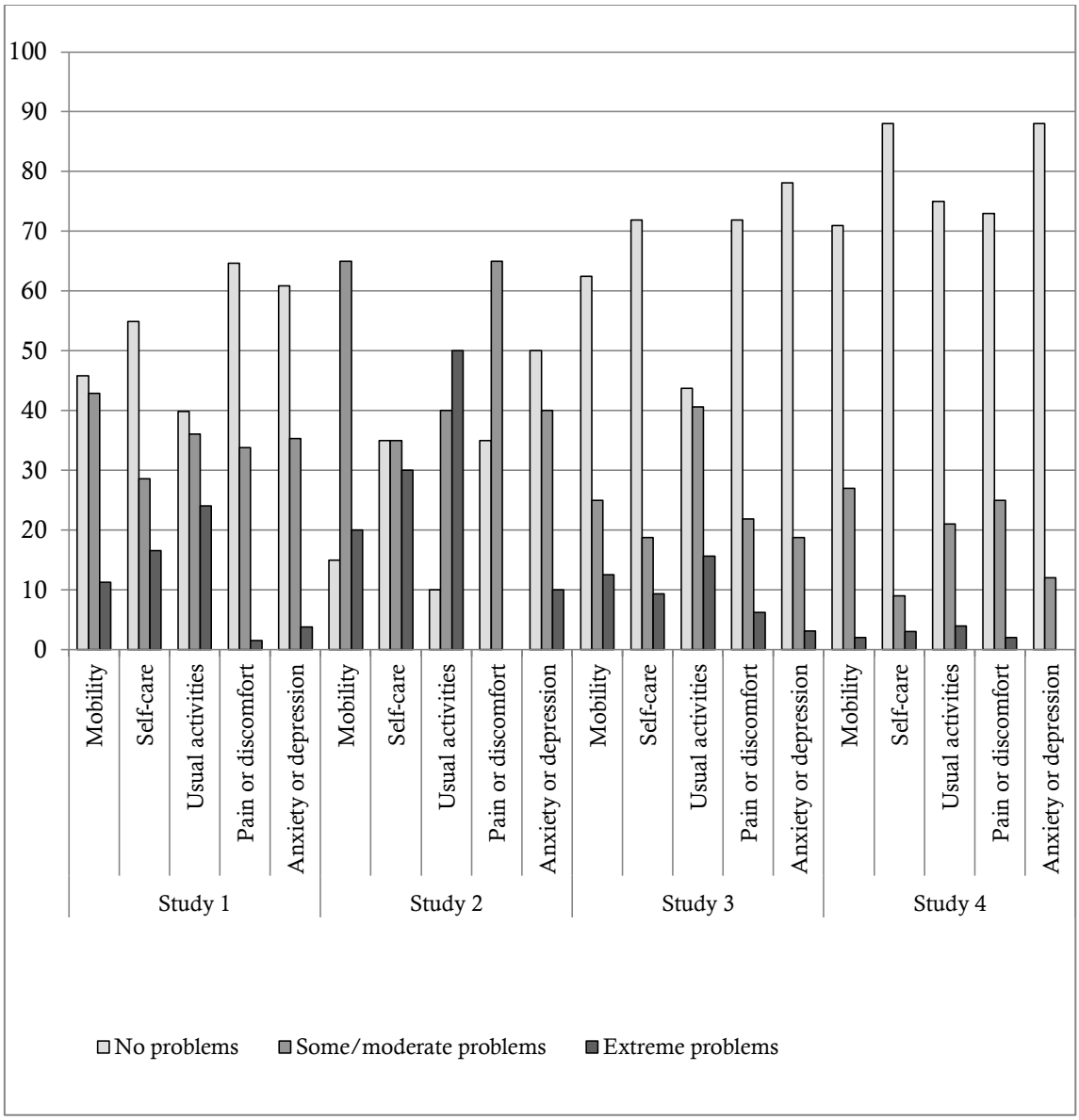

Figure 12. EQ-5D health states in all 4 studies of all survivors included in follow-up.

Besides the main interest of cost-effectiveness, we discovered some interesting additional findings.

1.) Recovery took longer than was expected

In Study 1, patients answered four questionnaires between 6 months and 5 years after the treatment. Based on these answers, we discovered that the patients experienced rehabilitation for longer than generally is expected. The usual opinion is that after traumatic brain injury, recovery is expected to be mostly achieved within 1.5 years (29).

2.) Complications of DC had no influence on the outcome

In Study 2, we found complications after either DC or cranioplasty to be fairly common, infection and hydrocephaly being the most frequent. The percentage of complications was 60% after DC and 35% after a cranioplasty. Complications, however, seemed to have had no influence on the overall outcome in this study. The mortality for those with complication was 44%, versus those without complications at 65%; both groups had the same percentage (12%) of good outcome (GOS 1–2).

3.) Alcohol abusers had a higher mortality and a worse outcome in TBI

In Study 3, we examined the patients' alcohol use before and at the time of the accident. We found that alcohol-related accidents were common, and of the study group, 50% were under the influence of alcohol at the time of injury and 30% had a history of habitual alcohol or substance abuse documented in their medical records. The habitual alcohol users had both a higher mortality (30% vs. 65%, $p<0.001$) and a worse outcome among the survivors (GOS1 17% vs. 37%, $p<0.001$). There were no explaining factors for this finding in the type of the accident, as alcohol abusers tend to have more common falls and assaults, whereas others had more high-energy trauma, such as traffic accidents.

4.) In SAH, the previous health status had no correlation with the outcome

In study 4, we examined several variables to find a correlation with the outcome. We found a statistically significant correlation between age and the outcome. But surprisingly no statistically significant correlation was found between the outcome and gender, hypertension, coronary artery disease, alcohol abuse or smoking status.

DISCUSSION

Based on these studies of four different groups of neurosurgical patients, we found that the treatment was cost-effective. We also found that despite the severity of the illnesses, the health-related quality of life of the study groups proved to be good, with one exception. The majority of the patients of each study were able to live at home (69%, 50%, 78%, and 88%) and a large portion were able to live independently (48%, 25%, 69%, and 75%).

ECONOMIC EVALUATION

Economic evaluation of health care has many advocates, but also opponents. There may be opinions that health care should not be subjected to economic evaluation or that decisions such as "to treat or not to treat" should not be affected by money. That is understandable at the individual level and eventually no one should be in the position that necessary treatment is denied solely by monetary reasons. These decisions should be determined at a different level.

When health care costs are paid from public funds, there has to be a common policy on what, when and how medical conditions are treated. The economic evaluation should be utilized to establish a bigger picture where it is a very valid and needed tool for resource allocation. The question is not who will be left without, but how the resources are divided in a way that a largest amount of health is achieved.

EVALUATING HEALTH-RELATED QUALITY OF LIFE

Although the concept of HRQoL has gained a lot of success and its use is highly recommendable, there are some questions in assessing the HRQoL. What is the influence of personality on HRQoL evaluation? How does the "bad day" affect assessment of HRQoL? How will several comorbidities affect estimations of a particular disease in research? Different methods of evaluation are influenced in a different way by the disturbing factors. The most sensitive method is VAS evaluation, in which respondents are asked to give a numerical value for their

HRQoL. On the other hand, more precise results are achieved with descriptive questionnaires, which are less influenced by other factors than HRQoL. The less complicated the questionnaire is, and the less freedom of choice there is, the less the result is affected by any other factors. This can be easily understood; if the questionnaire asks "can you walk or not?", the question most likely reflects the actual health status rather than personality, mood, life situation or other irrelevant concerns. Although uncomplicated questionnaires can be free from inappropriate influences, they are incapable of distinguishing fine distinctions between different health states.

QUALITY-ADJUSTED LIFE YEAR

As well as HRQoL, the concept of QALY is widely used, but it has also received a lot of criticism [Hirsky 2007]. Especially in drug research, the QALY has been judged as too rigid and not detecting small improvements of health. It does not take personal differences into account in the valuing of health and it does not regard willingness to take risks or to pay for an illness [Stevens 2012]. QALYs have also been considered to discriminate elderly patients, because their life expectancy is lower. There are also suspicions that in chronic diseases, psychiatric disorders or dementia or other memory disorders, QALYs are not reliable [Bosanquet 2005]. However, QALYs do not, of themselves, provide a measure of cost-effectiveness. For example, the calculation of a ratio – the incremental (ICER) cost per QALY – diminishes the effect of the age in calculations. If two interventions are compared and ICER costs are evaluated, the effect of age does not affect the results. It is true that the QALY might be rigid and does not consider any personal aspects of health status, but should they be taken into account? Is one's illness more important if its effect is greater because of personal characteristics?

Despite the criticism against the QALY, there have not been any suggestions for replacing the QALY. Finding a corresponding concept that is objective, rational, mathematical, universally valid, and which overcomes the deficiencies of what the QALY is accused of seems less than plausible.

EQ-5D

We selected the EQ-5D questionnaire because it is simple, clear, and quick to fill. We presumed that our study groups will find it easy to answer and therefore we expected a good response rate. There are no common recommendations or "a

golden standard" on which instrument to use in HRQoL studies, but in 2002, the Brussels Roundtable Consensus meeting recommended the SF-36 and EQ-5D as the preferred HRQoL instruments in the critical care setting [Angus 2002]. EQ-5D has had quite a few critical appraisals in the literature. In chronic pain assessment, EQ-5D was suspected to be influenced by the floor effect in pain assessment and therefore was not regarded to be sensitive enough [Dixon 2011]. Linde et al. compared 5 instruments, including EQ-5D, in rheumatoid arthritis and found all of them to be equally useful [Linde 2008]. The validity of EQ-5D has not been studied with acutely ill neurosurgical patients.

Before we chose EQ-5D, we examined other possible instruments. The 15D questionnaire was also found suitable for our purposes. 15D is a widely used instrument in Finland and some institutions have prioritized its use in HRQoL studies. The 15D group published a study in which they found 15D to be superior over EQ-5D [Vainiola 2010]. However, EQ-5D is short and concise and therefore easy to answer and yet manages to examine the clinical condition extensively. We suspected 15D to be too long and contain too personal questions for our patients.

COSTS ANALYSIS

One of the most challenging aspects in CE studies is the evaluation of the costs. Even though the direct costs are recorded, they might be far from the actual costs of the treatment and further of the illness. The direct costs from one institution can be evaluated with reasonable accuracy, as these costs are well recorded. The most reliable estimate of the total costs may be achieved from the register of the Social Insurance Institution of Finland, but even that estimation may be imprecise. The data is based on register information, the reliability of which depends on the accuracy of the announcements of the health care personnel. However, this is not the only fact which could distort the evaluations. Patients may suffer from multiple illnesses and conditions and the costs may be entangled with each other.

The complexity of the costs analysis is, however, a well-recognized and universal challenge. As this is difficult for all CE researchers, the most important thing in studies is to carefully report the methods of how and what is taken into account, how calculations are conducted and what the approximations are based on.

EFFECTIVENESS OF AN INTERVENTION

In elective surgery, the assessment of the effectiveness of the intervention can be straightforward. The patients can be interviewed before and after the operation and the estimation of QALYs gained can be executed after a single surgical intervention. Pharmaceutical research has also utilized QALYs in assessments of the effect of drugs, and this may also be quite straightforward. The assessment of QALYs gained by intervention in acute illnesses involves many challenges. The evaluation of HRQoL before the treatment in acute conditions is rarely available. How to estimate the quality of life – could HRQoL be reliably evaluated by retrospective interviews? Or is it even possible to evaluate the effect of the treatment by using QALYs in acute serious illnesses? When an otherwise healthy person comes down with a serious illness, the reduction of HRQoL is inevitable and the assumed positive effects of the intervention may not be evident due to the sudden course of the illness. Another factor is the effect of the illness on the life expectancy. If the intervention is performed as a life-saving procedure, one could assume that life expectancy before treatment is equal to zero, and therefore there is no need to evaluate HRQoL before treatment.

Finally, the question is how can the calculated QALYs be valued? In terms of medicine, are the achieved QALYs in accordance with the improvement of the clinical condition? How to value QALYs if there is no evidence of improvement of any measurable medical parameters? A weight loss study was published in NEJM in 2013, in which weight loss was compared between two groups, a regularly supported group and a control group [Nanchahal 2013]. There was no statistically significant difference in weight loss between the two groups, but the supported group reported improved HRQoL. Although there were no QALYs calculated, the improving HRQoL may yield QALYs. How to value QALYs achieved by this kind of intervention? Does the improvement of HRQoL justify the treatment even though the actual medical benefits of weight loss may not be achieved?

COST-EFFECTIVENESS THRESHOLD

The cost-effectiveness threshold is probably the most criticized component of the CE studies. Criticism is expressed from both sides of the table. The health care providers regard the limits as too low and the payers as too high, even though the limits are rarely expressed explicitly. The threshold limits, as well as the QALY concept, have faced severe criticism from the drug industry. Typically this has

occurred whenever a new developed drug has been declared not to be cost-effective. The criticism is partially justified; the declared limits of cost-effectiveness and the threshold are not based on any theoretical foundation. The limits are often vague and the decision process is not transparent. In an ideal world, the limits are well founded, transparent, equal, even-handed, the same to all people but still flexible. The theoretical bases may be impossible to establish, but since the eventual payers of the services are the citizens, the public opinion of willingness to pay should be somehow incorporated into the decision making.

CONSOLIDATED REPORTING STANDARDS

The health evaluation studies encounter many challenges as speculated previously. As the number of studies increases, the heterogeneity of the publications also increases. In order to be considered convincing, the study methods have to be valid and the reporting should be universal. Despite a growth in published studies, the existing reporting guidelines are not widely acknowledged or utilized. Therefore a panel of distinguished health economists have very recently published Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [Husereau 2013 (Value in Health), Husereau 2013 (BMC Medicine)]. They have published a user-friendly checklist with the purpose of helping authors, editors, and peer reviewers to use the guidelines to improve reporting. The checklist includes 24 items which give explicit instructions for every section, topics ranging from the title of the report to the source of funding and conflicts of interest. These kinds of universal guidelines are very welcome and it is in every researcher's interest to utilize these guidelines. The more consistent the methods and reporting standards are in publications, the more weight will publications and the whole field of health economics gain. Uniform methodology makes it possible to compare the results of studies, treatments and different fields of medicine, etc. Even though a major part of this research project has been conducted before the guidelines were published, all of the four studies in the research project fulfill the requirements of the guidelines for the most part.

The purpose of the Step-Down Unit study was to evaluate whether the treatment policy in our department was clinically justified and cost-effective or whether it was a worthless extension of humane suffering at high costs.

The main limitation of the Step-Down Unit study was the heterogeneity of the study group and lack of unambiguous inclusion criteria. We did not evaluate the outcome of a specific diagnosis, but had a study group of step-down unit patients in a poor condition with various neurosurgical diagnoses. The decision to withdraw patients from a neurosurgical intensive care unit and move them to the step-down unit was made by a senior neurosurgeon. There were no objective measures, such as a laboratory result, but the decision was based on an evaluation of whether the patients would benefit from ICU treatment or not. The baseline assumption was that these patients would have died without treatment and, furthermore, if these patients would have been disconnected from life-sustaining devices at the time of discharge from the ICU, they would have died. Therefore, we concluded that the combination of treatment including operational and intensive care treatment as well as extra time spent in a step-down unit was a life-saving intervention for survivors. This fundamental assumption was utilized in QALY calculations, and the high mortality of the study group indicates that our assumption was likely to be correct.

Another obvious shortcoming was the cost analysis in which only the direct neurosurgical costs were calculated, though most of the patients were transferred to other hospitals for further care, where cost data were not available. The total costs were assessed by using estimates presented in the literature and by performing estimations based on questionnaire data of the patient's type of residence (assisted at home, a nursing home, or a hospital) and continuance of the treatment (e.g. physical and speech therapy) and on detailed healthcare cost data from publications of the National Research and Development Centre for Welfare and Health. We calculated the approximations of the costs during study time. Furthermore, we made estimations for the future costs based on these same data. Finally, we included the approximated costs of the eventual non-survivors.

In the QALY calculations, we aimed to be as precise as possible. We calculated the reduction of HRQoL by age using the values of the standard population.The effect of the specific diagnosis on life expectancy was also taken into account. We performed a literature search for the most valid approximations and reduced the life expectancy accordingly.

Acknowledging these limitations, this study succeeded in showing that despite a poor prognosis, the treatment was justified and many patients experienced better

recovery than anticipated and, the treatment in the step-down unit has been developed further based on these findings.

DC AFTER SAH STUDY

As discussed previously, the status of DC has been controversial in the literature as long as it has been utilized. Before our study, there were no cost-effectiveness evaluations of DC of any underlying etiology. Our aim was to perform the first cost-effectiveness study on DC patients. This study focused on patients whose DC was performed in non-traumatic rise of ICP. DC has been relatively rarely used on SAH patients and literature on the topic is very limited, but the outcome is presumed to be poor.

The most obvious limitation in the DC after SAH study is the lack of any non-operative treatment group with which to compare the results. However, as discussed previously, conservative treatment would be hard to justify, knowing that DC often normalizes increased ICP in the acute phase, though the long-term effects are controversial.

The main challenge in this study was analyzing and interpreting the results because the underlying etiology leading to the DC was so heterogeneous, causing also large variation in the results. The study group had to be divided into two groups (SAH and other neurological emergencies), which further reduced the number of patients in the groups. The results of the SAH group were similar to previous results in the literature, but the other group lacked comparable references because of the rarity of the illnesses. Therefore, as the indications for DC in various situations were not established, the results cannot necessarily be generalized to cover different clinical situations.

There were no common and specific indications or contraindications in SAH or other neurological emergencies for performing DC. Our assumption was that DC was the last possible intervention when all other means had failed. The clinical condition of the patients before DC was poor; all were comatose, in respirators, ICP extremely high (over 35 mmHg), and many had either fixed, dilated pupils or herniation in the CT scan. There were no contraindications for DC other than death. From this point of view, the results could be considered quite acceptable. In the QALY calculations, we did not calculate QALYs before the illness because we assumed that life expectancy without treatment would be equal to zero, resulting in QALY before the illness being zero. Considering the poor condition of the patients before DC, this assumption seems to be justified.

Despite the limitations, the study implicated that patients with intractable ICP due to various underlying etiologies (other than SAH) may benefit from DC, as they seemed to recover fairly well. The HRQoL index for SAH patients was poor, only 0.15, and only one of the 11 SAH survivors had returned to work. On the other hand, 8 of the 11 were able to live at home. Then again, considering the fact that without the treatment they would most likely die, their outcome can be considered at least reasonable. The cost of neurosurgical treatment for one QALY was 11,000€ for SAH and 2,000€ for other emergencies. DC after other indications seems to be justified and cost-effective, but the use of DC for SAH patients should be predisposed for further evaluation. DC should be performed only after careful consideration, since there was no convincing evidence of its benefits.

DC AFTER TBI STUDY

Although there are studies on DC performed after TBI, no consensus exists of its benefits, and the economic aspects of the procedure have not been studied. We aimed to demonstrate that DC is a cost-effective procedure and its use is well grounded for vital indications.

As previously in the DC after SAH study, also in this study the most obvious limitation was the lack of any non-operative treatment group with which to compare the results. There are no randomized control trials on hemicraniectomy, and such studies will probably not appear until a major step forward is taken in conservative treatment. One subject of discussion was the indications and contraindications for DC. So called “prophylactic” DC was not performed in our study group. Each patient who underwent DC was considered to be fatally ill and therefore we presumed that DC was performed for vital indications. Before DC, patients had either ICP over 35, dilated pupils or brainstem herniation seen in a CT scan. The contraindication raised questions as well because we were not able to give exact boundaries or values for exclusion since there were none. Anyone who was expected to survive through the surgery received DC, except patients with a brainstem hematoma.

In the cost analysis, our goal was to create a more accurate approximation of total costs. We gathered information from patients and medical records about treatment after the acute treatment period, evaluated all the treatment costs of deceased, and we also estimated the future costs based on the information of the continuance of treatment.

This study indicated that DC is a beneficial procedure for TBI patients and the recovery of the patients was surprisingly good. The treatment was estimated to be both clinically justified and cost-effective, and therefore the use of DC could be recommended for treating similar patients.

SAH STUDY

The purpose was to perform a long-term outcome evaluation of SAH patients. Many studies focus on the outcome at 6-12 months after SAH, but we performed an evaluation of the outcome approximately 10 years after treatment. The cost-effectiveness of the treatments was also evaluated.

The most obvious limitation of the SAH study is the cost evaluation. The direct neurosurgical costs were collected from the actual hospital cost database and may therefore be considered reliable. However, most of the patients were transferred to other hospitals for further care and rehabilitation, and the exact cost data from these facilities were not available. The total costs were evaluated by estimations found in the literature. The recovery of the study patients was amazingly good and therefore the total costs are not expected to exceed these evaluations. Another issue for speculation was whether the good outcome was due to the strict inclusion criteria. The study group was originally recruited to study the effect of anticoagulant drugs on SAH patients, and therefore the exclusion criteria mainly concerned the drug administration. However, the case fatality of our patients was relatively high, suggesting that it represents well the hospital-based SAH population.

Acknowledging the shortcomings of the analysis, this study still managed to confirm the good recovery of the patients. After a ten-year follow-up, 75% of the survivors had a good outcome as evaluated on the GOS scale. Another measure of well-being is the ability to return to work. Of our survived patients, 63% returned to work after SAH, and at 10 years into the follow-up, 36% were still working and 27% had retired because of age. Only 24% reported that they do not work because of SAH. The EQ-5D index and the VAS value were similar or even better than the reference population's values. Reasons for this can be only speculated; it could be that after a serious illness, patients have a healthier life style, better control of chronic illnesses, or the evaluation and appreciation of one's health status may change after being seriously ill.

We found the treatment to be cost-effective, and this study may be encouraging for SAH patients and their next-of-kin, giving hope that the original survivors may have a good recovery.

CONCLUSIONS

The rising medical costs and the growing at-risk population will lead to increasing competition for health care resources. While competing for resources, different branches of medicine are forced to demonstrate the benefits of their treatments. The treatment of the most severely ill neurosurgical patients is highly resource-demanding and is therefore a potential target of doubts regarding whether the treatment of these patients is cost-effective or even clinically justified.

We have studied a total of 620 severely ill neurosurgical patients treated in the Helsinki Department of Neurosurgery between 1998 and 2006. We found the treatment of the severely ill neurosurgical patients to be cost-effective, which resulted in health-related quality of life that varied from acceptable to good when compared to the reference population. We found no evidence of unnecessary prolongation of human suffering when death was inevitable. The worst state of health-related quality of life did not occur among the survivors. However, the status of DC in the treatment of SAH patients should be subjected for further evaluation.

In summary, the current healthcare resources are utilized cost-effectively to achieve life that is meaningful. Allocation of healthcare resources to severely ill neurosurgical patients seems to be justified.

ACKNOWLEDGEMENTS

The present study was carried out at the Department of Neurosurgery of the Hospital District of Helsinki and Uusimaa during the years 2006-2013.

First, I would like to thank Professor of Neurosurgery and Chairman Juha Hernesniemi for giving the original idea for this research and for allowing me to conduct this research in the Helsinki Department of Neurosurgery.

I would like to express my sincere gratitude to my supervisor Docent Jari Siironen for his advice, guidance, and encouragement throughout this work. I would not have completed this work successfully without his incessant support and motivation. I also wish to thank Professor Juha Hernesniemi for his support as a thesis supervisor.

I would also like to extend my appreciation to all my co-authors: Docent Seppo Juvela, Professor Juha Öhman, MD, PhD Riku Kivisaari, M.Sc. Ritva Salmenperä, Docent Risto Roine, and MD, PhD Jaakko Lappalainen. In particular, I would like to address my gratitude to Seppo Juvela for his guidance in writing the final study of this thesis.

The reviewers of this thesis, Docent Antti Malmivaara and Docent Esa Heikkinen, are gratefully acknowledged for the valuable comments.

I am thankful for Docent Mika Niemelä and Docent Timo Koivisto for participating in the thesis committee. I thank MD, PhD Jussi Antinheimo, MD Hanna Lehto, and MD, PhD Johanna Kuhmonen for their help in the early phases of this project.

I want to express my gratitude to everyone who supported me during this project. I am thankful for the staff and patients of the Helsinki Department of Neurosurgery. In particular I wish to acknowledge Virpi Hakala for valuable help in practical matters.

Tremendous gratitude belongs to my mother Tellervo Honkavaara for taking care of everything while I was busy doing this research and to my father Seppo Koistinen.

Finally, my warmest thanks belong to my family; my husband, my soul (and sail) mate Mikko and my children, the best crew ever, Jerry and Erika.

The research was supported by the Maire Taponen Foundation, a research grant from Päijät-Häme Central hospital and The National Graduate School of Clinical Investigation.

REFERENCES

Aalto A-M, Aro S, Aro AR, Mähönen M. "RAND 36-item health survey 1.0". Suomenkielinen versio terveyteen liityvän elämänlaadun kyselystä. STAKES, Aiheita-sarja 2/1995.

Adamo MA, Deshaies EM. Emergency decompressive craniectomy for fulminating infectious encephalitis. *Journal of Neurosurgery* 2008;**108**:174-176.

Agrawal D, Hussain N. Decompressive craniectomy in cerebral toxoplasmosis. *European Journal of Clinical Microbiology and Infectious Diseases* 2005; **24**: 772–773.

Ahmed AI, Eynon CA, Kinton L, Nicoll JA, Belli A. Decompressive craniectomy for acute disseminated encephalomyelitis. *Neurocritical Care* 2010;**13**:393-395.

Al-Khindi T, Macdonald RL, Schweizer TA. Cognitive and functional outcome after aneurysmal subarachnoid haemorrhage. *Stroke* 2010;**41**:519-536.

Angus DC, Carlet J (2003) Surviving intensive care: a report from the 2002 Brussels Roundtable. Expert Panel 2003;**29(3)**:368–377.

Appelboom G, Zoller SD, Piazza MA, Szpalski C, Bruce SS, McDowell MM, Vaughan KA, Zacharia BE, Hickman Z, D'Ambrosio A, Feldstein NA, Anderson RC. Traumatic brain injury in pediatric patients: evidence for the effectiveness of decompressive surgery. *Neurosurgery Focus* 2011;**31**:E5.

Arac A, Blanchard V, Lee M, Steinberg GK: Assesment of outcome following decompressive craniectomy for malignant middle cerebral artery infarction in patients older than 60 years of age. *Neurosurgical Focus* 2009;**26(6)**:E3.

Bardach NS, Olson SJ, Elkins JS, Smith WS, Lawton MT, Johnston SC. Regionalization of treatment for subarachnoid hemorrhage: a cost-utility analysis. *Circulation* 2004;**109**:2207-2212.

Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, Rosenwasser RH. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 2000;**40**:994-1025.

Bor AS, Koffijberg H, Wermer MJ, Rinkel GJ. Optimal screening strategy for familial intracranial aneurysms: a cost-effectiveness analysis. *Neurology* 2010;**74**:1671-1679.

Bosanquet N, Rawlins M. The HSJ debate. Quality-adjusted life years are too rigid a yardstick for the NHS. *Health Services J* 2005;**115**:20-21.

Brooks R. EuroQol: The current state of play. *Health Policy* 1996;**37**:53-72.

Brown RD Jr, Piepgras DG. Screening for intracranial aneurysms after subarachnoid hemorrhage: do our patients benefit? *Neurology* 2004. 10;**62**:354-356.

Committee on Comparative Effectiveness Research Prioritization, Institute of Medicine: Initial National Priorities for Comparative Effectiveness Research. Washington, DC: National Academies Press, 2009.

Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, Kossmann T, Ponsford J, Seppelt I, Reilly P, Wolfe R; DECRA Trial Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. *New England Journal of Medicine* 2011;**364**:1493-1502.

Cotton BA, Kao LS, Kozar R, Holcomb JB. Cost-utility analysis of levetiracetam and phenytoin for posttraumatic seizure prophylaxis. *Journal of Trauma* 2011;**71**:375-9.

Cunningham SJ. An introduction to economic evaluation of health care. *Journal of Orthodontics* 2001;**28**:246-50.

Daboussi A, Minville V, Leclerc-Foucras S, et al. Cerebral hemodynamic changes in severe head injury patients undergoing decompressive craniectomy. *Journal of Neurosurgery and Anesthesiology* 2009; **21**: 339–345.

D'Ambrosio AL, Sughrue ME, Yorgason JG, Mocco JD, Kreiter KT, Mayer SA, McKhann GM 2nd, Connolly ES Jr. Decompressive hemicraniectomy for poor-grade aneurysmal subarachnoid hemorrhage patients with associated intracerebral hemorrhage: clinical outcome and quality of life assessment. *Neurosurgery* 2005;**56**:12-19.

Danish SF, Barone D, Bradley P.A-C, Lega BL, Stein SC. Quality of life after hemicraniectomy for traumatic brain injury in adults. *Neurosurgical Focus* 2009;**26(6)**:E2.

Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Critical Care Medicine* 2001;**29**:635-640.

Dixon S, Poole CD, Odeyemi I, Retsa P, Chambers C, Currie CJ. Deriving health state utilities for the numerical pain rating scale. *Health Quality Life Outcomes* 2011;**9**:96.

Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic Evaluation of Health Care Programmes*, 3rd edn. New York: Oxford University Press Inc., 2005.

Dunham CM, Carter KJ, Castro F, Erickson B. Impact of cervical spine management brain injury on functional survival outcomes in comatose, blunt trauma patients with extremity movement and negative cervical spine CT: application of the Monte Carlo simulation. *Journal of Neurotrauma* 2011;**28(6)**:1009-1019.

Feeny, David H., George W. Torrance, and William J. Furlong, "Health Utilities Index," Chapter 26 In Bert Spilker, ed. *Quality of Life and Pharmacoeconomics in Clinical Trials*. 2nd ed. Philadelphia: Lippincott-Raven Press, 1996, pp 239-252.

Ferro JM, Crassard I, Coutinho JM, Canhão P, Barinagarrementeria F, Cucchiara B, Derex L, Lichy C, Masjuan J, Massaro A, Matamala G, Poli S, Saadatnia M, Stolz E, Viana-Baptista M, Stam J, Bousser MG; Second International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT 2) Investigators. Decompressive surgery in cerebrovenous thrombosis: a multicenter registry and a systematic review of individual patient data. *Stroke* 2011;**42**:2825-31.

Fetter RB, Shin Y, Freeman JL, Averill RF, Thompson JD. Case mix definition by diagnosis related groups. *Medical Care* 1980;**18**(2):1–53.

Gaetani P, Rodriguez y Baena R, Klersy C, Adinolfi D, Infuso L. A cost-effectiveness analysis on different surgical strategies for intracranial aneurysms. *Journal of Neurosurg Science* 1998;**42**:69-78.

Gafni A. Economic Evaluation of Health-care Programmes: Is CEA Better than CBA? *Environmental & Resource Economics* 2006;**34**:407-418.

Galvagno SM Jr, Thomas S, Stephens C, Haut ER, Hirshon JM, Floccare D, Pronovost P. Helicopter emergency medical services for adults with major trauma. *Cochrane Database Systemic Reviews* 2013;**28**;**3**:CD009228.

Ghajar J. Traumatic brain injury. *Lancet* 2000;**356**:923-9.

Gold MR, Siegel JE, Russel LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.

Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. *Annual Review of Public Healt* 2002;**23**:115-34.

Graves N, Walker D, Raine R, Hutchings A, Roberts JA. Cost data for individual patients included in clinical studies: no amount of statistical analysis can compensate for inadequate costing methods. *Health Economics* 2002;**11**:735-9.

Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. *Expert Review of Pharmacoeconomics & Outcomes Research* 2008;**8**:165-78.

Guerra WK, Gaab MR, Dietz H, Mueller JU, Piek J, Fritsch MJ. Surgical decompression for traumatic brain swelling: indications and results. *Journal of Neurosurgery* 1999;**90**:187-96.

Gyrd-Hansen D. Willingness to pay for a QALY. *Health Economics* 2003;**12**:1049–1060.

Haagsma JA, van Beeck EF, Polinder S, Hoeymans N, Mulder S, Bonsel GJ. Novel empirical disability weights to assess the burden of non-fatal injury. *Injury Prevention* 2008 Feb;**14**:5-10.

Hackett ML, Anderson CS. Health outcomes 1 year after subarachnoid hemorrhage: An international population-based study. The Australian Cooperative Research on Subarachnoid Hemorrhage Study Group. *Neurology* 2000;**55**:658-662.

Hammitt J. QALYs versus WTP. *Risk Analysis* 2002;**22**:985-1001.

Harrison-Felix CL, Whiteneck GG, Jha A, DeVivo MJ, Hammond FM, Hart DM. Mortality over four decades after traumatic brain injury rehabilitation: a retrospective cohort study. *Archives of Physycal Medicine and Rehabilitation* 2009;**90**:1506-1513.

Hirsky P. QALY: an ethical issue that dare not speak its name. *Nursing Ethics* 2007;**14**:72-82.

Ho KM, Honeybul S, Lind CR, Gillett GR, Litton E. Cost-effectiveness of decompressive craniectomy as a lifesaving rescue procedure for patients with severe traumatic brain injury. *Journal of Trauma* 2011;**71**:1637-1644.

Hofmeijer J, van der Worp HB, Kappelle LJ, Eshuis S, Algra A, Greving JP. Cost-Effectiveness of Surgical Decompression for Space-Occupying Hemispheric Infarction. Stroke 2013; Aug 13. [Epub ahead of print]

Holmes MW, Goodacre S, Stevenson MD, Pandor A, Pickering A. The cost-effectiveness of diagnostic management strategies for adults with minor head injury. *Injury* 2012;**43**:1423-1431.

Honeybul S, Gillett G, Ho K, Lind C. Ethical considerations for performing decompressive craniectomy as a life-saving intervention for severe traumatic brain injury. *Journal of Medical Ethics* 2012;**38**:657-661.

Howard JL, Cipolle MD, Anderson M et al. Outcome after decompressive craniectomy for the treatment of severe traumatic brain injury. *Journal of Trauma* 2008;**65**:380-385.

Hujanen T, Kapiainen S, Tuominen U, Pekurinen M. Terveydenhuollon yksikkökustannukset Suomessa vuonna 2006, Stakes 2008, Helsinki 2008.

Hunt SM, McEwan J. The development of a subjective health indicator. *Sociology of Health and Illness* 1980;**2**:231-246.

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013;16:231-250.

Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMC Medicine 2013;11:80

Hutchinson P, Timofeev I, Kirkpatrick P. Surgery for brain edema. *Neurosurgical Focus* 2007;**22**:E14.

Hutchinson PJ, Timofeev I, Kolias AG, Corteen EA, Czosnyka M, Menon DK, Pickard JD, Kirkpatrick PJ. Decompressive craniectomy for traumatic brain injury: the jury is still out. *British Journal of Neurosurgery* 2011;**25**:441-442.

Hütter BO, Kreitschmann-Andermahr I, Gilsbach JM. Health-related quality of life after aneurysmal subarachnoid haemorrhage: impacts of bleeding severity, computerized tomography findings, surgery, vasospasm, and neurological grade. *Journal of Neurosurgery* 2000;**94**:241-251.

Jethwa PR, Punia V, Patel TD, Duffis EJ, Gandhi CD, Prestigiacomo CJ. Cost-effectiveness of digital subtraction angiography in the setting of computed tomographic angiography negative subarachnoid hemorrhage. *Neurosurgery* 2013;**72**:511-9.

Johnston SC, Gress DR, Kahn JG. Which unruptured cerebral aneurysms should be treated? A cost-utility analysis. *Neurology* 1999;**52**:1806-1815.

Kakar V, Nagaria J, John Kirkpatrick P. The current status of decompressive craniectomy. *British Journal of Neurosurgery* 2009;**23**:147-157.

Kallmes DF, Kallmes MH. Cost-effectiveness of angiography performed during surgery for ruptured intracranial aneurysms. *American Journal of Neuroradiology* 1997;**18**:1453-62.

Kaplan RM, Bush JW. Health-related quality of life measurement for evaluation research and policy analysis. *Health Psychology* 1982;**1**:61–80.

King JT Jr, Glick HA, Mason TJ, Flamm ES. Elective surgery for asymptomatic, unruptured, intracranial aneurysms: a cost-effectiveness analysis. *Journal of Neurosurgery* 1995;**83**:403-412.

King JT Jr, Ratcheson RA. Cost and outcomes analysis. *Neurosurgery Clinics of North American* 1998;**9**:629-640.

Koffijberg H, Buskens E, Rinkel GJ. Aneurysm occlusion in elderly patients with aneurysmal subarachnoid haemorrhage: a cost-utility analysis. *Journal of Neurology Neurosurgery and Psychiatry* 2011;**82**:718-727.

Kolias AG, Kirkpatrick PJ, Hutchinson PJ. Decompressive craniectomy: past, present and future. Nature Reviews in Neurolology 2013;9:405-415.

Korja M, Silventoinen K, Laatikainen T, Jousilahti P, Salomaa V, Kaprio J. Cause-specific mortality of 1-year survivors of subarachnoid hemorrhage. *Neurology* 2013;**80**:481-486.

Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? *Canadian Medical Association Journal* 1992;**146**:473–481.

Leach MJ, Gall SL, Dewey HM, Macdonell RA, Thrift AG. Factors associated with quality of life in 7-year survivors of stroke. *Journal of Neurology Neurosurgery Psychiatry* 2011;**82**:1365-1371.

Lemcke J, Ahmadi S, Meier U. Outcome of patients with severe head injury after decompressive craniectomy. *Acta Neurochirurgica Supplement* 2010;**106**:231-233.

Levi M, Ariani F, Baldasseroni A. Comparison between two different Disability Weights calculations: the case of occupational injuries. *Epidemiologic Prevention* 2011;**35**:307-314.

Linde L, Sørensen J, Ostergaard M, Hørslev-Petersen K, Hetland ML. Health-related quality of life: validity, reliability, and responsiveness of SF-36, 15D, EQ-5D [corrected] RAQoL, and HAQ in patients with rheumatoid arthritis. *Journal of Rheumatology* 2008;**35**:1528-1537.

Maas AI, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. *Journal of Neurotrauma* 2012;**29**:32–46.

Macran S, Kind P: "Death" and the valuation of health-related quality of life. *Medical Care* 2001, **39:**212-227.

Marko NF, Weil RJ: An introduction to comparative effectiveness research. *Neurosurgery* 2012;**70**:425–434.

Meier U, Zeilinger FS, Henzka O. The use of decompressive craniectomy for the management of severe head injuries. *Acta Neurochirurgica Supplement* 2000;**76**:475-478.

Meyer B, Ringel F, Winter Y, et al. Health-related quality of life in patients with subarachnoid haemorrhage. *Cerebrovascular Disease* 2010;**30**:423-431.

Mirski MA, Chang CW, Cowan R. Impact of a neuroscience intensive care unit on neurosurgical patient outcomes and cost of care: evidence-based support for an intensivist-directed specialty ICU model of care. *Journal of Neurosurgical Anesthesiology* 2001;**13**:83-92.

Morgalla MH, Will BE, Roser F, Tatagiba M. Do long-term results justify decompressive craniectomy after severe traumatic brain injury? *Journal of Neurosurgery* 2008;**109**:685-690.

Murphy B, Herrman H, Hawthorne G, Pinzone T, Evert H (2000). Australian WHOQoL instruments: User's manual and interpretation guide. Australian WHOQoL Field Study Centre, Melbourne, Australia.

Nanchahal K, Power T, Holdsworth E, et al. A pragmatic randomised controlled trial in primary care of the Camden Weight Loss (CAMWEL) programme. *BMJ Open* 2012;**2**:e000793

Newby D, Hill S. Use of pharmacoeconomics in prescribing research. Part 2: cost-minimization analysis--when are two therapies equal? *Journal Clinical Pharmacy and Therapeutics* 2003;**28**:145-50.

Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurology* 2009;**8**:635-42.

Nilsson P, Larsson EM , Kahlon B, Nordström C-H, Norrving B. Tumefactive demyelinating disease treated with decompressive craniectomy. *European Journal of Neurology* 2009;16:639–642.

Norum J, Ramsvik A, Tjeldnes K. Brain damage treated with non-proven intensive training 2003-2011: a Norwegian cost analysis. *Global Journal of Health Science* 2012;**4**:179-84.

Ohinmaa A, Eija H, Sintonen H. Modelling EuroQol values of Finnish adult population. In: Badia X, Herdman M, Segura A, editors. EuroQol Plenary Meeting Barcelona 1995. Discussion Papers. Institut Universitari de Salut Publica de Catalunya, 1996; 67-76.

Olesen J, Leonardi M. The burden of brain diseases in Europe. *European Journal of Neurology* 2003;**10**:471-477.

Parkin D, Devlin N. Is there a case for using visual analogue scale valuations in cost-utility analysis? *Health Economics* 2006;**15**:653-664.

Pérez-Bovet J, Garcia-Armengol R, Buxó-Pujolràs M, Lorite-Díaz N, Narváez-Martínez Y, Caro-Cardera JL, Rimbau-Muñoz J, Joly-Torta MC, Castellví-Joan M, Martín-Ferrer S. Decompressive craniectomy for encephalitis with brain herniation: case report and review of the literature. *Acta Neurochirurgica* 2012; **154**:1717-1724.

Pompucci A, De Bonis P, Pettorini B, Petrella G, Di Chirico A, Anile C. Decompressive craniectomy for traumatic brain injury: patient age and outcome. *Journal of Neurotrauma* 2007;**24**:1182-1188.

Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ* 2004;**329**:224-227.

Richardson Jeff. Cost Utility Analysis: *What Should be Measured; Utility, Value or Healthy Year Equivalents?* Second World Congress on Health Economics University of Zurich, Switzerland 1990.

Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J. General health status measures for people with cognitive impairment: learning disability and acquired brain injury. *Health Technology Assessment* 2001;**5**:1-100.

Rivero-Arias O, Gray A, Wolstenholme J. Burden of disease and costs of aneurysmal subarachnoid haemorrhage (aSAH) in the United Kingdom. *Cost Effectiveness and Resource Allocation* 2010;**27**:6.

Ronne-Engström E, Enblad P, Lundström E. Outcome after spontaneous subarachnoid haemorrhage measured with the EQ-5D. *Stroke* 2011;**42**:3284-3286.

Rosengart AJ, Schultheiss KE, Tolentino J, Macdonald RL. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2007;**38**:2315-21.

Ryynänen OP, Iirola T, Reitala J, Pälve H, Malmivaara A. Is advanced life support better than basic life support in prehospital care? A systematic review. *Scandinavian Journal of Trauma Resuscitation and Emergency Medicine* 2010;**18**:62.

Sahuquillo J, Arikan F. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. *Cochrane Database of Systematic Reviews* 2006;**1**:CD003983.

Sanelli PC, Gold RL, Greenberg ED, Reichman MB, Ugorec I, Segal AZ, Fink M. Work-in-progress toward incorporating patients' preferences in practice guidelines for imaging aneurysmal subarachnoid hemorrhage. *Academic Radiology* 2009;**16**:535-40.

Sassi F. Calculating QALYs, comparing QALY and DALY calculations. *Health Policy and Planning* 2006;**21**:402-8.

Schirmer CM, Hoit DA, Malek AM: Decompressive hemicraniectomy for the treatment of intractable intracranial hypertension after aneurysmal subarachnoid hemorrhage. *Stroke* 2007;**38**:987–992.

Siironen J, Juvela S, Varis J, et al. No effect of enoxaparin on outcome of aneurysmal subarachnoid haemorrhage: a randomized, double-blind, placebo-controlled clinical trial. *Journal of Neurosurgery* 2003;**99**:953-959.

Sintonen H, Pekurinen M. Uses of 15D-measure of health-related quality of life. In Health systems - the challenge of change. Proceedings of the 5th International Conference on System Science in Health Care. Prague June 29-July 3, 1992. Chytil MK, Duru G, van Eimeren W, Flagle CD (eds). Omnipress, Prague 1992, 1071-1074.

Sintonen H. An approach to measuring and valuing health states. *Social Science Medicine* 1981;**15C**: 55-65.

Stein SC, Burnett MG, Glick HA. Indications for CT scanning in mild traumatic brain injury: A cost-effectiveness study. *Journal of Trauma* 2006;**61**:558-566.

Stein SC, M.D. Comparative Effectiveness in Neurosurgery: What It Means, How It Is Measured, and Why It Matter. *Neurosurgical Focus* 2012;**33**:e1

Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European stroke organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovascular Disease* 2013;**35**:93-112.

Stevens A, Doyle N, Littlejohns P, Docherty M. National Institute for Health and Clinical Excellence appraisal and ageism. *Journal of Medical Ethics* 2012;**38**:258-262.

Suarez JI, Tarr RW, Selman WR. Aneurysmal subarachnoid hemorrhage. *New England Journal of Medicine* 2006;**354**:387-96.

Tagliaferri F, Zani G, Iaccarino C, Ferro S, Ridolfi L, Basaglia N, Hutchinson P, Servadei F. Decompressive craniectomies, facts and fiction: a retrospective analysis of 526 cases. *Acta Neurochirurgia* 2012;**154**:919-26.

Takao H, Nojo T, Ohtomo K. Screening for familial intracranial aneurysms: decision and cost-effectiveness analysis. *Academic Radiology* 2008;**15**:462-471.

Takao H, Nojo T, Ohtomo K. Treatment of ruptured intracranial aneurysms: a decision analysis. *British Journal of Radiology* 2008;**81**:299-303.

Tilford JM, Aitken ME, Goodman AC, Adelson PD. Measuring the cost-effectiveness of technologic change in the treatment of pediatric traumatic brain injury. *Journal of Trauma* 2007;**63**:S113-S120.

Tilford JM, Aitken ME, Goodman AC, Fiser DH, Killingsworth JB, Green JW, Adelson PD. Child health-related quality of life following neurocritical care for traumatic brain injury: an analysis of preference-weighted outcomes. *Neurocritical Care* 2007;**7**:64-75.

Timofeev I, Czosnyka M, Nortje J et al. Effect of decompressive craniectomy on intracranial pressure and cerebrospinal compensation following traumatic brain injury. *Journal of Neurosurgery* 2008;**108**:66-73.

Tolias CM, Choksey MS. Will increased awareness among physicians of the significance of sudden agonizing headache affect the outcome of subarachnoid hemorrhage? Coventry and Warwickshire Study: audit of subarachnoid hemorrhage (establishing historical controls), hypothesis, campaign layout, and cost estimation. *Stroke* 1996;**27**:807-812.

Torres R. DECRA…Where do we go from here? *Surgical Neurology International* 2012;**3**:54.

Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink G-J, Schmiedeck P, Schwab S, Rothwell PM, BousserM-G, van der Worp, HB Hacke W, DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurology* 2007;**6**:215-22.

Vainiola T, Pettilä V, Roine RP, Räsänen P, Rissanen AM, Sintonen H. Comparison of two utility instruments, the EQ-5D and the 15D, in the critical care setting. *Intensive Care Medicine* 2010;**36**:2090-2093.

Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: review of randomized controlled trials and meta-analyses in the literature. *World of Neurosurgery* 2011;**76**:446-54.

von Steinbuechel N, Richter S, Morawetz C, Riemsma R. Assessment of subjective health and health-related quality of life in persons with acquired or degenerative brain injury. *Current Opinion of Neurology* 2005;**18**:681-691.

Ward MJ, Bonomo JB, Adeoye O, Raja AS, Pines JM. Cost-effectiveness of diagnostic strategies for evaluation of suspected subarachnoid hemorrhage in the emergency department. *Academic Emergancy Medicine* 2012;**19**:1134-44.

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;**30**:473-83.

Weinstein MC, Torrance G, McGuire A. QALYs: the basics. *Value in Health* 2009;**12**:S5-9.

Wermer MJ, Buskens E, van der Schaaf IC, Bossuyt PM, Rinkel GJ. Yield of screening for new aneurysms after treatment for subarachnoid hemorrhage. *Neurology* 2004;**62**:369-375.

Wermer MJ, Koffijberg H, van der Schaaf IC; ASTRA Study Group. Effectiveness and costs of screening for aneurysms every 5 years after subarachnoid hemorrhage. *Neurology* 2007;**70**:2053-2062.

Whitfield PC, Kirkpatrick P. Timing of surgery for aneurysmal subarachnoid haemorrhage. *Cochrane Database of Systematic Reviews* 2001, Issue 2. Art. No.: CD001697.

Whitmore RG, Thawani JP, Grady MS, Levine JM, Sanborn MR, Stein SC. Is aggressive treatment of traumatic brain injury cost-effective? J *Neurosurgery* 2012;**116**:1106-13.

Williams A. QALYS and ethics: a health economist's perspective. *Social Science Medicine* 1996;**43**:1795-1804.

Wong GK, Poon WS, Boet R, et al. Health-related quality of life after aneurysmal subarachnoid haemorrhage: profile and clinical factors. *Neurosurgery* 2011;**68**:1556-1561.

Zubair Tahir M, Enam SA, Pervez Ali R, Bhatti A, ul Haq T. Cost-effectiveness of clipping vs coiling of intracranial aneurysms after subarachnoid haemorrhage in a developing country--a prospective study. *Surgical Neurology* 2009;**72**:355-360.

Zusman EE. Comparative effectiveness research: is it progress? *Neurosurgery* 2010; **67**:N21.

WEBSITES:

Center for the Evaluation of Value and Risk in Health (CEVR), Tufts-New England Medical Center, Institute for Clinical Research and Health Policy Studies: www.cearegistry.org.
(https://research.tufts-nemc.org/cear4/AboutUs/WhatistheCEARegistry.aspx)

Käypä hoito-suositus, aivovammat:
http://www.kaypahoito.fi/web/kh/suositukset/naytaartikkeli/tunnus/hoi18020