FORSCHUNGSBERICHTE DER ABTEILUNG MEDIZINISCHE BIOMETRIE, UNIVERSITÄT HEIDELBERG

Nr. 58

Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY)

Mai 2008

INSTITUT FÜR MEDIZINISCHE BIOMETRIE UND INFORMATIK

RUPRECHT-KARLS-UNIVERSITÄT HEIDELBERG

Forschungsberichte der
Abteilung Medizinische Biometrie, Universität Heidelberg

Nr. 58

Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY)

Biometrical final report

EKKEHART JENETZKY (1), CARMEN BAUER (1), ERIC JÜTTLER (2), STEFFEN WITTE (1)

(1) Institute of Medical Biometry and Informatics (IMBI), University of Heidelberg

Further contributors:

ULRICH MANSMANN (1,3), JUDITH MUNZINGER (1), NORBERT VICTOR (1), WERNER HACKE (2)

(2) Department of Neurology, University of Heidelberg
(3) Institute of Medical Informatics, Biometry, and Epidemiology, LM University of Munich

Heidelberg, Mai 2008

Impressum:
Reihentitel: Forschungsberichte der Abteilung Medizinische Biometrie,
Universität Heidelberg
Herausgeber: Prof. Dr. Meinhard Kieser
Anschrift: Im Neuenheimer Feld 305, 69120 Heidelberg
Druck: Hausdruckerei der Ruprecht-Karls-Universität Heidelberg
Elektronischer Bezug: http://www.biometrie.uni-heidelberg.de
ISSN: 1619-5833

1 Table of contents

1 Table of contents 1
2 Table of Listings, Tables, Figures 3
3 Summary 5
4 Abbreviations and Definitions 6
5 Introduction 7
5.1 Stroke 8
5.2 Interventions 8
5.3 Aim of the Study 9
6 Methods 9
6.1 Study Protocol, Ethics, Stroke Register 9
6.2 Organisation and Investigators 9
6.3 Trial Design 10
6.3.1 Randomisation 10
6.3.2 Blinding 10
6.4 Study Populations 10
6.4.1 Inclusion Criteria 10
6.4.2 Exclusion Criteria 11
6.5 Treatments 11
6.5.1 Conventional Treatment Group 11
6.5.2 Surgical Treatment Group 11
6.5.3 Pre- and Concomittant Diseases 12
6.6 Endpoints 12
6.6.1 Primary Endpoint 12
6.6.2 Secondary Endpoints 12
6.6.3 Further Endpoints 13
6.7 Quality Control 13
6.7.1 SOPs 13
6.7.2 Clinical Monitoring 13
6.7.3 Statistical Monitoring 13
6.7.4 Audits and inspections 14

6.8 Statistical Methods 14
6.9 Changes during the trial 14
7 Results 14
7.1 Recruitment of Investigators / Centres 14
7.2 Recruitment of Patients 15
7.3 Patient Data 16
7.3.1 Status of Data Collection 16
7.3.2 Protocol Violations and Compliance 16
7.3.3 Quality of Data 16
7.4 Analysis Sets 17
7.5 Demography, Baseline Characteristics and Homogeneity 17
7.6 Efficacy 18
7.6.1 Analysis of the Primary Endpoint 18
7.6.2 Sensitivity Analyses 19
7.6.3 Analysis of Secondary Endpoints 20
7.7 Safety (Adverse Events, AE) 30
7.7.1 Overview of Adverse Events 31
7.7.2 AEs by different classifications 31
7.7.3 Serious Adverse Events (SAE) 31
8 Discussion and Conclusion 33
9 Appendix 35
9.1 Tables and Listings 35
9.2 References 88
9.3 Study Protocol 91
9.4 Case Report Form 91
9.5 Statistical Analysis Plan 91

2 Table of Listings, Tables, Figures

Listing 7-1: Reasons for death 32
Listing 9-1: Reported Adverse Events 74
Listing 9-2: Reason for death 79
Listing 9-3: Further Medical Findings 80
Listing 9-4: Comments on neurological assessment 81
Listing 9-5: Comments on progression and treatment 86
Listing 9-6: Other comments 87

Table 7-1: Analysis sets and protocol compliance 17
Table 7-2: Primary analysis and sensitivity analyses 19
Table 7-3: 1 year after randomisation (FAS) - survivors only 30
Table 7-4: Mortality by group and time 32
Table 9-1: Recruitment by time or centre (FAS) 35
Table 9-2: Recruitment by time dichotomised in subgroups (FAS) 35
Table 9-3: Analysis sets and protocol compliance 36
Table 9-4: Baseline demographics by group (FAS) 36
Table 9-5: Baseline demographics by group (PP) 38
Table 9-6: First day after randomisation (FAS) 40
Table 9-7: First day after randomisation (PP) 42
Table 9-8: Day 7 after randomisation (FAS) 44
Table 9-9: Day 7 after randomisation (PP) 45
Table 9-10: Day 30 after randomisation (FAS) 47
Table 9-11: Day 30 after randomisation (PP) 49
Table 9-12: 6 months after randomisation (FAS) 51
Table 9-13: 6 months after randomisation (PP) 53
Table 9-14: 1 year after randomisation (FAS) 55
Table 9-15: 1 year after randomisation (PP) 56
Table 9-16: Barthel by group and visit (FAS) 58
Table 9-17: Barthel by group and visit (PP) 58
Table 9-18: NIHSS by group and visit (FAS) 59
Table 9-19: NIHSS by group and visit (PP) 59

Table 9-20: mRS by group and visit (FAS) 59
Table 9-21: mRS by group and visit (PP) 60
Table 9-22: Analyses of the primary endpoint (6-months) 60
Table 9-23: One, six twelve months mortality by group (Chi^2 and logrank-test) (FAS) 61
Table 9-24: One, six twelve months mortality by group (Chi^2 and logrank-test) (PP) 61
Table 9-25: SF36 - 1 year after randomisation (FAS) 62
Table 9-26: SF36 - 1 year after randomisation (PP) 64
Table 9-27: Adverse Events (FAS) 66
Table 9-28: Serious Adverse Events (FAS) 68
Table 9-29: Adverse Events (PP) 69
Table 9-30: Serious Adverse Events (PP) 72

Figure 7-1: Patient recruitment over time 15
Figure 7-2: Sequential plan 21
Figure 7-3: Survival curve by treatment group 22
Figure 7-4: Boxplot of mRS over time: surgical group (grey), standard group (white) 24
Figure 7-5: mRS over time: surgical group (OP) and standard group (ICU) 25
Figure 7-6: Boxplot of Barthel over time: surgical group (grey), standard group (white) 26
Figure 7-7: Barthel and median over time: surgical group (left), standard group (right) 27
Figure 7-8: Boxplot of NIHSS over time: surgical group (grey), standard group (white) 28
Figure 7-9: NIHSS with median over time: surgical group (left), standard group (right) 29

3 Summary

Introduction: The aim of the study was to evaluate usage and prognosis of extensive decompression surgery (hemicranectomy) compared to maximum standard therapy in case of serious malignant infarction.

Methods: In this randomized, controlled, sequential, parallel, multicentre, clinical trial (ISRCTN01258591), six centres randomised 32 patients to either standard care or decompression via a surgical intervention. The primary endpoint was the dichotomised modified Rankin Scale (mRS: 0-3, 4-6) after six months. Due to ethical reasons, the stopping rule was based on the mortality after 30 days.

Results: Hence, the recruitment was stopped after 32 randomised patients. Apart from NIHSS, all baseline measures were homogeneous over the two treatment groups. The primary endpoint was in favour of the surgical intervention but the two treatment groups did not differ significantly (OR=0.4091 [0.0923, 1.8130], p_{Chi}=0.2344). Overall six months survival was better in the surgical group (p_{Chi}=0.0339). Further outcome measurements at six months were in favour of the surgical group: NIHSS: $p_{U\text{-}test}$ = 0.0447; Barthel Index: $p_{U\text{-}test}$ = 0.0759; mRS: $p_{U\text{-}test}$ = 0.0417. Sensitivity analyses of the preliminary per-protocol set, adjustment for baseline NIHSS or centre as factor as well as analyses after 12 months did not influence the result remarkably. A difference in SF-36 after 12 months could not be shown in any subscale. NIHSS, Barthel Index or mRS showed no difference in the subgroup of survivors.

Limitations: The low number of patients was not sufficient enough to show superiority regarding the primary endpoint. The per-protocol analysis excluded two cases, but no complete per-protocol definition was performed.

Conclusion: The surgical method was superior in terms of survival. Regarding mRS, a superiority could not be shown. However, there was no evidence of any difference between both methods concerning survivors. Further randomised trials are ethically questionable. The results need to be discussed together with other trials in the same setting.

4 Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse event
BMI	Body mass index = weight (kg) / squared height (m^2)
BI	Barthel Index[28]
CAC	Case adjudication committee
CCT	Cranial computer tomography
CONSORT	Consolidated Standards of Reporting Trials; http://www.consort-statement.org/
CRF	Case Report Form
CT	Computer tomography
DESTINY	Trial title: Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery; http://www.strokecenter.org/trials/TrialDetail.aspx?tid=590
DSA	Digital subtraction sonography
DSMB	Data safety and monitoring board
FAS	Full analysis set
GCS	Glasgow coma scale
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; http://www.ich.org
IMBI	Institut für Medizinische Biometrie und Informatik, Universität Heidelberg; http://www.biometrie.uni-heidelberg.de
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to treat
MedDRA	MedDRA - the Medical Dictionary for Regulatory Activities: http://www.meddramsso.com
MRA	Magnet resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale[29]; http://www.strokecenter.org/trials/scales/rankin.html
NIHSS	National Institute of Health Stroke Scale; http://www.strokecenter.org/trials/scales/nihss.html
SAE	Serious adverse event; http://www.klinikum.uni-heidelberg.de/index.php?id=3252
SAP	Statistical analysis plan
SOP	Standard operating procedures
SF-36	Quality of life questionnaire; http://www.sf-36.org
PEST	"Planning and Evaluation of Sequential Trials," a type of software of the University of Reading[27]
PP	Per protocol

5 Introduction

The treatment of life-threatening space-occupying brain edema after massive cerebral infarction remains a controversial issue within neurology and neurosurgery. Such massive hemispheric infarctions occur in 1-10% of patients with as supratentorial infarct[1]. In large intensive care-based prospective series, case fatility rate was about 70-80% [2,3,4]. Therefore, the term 'malignant middle cerebral artery infarction' was introduced for these massive cerebral infarcts[2]. Several conservative treatment strategies, such as artificial coma, hyperventilation, steroids, barbiturates, and osmotic therapy with glycerol, mannitol or hypertonic hydroxyethyl starch have been proposed to reduce the development of brain edema and intracranial pressure. So far, though, not enough evidence of efficacy from randomised clinical trials is available to support any of these therapeutic strategies. Indeed, several reports suggest that these therapies are ineffective or even detrimental[5,6,7,8,9,10]. Despite this lack of evidence, they are widely recommended and used for patients with ischemic stroke and deterioration secondary to edema formation.

Because of the limitations of medical therapies, decompressive surgery has been proposed for patients with space-occupying hemispheric infarction. The rationale of this therapy is to create space to accommodate the swollen brain, so as to normalize intracranial pressure, revert brain tissue shifts and prevent secondary tissue damage[11,12]. This technique is relatively simple and can be performed in every neurosurgical centre.

Findings in numerous case reports were supported by a number of uncontrolled, non-randomised, prospective case series suggesting a substantial benefit of hemicraniectomy on mortality from 67-88% in controls to 0-34%[13]. This effect may even be more pronounced if the treatment is started earlier, and before any signs of herniation appear[14,15]. These studies also suggest that the treatment reduces poor functional outcome (mRS 4-6, Barthel-Index (BI) 0-25, or Glasgow Outcome Scale (GCS) 1-3) from 95% in conservatively treated patients to 8-50% in surgically treated patients[2,13,14,16].

Yet, most studies referred to historical controls with patients who were significantly older, with more co-morbidity, and more often lesions of the dominant hemisphere[14,16]. In most studies, information on long-term outcome is missing. Due to the lack of conclusive evidence of efficacy, controversy over the benefit of hemicraniectomy remains, leading to large regional differences in the use of the procedure. For more than a decade there have been calls for randomised trials.

Meanwhile, five randomised trials have been designed: The *Hemicraniectomy And Durotomy Upon Deterioration From Infarction Related Swelling Trial* (HeADDFIRST) randomised 26 patients between 2000 and 2003. The final results, however, have not been published [17,18]. A study from the Philippines (*Hemicraniectomy For Malignant Middle Cerebral Artery Infarcts (HeMMI)*) and three European studies (*Hemicraniectomy After Middle cerebral artery infarction with Life-threatening Edema Trial* (HAMLET)[19] from the Netherlands, *DEcompressive Craniectomy In MALignant middle cerebral artery infarcts* (DECIMAL) [20] from France, and *DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral arterY* (DESTINY)[21] from Germany) are still ongoing or just recently finished.[22, 23]

5.1 Stroke

Stroke is a disease affecting blood vessels that supply blood to the brain. There are two main types of stroke. One is caused by blockage of a blood vessel (ischemic stroke); the other is caused by bleeding (hemorrhagic stroke).

A stroke occurs when a blood vessel that supplies the brain with oxygen and nutrients either bursts or is clogged by a blood clot or some other mass. Because of this rupture or blockage, parts of the brain do not get blood and oxygen needed. Deprived of oxygen, nerve cells in the affected area of the brain are not able to work any longer and die within minutes. And if nerve cells cannot work, the part of the body they control cannot work either. The devastating effects of a severe stroke are often permanent because dead brain cells cannot be replaced.

Each year, about 700.000 Americans experience a new or recurrent stroke. About 500.000 of these strokes are first attacks, and 200.000 are recurrent attacks. That means, on average, that a stroke occurs every 45 seconds. Stroke kills nearly 157.000 people a year, about 1 of every 15 deaths. It is the third most common cause of death, placed only behind heart diseases and cancer[24]. Ischemic stroke is the most common type. It accounts for about 88 percent of all strokes. It occurs when a blood clot (thrombus) forms and blocks the blood flow in an artery that supplies blood to the brain. If this ischemic stroke occurs for a complete hemisphere, it must be considered a serious condition.

5.2 Interventions

The investigated treatments are two neurosurgery techniques, one for removal and one for replacement of a major part of the skull bone. This procedure, called extensive decompression surgery (hemicranectomy) with duraplasty, is well known for treatment of epidural haematoma[25]. The standard therapy is specifically explained in chapter 6.5.

5.3 Aim of the Study

Aim of the study was to achieve more knowledge or even evidence regarding the advantage of the surgical decompressive treatment (hemicraniectomy) in comparison to conservative treatment of an intensive care unit regarding mortality, functional outcome and degree of remaining disability.

6 Methods

6.1 Study Protocol, Ethics, Stroke Register

The trial protocol was finalized on 31.07.2003 (see 9.3). No amendments were necessary. The trial was submitted to the ethics committees of the Universities of Greifswald, Heidelberg, Köln, Leipzig, Mannheim and Würzburg. Due to prespecification and quality control of the results, the trial was registered in the stroke register (http://www.strokecenter.org/trials/) and was also registered in the Controlled Clinical Trials Register (http://www.controlled-trials.com), receiving the identification number ISRCTN 01258591 in April 2006.

6.2 Organisation and Investigators

Organisation: In the planning phase, the steering committee consisted of all principal investigators and the members of the executive committee. Members of the executive committee were Prof. Dr. Hacke, Prof. Dr. Schmiedek, PD Dr. Schwab, PD Dr. Mansmann and Dr. Jüttler. During the trial, Prof. Dr. Stefan Schwab and Prof. Dr. Ulrich Mansmann left (both became Full Professor in the meantime). The role of the responsible biometrician was handed over to Dr. Steffen Witte with Dr. Ekkehart Jenetzky as his representative. The trial coordinator is Dr. Eric Jüttler. There were two further committees: the safety committee (Prof. Dr. Schuchardt, Prof. Dr. Bluhmki, Prof. Dr. Karimi) and the case adjudication committee (Prof. Dr. von Kummer, Prof. Dr. Busse, Prof. Dr. Kunze) were incumbent on safety issues and assuring protocol compliance.

Sponsor regarding GCP was the University Clinic of Heidelberg. Biometry and data management was done by the Institute of Medical Biometry and Informatics (IMBI) of the University of Heidelberg. In contrast to specifications in the trial protocol, the data management was performed by the IMBI (Carmen Bauer and Judith Munzinger). Monitoring was done by the Coordination Centre for Clinical Trials (KKS), Heidelberg. The trial was not financially supported by any company and no grant was given. No conflict of interest is stated.

Investigators: Investigators from six cities were involved in the trial and randomised at least one patient: Greifswald, Heidelberg, Köln, Leipzig, Mannheim and Würzburg.

6.3 Trial Design

DESTINY was a prospective, multicentre, open, randomised, clinical trial based on a sequential design (using mortality after 30 days) with a one-year follow-up and a patient related neurologic outcome (mRS) after six months as primary endpoint.

6.3.1 Randomisation

A randomisation list was compiled by a former member of the IMBI (Ulrich Mansmann), who was not involved in the treatment. It was stratified for centres with an hidden block length. In total it could have been up to 15 centres with each up to 24 patients. The neurological unit of Heidelberg received sealed envelopes and provided the 24-hour-availability for randomization. In retrospective analyses, the block size was six, but it was initially not known to any other person.

6.3.2 Blinding

Blinding of patients or investigators was not possible. Observer blinding of primary endpoint was not applied. Hence, the trial was open, not blinded.

6.4 Study Populations

The study population was defined as follows:

6.4.1 Inclusion Criteria

- age 18-60 years
- CT documented unilateral ischemic infarction of at least 2/3 of the middle cerebral artery (MCA) territory at least partly including the basal ganglia
- informed consent of the patient or the legal representative
- onset of symptoms >12 and <36 hours previous to a possible surgical intervention
- possibility to start treatment/surgery within six hours after randomization and before 36 hours after start of symptoms
- a score on the National Institutes of Health Stroke Scale (NIHSS) >18 (non-dominant hemisphere) or >20 (dominant hemisphere), respectively
- Level of Consciousness of at least 1 (loc≥1)

6.4.2 Exclusion Criteria

- pre-stroke score on the modified Rankin Scale (mRS) ≥2
- pre-stroke Barthel Index (BI) <95
- ambilateral missing pupillary reflex on light exposure.
- a score on the Glasgow Coma Scale (GCS) <6 at randomization
- secondary bleeding in the area of infarction
- coincidental other brain lesion (i.e. trauma, haemorrhage)
- life expectancy <3 years
- any other serious illness that may have confounded treatment assessment
- other contraindications for treatment

6.5 Treatments

6.5.1 Conventional Treatment Group

The control group received the usual treatment following massive cerebral infarction in an intensive care unit. Treatment recommendations were given in the protocol for following aspects:

- serum osmosis
- intubation, artificial ventilation and hyperventilation
- intra cranial pressure measurement
- sedation
- blood pressure
- positioning
- body temperature
- blood sugar homeostasis
- haemoglobin concentration
- thrombosis prophylaxis

6.5.2 Surgical Treatment Group

The experimental group received a surgery with hemicranectomy of nearly half the skull bone (diameter at least 12 cm) for decompressive treatment. Resection of dead brain substance is possible but not recommended. After a period of between six weeks and six months, this bone part was replaced. The experimental group received two cranial surgeries (removal and implantation of skull bone) with the purpose to relieve marring intracranial pressure effectively.

6.5.3 Pre- and Concomitant Diseases

According to EMEAs *Points to Consider on Clinical Investigation on Medicinal Products for the Treatment of Acute Stroke* (CPMP/EWP/560/98) [26], chapter 4.3 of the prestroke disorders of the study population should be carefully assessed. In DESTINY, this happened on a global basis through evaluation of premorbid Barthel and mRS by patient or, in case of necessity, by next of kin and investigator on study begin. Already severely handicapped patients were excluded a priori as suggested in chapter 4.2 of the "Points to Consider"[26]. But in the CRF pre- and concomittant diseases were not assessed in detail.

6.6 Endpoints

All endpoints were documented in the CRF.

6.6.1 Primary Endpoint

Dichotomised modified Rankin Scale after six months (success: 0-3; failure:4-6).

6.6.2 Secondary Endpoints

- mortality after 30 days
- mortality after six months
- mortality after twelve months
- dichotomised modified Rankin Scale on each visit (success: 0-3; failure: 4-6)
- post-hoc included: dichotomised modified Rankin Scale on each visit (success: 0-4; failure: 5-6)
- dichotomised Barthel-Index each visit (success: >80; failure ≤80)
- modified Rankin Scale on each visit
- Barthel-Index (ordinal 0-100) on each visit
- NIH Stroke Scale (ordinal 0-42) on each visit
- quality of life SF-36 (ordinal raw-scores) after12 month
- size of infarction: CT (in cm^3) on day 2-3 to 4-8
- surgical complications (yes/no) each visit:
    - anaesthetics
    - bleeding
    - wound infection
    - problems with wound healing
    - postoperative pain

- others

6.6.3 Further Endpoints

None.

6.7 Quality Control

To ensure quality of the trial, a study protocol and a statistical analysis plan were written, SOPs were used, and clinical as well as statistical monitoring were applied. As external inspection, a case adjudication committee (CAC) was planned. But this CAC did not assemble until final database freeze.

6.7.1 SOPs

The SOPs of the IMBI were used for all biometry- and data management-related activities of the trial.

6.7.2 Clinical Monitoring

The clinical monitoring has been conducted by the KKS Heidelberg according to their Standard Operation Procedures (SOPs). Final close-out-visit was performed on 20.11.2007 without open questions regarding CRF or SAE/AE. In most circumstances, source data verification was not possible, because most scales (NIH, mRS) and some visits (e.g. 4 and 5) were documented exclusively in the CRF. The visits four and five were performed exclusively by one investigator (Eric Jüttler). Further details can be read in the monitoring manual (KKS, 3.1.06, v2).
No monitoring was performed by case adjudication committee before database freeze in November 2007.
A complete monitoring of all available data was done for the 26 patients of centres in Heidelberg and Mannheim. In case of the other six patients, monitoring included only a control of completeness of CRF pages. The IMBI provided statistical monitoring via query-handling for all patients (see 6.7.3).

6.7.3 Statistical Monitoring

The trial centre in Heidelberg (IMBI) developed a validation plan. Queries were generated using SAS®. In total, 185 quality checks were programmed. The queries were sent to the monitor or directly to the study site. After the data check at the trial site, the query sheet was

sent back to the IMBI and the answers were used to modify the database. Until the end of the study, 433 queries were generated in total, but more than 300 (70%) were just missing sheets. All queries could be solved. The only incomplete data due to missing meeting of case adjudication committee are left.

6.7.4 Audits and inspections

Neither audits nor inspections were done. A cases adjudication committee should check the validity of diagnosis and treatment.

6.8 Statistical Methods

See Statistical Analysis Plan in the Appendix (chapter 9.5).

6.9 Changes during the trial

- More specified endpoints: Due to the initial study protocol, the 6-month-mortality (page 2) and the 12-month-mortality (page 12) were endpoints. We used 6-month-mortality as well as the 12-month-mortality as secondary endpoint. We also analysed for each visit mRS, NIHSS and Barthel as secondary outcome (ordinal and dichotomous if applicable).
- In this trial we refrain from performing a confirmatory second stage; and used the whole one-sided α-level (5%) for the first stage. To estimate a sample size for a possible exploratory second stage, we used α_{global}=10%, β=10% just for ad-hoc calculation purposes.
- There were four more centres which contributed six patients in total than the two major centres mentioned on page 14 in the initial study protocol.
- A real per-protocol set was not defined, only two patients were excluded (see Analysis Sets). Sizes of infarction were not measured; hence, we discarded these analyses.

7 Results

7.1 Recruitment of Investigators / Centres

In the trial protocol, two centres were mentioned (Heidelberg and Mannheim) with the aim to extend the number of centres. Finally, six centres were initiated and all six centres

(Greifswald n=2, Heidelberg n=20, Köln n=1, Leipzig n=2, Mannheim n=6, and Würzburg n=1) randomised at least one patient (Table 9-1).

7.2 Recruitment of Patients

The first patient was randomised on 17.01.2004 and the 32nd on 14.12. 2005. In each quarter, three to five patients were randomised (Table 9-1 and Figure 7-1). The recruitment of patients was slower than expected. The recruitment was interrupted (due to the criteria of the sequential testing procedure) on 05.01.2006 (sent via email to the investigators). The software PEST[27] was used for sequential analysis..

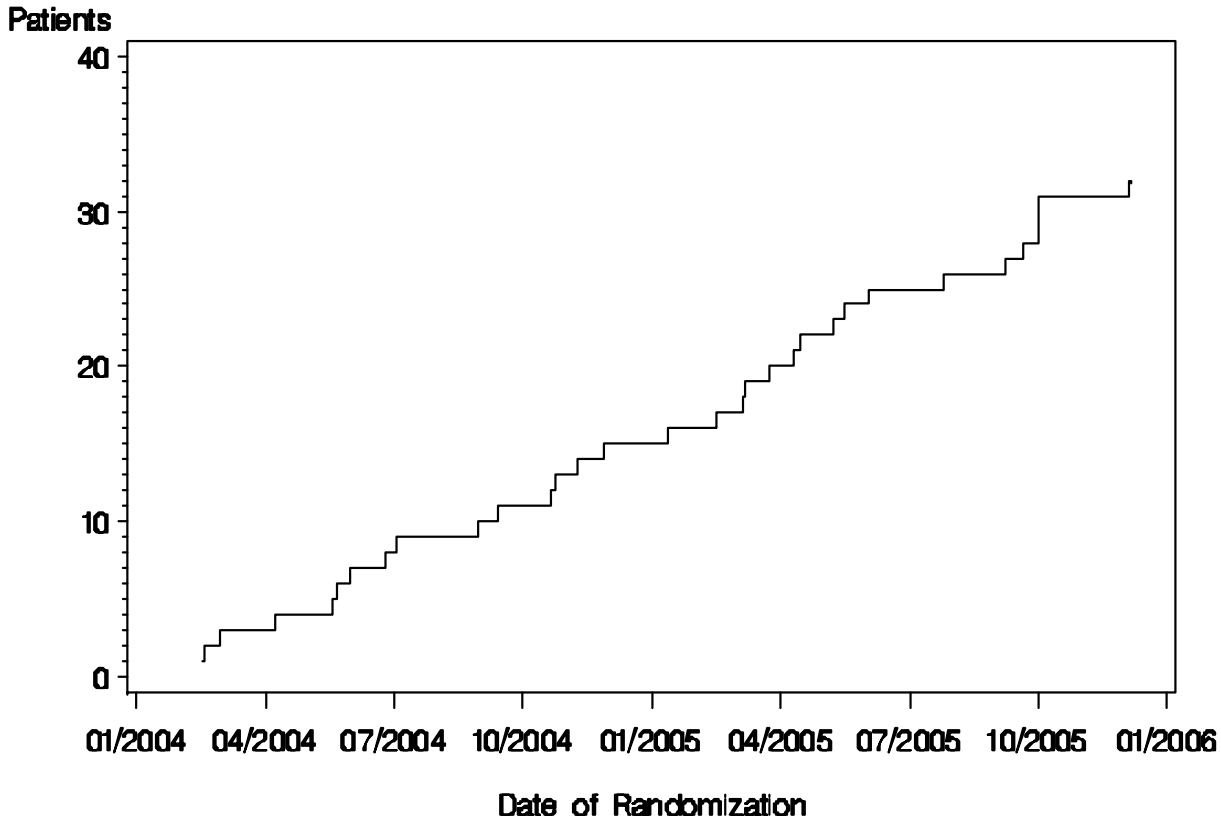

Figure 7-1: Patient recruitment over time

On 20.06.2006, a meeting of the steering committee was held to discuss whether to continue with the study (in terms of recruiting new patients) or not. The steering committee decided to stop the recruitment of the trial and to publish the six-month-data as soon as possible. Feasibility would not be achieved, a meaningful sample size for a second stage would be very large. Assuming a success rates of 7/17 (or 8/17) (surgical group) and 4/15 (conservative group), a sample size of 2x181 (or 2x94) would be needed (α=0.05, β=0.10, one-sided χ^2-test) for a new trial (Nquery®). A second stage would even demand more patients (even if that sounds paradox), but these results would only be exploratory rather than confirmatory (a

confirmatory second stage was not planned a priori, see protocol and statistical analysis plan for details).

7.3 Patient Data

7.3.1 Status of Data Collection

Thirty-two patients were randomised and were included in the analysis. The database was locked for the interim analysis on 03.08.2006, including the six-month follow-up of all patients. The decision was to wait for the complete 12-month follow up (15.12.2006) and for the meeting of the case adjudication committee and the radiologic measurement of the bleeding size. But a meeting of the case adjudication committee did not take place.. By this time the database was finally locked on 30.11.2007 without an appropriate per-protocol definition.

7.3.2 Protocol Violations and Compliance

The case adjudication committee did not hold a meeting. But two protocol violations are known to the authors so far: One patient (502) was randomised to the standard group but was treated in the surgical group (reason specified on the CRF: "Trotz max. antioedematöser Therapie zunehmender Hirndruck und Zeichen der Einklemmung. Am Tag 1 wurde als schwere Protokollverletzung Dekompressions-OP durchgeführt"). For another patient (601), surgery was not sufficient according to the procedure described in the trial protocol; trepanation was too small and the patient was operated again (reason specified on the CRF for day 1: "Revision der Hemikraniektomie, da Knochenfenster zu klein und Patientin war Vigilanzgemindert mit Anisocoria"; and for day 30: "Pat. hatte ein Duraleck, welches 2mal revidiert wurde").

7.3.3 Quality of Data

The main deficiency with impact on this final report is that a valid per-protocol analysis does not exist. A case adjudication committee should have met to review treatment and diagnostic decisions (see 7.3.2 and 7.6.3.12). Therefore, page 38 and the item “PR04” on page 7 and 13 of the CRF is omitted.

Furthermore, our SF-36 questionnaire was not used with the layout of the original and validated version. Question 2 was, due to a copy mistake, in the same scale as question 1, the second question 3.i „eine Straßenkreuzung weit zu Fuß gehen“ is completely missing in most cases and only available in the six cases from other centres than Heidelberg or Mannheim.

Therefore, the scale “physical functioning” can be calculated with only nine and not ten items!

SOPs (Standard Operating procedures) of the IMBI were used for biometry and data management; for monitoring, the SOP of KKS was used. According GCP, double data entry was done in DOS-Software DATA ENTRY 90. In SAS®, 185 plausibility checks were programmed (see 6.7.3), so that 423 queries could be generated. All queries were solved.

7.4 Analysis Sets

The full analysis set consists of all 32 randomised patients (as randomised), the preliminary per-protocol-set consists of 30 patients without protocol violation.

The patient without sufficient surgery (601) was left out of the per-protocol set (see chapter 7.3.2). The patient who received surgical intervention – although randomised to the standard group – (502) does not belong to the per-protocol analysis (as treated) due to delayed surgery.

	Surgery	**Standard**	**Total**
Randomised Patients			
- yes	17 (100.0%)	15 (100.0%)	32 (100.0%)
FAS (=SAF)			
- yes	17 (100.0%)	15 (100.0%)	32 (100.0%)
No final examination	3 (17.6%)	0 (0.0%)	3 (9.4%)
Change of randomisation group, but surgery too late	0 (0.0%)	1 (6.7%)	1 (3.1%)
Trepanation not sufficient	1 (5.9%)	0 (0.0%)	1 (3.1%)
PP			
- no	1 (5.9%)	1 (6.7%)	2 (6.3%)
- yes	16 (94.1%)	14 (93.3%)	30 (93.8%)

Table 7-1: Analysis sets and protocol compliance

7.5 Demography, Baseline Characteristics and Homogeneity

From the 32 randomised patients (Table 9-4), 17 (53%) were female. The patients had a mean age of 44.6 +/–9.1 years, a BMI of 26.6 +/– 5.2, the mRS was mainly 0, only 4 (13%) patients had a score of 1, the pre-morbid BI was 100 for all patients apart from one 56-year old man (110) in the standard group with an index of 95. Furthermore, the median time from the onset of symptoms was 24 hours with a minimum of 12 and a maximum of 36 hours, and in 20

(63%) of the patients, the dominant hemisphere was affected. In all variables but one, no group difference could be found. A notable difference between the treatment groups occurs only in one of the measured 11 variables. The mean NIHSS was lower (better) in the surgical group (surgical 21.2 +/– 2.0, standard 24.0 +/– 2.9) than in the standard group (U-Test p=0.004). The same picture was seen in the PP set. Overall there is not enough evidence that the randomisation procedure did *not* work. Due to the difference in NIHSS, a sensitivity analysis was added post-hoc (7.6.2.4).

7.6 Efficacy

The efficacy is mainly analysed based on the full-analysis set (FAS) with the intention-to-treat (ITT) principles. If a patient died, the subsequent BI score or NIHSS were set to the worst case (BI=0, NIHSS=42), the mRS is already defined like that (mRS=6 for died patients). The existing per-protocol set is used for sensitivity analyses.

7.6.1 Analysis of the Primary Endpoint

The dichotomised mRS (success: 0-3; failure: 4-6) after six months was defined as the primary endpoint. There were 8/17 (47.1%) patients counted as success in the surgical group but only 4/15 (27%) successes in the standard group, RR=0.7219 [0.4198, 1.2416], OR=0.4091 [0.0923, 1.8130] in favour of the surgical group. Although the point estimates are quite different, the difference is not statistically significant (pChi=0.2344) due to low power with 32 patients (Table 7-2 respectively Table 9-22). The statistical necessity to adjust this p-value due to a data driven stop of recruitment leads to the same p-value, p_{adj}=max(0.0195, 0.2344)=0.2344, see statistical analysis plan, page 9. No median unbiased estimates were calculated.

	Surgery	Standard	Total	Croup Comparison
mRS (FAS)	N=17	N=15	N=32	p_{Chi} =0.2344
- failure (4-6)	9 (52.9%)	11 (73.3%)	20 (62.5%)	p_{Fisher} =0.2907
- success (0-3)	8 (47.1%)	4 (26.7%)	12 (37.5%)	OR=0.409 [0.092, 1.813]
mRS (FAS, survivors only)	N=14	N=7	N=21	p_{Chi} =1.0000
- failure (4-5)	6 (42.9%)	3 (42.9%)	9 (42.9%)	p_{Fisher} =1.0000
- success (0-3)	8 (57.1%)	4 (57.1%)	12 (57.1%)	OR=1.000 [0.160, 6.255]
mRS (PP)	N=16	N=14	N=30	p_{Chi} =0.2930
- failure (4-6)	9 (52.9%)	10 (71.4%)	19 (61.3%)	p_{Fisher} =0.4607
- success (0-3)	8 (47.1%)	4 (28.6%)	12 (38.7%)	OR=0.450 [0.100, 2.018]
mRS (PP, survivors only)	N=14	N=6	N=20	p_{Chi} =0.6903
- failure (4-5)	6 (42.9%)	2 (33.3%)	8 (40.0%)	p_{Fisher} =1.0000
- success (0-3)	8 (57.1%)	4 (66.7%)	12 (60.0%)	OR=1.500 [0.203, 11.09]
mRS (FAS, incl. centre as factor)	N=17	N=15	N=32	p_{CMH} =0.2388
number of successes				OR=0.397 [0.088, 1.787]
HD/MA (N=26)	6 (42.9%)	3 (25.0%)	9 (34.6%)	
WÜ/GR/L/K (N=6)	2 (66.7%)	1 (33.3%)	3 (50.0%)	
mRS (PP, incl. centre as factor)	N=16	N=14	N=30	p_{CMH} =0.3236
number of successes				OR=0.453 [0.098, 2.090]
HD/MA (N=26)	6 (42.9%)	3 (25.0%)	9 (34.6%)	
WÜ/GR/L/K (N=5)	2 (66.7%)	1 (50.0%)	3 (60.0%)	

Table 7-2: Primary analysis and sensitivity analyses

7.6.2 Sensitivity Analyses

The sensitivity analyses ought give more information about the primary endpoint.

All p-values and 95% confidence intervals are two-sided (although the primary hypothesis was one-sided).

7.6.2.1 Differences in Analysis Sets (FAS-PP)

As described in chapter 7.4, only two patients are left out of the preliminary PP analysis.
There was no major difference between the two analyses, the PP analysis supports the FAS analysis, six (Table 9-12, Table 9-13) and twelve (Table 9-14, Table 9-15) months after randomisation.

7.6.2.2 Subgroup analysis: Survivors only

The data were very sparse when only survivors were used for the analysis (FAS N=21, PP N=20). The point estimates of the success rates are the same (FAS) or very similar (PP) in both groups (cf. Table 7-2) . Even knowing that any implication of this data is very weak, no difference between the groups can be found OR=1.00 95% CI [0.160; 6.255] (p_{Chi}=1.000) for FAS (and PP as well).

7.6.2.3 Centre effects

A centre effect was added in the model. The centres were classified in Heidelberg/Mannheim (n=26) and others (n=5). The Cochrane-Mantel-Haenszel test gave a stratified relative risk of RR=0.751 [0.440, 1.298] (OR=0.453 [0.098, 2.090]), also without any statistical difference between the treatment group (p_{CMH}=0.324). A logistic regression with group and centre as fixed factors leads to the same result OR=0.395 [0.087, 1.787] p_{Wald}=0.228. A logistic regression model were the centre * group interaction was added: No interaction could be found in this small data set (p_{Wald}=0.766).
The centre effect does not change the interpretation of the primary analysis. A difference between the centres could not be found.

7.6.2.4 Adjustment with other covariates

Due to baseline differences, a post-hoc (!) adjustment was done with baseline NIHSS as covariate in a logistic regression. The group difference without the covariate was OR=0.409 [0.092, 1.813] p_{logit}=0.2393 and with the covariate OR=0.485 [0.088, 2.689] p_{logit}=0.4081. The adjustment therefore did not change the major result, but due to the fact that the more severe cases were in the standard group, the adjusted OR was less in favour of the surgical group and the p-value was higher.

7.6.3 Analysis of Secondary Endpoints

The analysis of the secondary endpoints was exploratory only. All p-values have to be interpreted descriptively.

7.6.3.1 Mortality after 30 days

Mortality after 30 days was used to define a rule to interrupt the recruitment of patients. The analysis was done sequentially. The IMBI was not immediately informed about the results of the thirty-days-assessment in each case, but after a small amount of patients. Those groups were irregular and no rule was defined for that in advance (Figure 7-2). However, the results of the following sequential analysis would change only very slightly using the original data from each patient and methodologically the results (estimates, p-values) are valid.

Less patients died until day 30 in the surgical group (surgical 2/17, standard 8/15); all patients who died in the standard group already died within the first week after operation. The median unbiased estimates of mortality rates are (surgery 0.1397, standard 0.5083). The Median unbiased estimate of exp(θ)=OR was 6.366 in favour of the surgical group with a 95% confidence interval for exp(θ)=OR of (1.3542, 29.1659). There was a difference between both groups (sequential p=0.0195) in favour of the surgical group. The figure shows Z (test statistic, efficient score for θ, measure of the observed advantage of the surgical group) against V (Fisher's information, measure of information, roughly proportional to sample size).

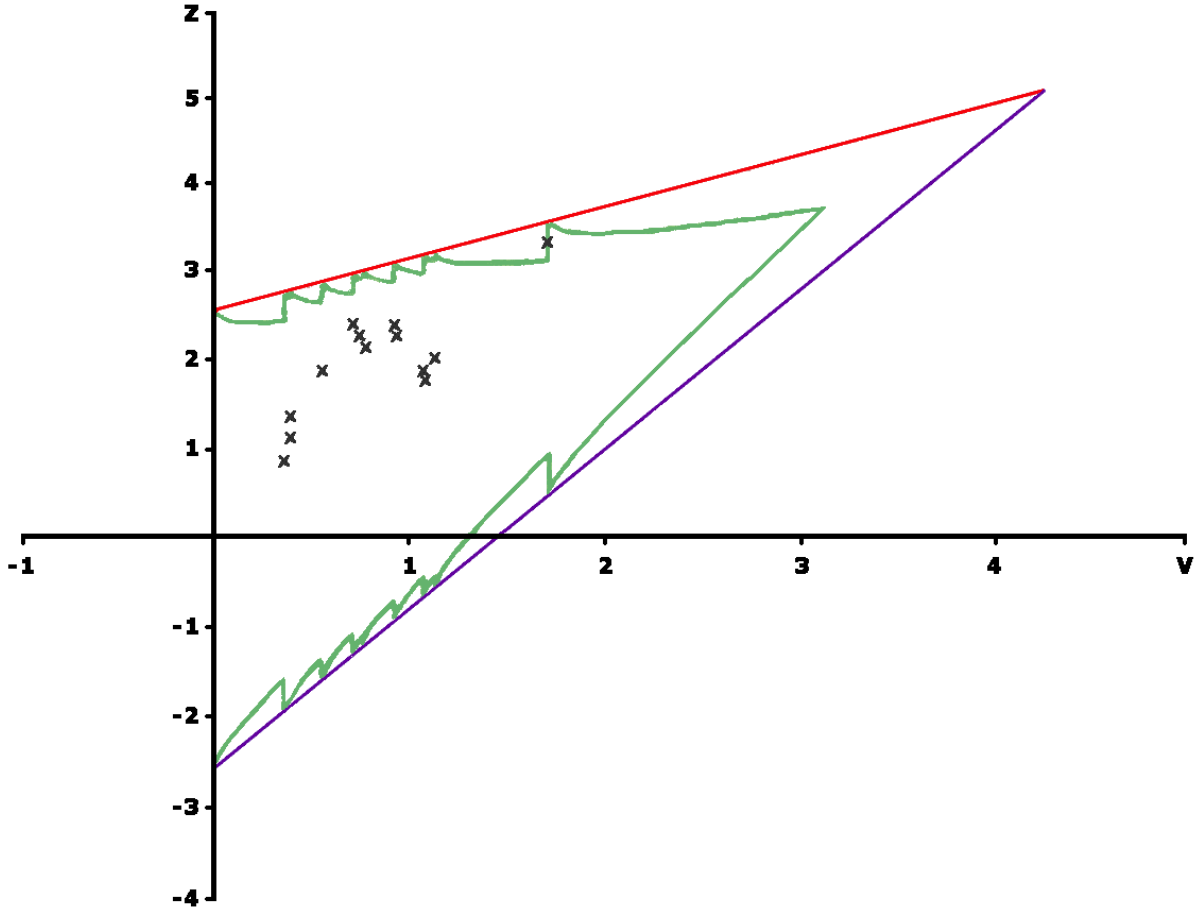

Figure 7-2: Sequential plan

There is an **x** in the figure for each analysis, 13 analyses were done in total. An analysis was performed by the biometrician when the next data were supported by the study coordinator. It can be seen that there are two gaps on the V-axis: from V=0 to the first **x** and from the penultimate to the last **x**. The reason is that before the first analysis had already 7 patients their 30-day mortality assessment and in the last analysis 8 patients were added. This has only an organizational background and does not influence the analysis itself.

7.6.3.2 Mortality after six months

One patient of the surgical group (Pat.No 106) died between the 30-day visit and the six-month visit, five months after the operation. The reason of death was pulmonary embolism. Therefore, in the surgical group 3/17 (18%) died, whereas in the standard group 8/15 (53%) died (p_{Chi}=0.0339), see Figure 7-3 and Table 9-23.

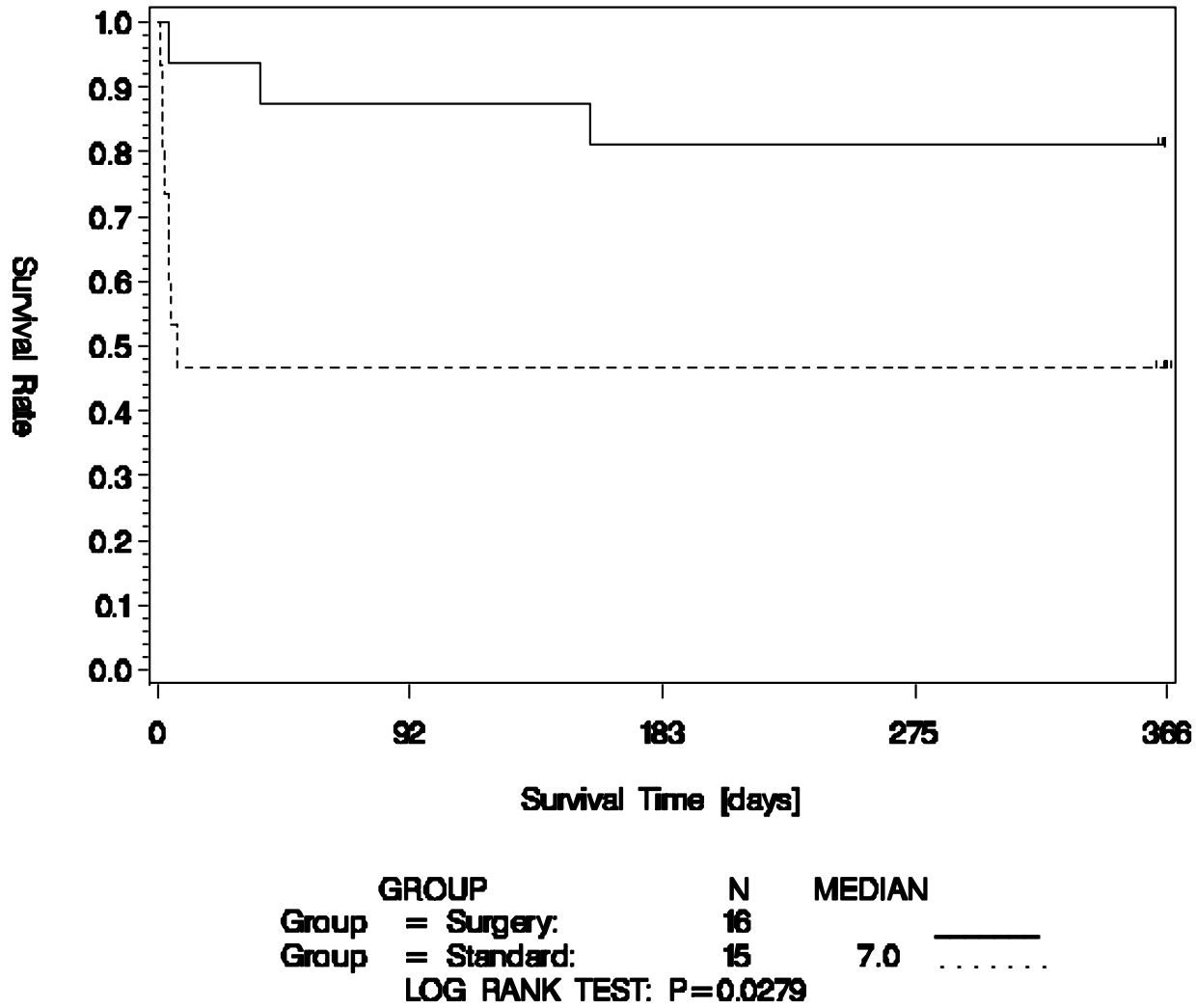

Figure 7-3: Survival curve by treatment group

7.6.3.3 Mortality after twelve months

As it can be seen in Figure 7-5, no death occurred between six and twelve months. Therefore the significant difference is kept stable (p_{Chi}=0.0339). Further information and reason for mortality is explained in 7.7.3.1.

7.6.3.4 Modified Rankin Scale each visit

The mRS[29] (0-6) was analysed by visit, Wilcoxon-tests (U-tests) lead to the following results in favour of the surgical treatment: after 1 day p_U=0.3164, after 7 days p_U=0.0030, after 30 days p_U=0.0166, after six months p_U=0.0417, after 12 months p_U=0.0370. This difference was mainly triggered by the higher mortality (mRS=6) in the standard group: Analyzing the survivors at each visit (mRS<6), no difference was found (after 1 day p_U=0.3164, after 7 days p_U=0.5708, after 30 days p_U=0.5741, after six months p_U=0.6236, after 12 months p_U=0.5350).

A post-hoc (!) longitudinal analysis using SAS ‘proc mixed’ showed a difference between the treatment groups over time (group*visit interaction) in the FAS in favour of the surgical group (mean change of mRS per visit: surgical -0.3448 [-0.4536, -0.2359], standard: -0.9867 [-2.1093, 0.1359], group difference: -0.2714 [-0.4268, -0.1161] p=0.0007), see Figure 7-4. This was mainly due to the higher mortality in the standard group: Analysing survivors only, both groups had a similar improvement over time (mean change of mRS per visit: surgical -0.4874 [-0.5799, -0.3949], standard: -0.3777 [-0.4930, -0.2623], group difference: -0.1097 [-0.2576, 0.0381] p=0.1437). The model assumptions were met.

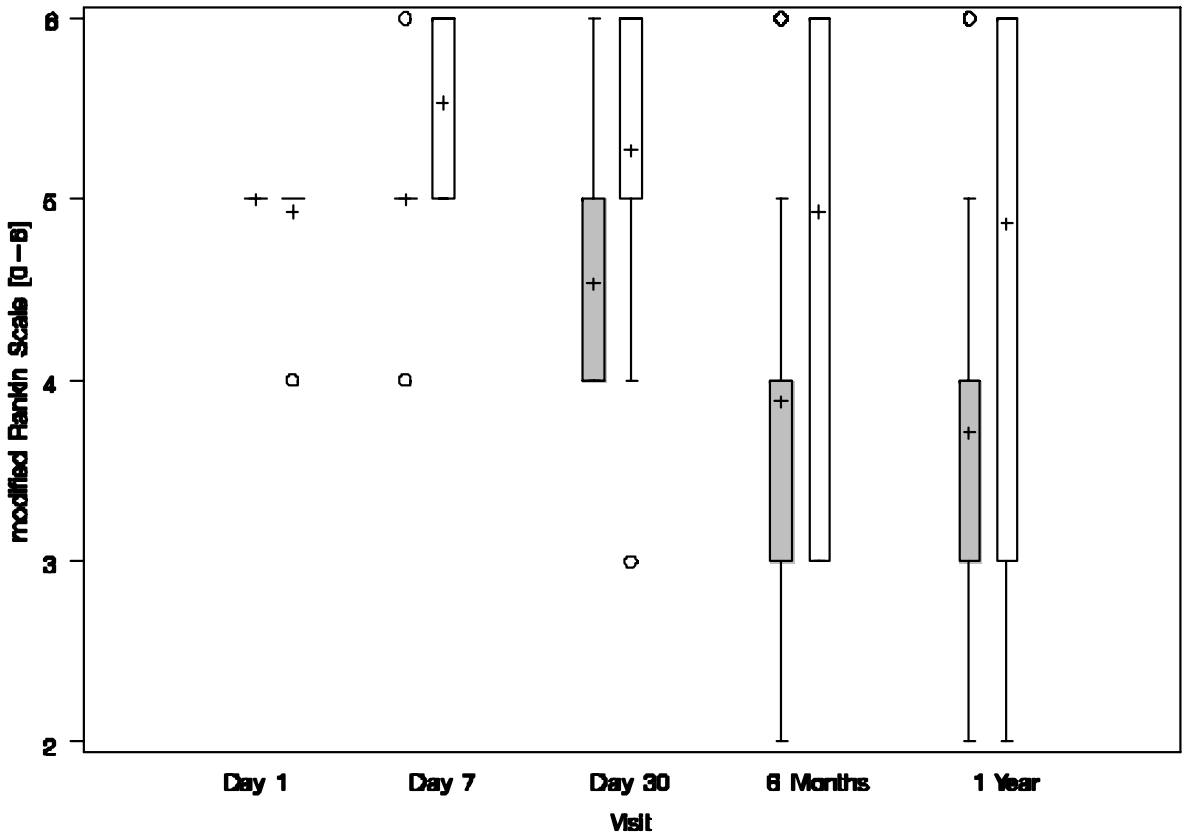

Figure 7-4: Boxplot of mRS over time: surgical group (grey), standard group (white)

7.6.3.5 Dichotomised modified Rankin Scale each visit (0-3/4-6)

Until visit 2 (7 days after operation), none of the patients was a success regarding mRS (success: 0-3; failure: 4-6) and only one patient was a success (standard group) after 30 days. But after six months, more successes occurred in the surgical group (8/17, 47%) than in the standard group (4/15, 27%) with p_{Chi}=0.234. Changes after twelve months did not occur (Table 9-14). The mRS over time is shown in Figure 7-5.

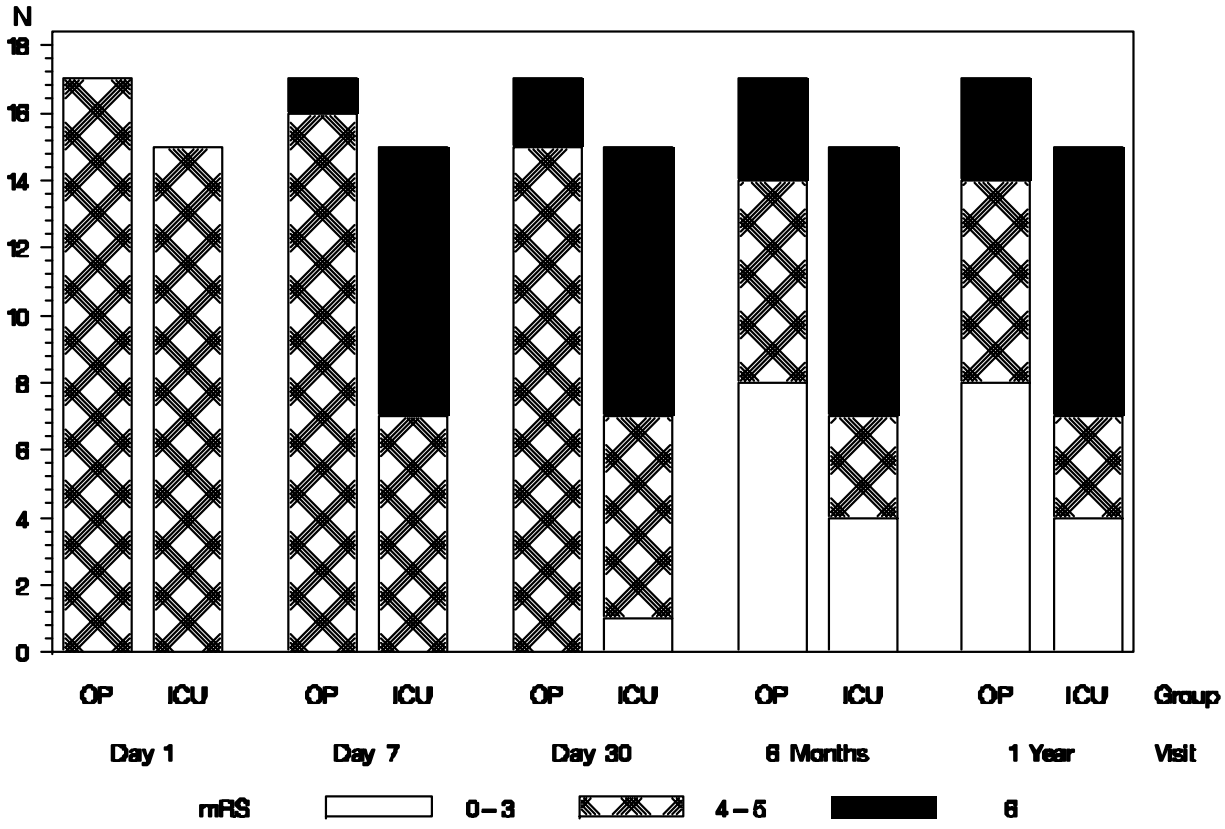

Figure 7-5: mRS over time: surgical group (OP) and standard group (ICU)

7.6.3.6 Dichotomised modified Rankin Scale each visit (0-4/5-6)

Another dichotomization was used post-hoc to split the group of patients into very strong failure (mRS 5 or 6) and others (success: 0-4; failure: 5-6). The usefulness of this dichotomization was underlined elsewhere[30].

Until visit 1 (1 day after operation), one patient was counted as success in the standard group (Table 9-6) but was a failure again at visit 2 (7 days after operation). On the other hand, one patient was a success at visit 2 in the surgical group (Table 9-8). However, thirty days after the operation 10/17 (59%) successes were in the surgical group whereas only 3/15 (20%) successes were in the standard group (p_{Chi}=0.026), see Table 9-10. After six months, the difference between the two groups was still valid, 13/17 (77%) surgical group, 5/15 (33%) standard group (p_{Chi}=0.014). The results kept stable until twelve months and did not alter any more (Table 9-14).

In this small sample, the surgical method created less severe cases (in terms of mRS 5 or 6) than the standard group.

7.6.3.7 Barthel-Index after each visit

Due to a high amount of deaths, the median BI [28] (measured on a 0-100 scale) was constant 0. In the standard group, the BI increased in the surgical group from 0 to 20 (95% CI [0, 30]) after 30 day, to 50 (95% CI [20, 75]) after six months and to 45 (95% CI [0, 85]) after twelve months (Table 9-16, Table 9-14). In both treatment groups, patients with maximum result of 95 after twelve months were viewed, see Figure 7-7. After analysing the visits separately, no statistical difference could be found, although the point estimates (median) differed as mentioned above (after 1 day p_U=0.250, after 7 days p_U=0.188, after 30 days p_U=0.050, 6 months p_U=0.076, after 12 months p_U=0.069), see Figure 7-6. The BI estimates favours the surgical treatment as well.

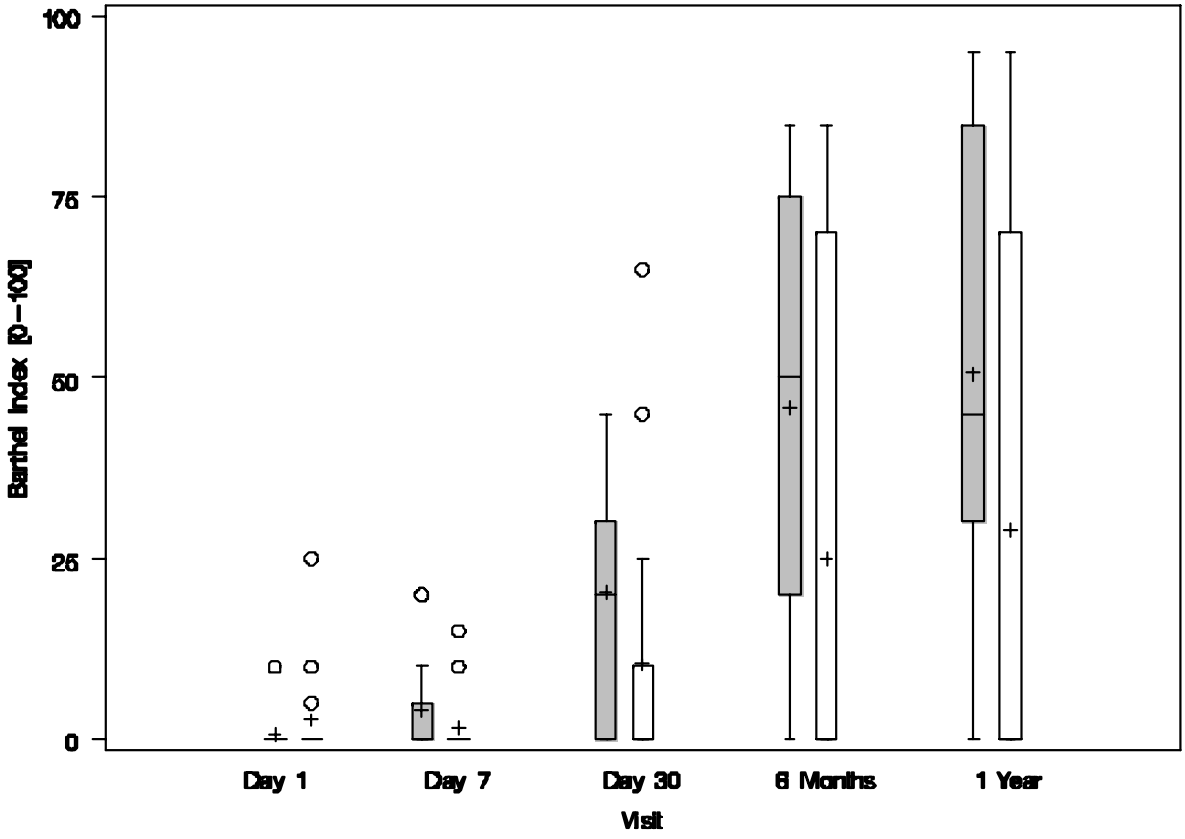

Figure 7-6: Boxplot of Barthel over time: surgical group (grey), standard group (white)

A post-hoc (!) longitudinal analysis did not result in a statistical difference between the treatment groups over time, but model assumptions were questionable. The PP analysis was not performed.

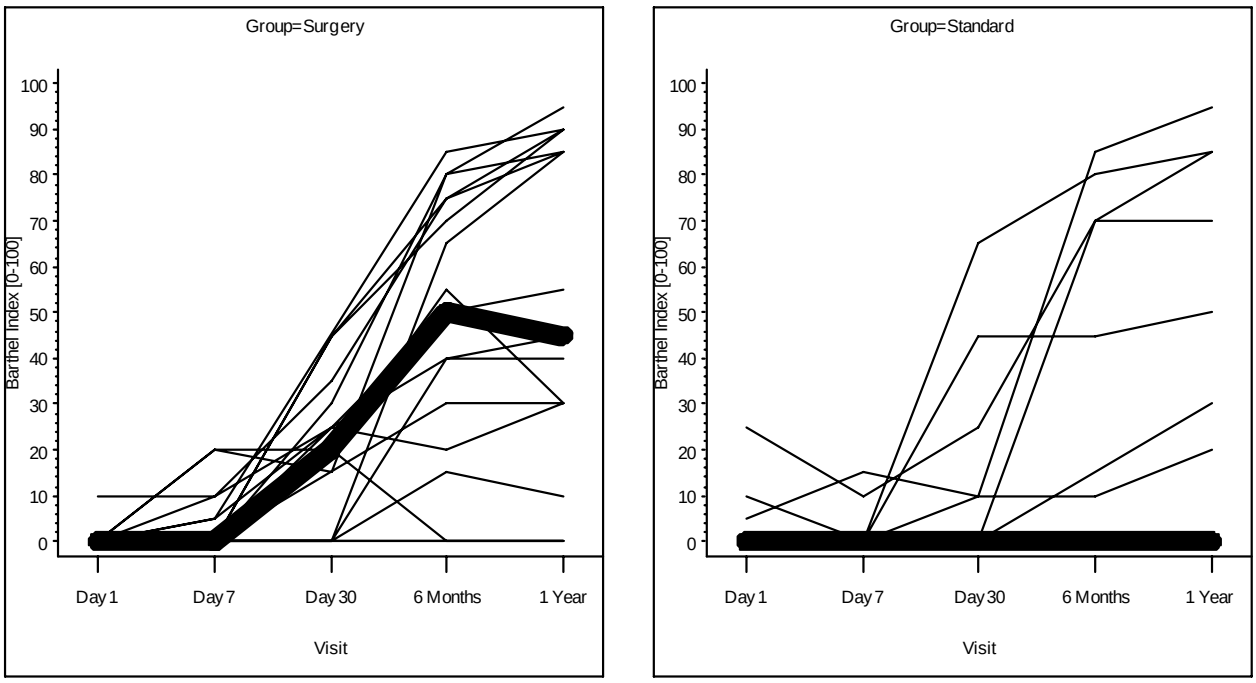

Figure 7-7: Barthel and median over time: surgical group (left), standard group (right)

7.6.3.8 Dichotomised Barthel-Index each visit

The dichotomised BI (success: >80; failure ≤80) was ≤80 for all patients until day 30 (Table 9-16). After six months, there was one success in each treatment group (Table 9-12). Regarding this binary endpoint, no difference between both group could be found (p_{Chi}=0.927). After one year, 7/17 (41%) in the surgical group and 3/15 (20%) in the conservative group achieved a Barthel Index above 80 (p_{Chi}=0.197). A post-hoc (!) longitudinal analysis could not be done due to sparse binary data.

7.6.3.9 NIH Stroke Scale each visit

The median NIHSS (ordinal 0-42) was in the surgical group [or standard group] 31 [31] (day 1 post OP), 19 [42] (day 7 post OP), 15 [42] (day 30 post OP), 14 [42] (month 6 post OP), 13 [42] (month 12 post OP). Pairwise comparisons for each time point showed that there were group differences in favour of the surgical therapy at some time points (p_U=0.835, p_U=0.001, p_U=0.005, p_U=0.045, p_U=0.053), see Figure 7-8 (and Table 9-6, Table 9-8, Table 9-10, Table 9-12, Table 9-14).

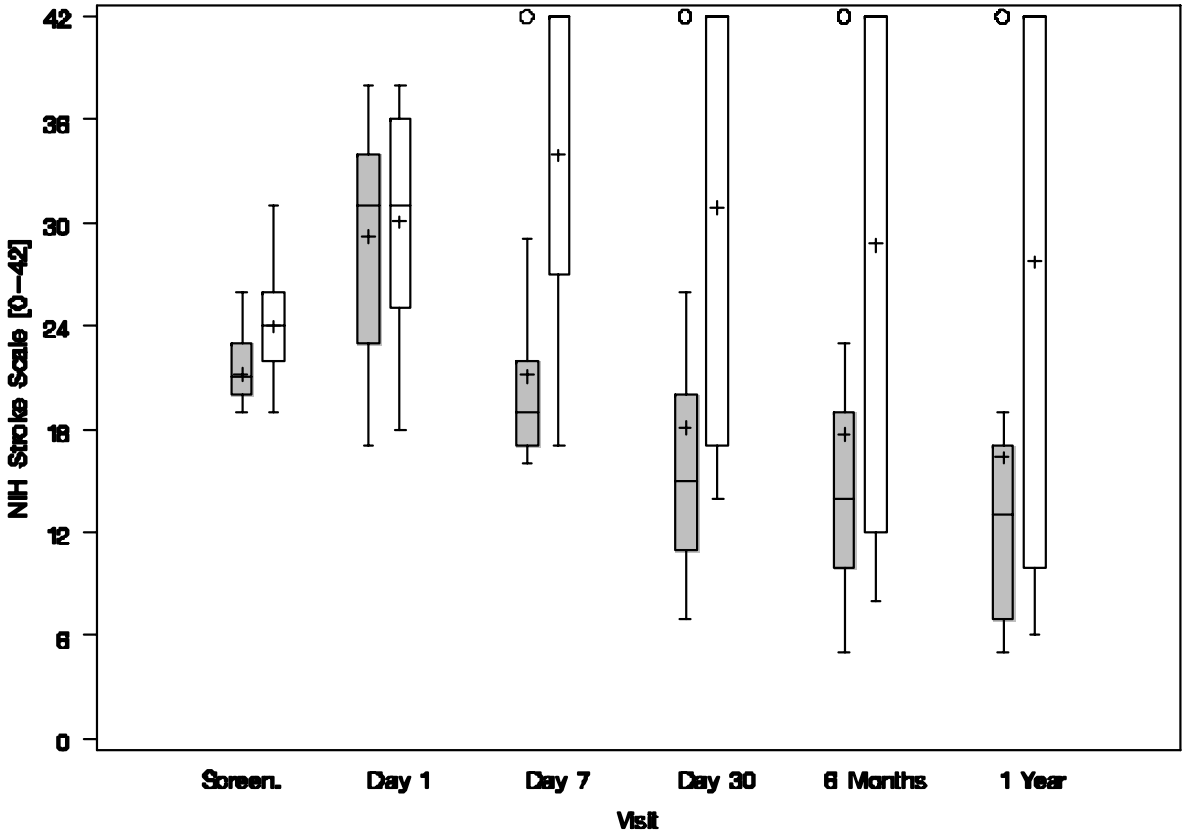

Figure 7-8: Boxplot of NIHSS over time: surgical group (grey), standard group (white)

A post-hoc (!) longitudinal analysis using SAS 'proc mixed' showed a difference between the treatment groups over time (group*visit interaction) in the FAS in favour of the surgical group (change of NIHSS per visit: surgical -2.6847 [-3.7879, -1.5815], standard: -0.9867 [-2.1093, 0.1359], group difference: -1.6981 [-3.2720, -0.1241] p=0.0347), see Figure 7-9. This was mainly due to higher mortality in the standard group: Analysing the survivors only, both groups had a similar improvement over time. The point estimate was actually very slightly in favour of the standard group (change of NIHSS per visit: surgical -4.3909 [-5.1955, -3.5863], standard: -4.7277 [-5.7360, -3.7195], group difference: 0.3368 [-0.9531, 1.6268] p=0.6048). The model assumptions were met.

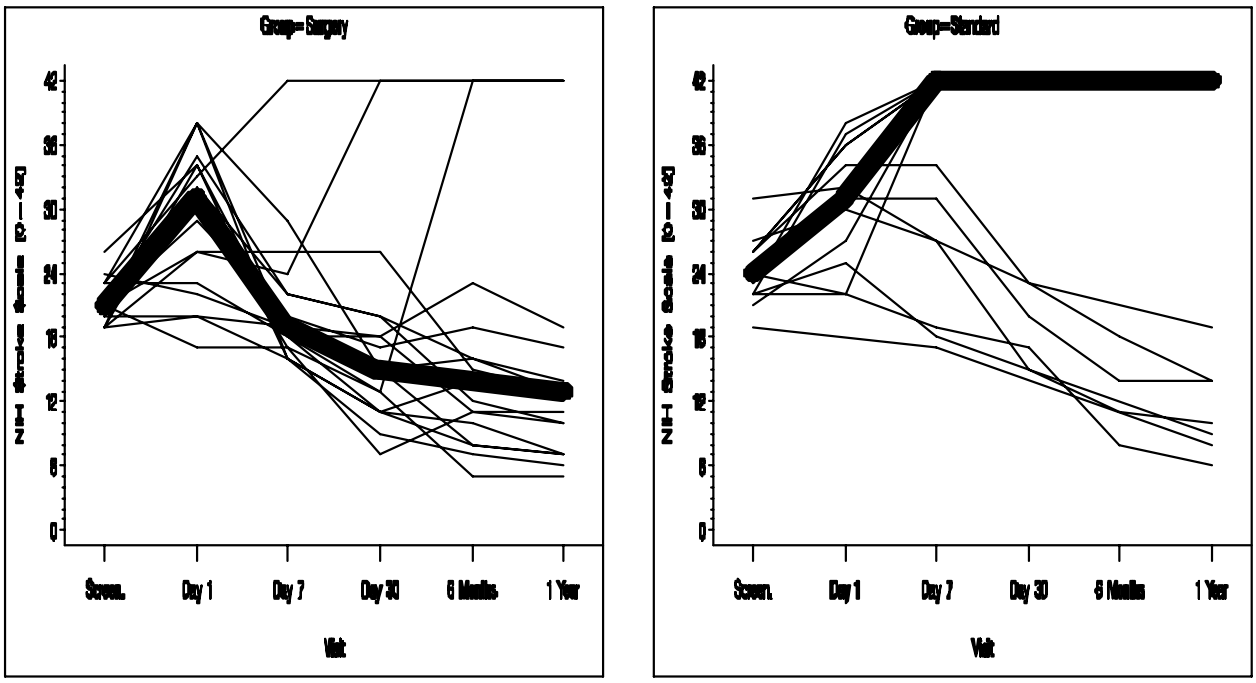

Figure 7-9: NIHSS with median over time: surgical group (left), standard group (right)

7.6.3.10 Barthel and NIHSS after 12 month constraint for survivors

Extending the sensitivity analyses at six months (cf. 7.6.2.2 and Table 7-2), as well no difference after twelve months could be stated.

	Surgery N=14	**Standard N=7**	**Total N=21**	**p-value**
Barthel Index [0-100]				
- N	14	7	21	0.9099 *[2]
- Mean +/- SD	61.4 +/- 29.9	62.1 +/- 29.3	61.7 +/-29.0	
- p5, p25, p75, p95	10.0, 30.0, 90.0, 95.0	20.0, 30.0, 85.0, 95.0	20.0, 30.0, 85.0, 95.0	
- Median	70.0	70.0	70.0	
- Min, Max	10.0, 95.0	20.0, 95.0	10.0, 95.0	
- 95% CI Median	[30.0;90.0]	[20.0;95.0]	[30.0;85.0]	
Barthel Index [dichotomised]				
- failure (<=80%)	7 (50.0%) [23.0%;77.0%]	4 (57.1%) [18.4%;90.1%]	11 (52.4%) [29.8%;74.3%]	0.7574 *[1]
- success (>80%)	7 (50.0%) [23.0%;77.0%]	3 (42.9%) [9.9%;81.6%]	10 (47.6%) [25.7%;70.2%]	
NIH Stroke Scale [0-42]				
- N	14	7	21	0.7356 *[2]
- Mean +/- SD	10.9 +/- 4.2	11.4 +/- 4.5	11.0 +/-4.2	
- p5, p25, p75, p95	5.0, 7.0, 13.0, 19.0	6.0, 8.0, 14.0, 19.0	6.0, 7.0, 14.0, 19.0	
- Median	10.5	10.0	10.0	
- Min, Max	5.0, 19.0	6.0, 19.0	5.0, 19.0	
- 95% CI Median	[7.0;14.0]	[6.0;19.0]	[7.0;14.0]	

*[1] = Chi[2]-Test *[2] = U-Test

Table 7-3: 1 year after randomisation (FAS) - survivors only

7.6.3.11 Quality of life SF-36 after12 months

After one year, the quality of life of the surviving patients was assessed by using the SF-36. No major differences could be found between both treatment groups in one of the ten sub-scales, neither in FAS (Table 9-25) nor in PPS (Table 9-26). Imputation for missing values or correction of mistakes in the questionnaire layout (cf. 7.3.3) was not performed. A difference in quality of life could not be stated after twelve months.

7.6.3.12 Size of infarction: CT on day 2-3 to 4-8 (in cm³)

Up to now, there are no data in the database regarding the size of infarction because this size should have been measured by the case adjudication committee, whose members did not hold a meeting. Hence, we had to omit these results in the report. Regarding the appropriate size of trepanation, it is mentioned in 7.3.2 that one patient had an osseous window too small, which had to be revised. The size of infarction was not used for any analysis.

7.6.3.13 Surgical complications (yes/no) each visit

It is not superfluous to mention that there were no surgical complications in the standard group. The converter (randomised to standard, received surgery, cf. 7.3.2) had no surgical complications. Surgical complications in the surgical group did happen, but only scarcely. The number of patients with at least one surgical complication until twelve months after the operation were as follows: Anaesthetics 0/17, bleeding 2/17, wound infection 1/17, problems with wound healing 3/17, post OP pain 6/17. Three other complications were entered: (day 1 post OP) lentil nucleus bleeding + subgaleal haematoma (401), (day 30 post OP) one patient with dura leakage twice revised (111) and (month 6 post OP) spastic leg pain (102). Most complications occurred during the first month, only the ‘spastic leg pain’ occurred at six month, no complications were recorded at 12 months (cf. Table 9-6, Table 9-8, Table 9-10, Table 9-12, Table 9-14).

7.7 Safety (Adverse Events, AE)

Adverse events were coded in ‘Preferred Term’ and ‘System Organ Classes’ according Med-DRA version 7.0. The ‘Points to Consider’ of EMEA for acute stroke trials[38] (chapter seven) suggest special attention on following potential adverse events: death, herniation, epileptic

seizures, arhythmias, effects on coagulation and fibrinolysis, hyper- or hypotension, hyperthermia, hyperglycaemia, severe infections, deep vein thrombosis and pulmonary embolism, vomiting, anxiety, hallucinations, agitations.
The studied population suffered from a very severe disease, but only few of the suggested adverse events were reported (cf. Listing 9-1), therefore an underreporting of AEs is expected. However, the main focus was on the serious adverse events (SAE).

7.7.1 Overview of Adverse Events

In total, there are 57 adverse events reported in 27 (84%) patients with one to four events in each patient and one surgical patient with nine events. All patients (100%) of the standard group and 12/17 (71%) of the surgical group report at least of AE (p_{Chi}=0.022). With 33 to 24, the absolute number of AE is higher in the surgical group (p_{Chi}=0.047). A complete listing can be found in Listing 9-1.

7.7.2 AEs by different classifications

The severity of the AE is more likely in the standard than in the surgical group (p_{Chi}=0.0298). In most cases, there seems to be no causality with the standard (79%) or surgical (73%) therapy (p_{Chi}=0.803). In the beginning, the AEs are more likely in the standard group (day1: 5/15; day7: 8/15; day30: 2/15; 6 month: 2/15, 12 month 1/15) than in the surgical group (day1: 1/17; day7: 3/17; day30: 7/17; 6 month: 4/17, 12 month 1/17). After one month or more, survivors in the surgical group could report more events. The ‘System Organ Class’ according MedDRA differed slightly (p_{Chi}=0.0937; cf. Table 9-27). But an increase in only one group of specific AEs is not evident.

7.7.3 Serious Adverse Events (SAE)

In total, 23/32 (72%) patients had at least one SAE, and there were 28 SAEs. In the surgical group, there were 8/17 (47%) patients without an SAE, whereas only 1/15 (7%) patients in the standard group had no SAE (p_{Chi}=0.011), see Table 9-28.

7.7.3.1 Deaths

In total, 11 of 32 patients died until the six month follow-up, 8 patients in the standard group and 3 in the surgical group (Table 7-4). The p-values are simply descriptive measures and do not apply to confirmatory statistics. The day-30-mortality was analysed using a sequential

design, see chapter 7.6.3.1 and chapter 7.6.3.2 for 6-months mortality. One patient died between one and six months in the surgical group, during replacement. No patients died between six and twelve months.

Visit	Surgery N=17	Standard N=15	Total N=32	Chi^2	Log Rank
Day 30	2 (11.8%)	8 (53.3%)	10 (31.3%)	0.0114 *[1]	0.0031
6 Months	3 (17.6%)	8 (53.3%)	11 (34.4%)	0.0339 *[1]	0.0207
1 Year	3 (17.6%)	8 (53.3%)	11 (34.4%)	0.0339 *[1]	0.0279

Table 7-4: Mortality by group and time

The reasons for death are given below (Listing 7-1).

Pat.No.	Group	Random.date	Date of death	Reason for death
103	Standard	21/05/2004	25/05/2004	unkontrollierbarer Hirndruck
105	Standard	02/06/2004	06/06/2004	unkontrollierbarer Hirndruck mit Herniation
106	Surgery	28/06/2004	02/12/2004	Lungenembolie
110	Standard	01/12/2004	08/12/2004	Hirndruck und Herniation
113	Standard	30/03/2005	01/04/2005	Herniation
115	Surgery	21/04/2005	28/05/2005	Herniation
118	Standard	09/10/2005	14/10/2005	Herniation
120	Surgery	14/12/2005	18/12/2005	Herniation
203	Standard	28/10/2004	30/10/2004	Oedem, Einklemmung
206	Standard	16/09/2005	19/09/2005	Oedem, Einklemmung
602	Standard	29/09/2005	01/10/2005	maligner Mediainfarkt links

Listing 7-1: Reasons for death

7.7.3.2 Other SAEs

Other SAEs are in most cases (Pat.No: 101; 108; 111;112; 202; 401; 1001) convulsion on different time points or impaired healing (Pat.No: 202; 204), amaurosis (Pat.No: 201) or pulmonary infarction (Pat.No: 501). The centre-specific reporting suggests a centre dependent reporting bias.

Both cases excluded from the PP set are also reported as SAEs due to insufficient decompression therapy (Pat.No: 502; 601) in the beginning.

8 Discussion and Conclusion

It was the aim of this study to test the advantage of surgical decompressive treatment (hemicraniectomy) in comparison to conservative treatment of an intensive care unit in case of malignant infarction of the middle cerebral artery regarding functional outcome six months after the stroke event.

This trial with 32 patients shows no evidence that there is a better functional outcome in view of the primary endpoint: dichotomised mRS 0-3 versus 4-6 (p_{Chi}=0.2344). But the surgical decompressive treatment is superior in terms of survival (p_{Chi}=0.0339). Regarding the ordinal mRS, superiority could not be shown (p_U=0.1362), but is likely at least. However, the interrater reliability of the ordinal mRS is limited according to van Swieten et al. (1988)[31] and Wilson et al. (2002, 2005) [32,33] with a κ_{uw} between 0.25 and 0.56 and an interrater agreement of 43 to 65%. The chosen dichotomised mRS (0-3 versus 4-6) is much more reliable with a κ_{uw} between 0.55 and 0.86 and an interrater agreement of 83 to 92%[33,34]. There is an ongoing discussion regarding the appropriate cut-off for mRS and some researchers suggest a cut-off between 4 and 5[30]. This discussion and the ITT analysis of the primary endpoint was already discussed in Jüttler et al. (2007)[21]. As sensitivity analyses of the primary endpoint, we inspected centre effect, baseline NIHSS, per-protocol set and subgroups of survivors. We found no difference between both groups in any of these analyses. The sparse subgroup of survivors (N=21) showed no difference (p_{Chi}=1.00), hence, the reduction of mortality could be considered as main effect. It can be concluded that an explorative analysis favours surgery in all endpoints, but there is no difference regarding the survivors.

Further points in time (1 week, 1 month, 1 year) and further outcome scales (NIHSS, Barthel Index, SF-36) were analysed as secondary endpoints. Fatal incidents occurred mainly during the first month, but one death in the surgical group occurred during a re-operation after four months. Therefore, mortality was significantly reduced in the surgical group at each point in time. Defining death as worst outcome in NIHSS, Barthel Index and mRS achieved low p-values at each point in time. However, when calculating survivors exclusively, there is no evidence of functional difference regarding mRS, NIHSS, and Barthel Index. No scale of SF-36 differs between both groups after one year.

Adverse events were reported by a vast majority of patients, but more severe adverse events were reported in the standard group. Beside death, further serious adverse events are convul-

sion, impaired healing, amaurosis and pulmonary infarction. Surgical complications were rare; Post OP pain and problems with wound healing mostly occurred.

DESTINY has some shortcomings: 81% of patients were enrolled from two centres only. As a matter of fact, this makes DESTINY an bi-centre rather than a proper multi-centre trial. Observer-blinding is not possible in such studies. Due to a lack of input from the case adjudication committee meeting, a proper PP set could not be defined. Anywhere, preliminary PP analyses showed no major differences. Patients above the age of 60 were excluded, hence, for this age group a treatment recommendation could not be made.

The intended primary endpoint of functional outcome could not be proved, but superiority of decompression regarding mortality was indeed shown. Hence, the results need to be discussed together with the other four randomised trials (HeADDFIRST, HeMMI, HAMLET, DECIMAL) in the comparable setting (Vahedi et al. 2007) [23].

9 Appendix

9.1 Tables and Listings

Table 9-1: Recruitment by time or centre (FAS)

	Surgery N=17	Standard N=15	Total N=32
Recruitment by quarters			
- 01/2004	1 (5.9%)	2 (13.3%)	3 (9.4%)
- 02/2004	3 (17.6%)	2 (13.3%)	5 (15.6%)
- 03/2004	3 (17.6%)	0 (0.0%)	3 (9.4%)
- 04/2004	2 (11.8%)	2 (13.3%)	4 (12.5%)
- 01/2005	0 (0.0%)	5 (33.3%)	5 (15.6%)
- 02/2005	4 (23.5%)	1 (6.7%)	5 (15.6%)
- 03/2005	1 (5.9%)	2 (13.3%)	3 (9.4%)
- 04/2005	3 (17.6%)	1 (6.7%)	4 (12.5%)
Recruitment by centre			
- 100 - Heidelberg	11 (64.7%)	9 (60.0%)	20 (62.5%)
- 200 - Mannheim	3 (17.6%)	3 (20.0%)	6 (18.8%)
- 400 - Würzburg	1 (5.9%)	0 (0.0%)	1 (3.1%)
- 500 - Greifswald	1 (5.9%)	1 (6.7%)	2 (6.3%)
- 600 - Leipzig	1 (5.9%)	1 (6.7%)	2 (6.3%)
- 1000 – Köln	0 (0.0%)	1 (6.7%)	1 (3.1%)

Table 9-2: Recruitment by time dichotomised in subgroups (FAS)

	Heidelberg N=20	Others N=12	Total N=32
Recruitment by quarters			
- 01/2004	1 (5.0%)	2 (16.7%)	3 (9.4%)
- 02/2004	5 (25.0%)	0 (0.0%)	5 (15.6%)
- 03/2004	1 (5.0%)	2 (16.7%)	3 (9.4%)
- 04/2004	3 (15.0%)	1 (8.3%)	4 (12.5%)
- 01/2005	3 (15.0%)	2 (16.7%)	5 (15.6%)
- 02/2005	3 (15.0%)	2 (16.7%)	5 (15.6%)
- 03/2005	0 (0.0%)	3 (25.0%)	3 (9.4%)
- 04/2005	4 (20.0%)	0 (0.0%)	4 (12.5%)

Table 9-3: Analysis sets and protocol compliance

	Surgery	Standard	Total
Randomized Patients			
- yes	17 (100.0%)	15 (100.0%)	32 (100.0%)
FAS (=SAF)			
- yes	17 (100.0%)	15 (100.0%)	32 (100.0%)
No final examination	3 (17.6%)	0 (0.0%)	3 (9.4%)
Change of randomization group, but surgery too late	0 (0.0%)	1 (6.7%)	1 (3.1%)
Trepanation not sufficient	1 (5.9%)	0 (0.0%)	1 (3.1%)
PP			
- no	1 (5.9%)	1 (6.7%)	2 (6.3%)
- yes	16 (94.1%)	14 (93.3%)	30 (93.8%)

Table 9-4: Baseline demographics by group (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Sex				
- male	8 (47.1%) [23.0%;72.2%]	7 (46.7%) [21.3%;73.4%]	15 (46.9%) [29.1%;65.3%]	0.9823 *[1]
- female	9 (52.9%) [27.8%;77.0%]	8 (53.3%) [26.6%;78.7%]	17 (53.1%) [34.7%;70.9%]	
Age [years]				
- N	17	15	32	0.4384 *[2]
- Mean +/- SD	43.2 +/- 9.7	46.1 +/- 8.4	44.6 +/-9.1	
- p5, p25, p75, p95	30.0, 34.0, 49.0, 60.0	29.0, 39.0, 54.0, 59.0	30.0, 38.5, 51.5, 59.0	
- Median	43.0	46.0	44.5	
- Min, Max	30.0, 60.0	29.0, 59.0	29.0, 60.0	
- 95% CI Median	[34.0;49.0]	[39.0;54.0]	[40.0;49.0]	
Weight [kg]				
- N	14	11	25	0.8906 *[2]
- Mean +/- SD	80.3 +/- 16.5	82.8 +/- 23.7	81.4 +/-19.6	
- p5, p25, p75, p95	45.0, 70.0, 89.0, 110.0	60.0, 70.0, 90.0, 145.0	60.0, 70.0, 90.0, 110.0	
- Median	85.0	75.0	80.0	
- Min, Max	45.0, 110.0	60.0, 145.0	45.0, 145.0	
- 95% CI Median	[70.0;90.0]	[70.0;95.0]	[71.0;89.0]	
Height [cm]				
- N	14	11	25	0.6983 *[2]
- Mean +/- SD	173.3 +/- 9.2	175.6 +/- 8.5	174.3 +/-8.8	
- p5, p25, p75, p95	158.0, 170.0, 180.0, 185.0	165.0, 170.0, 183.0, 191.0	160.0, 170.0, 180.0, 185.0	

	Surgery N=17	Standard N=15	Total N=32	p-value
- Median	175.0	175.0	175.0	
- Min, Max	158.0, 185.0	165.0, 191.0	158.0, 191.0	
- 95% CI Median	[170.0;185.0]	[170.0;185.0]	[170.0;180.0]	
BMI [kg/m^2]				
- N	14	11	25	0.7220 *[2]
- Mean +/- SD	26.7 +/- 5.5	26.5 +/- 5.2	26.6 +/-5.2	
- p5, p25, p75, p95	17.6, 23.4, 29.4, 40.1	20.8, 22.0, 28.4, 39.7	20.8, 23.4, 29.1, 39.7	
- Median	25.5	26.0	26.0	
- Min, Max	17.6, 40.1	20.8, 39.7	17.6, 40.1	
- 95% CI Median	[23.4;31.1]	[22.0;29.4]	[23.4;28.4]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.0035 *[2]
- Mean +/- SD	21.2 +/- 2.0	24.0 +/- 2.9	22.5 +/-2.8	
- p5, p25, p75, p95	19.0, 20.0, 23.0, 26.0	19.0, 22.0, 26.0, 31.0	19.0, 20.5, 24.0, 27.0	
- Median	21.0	24.0	22.0	
- Min, Max	19.0, 26.0	19.0, 31.0	19.0, 31.0	
- 95% CI Median	[20.0;23.0]	[22.0;26.0]	[21.0;24.0]	
premorbid Modified Rankin Scale [0-6]				
- N	17	15	32	0.9213 *[2]
- Mean +/- SD	0.1 +/- 0.3	0.1 +/- 0.4	0.1 +/-0.3	
- p5, p25, p75, p95	0.0, 0.0, 0.0, 1.0	0.0, 0.0, 0.0, 1.0	0.0, 0.0, 0.0, 1.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 1.0	0.0, 1.0	0.0, 1.0	
- 95% CI Median	[0.0;0.0]	[0.0;0.0]	[0.0;0.0]	
premorbid Modified Rankin Scale [0-6]				
- 0	15 (88.2%) [63.6%;98.5%]	13 (86.7%) [59.5%;98.3%]	28 (87.5%) [71.0%;96.5%]	0.8935 *[1]
- 1	2 (11.8%) [1.5%;36.4%]	2 (13.3%) [1.7%;40.5%]	4 (12.5%) [3.5%;29.0%]	
premorbid Barthel Index [0-100]				
- N	17	15	32	0.3164 *[2]
- Mean +/- SD	100.0 +/- 0.0	99.7 +/- 1.3	99.8 +/-0.9	
- p5, p25, p75, p95	100.0, 100.0, 100.0, 100.0	95.0, 100.0, 100.0, 100.0	100.0, 100.0, 100.0, 100.0	
- Median	100.0	100.0	100.0	
- Min, Max	100.0, 100.0	95.0, 100.0	95.0, 100.0	
- 95% CI Median	[100.0;100.0]	[100.0;100.0]	[100.0;100.0]	
Source of Information				
- Patient	2 (11.8%) [1.5%;36.4%]	0 (0.0%) [0.0%;21.8%]	2 (6.3%) [0.8%;20.8%]	0.4235 *[1]

	Surgery N=17	Standard N=15	Total N=32	p-value
- Relative	11 (64.7%) [38.3%;85.8%]	12 (80.0%) [51.9%;95.7%]	23 (71.9%) [53.3%;86.3%]	
- Examiner	0 (0.0%) [0.0%;19.5%]	1 (6.7%) [0.2%;31.9%]	1 (3.1%) [0.1%;16.2%]	
- Pat.+Exam.	2 (11.8%) [1.5%;36.4%]	0 (0.0%) [0.0%;21.8%]	2 (6.3%) [0.8%;20.8%]	
- Pat.+Rel.+Exam.	1 (5.9%) [0.1%;28.7%]	1 (6.7%) [0.2%;31.9%]	2 (6.3%) [0.8%;20.8%]	
- Pat.+Rel.	1 (5.9%) [0.1%;28.7%]	1 (6.7%) [0.2%;31.9%]	2 (6.3%) [0.8%;20.8%]	
Time from symptom onset [h]				
- N	17	15	32	0.6640 *[2]
- Mean +/- SD	24.4 +/- 6.9	23.8 +/- 7.8	24.1 +/-7.2	
- p5, p25, p75, p95	13.5, 18.3, 29.0, 36.0	12.0, 17.3, 32.5, 35.0	13.0, 17.7, 29.1, 35.0	
- Median	24.0	22.5	24.0	
- Min, Max	13.5, 36.0	12.0, 35.0	12.0, 36.0	
- 95% CI Median	[18.3;29.0]	[17.3;32.5]	[18.5;28.0]	
Hemisphere				
- dominant	9 (52.9%) [27.8%;77.0%]	11 (73.3%) [44.9%;92.2%]	20 (62.5%) [43.7%;78.9%]	0.2344 *[1]
- non-dominant	8 (47.1%) [23.0%;72.2%]	4 (26.7%) [7.8%;55.1%]	12 (37.5%) [21.1%;56.3%]	

*[1] = chi^2-Test *[2] = U-Test

Table 9-5: Baseline demographics by group (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Sex				
- male	8 (50.0%) [24.7%;75.3%]	7 (50.0%) [23.0%;77.0%]	15 (50.0%) [31.3%;68.7%]	1.0000 *[1]
- female	8 (50.0%) [24.7%;75.3%]	7 (50.0%) [23.0%;77.0%]	15 (50.0%) [31.3%;68.7%]	
Age [years]				
- N	16	14	30	0.4538 *[2]
- Mean +/- SD	43.3 +/- 10.0	46.1 +/- 8.7	44.6 +/-9.4	
- p5, p25, p75, p95	30.0, 33.5, 51.0, 60.0	29.0, 39.0, 54.0, 59.0	30.0, 38.0, 53.0, 59.0	
- Median	43.5	47.0	45.0	
- Min, Max	30.0, 60.0	29.0, 59.0	29.0, 60.0	
- 95% CI Median	[34.0;53.0]	[39.0;56.0]	[39.0;49.0]	
Weight [kg]				
- N	13	11	24	0.6413 *[2]
- Mean +/- SD	83.0 +/- 13.6	82.8 +/- 23.7	82.9 +/-18.4	
- p5, p25, p75, p95	60.0, 75.0, 89.0, 110.0	60.0, 70.0, 90.0, 145.0	60.0, 70.5, 90.0, 110.0	
- Median	85.0	75.0	82.5	
- Min, Max	60.0, 110.0	60.0, 145.0	60.0, 145.0	
- 95% CI Median	[70.0;90.0]	[70.0;95.0]	[75.0;90.0]	
Height [cm]				

	Surgery N=16	Standard N=14	Total N=30	p-value
- N	13	11	24	0.9299 *[2]
- Mean +/- SD	174.3 +/- 8.7	175.6 +/- 8.5	174.9 +/-8.5	
- p5, p25, p75, p95	158.0, 170.0, 180.0, 185.0	165.0, 170.0, 183.0, 191.0	160.0, 170.0, 181.5, 185.0	
- Median	175.0	175.0	175.0	
- Min, Max	158.0, 185.0	165.0, 191.0	158.0, 191.0	
- 95% CI Median	[170.0;185.0]	[170.0;185.0]	[170.0;180.0]	
BMI [kg/m^2]				
- N	13	11	24	0.4869 *[2]
- Mean +/- SD	27.4 +/- 5.0	26.5 +/- 5.2	27.0 +/-5.0	
- p5, p25, p75, p95	22.5, 23.4, 29.4, 40.1	20.8, 22.0, 28.4, 39.7	21.9, 23.4, 29.2, 39.7	
- Median	26.2	26.0	26.0	
- Min, Max	22.5, 40.1	20.8, 39.7	20.8, 40.1	
- 95% CI Median	[23.4;31.1]	[22.0;29.4]	[24.2;29.1]	
NIH Stroke Scale [0-42]				
- N	16	14	30	0.0091 *[2]
- Mean +/- SD	21.3 +/- 2.0	23.8 +/- 2.9	22.4 +/-2.8	
- p5, p25, p75, p95	19.0, 19.5, 23.0, 26.0	19.0, 22.0, 26.0, 31.0	19.0, 21.0, 24.0, 26.0	
- Median	21.0	23.5	22.0	
- Min, Max	19.0, 26.0	19.0, 31.0	19.0, 31.0	
- 95% CI Median	[20.0;23.0]	[22.0;26.0]	[21.0;23.0]	
premorbid Modified Rankin Scale [0-6]				
- N	16	14	30	0.9157 *[2]
- Mean +/- SD	0.1 +/- 0.3	0.1 +/- 0.4	0.1 +/-0.3	
- p5, p25, p75, p95	0.0, 0.0, 0.0, 1.0	0.0, 0.0, 0.0, 1.0	0.0, 0.0, 0.0, 1.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 1.0	0.0, 1.0	0.0, 1.0	
- 95% CI Median	[0.0;0.0]	[0.0;0.0]	[0.0;0.0]	
premorbid Modified Rankin Scale [0-6]				
- 0	14 (87.5%) [61.7%;98.4%]	12 (85.7%) [57.2%;98.2%]	26 (86.7%) [69.3%;96.2%]	0.8859 *[1]
- 1	2 (12.5%) [1.6%;38.3%]	2 (14.3%) [1.8%;42.8%]	4 (13.3%) [3.8%;30.7%]	
premorbid Barthel Index [0-100]				
- N	16	14	30	0.3162 *[2]
- Mean +/- SD	100.0 +/- 0.0	99.6 +/- 1.3	99.8 +/-0.9	
- p5, p25, p75, p95	100.0, 100.0, 100.0, 100.0	95.0, 100.0, 100.0, 100.0	100.0, 100.0, 100.0, 100.0	
- Median	100.0	100.0	100.0	
- Min, Max	100.0, 100.0	95.0, 100.0	95.0, 100.0	
- 95% CI Median	[100.0;100.0]	[100.0;100.0]	[100.0;100.0]	

	Surgery N=16	Standard N=14	Total N=30	p-value
Source of Information				
- Patient	2 (12.5%) [1.6%;38.3%]	0 (0.0%) [0.0%;23.2%]	2 (6.7%) [0.8%;22.1%]	0.4237 *[1]
- Relative	10 (62.5%) [35.4%;84.8%]	11 (78.6%) [49.2%;95.3%]	21 (70.0%) [50.6%;85.3%]	
- Examiner	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	
- Pat.+Exam.	2 (12.5%) [1.6%;38.3%]	0 (0.0%) [0.0%;23.2%]	2 (6.7%) [0.8%;22.1%]	
- Pat.+Rel.+Exam.	1 (6.3%) [0.2%;30.2%]	1 (7.1%) [0.2%;33.9%]	2 (6.7%) [0.8%;22.1%]	
- Pat.+Rel.	1 (6.3%) [0.2%;30.2%]	1 (7.1%) [0.2%;33.9%]	2 (6.7%) [0.8%;22.1%]	
Time from symptom onset [h]				
- N	16	14	30	0.5058 *[2]
- Mean +/- SD	24.4 +/- 7.1	23.1 +/- 7.5	23.8 +/-7.2	
- p5, p25, p75, p95	13.5, 18.1, 29.1, 36.0	12.0, 17.3, 28.0, 35.0	13.0, 17.4, 29.0, 35.0	
- Median	24.0	22.3	23.8	
- Min, Max	13.5, 36.0	12.0, 35.0	12.0, 36.0	
- 95% CI Median	[18.3;29.3]	[17.3;32.5]	[18.3;27.7]	
Hemisphere				
- dominant	8 (50.0%) [24.7%;75.3%]	10 (71.4%) [41.9%;91.6%]	18 (60.0%) [40.6%;77.3%]	0.2320 *[1]
- non-dominant	8 (50.0%) [24.7%;75.3%]	4 (28.6%) [8.4%;58.1%]	12 (40.0%) [22.7%;59.4%]	

*[1] = chi^2-Test *[2] = U-Test

Table 9-6: First day after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [0-100]				
- N	17	15	32	0.2501 *[2]
- Mean +/- SD	0.6 +/- 2.4	2.7 +/- 6.8	1.6 +/-5.0	
- p5, p25, p75, p95	0.0, 0.0, 0.0, 10.0	0.0, 0.0, 0.0, 25.0	0.0, 0.0, 0.0, 10.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 10.0	0.0, 25.0	0.0, 25.0	
Barthel Index [dichotomized]				
- failure (<=80%)	17 (100.0%) [80.5%;100.0%]	15 (100.0%) [78.2%;100.0%]	32 (100.0%) [89.1%;100.0%]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.8350 *[2]
- Mean +/- SD	29.2 +/- 6.9	30.1 +/- 6.1	29.6 +/-6.5	
- p5, p25, p75, p95	17.0, 23.0, 34.0, 38.0	18.0, 25.0, 36.0, 38.0	18.0, 24.0, 34.5, 38.0	
- Median	31.0	31.0	31.0	
- Min, Max	17.0, 38.0	18.0, 38.0	17.0, 38.0	
Modified Rankin Scale [0-6]				

	Surgery N=17	Standard N=15	Total N=32	p-value
- N	17	15	32	0.3164 *[2]
- Mean +/- SD	5.0 +/- 0.0	4.9 +/- 0.3	5.0 +/-0.2	
- p5, p25, p75, p95	5.0, 5.0, 5.0, 5.0	4.0, 5.0, 5.0, 5.0	5.0, 5.0, 5.0, 5.0	
- Median	5.0	5.0	5.0	
- Min, Max	5.0, 5.0	4.0, 5.0	4.0, 5.0	
- 95% CI Median	[5.0;5.0]	[5.0;5.0]	[5.0;5.0]	
Modified Rankin Scale [0-6]				
- 4	0 (0.0%) [0.0%;19.5%]	1 (6.7%) [0.2%;31.9%]	1 (3.1%) [0.1%;16.2%]	0.2794 *[1]
- 5	17 (100.0%) [80.5%;100.0%]	14 (93.3%) [68.1%;99.8%]	31 (96.9%) [83.8%;99.9%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	17 (100.0%) [80.5%;100.0%]	15 (100.0%) [78.2%;100.0%]	32 (100.0%) [89.1%;100.0%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	17 (100.0%) [80.5%;100.0%]	14 (93.3%) [68.1%;99.8%]	31 (96.9%) [83.8%;99.9%]	0.2794 *[1]
- success (0-4)	0 (0.0%) [0.0%;19.5%]	1 (6.7%) [0.2%;31.9%]	1 (3.1%) [0.1%;16.2%]	
Hemorrhage (PH1,PH2)				
- no	15 (88.2%) [63.6%;98.5%]	11 (78.6%) [49.2%;95.3%]	26 (83.9%) [66.3%;94.5%]	0.4666 *[1]
- yes	2 (11.8%) [1.5%;36.4%]	3 (21.4%) [4.7%;50.8%]	5 (16.1%) [5.5%;33.7%]	
Dislocation of axis				
- no	11 (64.7%) [38.3%;85.8%]	3 (21.4%) [4.7%;50.8%]	14 (45.2%) [27.3%;64.0%]	0.0160 *[1]
- yes	6 (35.3%) [14.2%;61.7%]	11 (78.6%) [49.2%;95.3%]	17 (54.8%) [36.0%;72.7%]	
Signs of incarceration				
- no	17 (100.0%) [80.5%;100.0%]	8 (57.1%) [28.9%;82.3%]	25 (80.6%) [62.5%;92.5%]	0.0026 *[1]
- yes	0 (0.0%) [0.0%;19.5%]	6 (42.9%) [17.7%;71.1%]	6 (19.4%) [7.5%;37.5%]	
Anaesthetics				
- no	17 (100.0%) [80.5%;100.0%]			
Bleeding				
- no	15 (88.2%) [63.6%;98.5%]			
- yes	2 (11.8%) [1.5%;36.4%]			
Wound infection				
- no	17 (100.0%) [80.5%;100.0%]			
Problems with wound healing				
- no	17 (100.0%) [80.5%;100.0%]			

	Surgery N=17	Standard N=15	Total N=32	p-value
Postoperative pain				
- no	14 (82.4%) [56.6%;96.2%]			
- yes	3 (17.6%) [3.8%;43.4%]			
Others				
- no	16 (94.1%) [71.3%;99.9%]			
- yes	1 (5.9%) [0.1%;28.7%]			

*[1] = chi[2] -Test *[2] = U-Test

Table 9-7: First day after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Barthel Index [0-100]				
- N	16	14	30	0.2457 *[2]
- Mean +/- SD	0.6 +/- 2.5	2.9 +/- 7.0	1.7 +/-5.1	
- p5, p25, p75, p95	0.0, 0.0, 0.0, 10.0	0.0, 0.0, 0.0, 25.0	0.0, 0.0, 0.0, 10.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 10.0	0.0, 25.0	0.0, 25.0	
Barthel Index [dichotomized]				
- failure (<=80%)	16 (100.0%) [79.4%;100.0%]	14 (100.0%) [76.8%;100.0%]	30 (100.0%) [88.4%;100.0%]	
NIH Stroke Scale [0-42]				
- N	16	14	30	1.0000 *[2]
- Mean +/- SD	29.8 +/- 6.7	30.1 +/- 6.3	29.9 +/-6.4	
- p5, p25, p75, p95	17.0, 24.5, 34.5, 38.0	18.0, 25.0, 36.0, 38.0	18.0, 25.0, 35.0, 38.0	
- Median	31.5	31.5	31.5	
- Min, Max	17.0, 38.0	18.0, 38.0	17.0, 38.0	
Modified Rankin Scale [0-6]				
- N	16	14	30	0.3162 *[2]
- Mean +/- SD	5.0 +/- 0.0	4.9 +/- 0.3	5.0 +/-0.2	
- p5, p25, p75, p95	5.0, 5.0, 5.0, 5.0	4.0, 5.0, 5.0, 5.0	5.0, 5.0, 5.0, 5.0	
- Median	5.0	5.0	5.0	
- Min, Max	5.0, 5.0	4.0, 5.0	4.0, 5.0	
- 95% CI Median	[5.0;5.0]	[5.0;5.0]	[5.0;5.0]	
Modified Rankin Scale [0-6]				
- 4	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	0.2769 *[1]
- 5	16 (100.0%) [79.4%;100.0%]	13 (92.9%) [66.1%;99.8%]	29 (96.7%) [82.8%;99.9%]	
Modified Rankin Scale [dichotomized]				

	Surgery N=16	Standard N=14	Total N=30	p-value
- failure (4-6)	16 (100.0%) [79.4%;100.0%]	14 (100.0%) [76.8%;100.0%]	30 (100.0%) [88.4%;100.0%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	16 (100.0%) [79.4%;100.0%]	13 (92.9%) [66.1%;99.8%]	29 (96.7%) [82.8%;99.9%]	0.2769 *[1]
- success (0-4)	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	
Hemorrhage (PH1,PH2)				
- no	14 (87.5%) [61.7%;98.4%]	10 (76.9%) [46.2%;95.0%]	24 (82.8%) [64.2%;94.2%]	0.4533 *[1]
- yes	2 (12.5%) [1.6%;38.3%]	3 (23.1%) [5.0%;53.8%]	5 (17.2%) [5.8%;35.8%]	
Dislocation of axis				
- no	11 (68.8%) [41.3%;89.0%]	3 (23.1%) [5.0%;53.8%]	14 (48.3%) [29.4%;67.5%]	0.0144 *[1]
- yes	5 (31.3%) [11.0%;58.7%]	10 (76.9%) [46.2%;95.0%]	15 (51.7%) [32.5%;70.6%]	
Signs of incarceration				
- no	16 (100.0%) [79.4%;100.0%]	8 (61.5%) [31.6%;86.1%]	24 (82.8%) [64.2%;94.2%]	0.0064 *[1]
- yes	0 (0.0%) [0.0%;20.6%]	5 (38.5%) [13.9%;68.4%]	5 (17.2%) [5.8%;35.8%]	
Anaesthetics				
- no	16 (100.0%) [79.4%;100.0%]			
Bleeding				
- no	14 (87.5%) [61.7%;98.4%]			
- yes	2 (12.5%) [1.6%;38.3%]			
Wound infection				
- no	16 (100.0%) [79.4%;100.0%]			
Problems with wound healing				
- no	16 (100.0%) [79.4%;100.0%]			
Postoperative pain				
- no	13 (81.3%) [54.4%;96.0%]			
- yes	3 (18.8%) [4.0%;45.6%]			
Others				
- no	15 (93.8%) [69.8%;99.8%]			
- yes	1 (6.3%) [0.2%;30.2%]			

*[1] = chi^2-Test *[2] = U-Test

Table 9-8: Day 7 after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [0-100]				
- N	17	15	32	0.1878 *[2]
- Mean +/- SD	4.1 +/- 6.9	1.7 +/- 4.5	3.0 +/-5.9	
- p5, p25, p75, p95	0.0, 0.0, 5.0, 20.0	0.0, 0.0, 0.0, 15.0	0.0, 0.0, 2.5, 20.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 20.0	0.0, 15.0	0.0, 20.0	
Barthel Index [dichotomized]				
- failure (<=80%)	17 (100.0%) [80.5%;100.0%]	15 (100.0%) [78.2%;100.0%]	32 (100.0%) [89.1%;100.0%]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.0011 *[2]
- Mean +/- SD	21.1 +/- 6.5	33.9 +/- 10.0	27.1 +/-10.4	
- p5, p25, p75, p95	16.0, 17.0, 22.0, 42.0	17.0, 27.0, 42.0, 42.0	16.0, 18.0, 42.0, 42.0	
- Median	19.0	42.0	23.0	
- Min, Max	16.0, 42.0	17.0, 42.0	16.0, 42.0	
Modified Rankin Scale [0-6]				
- N	17	15	32	0.0030 *[2]
- Mean +/- SD	5.0 +/- 0.4	5.5 +/- 0.5	5.3 +/-0.5	
- p5, p25, p75, p95	4.0, 5.0, 5.0, 6.0	5.0, 5.0, 6.0, 6.0	5.0, 5.0, 6.0, 6.0	
- Median	5.0	6.0	5.0	
- Min, Max	4.0, 6.0	5.0, 6.0	4.0, 6.0	
- 95% CI Median	[5.0;5.0]	[5.0;6.0]	[5.0;5.0]	
Modified Rankin Scale [0-6]				
- 4	1 (5.9%) [0.1%;28.7%]	0 (0.0%) [0.0%;21.8%]	1 (3.1%) [0.1%;16.2%]	0.0097 *[1]
- 5	15 (88.2%) [63.6%;98.5%]	7 (46.7%) [21.3%;73.4%]	22 (68.8%) [50.0%;83.9%]	
- 6	1 (5.9%) [0.1%;28.7%]	8 (53.3%) [26.6%;78.7%]	9 (28.1%) [13.7%;46.7%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	17 (100.0%) [80.5%;100.0%]	15 (100.0%) [78.2%;100.0%]	32 (100.0%) [89.1%;100.0%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	16 (94.1%) [71.3%;99.9%]	15 (100.0%) [78.2%;100.0%]	31 (96.9%) [83.8%;99.9%]	0.3399 *[1]
- success (0-4)	1 (5.9%) [0.1%;28.7%]	0 (0.0%) [0.0%;21.8%]	1 (3.1%) [0.1%;16.2%]	
Hemorrhage (PH1,PH2)				
- no	14 (87.5%) [61.7%;98.4%]	6 (75.0%) [34.9%;96.8%]	20 (83.3%) [62.6%;95.3%]	0.4386 *[1]
- yes	2 (12.5%) [1.6%;38.3%]	2 (25.0%) [3.2%;65.1%]	4 (16.7%) [4.7%;37.4%]	
- missing	1	7	8	
Dislocation of axis				

	Surgery N=17	Standard N=15	Total N=32	p-value
- no	10 (62.5%) [35.4%;84.8%]	3 (37.5%) [8.5%;75.5%]	13 (54.2%) [32.8%;74.4%]	0.2466 *[1]
- yes	6 (37.5%) [15.2%;64.6%]	5 (62.5%) [24.5%;91.5%]	11 (45.8%) [25.6%;67.2%]	
- missing	1	7	8	
Signs of incarceration				
- no	15 (93.8%) [69.8%;99.8%]	6 (75.0%) [34.9%;96.8%]	21 (87.5%) [67.6%;97.3%]	0.1904 *[1]
- yes	1 (6.3%) [0.2%;30.2%]	2 (25.0%) [3.2%;65.1%]	3 (12.5%) [2.7%;32.4%]	
- missing	1	7	8	
Anaesthetics				
- no	16 (100.0%) [79.4%;100.0%]			
- missing	1			
Bleeding				
- no	14 (87.5%) [61.7%;98.4%]			
- yes	2 (12.5%) [1.6%;38.3%]			
- missing	1			
Wound infection				
- no	16 (100.0%) [79.4%;100.0%]			
- missing	1			
Problems with wound healing				
- no	14 (87.5%) [61.7%;98.4%]			
- yes	2 (12.5%) [1.6%;38.3%]			
- missing	1			
Postoperative pain				
- no	14 (87.5%) [61.7%;98.4%]			
- yes	2 (12.5%) [1.6%;38.3%]			
- missing	1			
Others				
- no	16 (100.0%) [79.4%;100.0%]			
- missing	1			

*[1] = chi^2-Test *[2] = U-Test

Table 9-9: Day 7 after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Barthel Index [0-100]				
- N	16	14	30	0.1903 *[2]
- Mean +/- SD	4.4 +/- 7.0	1.8 +/- 4.6	3.2 +/-6.1	

	Surgery N=16	Standard N=14	Total N=30	p-value
- p5, p25, p75, p95	0.0, 0.0, 7.5, 20.0	0.0, 0.0, 0.0, 15.0	0.0, 0.0, 5.0, 20.0	
- Median	0.0	0.0	0.0	
- Min, Max	0.0, 20.0	0.0, 15.0	0.0, 20.0	
Barthel Index [dichotomized]				
- failure (<=80%)	16 (100.0%) [79.4%;100.0%]	14 (100.0%) [76.8%;100.0%]	30 (100.0%) [88.4%;100.0%]	
NIH Stroke Scale [0-42]				
- N	16	14	30	0.0017 *[2]
- Mean +/- SD	21.3 +/- 6.7	34.4 +/- 10.1	27.4 +/-10.7	
- p5, p25, p75, p95	16.0, 17.0, 23.0, 42.0	17.0, 27.0, 42.0, 42.0	16.0, 18.0, 42.0, 42.0	
- Median	18.5	42.0	23.0	
- Min, Max	16.0, 42.0	17.0, 42.0	16.0, 42.0	
Modified Rankin Scale [0-6]				
- N	16	14	30	0.0027 *[2]
- Mean +/- SD	5.0 +/- 0.4	5.6 +/- 0.5	5.3 +/-0.5	
- p5, p25, p75, p95	4.0, 5.0, 5.0, 6.0	5.0, 5.0, 6.0, 6.0	5.0, 5.0, 6.0, 6.0	
- Median	5.0	6.0	5.0	
- Min, Max	4.0, 6.0	5.0, 6.0	4.0, 6.0	
- 95% CI Median	[5.0;5.0]	[5.0;6.0]	[5.0;5.0]	
Modified Rankin Scale [0-6]				
- 4	1 (6.3%) [0.2%;30.2%]	0 (0.0%) [0.0%;23.2%]	1 (3.3%) [0.1%;17.2%]	0.0084 *[1]
- 5	14 (87.5%) [61.7%;98.4%]	6 (42.9%) [17.7%;71.1%]	20 (66.7%) [47.2%;82.7%]	
- 6	1 (6.3%) [0.2%;30.2%]	8 (57.1%) [28.9%;82.3%]	9 (30.0%) [14.7%;49.4%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	16 (100.0%) [79.4%;100.0%]	14 (100.0%) [76.8%;100.0%]	30 (100.0%) [88.4%;100.0%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	15 (93.8%) [69.8%;99.8%]	14 (100.0%) [76.8%;100.0%]	29 (96.7%) [82.8%;99.9%]	0.3414 *[1]
- success (0-4)	1 (6.3%) [0.2%;30.2%]	0 (0.0%) [0.0%;23.2%]	1 (3.3%) [0.1%;17.2%]	
Hemorrhage (PH1,PH2)				
- no	13 (86.7%) [59.5%;98.3%]	5 (71.4%) [29.0%;96.3%]	18 (81.8%) [59.7%;94.8%]	0.3881 *[1]
- yes	2 (13.3%) [1.7%;40.5%]	2 (28.6%) [3.7%;71.0%]	4 (18.2%) [5.2%;40.3%]	
- missing	1	7	8	
Dislocation of axis				
- no	10 (66.7%) [38.4%;88.2%]	3 (42.9%) [9.9%;81.6%]	13 (59.1%) [36.4%;79.3%]	0.2901 *[1]
- yes	5 (33.3%) [11.8%;61.6%]	4 (57.1%) [18.4%;90.1%]	9 (40.9%) [20.7%;63.6%]	
- missing	1	7	8	
Signs of incarceration				

	Surgery N=16	Standard N=14	Total N=30	p-value
- no	14 (93.3%) [68.1%;99.8%]	5 (71.4%) [29.0%;96.3%]	19 (86.4%) [65.1%;97.1%]	0.1632 *[1]
- yes	1 (6.7%) [0.2%;31.9%]	2 (28.6%) [3.7%;71.0%]	3 (13.6%) [2.9%;34.9%]	
- missing	1	7	8	
Anaesthetics				
- no	15 (100.0%) [78.2%;100.0%]			
- missing	1			
Bleeding				
- no	13 (86.7%) [59.5%;98.3%]			
- yes	2 (13.3%) [1.7%;40.5%]			
- missing	1			
Wound infection				
- no	15 (100.0%) [78.2%;100.0%]			
- missing	1			
Problems with wound healing				
- no	14 (93.3%) [68.1%;99.8%]			
- yes	1 (6.7%) [0.2%;31.9%]			
- missing	1			
Postoperative pain				
- no	13 (86.7%) [59.5%;98.3%]			
- yes	2 (13.3%) [1.7%;40.5%]			
- missing	1			
Others				
- no	15 (100.0%) [78.2%;100.0%]			
- missing	1			

*[1] = chi^2-Test *[2] = U-Test

Table 9-10: Day 30 after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [0-100]				
- N	17	15	32	0.0502 *[2]
- Mean +/- SD	20.3 +/- 16.4	10.3 +/- 19.8	15.6 +/-18.5	
- p5, p25, p75, p95	0.0, 0.0, 30.0, 45.0	0.0, 0.0, 10.0, 65.0	0.0, 0.0, 25.0, 45.0	
- Median	20.0	0.0	10.0	
- Min, Max	0.0, 45.0	0.0, 65.0	0.0, 65.0	
- 95% CI Median	[0.0;30.0]	[0.0;10.0]	[0.0;25.0]	

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [dichotomized]				
- failure (<=80%)	17 (100.0%) [80.5%;100.0%]	15 (100.0%) [78.2%;100.0%]	32 (100.0%) [89.1%;100.0%]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.0047 *[2]
- Mean +/- SD	18.1 +/- 10.1	30.9 +/- 12.6	24.1 +/-12.9	
- p5, p25, p75, p95	7.0, 11.0, 20.0, 42.0	14.0, 17.0, 42.0, 42.0	9.0, 14.5, 42.0, 42.0	
- Median	15.0	42.0	19.0	
- Min, Max	7.0, 42.0	14.0, 42.0	7.0, 42.0	
- 95% CI Median	[11.0;20.0]	[17.0;42.0]	[15.0;42.0]	
Modified Rankin Scale [0-6]				
- N	17	15	32	0.0166 *[2]
- Mean +/- SD	4.5 +/- 0.7	5.3 +/- 1.0	4.9 +/-0.9	
- p5, p25, p75, p95	4.0, 4.0, 5.0, 6.0	3.0, 5.0, 6.0, 6.0	4.0, 4.0, 6.0, 6.0	
- Median	4.0	6.0	5.0	
- Min, Max	4.0, 6.0	3.0, 6.0	3.0, 6.0	
- 95% CI Median	[4.0;5.0]	[5.0;6.0]	[4.0;6.0]	
Modified Rankin Scale [0-6]				
- 3	0 (0.0%) [0.0%;19.5%]	1 (6.7%) [0.2%;31.9%]	1 (3.1%) [0.1%;16.2%]	0.0189 *[1]
- 4	10 (58.8%) [32.9%;81.6%]	2 (13.3%) [1.7%;40.5%]	12 (37.5%) [21.1%;56.3%]	
- 5	5 (29.4%) [10.3%;56.0%]	4 (26.7%) [7.8%;55.1%]	9 (28.1%) [13.7%;46.7%]	
- 6	2 (11.8%) [1.5%;36.4%]	8 (53.3%) [26.6%;78.7%]	10 (31.3%) [16.1%;50.0%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	17 (100.0%) [80.5%;100.0%]	14 (93.3%) [68.1%;99.8%]	31 (96.9%) [83.8%;99.9%]	0.2794 *[1]
- success (0-3)	0 (0.0%) [0.0%;19.5%]	1 (6.7%) [0.2%;31.9%]	1 (3.1%) [0.1%;16.2%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	7 (41.2%) [18.4%;67.1%]	12 (80.0%) [51.9%;95.7%]	19 (59.4%) [40.6%;76.3%]	0.0256 *[1]
- success (0-4)	10 (58.8%) [32.9%;81.6%]	3 (20.0%) [4.3%;48.1%]	13 (40.6%) [23.7%;59.4%]	
Mortality				
- alive	15 (88.2%) [63.6%;98.5%]	7 (46.7%) [21.3%;73.4%]	22 (68.8%) [50.0%;83.9%]	0.0114 *[1]
- death	2 (11.8%) [1.5%;36.4%]	8 (53.3%) [26.6%;78.7%]	10 (31.3%) [16.1%;50.0%]	
Anaesthetics				
- no	15 (100.0%) [78.2%;100.0%]			
- missing	2			
Bleeding				
- no	15 (100.0%) [78.2%;100.0%]			
- missing	2			

	Surgery N=17	Standard N=15	Total N=32	p-value
Wound infection				
- no	14 (93.3%) [68.1%;99.8%]			
- yes	1 (6.7%) [0.2%;31.9%]			
- missing	2			
Problems with wound healing				
- no	12 (80.0%) [51.9%;95.7%]			
- yes	3 (20.0%) [4.3%;48.1%]			
- missing	2			
Postoperative pain				
- no	14 (93.3%) [68.1%;99.8%]			
- yes	1 (6.7%) [0.2%;31.9%]			
- missing	2			
Others				
- no	14 (93.3%) [68.1%;99.8%]			
- yes	1 (6.7%) [0.2%;31.9%]			
- missing	2			

*[1] = chi^2-Test *[2] = U-Test

Table 9-11: Day 30 after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Barthel Index [0-100]				
- N	16	14	30	0.0246 *[2]
- Mean +/- SD	20.0 +/- 16.9	7.9 +/- 17.9	14.3 +/-18.2	
- p5, p25, p75, p95	0.0, 0.0, 32.5, 45.0	0.0, 0.0, 10.0, 65.0	0.0, 0.0, 25.0, 45.0	
- Median	20.0	0.0	5.0	
- Min, Max	0.0, 45.0	0.0, 65.0	0.0, 65.0	
- 95% CI Median	[0.0;35.0]	[0.0;10.0]	[0.0;20.0]	
Barthel Index [dichotomized]				
- failure (<=80%)	16 (100.0%) [79.4%;100.0%]	14 (100.0%) [76.8%;100.0%]	30 (100.0%) [88.4%;100.0%]	
NIH Stroke Scale [0-42]				
- N	16	14	30	0.0030 *[2]
- Mean +/- SD	18.1 +/- 10.5	32.0 +/- 12.2	24.6 +/-13.2	
- p5, p25, p75, p95	7.0, 11.0, 20.0, 42.0	14.0, 20.0, 42.0, 42.0	9.0, 14.0, 42.0, 42.0	
- Median	15.0	42.0	20.0	
- Min, Max	7.0, 42.0	14.0, 42.0	7.0, 42.0	
- 95% CI Median	[11.0;20.0]	[20.0;42.0]	[15.0;42.0]	

	Surgery N=16	Standard N=14	Total N=30	p-value
Modified Rankin Scale [0-6]				
- N	16	14	30	0.0251 *[2]
- Mean +/- SD	4.6 +/- 0.7	5.3 +/- 1.0	4.9 +/-0.9	
- p5, p25, p75, p95	4.0, 4.0, 5.0, 6.0	3.0, 5.0, 6.0, 6.0	4.0, 4.0, 6.0, 6.0	
- Median	4.0	6.0	5.0	
- Min, Max	4.0, 6.0	3.0, 6.0	3.0, 6.0	
- 95% CI Median	[4.0;5.0]	[5.0;6.0]	[4.0;6.0]	
Modified Rankin Scale [0-6]				
- 3	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	0.0237 *[1]
- 4	9 (56.3%) [29.9%;80.2%]	2 (14.3%) [1.8%;42.8%]	11 (36.7%) [19.9%;56.1%]	
- 5	5 (31.3%) [11.0%;58.7%]	3 (21.4%) [4.7%;50.8%]	8 (26.7%) [12.3%;45.9%]	
- 6	2 (12.5%) [1.6%;38.3%]	8 (57.1%) [28.9%;82.3%]	10 (33.3%) [17.3%;52.8%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	16 (100.0%) [79.4%;100.0%]	13 (92.9%) [66.1%;99.8%]	29 (96.7%) [82.8%;99.9%]	0.2769 *[1]
- success (0-3)	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	7 (43.8%) [19.8%;70.1%]	11 (78.6%) [49.2%;95.3%]	18 (60.0%) [40.6%;77.3%]	0.0521 *[1]
- success (0-4)	9 (56.3%) [29.9%;80.2%]	3 (21.4%) [4.7%;50.8%]	12 (40.0%) [22.7%;59.4%]	
Mortality				
- alive	14 (87.5%) [61.7%;98.4%]	6 (42.9%) [17.7%;71.1%]	20 (66.7%) [47.2%;82.7%]	0.0097 *[1]
- death	2 (12.5%) [1.6%;38.3%]	8 (57.1%) [28.9%;82.3%]	10 (33.3%) [17.3%;52.8%]	
Anaesthetics				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	2			
Bleeding				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	2			
Wound infection				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	2			
Problems with wound healing				
- no	12 (85.7%) [57.2%;98.2%]			
- yes	2 (14.3%) [1.8%;42.8%]			
- missing	2			
Postoperative pain				
- no	14 (100.0%) [76.8%;100.0%]			

	Surgery N=16	Standard N=14	Total N=30	p-value
- missing	2			
Others				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	2			

*[1] = chi[2] -Test *[2] = U-Test

Table 9-12: 6 months after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [ordinal 100-0]				
- N	17	15	32	0.0759 *[2]
- Mean +/- SD	45.9 +/- 30.5	25.0 +/- 34.2	36.1 +/-33.5	
- p5, p25, p75, p95	0.0, 20.0, 75.0, 85.0	0.0, 0.0, 70.0, 85.0	0.0, 0.0, 70.0, 85.0	
- Median	50.0	0.0	35.0	
- Min, Max	0.0, 85.0	0.0, 85.0	0.0, 85.0	
- 95% CI Median	[20.0;75.0]	[0.0;70.0]	[0.0;70.0]	
Barthel Index [dichotomized]				
- failure (<=80%)	16 (94.1%) [71.3%;99.9%]	14 (93.3%) [68.1%;99.8%]	30 (93.8%) [79.2%;99.2%]	0.9271 *[1]
- success (>80%)	1 (5.9%) [0.1%;28.7%]	1 (6.7%) [0.2%;31.9%]	2 (6.3%) [0.8%;20.8%]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.0447 *[2]
- Mean +/- SD	17.7 +/- 12.4	28.7 +/- 15.0	22.9 +/-14.6	
- p5, p25, p75, p95	5.0, 10.0, 19.0, 42.0	8.0, 12.0, 42.0, 42.0	7.0, 11.0, 42.0, 42.0	
- Median	14.0	42.0	16.0	
- Min, Max	5.0, 42.0	8.0, 42.0	5.0, 42.0	
- 95% CI Median	[10.0;19.0]	[12.0;42.0]	[12.0;42.0]	
Modified Rankin Scale [0-6]				
- N	17	15	32	0.0417 *[2]
- Mean +/- SD	3.9 +/- 1.2	4.9 +/- 1.3	4.4 +/-1.4	
- p5, p25, p75, p95	2.0, 3.0, 4.0, 6.0	3.0, 3.0, 6.0, 6.0	3.0, 3.0, 6.0, 6.0	
- Median	4.0	6.0	4.0	
- Min, Max	2.0, 6.0	3.0, 6.0	2.0, 6.0	
- 95% CI Median	[3.0;4.0]	[3.0;6.0]	[3.0;6.0]	
Modified Rankin Scale [0-6]				
- 2	1 (5.9%) [0.1%;28.7%]	0 (0.0%) [0.0%;21.8%]	1 (3.1%) [0.1%;16.2%]	0.1362 *[1]
- 3	7 (41.2%) [18.4%;67.1%]	4 (26.7%) [7.8%;55.1%]	11 (34.4%) [18.6%;53.2%]	
- 4	5 (29.4%) [10.3%;56.0%]	1 (6.7%) [0.2%;31.9%]	6 (18.8%) [7.2%;36.4%]	
- 5	1 (5.9%) [0.1%;28.7%]	2 (13.3%) [1.7%;40.5%]	3 (9.4%) [2.0%;25.0%]	
- 6	3 (17.6%) [3.8%;43.4%]	8 (53.3%) [26.6%;78.7%]	11 (34.4%) [18.6%;53.2%]	

	Surgery N=17	Standard N=15	Total N=32	p-value
Modified Rankin Scale [dichotomized]				
- failure (4-6)	9 (52.9%) [27.8%;77.0%]	11 (73.3%) [44.9%;92.2%]	20 (62.5%) [43.7%;78.9%]	0.2344 *[1]
- success (0-3)	8 (47.1%) [23.0%;72.2%]	4 (26.7%) [7.8%;55.1%]	12 (37.5%) [21.1%;56.3%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	4 (23.5%) [6.8%;49.9%]	10 (66.7%) [38.4%;88.2%]	14 (43.8%) [26.4%;62.3%]	0.0141 *[1]
- success (0-4)	13 (76.5%) [50.1%;93.2%]	5 (33.3%) [11.8%;61.6%]	18 (56.3%) [37.7%;73.6%]	
Mortality				
- alive	14 (82.4%) [56.6%;96.2%]	7 (46.7%) [21.3%;73.4%]	21 (65.6%) [46.8%;81.4%]	0.0339 *[1]
- death	3 (17.6%) [3.8%;43.4%]	8 (53.3%) [26.6%;78.7%]	11 (34.4%) [18.6%;53.2%]	
Anaesthetics				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Bleeding				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Wound infection				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Problems with wound healing				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Postoperative pain				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Others				
- no	13 (92.9%) [66.1%;99.8%]			
- yes	1 (7.1%) [0.2%;33.9%]			
- missing	3			
Patients with at least one complication during 6 months				
Bleeding	2 (11.8%) [1.5%;36.4%]			
Wound infection	1 (5.9%) [0.1%;28.7%]			
Problems with wound healing	3 (17.6%) [3.8%;43.4%]			
Postoperative pain	6 (35.3%) [14.2%;61.7%]			

	Surgery N=17	Standard N=15	Total N=32	p-value
Other	3 (17.6%) [3.8%;43.4%]			

*[1] = chi[2] -Test *[2] = U-Test

Table 9-13: 6 months after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Barthel Index [ordinal 100-0]				
- N	16	14	30	0.0696 *[2]
- Mean +/- SD	47.5 +/- 30.7	23.6 +/- 35.1	36.3 +/-34.4	
- p5, p25, p75, p95	0.0, 22.5, 75.0, 85.0	0.0, 0.0, 70.0, 85.0	0.0, 0.0, 70.0, 85.0	
- Median	52.5	0.0	35.0	
- Min, Max	0.0, 85.0	0.0, 85.0	0.0, 85.0	
- 95% CI Median	[30.0;75.0]	[0.0;70.0]	[0.0;70.0]	
Barthel Index [dichotomized]				
- failure (<=80%)	15 (93.8%) [69.8%;99.8%]	13 (92.9%) [66.1%;99.8%]	28 (93.3%) [77.9%;99.2%]	0.9221 *[1]
- success (>80%)	1 (6.3%) [0.2%;30.2%]	1 (7.1%) [0.2%;33.9%]	2 (6.7%) [0.8%;22.1%]	
NIH Stroke Scale [0-42]				
- N	16	14	30	0.0264 *[2]
- Mean +/- SD	17.4 +/- 12.8	29.9 +/- 14.8	23.2 +/-14.9	
- p5, p25, p75, p95	5.0, 9.0, 17.5, 42.0	8.0, 14.0, 42.0, 42.0	7.0, 11.0, 42.0, 42.0	
- Median	13.0	42.0	16.0	
- Min, Max	5.0, 42.0	8.0, 42.0	5.0, 42.0	
- 95% CI Median	[10.0;19.0]	[14.0;42.0]	[11.0;42.0]	
Modified Rankin Scale [0-6]				
- N	16	14	30	0.0415 *[2]
- Mean +/- SD	3.9 +/- 1.3	5.0 +/- 1.4	4.4 +/-1.4	
- p5, p25, p75, p95	2.0, 3.0, 4.5, 6.0	3.0, 3.0, 6.0, 6.0	3.0, 3.0, 6.0, 6.0	
- Median	3.5	6.0	4.0	
- Min, Max	2.0, 6.0	3.0, 6.0	2.0, 6.0	
- 95% CI Median	[3.0;5.0]	[3.0;6.0]	[3.0;6.0]	
Modified Rankin Scale [0-6]				
- 2	1 (6.3%) [0.2%;30.2%]	0 (0.0%) [0.0%;23.2%]	1 (3.3%) [0.1%;17.2%]	0.0803 *[1]
- 3	7 (43.8%) [19.8%;70.1%]	4 (28.6%) [8.4%;58.1%]	11 (36.7%) [19.9%;56.1%]	
- 4	4 (25.0%) [7.3%;52.4%]	0 (0.0%) [0.0%;23.2%]	4 (13.3%) [3.8%;30.7%]	
- 5	1 (6.3%) [0.2%;30.2%]	2 (14.3%) [1.8%;42.8%]	3 (10.0%) [2.1%;26.5%]	
- 6	3 (18.8%) [4.0%;45.6%]	8 (57.1%) [28.9%;82.3%]	11 (36.7%) [19.9%;56.1%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	8 (50.0%) [24.7%;75.3%]	10 (71.4%) [41.9%;91.6%]	18 (60.0%) [40.6%;77.3%]	0.2320 *[1]
- success (0-3)	8 (50.0%) [24.7%;75.3%]	4 (28.6%) [8.4%;58.1%]	12 (40.0%) [22.7%;59.4%]	

	Surgery N=16	Standard N=14	Total N=30	p-value
Modified Rankin Scale [dichotomized]				
- failure (5+6)	4 (25.0%) [7.3%;52.4%]	10 (71.4%) [41.9%;91.6%]	14 (46.7%) [28.3%;65.7%]	0.0110 *[1]
- success (0-4)	12 (75.0%) [47.6%;92.7%]	4 (28.6%) [8.4%;58.1%]	16 (53.3%) [34.3%;71.7%]	
Mortality				
- alive	13 (81.3%) [54.4%;96.0%]	6 (42.9%) [17.7%;71.1%]	19 (63.3%) [43.9%;80.1%]	0.0295 *[1]
- death	3 (18.8%) [4.0%;45.6%]	8 (57.1%) [28.9%;82.3%]	11 (36.7%) [19.9%;56.1%]	
Anaesthetics				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Bleeding				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Wound infection				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Problems with wound healing				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Postoperative pain				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Others				
- no	12 (92.3%) [64.0%;99.8%]			
- yes	1 (7.7%) [0.2%;36.0%]			
- missing	3			
Patients with at least one complication during 6 months				
Bleeding	2 (12.5%) [1.6%;38.3%]			
Problems with wound healing	2 (12.5%) [1.6%;38.3%]			
Postoperative pain	5 (31.3%) [11.0%;58.7%]			
Other	2 (12.5%) [1.6%;38.3%]			

*[1] = chi^2-Test *[2] = U-Test

Table 9-14: 1 year after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Barthel Index [0-100]				
- N	17	15	32	0.0691 *[2]
- Mean +/- SD	50.6 +/- 36.2	29.0 +/- 37.4	40.5 +/-37.8	
- p5, p25, p75, p95	0.0, 30.0, 85.0, 95.0	0.0, 0.0, 70.0, 95.0	0.0, 0.0, 85.0, 95.0	
- Median	45.0	0.0	30.0	
- Min, Max	0.0, 95.0	0.0, 95.0	0.0, 95.0	
- 95% CI Median	[30.0;85.0]	[0.0;70.0]	[0.0;85.0]	
Barthel Index [dichotomized]				
- failure (<=80%)	10 (58.8%) [32.9%;81.6%]	12 (80.0%) [51.9%;95.7%]	22 (68.8%) [50.0%;83.9%]	0.1972 *[1]
- success (>80%)	7 (41.2%) [18.4%;67.1%]	3 (20.0%) [4.3%;48.1%]	10 (31.3%) [16.1%;50.0%]	
NIH Stroke Scale [0-42]				
- N	17	15	32	0.0535 *[2]
- Mean +/- SD	16.4 +/- 12.8	27.7 +/- 16.1	21.7 +/-15.3	
- p5, p25, p75, p95	5.0, 7.0, 17.0, 42.0	6.0, 10.0, 42.0, 42.0	6.0, 9.5, 42.0, 42.0	
- Median	13.0	42.0	14.0	
- Min, Max	5.0, 42.0	6.0, 42.0	5.0, 42.0	
- 95% CI Median	[7.0;17.0]	[10.0;42.0]	[10.0;42.0]	
Modified Rankin Scale [0-6]				
- N	17	15	32	0.0370 *[2]
- Mean +/- SD	3.7 +/- 1.4	4.9 +/- 1.5	4.3 +/-1.5	
- p5, p25, p75, p95	2.0, 3.0, 4.0, 6.0	2.0, 3.0, 6.0, 6.0	2.0, 3.0, 6.0, 6.0	
- Median	4.0	6.0	4.0	
- Min, Max	2.0, 6.0	2.0, 6.0	2.0, 6.0	
- 95% CI Median	[3.0;4.0]	[3.0;6.0]	[3.0;6.0]	
Modified Rankin Scale [0-6]				
- 2	4 (23.5%) [6.8%;49.9%]	1 (6.7%) [0.2%;31.9%]	5 (15.6%) [5.3%;32.8%]	0.1298 *[1]
- 3	4 (23.5%) [6.8%;49.9%]	3 (20.0%) [4.3%;48.1%]	7 (21.9%) [9.3%;40.0%]	
- 4	5 (29.4%) [10.3%;56.0%]	1 (6.7%) [0.2%;31.9%]	6 (18.8%) [7.2%;36.4%]	
- 5	1 (5.9%) [0.1%;28.7%]	2 (13.3%) [1.7%;40.5%]	3 (9.4%) [2.0%;25.0%]	
- 6	3 (17.6%) [3.8%;43.4%]	8 (53.3%) [26.6%;78.7%]	11 (34.4%) [18.6%;53.2%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	9 (52.9%) [27.8%;77.0%]	11 (73.3%) [44.9%;92.2%]	20 (62.5%) [43.7%;78.9%]	0.2344 *[1]
- success (0-3)	8 (47.1%) [23.0%;72.2%]	4 (26.7%) [7.8%;55.1%]	12 (37.5%) [21.1%;56.3%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	4 (23.5%) [6.8%;49.9%]	10 (66.7%) [38.4%;88.2%]	14 (43.8%) [26.4%;62.3%]	0.0141 *[1]
- success (0-4)	13 (76.5%) [50.1%;93.2%]	5 (33.3%) [11.8%;61.6%]	18 (56.3%) [37.7%;73.6%]	

	Surgery N=17	Standard N=15	Total N=32	p-value
Mortality				
- alive	14 (82.4%) [56.6%;96.2%]	7 (46.7%) [21.3%;73.4%]	21 (65.6%) [46.8%;81.4%]	0.0339 *[1]
- death	3 (17.6%) [3.8%;43.4%]	8 (53.3%) [26.6%;78.7%]	11 (34.4%) [18.6%;53.2%]	
Anaesthetics				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Bleeding				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Wound infection				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Problems with wound healing				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Postoperative pain				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			
Others				
- no	14 (100.0%) [76.8%;100.0%]			
- missing	3			

*[1] = chi^2-Test *[2] = U-Test

Table 9-15: 1 year after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Barthel Index [0-100]				
- N	16	14	30	0.0543 *[2]
- Mean +/- SD	51.9 +/- 37.0	27.5 +/- 38.3	40.5 +/-39.0	
- p5, p25, p75, p95	0.0, 20.0, 87.5, 95.0	0.0, 0.0, 70.0, 95.0	0.0, 0.0, 85.0, 95.0	
- Median	50.0	0.0	30.0	
- Min, Max	0.0, 95.0	0.0, 95.0	0.0, 95.0	
- 95% CI Median	[30.0;90.0]	[0.0;85.0]	[0.0;85.0]	
Barthel Index [dichotomized]				
- failure (<=80%)	9 (56.3%) [29.9%;80.2%]	11 (78.6%) [49.2%;95.3%]	20 (66.7%) [47.2%;82.7%]	0.1957 *[1]
- success (>80%)	7 (43.8%) [19.8%;70.1%]	3 (21.4%) [4.7%;50.8%]	10 (33.3%) [17.3%;52.8%]	

	Surgery N=16	Standard N=14	Total N=30	p-value
NIH Stroke Scale [0-42]				
- N	16	14	30	0.0264 *[2]
- Mean +/- SD	16.2 +/- 13.2	29.1 +/- 15.8	22.2 +/-15.6	
- p5, p25, p75, p95	5.0, 7.0, 15.5, 42.0	6.0, 14.0, 42.0, 42.0	6.0, 10.0, 42.0, 42.0	
- Median	12.0	42.0	14.0	
- Min, Max	5.0, 42.0	6.0, 42.0	5.0, 42.0	
- 95% CI Median	[7.0;17.0]	[14.0;42.0]	[10.0;42.0]	
Modified Rankin Scale [0-6]				
- N	16	14	30	0.0367 *[2]
- Mean +/- SD	3.7 +/- 1.4	4.9 +/- 1.5	4.3 +/-1.6	
- p5, p25, p75, p95	2.0, 2.5, 4.5, 6.0	2.0, 3.0, 6.0, 6.0	2.0, 3.0, 6.0, 6.0	
- Median	3.5	6.0	4.0	
- Min, Max	2.0, 6.0	2.0, 6.0	2.0, 6.0	
- 95% CI Median	[3.0;5.0]	[3.0;6.0]	[3.0;6.0]	
Modified Rankin Scale [0-6]				
- 2	4 (25.0%) [7.3%;52.4%]	1 (7.1%) [0.2%;33.9%]	5 (16.7%) [5.6%;34.7%]	0.0763 *[1]
- 3	4 (25.0%) [7.3%;52.4%]	3 (21.4%) [4.7%;50.8%]	7 (23.3%) [9.9%;42.3%]	
- 4	4 (25.0%) [7.3%;52.4%]	0 (0.0%) [0.0%;23.2%]	4 (13.3%) [3.8%;30.7%]	
- 5	1 (6.3%) [0.2%;30.2%]	2 (14.3%) [1.8%;42.8%]	3 (10.0%) [2.1%;26.5%]	
- 6	3 (18.8%) [4.0%;45.6%]	8 (57.1%) [28.9%;82.3%]	11 (36.7%) [19.9%;56.1%]	
Modified Rankin Scale [dichotomized]				
- failure (4-6)	8 (50.0%) [24.7%;75.3%]	10 (71.4%) [41.9%;91.6%]	18 (60.0%) [40.6%;77.3%]	0.2320 *[1]
- success (0-3)	8 (50.0%) [24.7%;75.3%]	4 (28.6%) [8.4%;58.1%]	12 (40.0%) [22.7%;59.4%]	
Modified Rankin Scale [dichotomized]				
- failure (5+6)	4 (25.0%) [7.3%;52.4%]	10 (71.4%) [41.9%;91.6%]	14 (46.7%) [28.3%;65.7%]	0.0110 *[1]
- success (0-4)	12 (75.0%) [47.6%;92.7%]	4 (28.6%) [8.4%;58.1%]	16 (53.3%) [34.3%;71.7%]	
Mortality				
- alive	13 (81.3%) [54.4%;96.0%]	6 (42.9%) [17.7%;71.1%]	19 (63.3%) [43.9%;80.1%]	0.0295 *[1]
- death	3 (18.8%) [4.0%;45.6%]	8 (57.1%) [28.9%;82.3%]	11 (36.7%) [19.9%;56.1%]	
Anaesthetics				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Bleeding				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			

	Surgery N=16	Standard N=14	Total N=30	p-value
Wound infection				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Problems with wound healing				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Postoperative pain				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			
Others				
- no	13 (100.0%) [75.3%;100.0%]			
- missing	3			

*[1] = chi^2-Test *[2] = U-Test

Table 9-16: Barthel by group and visit (FAS)

	Surgery N=17			Standard N=15		
Visit	N	Median	Prop. Success >80	N	Median	Prop. Success >80
Day 1	17	0.0	0 (0.0%)	15	0.0	0 (0.0%)
Day 7	17	0.0	0 (0.0%)	15	0.0	0 (0.0%)
Day 30	17	20.0	0 (0.0%)	15	0.0	0 (0.0%)
6 Months	17	50.0	1 (5.9%)	15	0.0	1 (6.7%)
1 Year	17	45.0	7 (41.2%)	15	0.0	3 (20.0%)

Table 9-17: Barthel by group and visit (PP)

	Surgery N=16			Standard N=14		
Visit	N	Median	Prop. Success >80	N	Median	Prop. Success >80
Day 1	16	0.0	0 (0.0%)	14	0.0	0 (0.0%)
Day 7	16	0.0	0 (0.0%)	14	0.0	0 (0.0%)
Day 30	16	20.0	0 (0.0%)	14	0.0	0 (0.0%)
6 Months	16	52.5	1 (6.3%)	14	0.0	1 (7.1%)
1 Year	16	50.0	7 (43.8%)	14	0.0	3 (21.4%)

Table 9-18: NIHSS by group and visit (FAS)

	Surgery N=17		Standard N=15	
Visit	**N**	**Median**	**N**	**Median**
Screen.	17	21.0	15	24.0
Day 1	17	31.0	15	31.0
Day 7	17	19.0	15	42.0
Day 30	17	15.0	15	42.0
6 Months	17	14.0	15	42.0
1 Year	17	13.0	15	42.0

Table 9-19: NIHSS by group and visit (PP)

	Surgery N=16		Standard N=14	
Visit	**N**	**Median**	**N**	**Median**
Screen.	16	21.0	14	23.5
Day 1	16	31.5	14	31.5
Day 7	16	18.5	14	42.0
Day 30	16	15.0	14	42.0
6 Months	16	13.0	14	42.0
1 Year	16	12.0	14	42.0

Table 9-20: mRS by group and visit (FAS)

	Surgery N=17			Standard N=15		
Visit	**N**	**Median**	**Prop. Success <4**	**N**	**Median**	**Prop. Success <4**
Day 1	17	5.0	0 (0.0%)	15	5.0	0 (0.0%)
Day 7	17	5.0	0 (0.0%)	15	6.0	0 (0.0%)
Day 30	17	4.0	0 (0.0%)	15	6.0	1 (6.7%)
6 Months	17	4.0	8 (47.1%)	15	6.0	4 (26.7%)
1 Year	17	4.0	8 (47.1%)	15	6.0	4 (26.7%)

Table 9-21: mRS by group and visit (PP)

	Surgery N=16			Standard N=14		
Visit	N	Median	Prop. Success <4	N	Median	Prop. Success <4
Day 1	16	5.0	0 (0.0%)	14	5.0	0 (0.0%)
Day 7	16	5.0	0 (0.0%)	14	6.0	0 (0.0%)
Day 30	16	4.0	0 (0.0%)	14	6.0	1 (7.1%)
6 Months	16	3.5	8 (50.0%)	14	6.0	4 (28.6%)
1 Year	16	3.5	8 (50.0%)	14	6.0	4 (28.6%)

Table 9-22: Analyses of the primary endpoint (6-months)

	Surgery	Standard	Total	Croup Comparison
mRS (FAS)	N=17	N=15	N=32	p_{Chi} =0.2344
- failure (4-6)	9 (52.9%)	11 (73.3%)	20 (62.5%)	p_{Fisher} =0.2907
- success (0-3)	8 (47.1%)	4 (26.7%)	12 (37.5%)	OR=0.409 [0.092, 1.813]
mRS (FAS, survivors only)	N=14	N=7	N=21	p_{Chi} =1.0000
- failure (4-5)	6 (42.9%)	3 (42.9%)	9 (42.9%)	p_{Fisher} =1.0000
- success (0-3)	8 (57.1%)	4 (57.1%)	12 (57.1%)	OR=1.000 [0.160, 6.255]
mRS (PP)	N=16	N=14	N=30	p_{Chi} =0.2930
- failure (4-6)	9 (52.9%)	10 (71.4%)	19 (61.3%)	p_{Fisher} =0.4607
- success (0-3)	8 (47.1%)	4 (28.6%)	12 (38.7%)	OR=0.450 [0.100, 2.018]
mRS (PP, survivors only)	N=14	N=6	N=20	p_{Chi} =0.6903
- failure (4-5)	6 (42.9%)	2 (33.3%)	8 (40.0%)	p_{Fisher} =1.0000
- success (0-3)	8 (57.1%)	4 (66.7%)	12 (60.0%)	OR=1.500 [0.203, 11.09]
mRS (FAS, incl. centre as factor)	N=17	N=15	N=32	p_{CMH} =0.2388
number of successes				OR=0.397 [0.088, 1.787]
HD/MA (N=26)	6 (42.9%)	3 (25.0%)	9 (34.6%)	
WÜ/GR/L/K (N=6)	2 (66.7%)	1 (33.3%)	3 (50.0%)	

	Surgery	Standard	Total	Croup Comparison
mRS (PP, incl. centre as factor)	N=16	N=14	N=30	p_{CMH} =0.3236
number of successes				OR=0.453 [0.098, 2.090]
HD/MA (N=26)	6 (42.9%)	3 (25.0%)	9 (34.6%)	
WÜ/GR/L/K (N=5)	2 (66.7%)	1 (50.0%)	3 (60.0%)	

p-value for sequential test procedure was 0.0195, therefore adjusted p-values (max(p-value,0.0195)) do not differ. (SAP page 9)

Table 9-23: One, six twelve months mortality by group (Chi^2 and logrank-test) (FAS)

Visit	Surgery N=17	Standard N=15	Total N=32	Chi^2	Log Rank
Day 30	2 (11.8%)	8 (53.3%)	10 (31.3%)	0.0114 *[1]	0.0031
6 Months	3 (17.6%)	8 (53.3%)	11 (34.4%)	0.0339 *[1]	0.0207
1 Year	3 (17.6%)	8 (53.3%)	11 (34.4%)	0.0339 *[1]	0.0279

Table 9-24: One, six twelve months mortality by group (Chi^2 and logrank-test) (PP)

Visit	Surgery N=16	Standard N=14	Total N=30	Chi^2	Log Rank
Day 30	2 (12.5%)	8 (57.1%)	10 (33.3%)	0.0097 *[1]	0.0026
6 Months	3 (18.8%)	8 (57.1%)	11 (36.7%)	0.0295 *[1]	0.0167
1 Year	3 (18.8%)	8 (57.1%)	11 (36.7%)	0.0295 *[1]	0.0232

Table 9-25: SF36 - 1 year after randomisation (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Physical Function [0-100]				
- N	14	7	21	0.7474 *[3]
- Mean +/- SD	17.5 +/- 23.7	21.3 +/- 27.9	18.7 +/-24.5	[-28.1;20.5]
- p5, p25, p75, p95	0.0, 0.0, 33.3, 70.0	0.0, 0.0, 25.0, 80.0	0.0, 0.0, 33.3, 70.0	
- Median	5.6	16.7	5.6	
- Min, Max	0.0, 70.0	0.0, 80.0	0.0, 80.0	
- 95% CI Mean	[3.8;31.2]	[-4.5;47.0]	[7.6;29.9]	
Physical Role Function [0-100]				
- N	14	7	21	0.8960 *[3]
- Mean +/- SD	30.4 +/- 32.8	32.1 +/- 18.9	31.0 +/-28.4	[-30;26.4]
- p5, p25, p75, p95	0.0, 0.0, 50.0, 100.0	0.0, 25.0, 50.0, 50.0	0.0, 0.0, 50.0, 75.0	
- Median	25.0	25.0	25.0	
- Min, Max	0.0, 100.0	0.0, 50.0	0.0, 100.0	
- 95% CI Mean	[11.4;49.3]	[14.7;49.6]	[18.0;43.9]	
Pain [0-100]				
- N	14	7	21	0.2327 *[3]
- Mean +/- SD	73.8 +/- 30.0	89.1 +/- 18.5	78.9 +/-27.3	[-41.4;10.7]
- p5, p25, p75, p95	12.0, 51.0, 100.0, 100.0	62.0, 62.0, 100.0, 100.0	41.0, 54.0, 100.0, 100.0	
- Median	87.0	100.0	100.0	
- Min, Max	12.0, 100.0	62.0, 100.0	12.0, 100.0	
- 95% CI Mean	[56.5;91.1]	[72.0;106.3]	[66.5;91.3]	
General Health Assessment [0-100]				
- N	14	7	21	0.7595 *[3]
- Mean +/- SD	49.4 +/- 19.2	52.3 +/- 21.3	50.4 +/-19.4	[-22.1;16.4]
- p5, p25, p75, p95	10.0, 40.0, 62.0, 87.0	25.0, 40.0, 67.0, 90.0	25.0, 40.0, 62.0, 87.0	
- Median	46.0	45.0	45.0	
- Min, Max	10.0, 87.0	25.0, 90.0	10.0, 90.0	
- 95% CI Mean	[38.3;60.5]	[32.6;72.0]	[41.5;59.2]	
Vitality [0-100]				
- N	14	7	21	0.9369 *[3]
- Mean +/- SD	47.9 +/- 22.0	48.6 +/- 11.1	48.1 +/-18.7	[-19.3;17.9]
- p5, p25, p75, p95	25.0, 35.0, 60.0, 100.0	35.0, 40.0, 50.0, 70.0	25.0, 35.0, 60.0, 80.0	
- Median	37.5	50.0	45.0	
- Min, Max	25.0, 100.0	35.0, 70.0	25.0, 100.0	
- 95% CI Mean	[35.2;60.6]	[38.3;58.8]	[39.6;56.6]	
Social Function [0-100]				
- N	14	7	21	0.4597 *[3]

	Surgery N=17	Standard N=15	Total N=32	p-value
- Mean +/- SD	62.5 +/- 27.3	71.4 +/- 21.3	65.5 +/-25.3	[-33.7;15.8]
- p5, p25, p75, p95	12.5, 37.5, 75.0, 100.0	50.0, 50.0, 100.0, 100.0	37.5, 50.0, 75.0, 100.0	
- Median	62.5	62.5	62.5	
- Min, Max	12.5, 100.0	50.0, 100.0	12.5, 100.0	
- 95% CI Mean	[46.7;78.3]	[51.7;91.1]	[54.0;77.0]	
Emotional Role Function [0-100]				
- N	14	7	21	0.5507 *[3]
- Mean +/- SD	69.0 +/- 46.2	81.0 +/- 32.5	73.0 +/-41.7	[-52.9;29.1]
- p5, p25, p75, p95	0.0, 0.0, 100.0, 100.0	33.3, 33.3, 100.0, 100.0	0.0, 33.3, 100.0, 100.0	
- Median	100.0	100.0	100.0	
- Min, Max	0.0, 100.0	33.3, 100.0	0.0, 100.0	
- 95% CI Mean	[42.4;95.7]	[50.9;111.0]	[54.1;92.0]	
Mental Well-beeing [0-100]				
- N	14	7	21	0.1160 *[3]
- Mean +/- SD	66.6 +/- 14.9	74.3 +/- 6.5	69.1 +/-13.1	[-20.2;4.8]
- p5, p25, p75, p95	44.0, 52.0, 76.0, 88.0	60.0, 76.0, 76.0, 80.0	48.0, 60.0, 76.0, 84.0	
- Median	68.0	76.0	76.0	
- Min, Max	44.0, 88.0	60.0, 80.0	44.0, 88.0	
- 95% CI Mean	[57.9;75.2]	[68.3;80.3]	[63.2;75.1]	
Physical Sum Scale [0-100]				
- N	14	7	21	0.7022 *[3]
- Mean +/- SD	30.9 +/- 9.6	32.5 +/- 8.3	31.4 +/-9.0	[-10.6;7.3]
- p5, p25, p75, p95	17.2, 24.5, 36.4, 50.7	25.2, 26.0, 32.7, 50.3	20.1, 25.2, 32.7, 50.3	
- Median	29.9	31.4	30.3	
- Min, Max	17.2, 50.7	25.2, 50.3	17.2, 50.7	
- 95% CI Mean	[25.3;36.4]	[24.8;40.2]	[27.3;35.5]	
Mental Sum Scale [0-100]				
- N	14	7	21	0.2862 *[3]
- Mean +/- SD	51.0 +/- 8.1	54.7 +/- 5.1	52.2 +/-7.3	[-10.7;3.4]
- p5, p25, p75, p95	36.6, 44.1, 56.4, 63.5	44.2, 52.5, 57.7, 59.0	41.5, 47.5, 57.2, 62.1	
- Median	49.9	56.2	55.3	
- Min, Max	36.6, 63.5	44.2, 59.0	36.6, 63.5	
- 95% CI Mean	[46.3;55.6]	[50.0;59.3]	[48.9;55.5]	

*[3] = T-Test

Table 9-26: SF36 - 1 year after randomisation (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Physical Function [0-100]				
- N	13	6	19	0.6904 *[3]
- Mean +/- SD	18.8 +/- 24.2	24.0 +/- 29.5	20.4 +/-25.2	[-32.1;21.7]
- p5, p25, p75, p95	0.0, 0.0, 33.3, 70.0	0.0, 0.0, 25.0, 80.0	0.0, 0.0, 33.3, 80.0	
- Median	5.6	19.4	5.6	
- Min, Max	0.0, 70.0	0.0, 80.0	0.0, 80.0	
- 95% CI Mean	[4.2;33.4]	[-7.0;54.9]	[8.3;32.6]	
Physical Role Function [0-100]				
- N	13	6	19	0.8113 *[3]
- Mean +/- SD	32.7 +/- 32.9	29.2 +/- 18.8	31.6 +/-28.7	[-27.1;34.2]
- p5, p25, p75, p95	0.0, 0.0, 50.0, 100.0	0.0, 25.0, 50.0, 50.0	0.0, 0.0, 50.0, 100.0	
- Median	25.0	25.0	25.0	
- Min, Max	0.0, 100.0	0.0, 50.0	0.0, 100.0	
- 95% CI Mean	[12.8;52.6]	[9.4;48.9]	[17.8;45.4]	
Pain [0-100]				
- N	13	6	19	0.4616 *[3]
- Mean +/- SD	78.5 +/- 25.1	87.3 +/- 19.6	81.3 +/-23.4	[-33.4;15.8]
- p5, p25, p75, p95	41.0, 51.0, 100.0, 100.0	62.0, 62.0, 100.0, 100.0	41.0, 54.0, 100.0, 100.0	
- Median	100.0	100.0	100.0	
- Min, Max	41.0, 100.0	62.0, 100.0	41.0, 100.0	
- 95% CI Mean	[63.3;93.7]	[66.7;107.9]	[70.1;92.6]	
General Health Assessment [0-100]				
- N	13	6	19	0.8669 *[3]
- Mean +/- SD	52.5 +/- 16.1	54.0 +/- 22.8	52.9 +/-17.8	[-20.6;17.5]
- p5, p25, p75, p95	30.0, 40.0, 62.0, 87.0	25.0, 40.0, 67.0, 90.0	25.0, 40.0, 62.0, 90.0	
- Median	47.0	51.0	47.0	
- Min, Max	30.0, 87.0	25.0, 90.0	25.0, 90.0	
- 95% CI Mean	[42.7;62.2]	[30.1;77.9]	[44.4;61.5]	
Vitality [0-100]				
- N	13	6	19	0.8955 *[3]
- Mean +/- SD	49.6 +/- 21.8	48.3 +/- 12.1	49.2 +/-18.9	[-19;21.6]
- p5, p25, p75, p95	25.0, 35.0, 60.0, 100.0	35.0, 40.0, 50.0, 70.0	25.0, 35.0, 60.0, 100.0	
- Median	40.0	47.5	45.0	
- Min, Max	25.0, 100.0	35.0, 70.0	25.0, 100.0	
- 95% CI Mean	[36.4;62.8]	[35.6;61.0]	[40.1;58.3]	
Social Function [0-100]				
- N	13	6	19	0.3132 *[3]
- Mean +/- SD	61.5 +/- 28.2	75.0 +/- 20.9	65.8 +/-26.3	[-40.8;13.9]

	Surgery N=16	Standard N=14	Total N=30	p-value
- p5, p25, p75, p95	12.5, 37.5, 75.0, 100.0	50.0, 62.5, 100.0, 100.0	12.5, 50.0, 100.0, 100.0	
- Median	50.0	68.8	62.5	
- Min, Max	12.5, 100.0	50.0, 100.0	12.5, 100.0	
- 95% CI Mean	[44.5;78.6]	[53.0;97.0]	[53.1;78.5]	
Emotional Role Function [0-100]				
- N	13	6	19	0.8676 *[3]
- Mean +/- SD	74.4 +/- 43.4	77.8 +/- 34.4	75.4 +/-39.8	[-46;39.2]
- p5, p25, p75, p95	0.0, 66.7, 100.0, 100.0	33.3, 33.3, 100.0, 100.0	0.0, 33.3, 100.0, 100.0	
- Median	100.0	100.0	100.0	
- Min, Max	0.0, 100.0	33.3, 100.0	0.0, 100.0	
- 95% CI Mean	[48.2;100.6]	[41.6;113.9]	[56.2;94.6]	
Mental Well-beeing [0-100]				
- N	13	6	19	0.3548 *[3]
- Mean +/- SD	68.0 +/- 14.5	74.0 +/- 7.0	69.9 +/-12.7	[-19.3;7.3]
- p5, p25, p75, p95	44.0, 56.0, 76.0, 88.0	60.0, 76.0, 76.0, 80.0	44.0, 60.0, 76.0, 88.0	
- Median	72.0	76.0	76.0	
- Min, Max	44.0, 88.0	60.0, 80.0	44.0, 88.0	
- 95% CI Mean	[59.2;76.8]	[66.6;81.4]	[63.8;76.0]	
Physical Sum Scale [0-100]				
- N	13	6	19	0.8315 *[3]
- Mean +/- SD	31.9 +/- 9.1	32.9 +/- 9.1	32.2 +/-8.8	[-10.4;8.5]
- p5, p25, p75, p95	20.1, 25.0, 36.4, 50.7	25.2, 26.0, 32.7, 50.3	20.1, 25.2, 36.4, 50.7	
- Median	30.1	31.5	30.8	
- Min, Max	20.1, 50.7	25.2, 50.3	20.1, 50.7	
- 95% CI Mean	[26.4;37.4]	[23.4;42.4]	[28.0;36.5]	
Mental Sum Scale [0-100]				
- N	13	6	19	0.4523 *[3]
- Mean +/- SD	51.7 +/- 7.9	54.5 +/- 5.5	52.6 +/-7.2	[-10.4;4.8]
- p5, p25, p75, p95	36.6, 47.5, 56.4, 63.5	44.2, 52.5, 57.7, 59.0	36.6, 47.5, 57.7, 63.5	
- Median	50.5	56.7	55.3	
- Min, Max	36.6, 63.5	44.2, 59.0	36.6, 63.5	
- 95% CI Mean	[46.9;56.5]	[48.7;60.3]	[49.1;56.1]	

*[3] = T-Test

Table 9-27: Adverse Events (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Patients with				
- no AE	5 (29.4%) [10.3%;56.0%]	0 (0.0%) [0.0%;21.8%]	5 (15.6%) [5.3%;32.8%]	0.0222 *[1]
- at least one AE	12 (70.6%) [44.0%;89.7%]	15 (100.0%) [78.2%;100.0%]	27 (84.4%) [67.2%;94.7%]	
Number of AEs per patient				
- 0	5 (29.4%) [10.3%;56.0%]	0 (0.0%) [0.0%;21.8%]	5 (15.6%) [5.3%;32.8%]	0.0470 *[1]
- 1	5 (29.4%) [10.3%;56.0%]	8 (53.3%) [26.6%;78.7%]	13 (40.6%) [23.7%;59.4%]	
- 2	2 (11.8%) [1.5%;36.4%]	5 (33.3%) [11.8%;61.6%]	7 (21.9%) [9.3%;40.0%]	
- 3	1 (5.9%) [0.1%;28.7%]	2 (13.3%) [1.7%;40.5%]	3 (9.4%) [2.0%;25.0%]	
- 4	3 (17.6%) [3.8%;43.4%]	0 (0.0%) [0.0%;21.8%]	3 (9.4%) [2.0%;25.0%]	
- 9	1 (5.9%) [0.1%;28.7%]	0 (0.0%) [0.0%;21.8%]	1 (3.1%) [0.1%;16.2%]	
Total number of AEs	33	24	57	
Severity				
- mild	15 (45.5%) [28.1%;63.6%]	5 (20.8%) [7.1%;42.2%]	20 (35.1%) [22.9%;48.9%]	0.0298 *[1]
- moderate	11 (33.3%) [18.0%;51.8%]	6 (25.0%) [9.8%;46.7%]	17 (29.8%) [18.4%;43.4%]	
- severe	7 (21.2%) [9.0%;38.9%]	13 (54.2%) [32.8%;74.4%]	20 (35.1%) [22.9%;48.9%]	
Causality				
- none	24 (72.7%) [54.5%;86.7%]	19 (79.2%) [57.8%;92.9%]	43 (75.4%) [62.2%;85.9%]	0.8025 *[1]
- unlikely	1 (3.0%) [0.1%;15.8%]	0 (0.0%) [0.0%;14.2%]	1 (1.8%) [0.0%;9.4%]	
- assumed	4 (12.1%) [3.4%;28.2%]	3 (12.5%) [2.7%;32.4%]	7 (12.3%) [5.1%;23.7%]	
- certain	4 (12.1%) [3.4%;28.2%]	2 (8.3%) [1.0%;27.0%]	6 (10.5%) [4.0%;21.5%]	
Preferred Term (PT)				
- missing	6	2	8	0.2574 *[1]
- Amaurosis	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Arthralgia	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Back pain	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Brain compression	2 (7.4%) [0.9%;24.3%]	4 (18.2%) [5.2%;40.3%]	6 (12.2%) [4.6%;24.8%]	
- Brain herniation	2 (7.4%) [0.9%;24.3%]	7 (31.8%) [13.9%;54.9%]	9 (18.4%) [8.8%;32.0%]	
- Brain stem auditory evoked response abnormal	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Breast necrosis	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Bronchial infection	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Cardiac pacemaker insertion	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Cataract nuclear	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Cerebral infarction	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Cerebrospinal fluid leakage	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	
- Complex partial seizures	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Convulsion	1 (3.7%) [0.1%;19.0%]	3 (13.6%) [2.9%;34.9%]	4 (8.2%) [2.3%;19.6%]	
- Grand mal convulsion	1 (3.7%) [0.1%;19.0%]	1 (4.5%) [0.1%;22.8%]	2 (4.1%) [0.5%;14.0%]	
- Hypokalaemia	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	

	Surgery N=17	Standard N=15	Total N=32	p-value
- Hyponatraemia	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Impaired healing	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Infection	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Joint dislocation	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Pneumothorax	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	
- Post procedural haematoma	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Pulmonary arteriovenous fistula	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Pulmonary infarction	3 (11.1%) [2.4%;29.2%]	0 (0.0%) [0.0%;15.4%]	3 (6.1%) [1.3%;16.9%]	
- Pyrexia	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Secondary hypertension	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Urinary tract infection	1 (3.7%) [0.1%;19.0%]	1 (4.5%) [0.1%;22.8%]	2 (4.1%) [0.5%;14.0%]	
System Organ Class (SOC)				
- missing	6	2	8	0.0937 *[1]
- Eye disorders	1 (3.7%) [0.1%;19.0%]	1 (4.5%) [0.1%;22.8%]	2 (4.1%) [0.5%;14.0%]	
- General disorders and administration site conditions	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	
- Infections and infestations	2 (7.4%) [0.9%;24.3%]	2 (9.1%) [1.1%;29.2%]	4 (8.2%) [2.3%;19.6%]	
- Injury, poisoning and procedural complications	5 (18.5%) [6.3%;38.1%]	8 (36.4%) [17.2%;59.3%]	13 (26.5%) [14.9%;41.1%]	
- Investigations	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Metabolism and nutrition disorders	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	
- Musculoskeletal and connective tissue disorders	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	
- Nervous system disorders	5 (18.5%) [6.3%;38.1%]	9 (40.9%) [20.7%;63.6%]	14 (28.6%) [16.6%;43.3%]	
- Reproductive system and breast disorders	1 (3.7%) [0.1%;19.0%]	0 (0.0%) [0.0%;15.4%]	1 (2.0%) [0.1%;10.9%]	
- Respiratory, thoracic and mediastinal disorders	5 (18.5%) [6.3%;38.1%]	0 (0.0%) [0.0%;15.4%]	5 (10.2%) [3.4%;22.2%]	
- Surgical and medical procedures	0 (0.0%) [0.0%;12.8%]	1 (4.5%) [0.1%;22.8%]	1 (2.0%) [0.1%;10.9%]	
- Vascular disorders	2 (7.4%) [0.9%;24.3%]	0 (0.0%) [0.0%;15.4%]	2 (4.1%) [0.5%;14.0%]	

*[1] = chi^2-Test

Table 9-28: Serious Adverse Events (FAS)

	Surgery N=17	Standard N=15	Total N=32	p-value
Patients with				
- no SAE	8 (47.1%) [23.0%;72.2%]	1 (6.7%) [0.2%;31.9%]	9 (28.1%) [13.7%;46.7%]	0.0112 *[1]
- at least one SAE	9 (52.9%) [27.8%;77.0%]	14 (93.3%) [68.1%;99.8%]	23 (71.9%) [53.3%;86.3%]	
Number of SAEs per patient				
- 0	8 (47.1%) [23.0%;72.2%]	1 (6.7%) [0.2%;31.9%]	9 (28.1%) [13.7%;46.7%]	0.0401 *[1]
- 1	7 (41.2%) [18.4%;67.1%]	11 (73.3%) [44.9%;92.2%]	18 (56.3%) [37.7%;73.6%]	
- 2	2 (11.8%) [1.5%;36.4%]	3 (20.0%) [4.3%;48.1%]	5 (15.6%) [5.3%;32.8%]	
Total number of SAEs	11	17	28	
Severity				
- mild	1 (9.1%) [0.2%;41.3%]	1 (5.9%) [0.1%;28.7%]	2 (7.1%) [0.9%;23.5%]	0.6877 *[1]
- moderate	4 (36.4%) [10.9%;69.2%]	4 (23.5%) [6.8%;49.9%]	8 (28.6%) [13.2%;48.7%]	
- severe	6 (54.5%) [23.4%;83.3%]	12 (70.6%) [44.0%;89.7%]	18 (64.3%) [44.1%;81.4%]	
Causality				
- none	5 (45.5%) [16.7%;76.6%]	14 (82.4%) [56.6%;96.2%]	19 (67.9%) [47.6%;84.1%]	0.1928 *[1]
- unlikely	1 (9.1%) [0.2%;41.3%]	0 (0.0%) [0.0%;19.5%]	1 (3.6%) [0.1%;18.3%]	
- assumed	2 (18.2%) [2.3%;51.8%]	1 (5.9%) [0.1%;28.7%]	3 (10.7%) [2.3%;28.2%]	
- certain	3 (27.3%) [6.0%;61.0%]	2 (11.8%) [1.5%;36.4%]	5 (17.9%) [6.1%;36.9%]	
Outcome				
- fatal	3 (27.3%) [6.0%;61.0%]	8 (47.1%) [23.0%;72.2%]	11 (39.3%) [21.5%;59.4%]	0.2951 *[1]
- non-fatal	8 (72.7%) [39.0%;94.0%]	9 (52.9%) [27.8%;77.0%]	17 (60.7%) [40.6%;78.5%]	
Preferred Term (PT)				
- missing	1	1	2	0.2772 *[1]
- Amaurosis	0 (0.0%) [0.0%;30.8%]	1 (6.3%) [0.2%;30.2%]	1 (3.8%) [0.1%;19.6%]	
- Brain compression	1 (10.0%) [0.3%;44.5%]	3 (18.8%) [4.0%;45.6%]	4 (15.4%) [4.4%;34.9%]	
- Brain herniation	2 (20.0%) [2.5%;55.6%]	7 (43.8%) [19.8%;70.1%]	9 (34.6%) [17.2%;55.7%]	
- Cerebral infarction	0 (0.0%) [0.0%;30.8%]	1 (6.3%) [0.2%;30.2%]	1 (3.8%) [0.1%;19.6%]	
- Cerebrospinal fluid leakage	1 (10.0%) [0.3%;44.5%]	0 (0.0%) [0.0%;20.6%]	1 (3.8%) [0.1%;19.6%]	
- Complex partial seizures	1 (10.0%) [0.3%;44.5%]	0 (0.0%) [0.0%;20.6%]	1 (3.8%) [0.1%;19.6%]	
- Convulsion	1 (10.0%) [0.3%;44.5%]	3 (18.8%) [4.0%;45.6%]	4 (15.4%) [4.4%;34.9%]	
- Grand mal convulsion	1 (10.0%) [0.3%;44.5%]	1 (6.3%) [0.2%;30.2%]	2 (7.7%) [0.9%;25.1%]	
- Impaired healing	1 (10.0%) [0.3%;44.5%]	0 (0.0%) [0.0%;20.6%]	1 (3.8%) [0.1%;19.6%]	
- Pulmonary infarction	2 (20.0%) [2.5%;55.6%]	0 (0.0%) [0.0%;20.6%]	2 (7.7%) [0.9%;25.1%]	
System Organ Class (SOC)				
- missing	1	1	2	0.2098 *[1]
- Eye disorders	0 (0.0%) [0.0%;30.8%]	1 (6.3%) [0.2%;30.2%]	1 (3.8%) [0.1%;19.6%]	

	Surgery N=17	Standard N=15	Total N=32	p-value
- General disorders and administration site conditions	1 (10.0%) [0.3%;44.5%]	0 (0.0%) [0.0%;20.6%]	1 (3.8%) [0.1%;19.6%]	
- Injury, poisoning and procedural complications	3 (30.0%) [6.7%;65.2%]	7 (43.8%) [19.8%;70.1%]	10 (38.5%) [20.2%;59.4%]	
- Nervous system disorders	4 (40.0%) [12.2%;73.8%]	8 (50.0%) [24.7%;75.3%]	12 (46.2%) [26.6%;66.6%]	
- Respiratory, thoracic and mediastinal disorders	2 (20.0%) [2.5%;55.6%]	0 (0.0%) [0.0%;20.6%]	2 (7.7%) [0.9%;25.1%]	

*[1] = chi^2-Test

Table 9-29: Adverse Events (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Patients with				
- no AE	5 (31.3%) [11.0%;58.7%]	0 (0.0%) [0.0%;23.2%]	5 (16.7%) [5.6%;34.7%]	0.0219 *[1]
- at least one AE	11 (68.8%) [41.3%;89.0%]	14 (100.0%) [76.8%;100.0%]	25 (83.3%) [65.3%;94.4%]	
Number of AEs per patient				
- 0	5 (31.3%) [11.0%;58.7%]	0 (0.0%) [0.0%;23.2%]	5 (16.7%) [5.6%;34.7%]	0.0362 *[1]
- 1	5 (31.3%) [11.0%;58.7%]	8 (57.1%) [28.9%;82.3%]	13 (43.3%) [25.5%;62.6%]	
- 2	2 (12.5%) [1.6%;38.3%]	5 (35.7%) [12.8%;64.9%]	7 (23.3%) [9.9%;42.3%]	
- 3	0 (0.0%) [0.0%;20.6%]	1 (7.1%) [0.2%;33.9%]	1 (3.3%) [0.1%;17.2%]	
- 4	3 (18.8%) [4.0%;45.6%]	0 (0.0%) [0.0%;23.2%]	3 (10.0%) [2.1%;26.5%]	
- 9	1 (6.3%) [0.2%;30.2%]	0 (0.0%) [0.0%;23.2%]	1 (3.3%) [0.1%;17.2%]	
Total number of AEs	30	21	51	
Severity				
- mild	15 (50.0%) [31.3%;68.7%]	3 (14.3%) [3.0%;36.3%]	18 (35.3%) [22.4%;49.9%]	0.0049 *[1]
- moderate	10 (33.3%) [17.3%;52.8%]	6 (28.6%) [11.3%;52.2%]	16 (31.4%) [19.1%;45.9%]	
- severe	5 (16.7%) [5.6%;34.7%]	12 (57.1%) [34.0%;78.2%]	17 (33.3%) [20.8%;47.9%]	
Causality				
- none	24 (80.0%) [61.4%;92.3%]	16 (76.2%) [52.8%;91.8%]	40 (78.4%) [64.7%;88.7%]	0.7905 *[1]
- unlikely	1 (3.3%) [0.1%;17.2%]	0 (0.0%) [0.0%;16.1%]	1 (2.0%) [0.0%;10.4%]	
- assumed	3 (10.0%) [2.1%;26.5%]	3 (14.3%) [3.0%;36.3%]	6 (11.8%) [4.4%;23.9%]	
- certain	2 (6.7%) [0.8%;22.1%]	2 (9.5%) [1.2%;30.4%]	4 (7.8%) [2.2%;18.9%]	
Preferred Term (PT)				
- missing	5	1	6	0.2821 *[1]

	Surgery N=16	Standard N=14	Total N=30	p-value
- Amaurosis	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Arthralgia	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Back pain	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Brain compression	1 (4.0%) [0.1%;20.4%]	3 (15.0%) [3.2%;37.9%]	4 (8.9%) [2.5%;21.2%]	
- Brain herniation	2 (8.0%) [1.0%;26.0%]	7 (35.0%) [15.4%;59.2%]	9 (20.0%) [9.6%;34.6%]	
- Brain stem auditory evoked response abnormal	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Breast necrosis	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Bronchial infection	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Cardiac pacemaker insertion	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Cataract nuclear	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Cerebral infarction	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Cerebrospinal fluid leakage	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Complex partial seizures	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Convulsion	1 (4.0%) [0.1%;20.4%]	3 (15.0%) [3.2%;37.9%]	4 (8.9%) [2.5%;21.2%]	
- Grand mal convulsion	1 (4.0%) [0.1%;20.4%]	1 (5.0%) [0.1%;24.9%]	2 (4.4%) [0.5%;15.1%]	
- Hypokalaemia	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Hyponatraemia	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Impaired healing	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Infection	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Pneumothorax	2 (8.0%) [1.0%;26.0%]	0 (0.0%) [0.0%;16.8%]	2 (4.4%) [0.5%;15.1%]	
- Post procedural haematoma	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Pulmonary arteriovenous fistula	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Pulmonary infarction	3 (12.0%) [2.5%;31.2%]	0 (0.0%) [0.0%;16.8%]	3 (6.7%) [1.4%;18.3%]	
- Pyrexia	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Secondary hypertension	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	
- Urinary tract infection	1 (4.0%) [0.1%;20.4%]	1 (5.0%) [0.1%;24.9%]	2 (4.4%) [0.5%;15.1%]	
System Organ Class (SOC)				
- missing	5	1	6	0.0860 *[1]
- Eye disorders	1 (4.0%) [0.1%;20.4%]	1 (5.0%) [0.1%;24.9%]	2 (4.4%) [0.5%;15.1%]	
- General disorders and administration site conditions	2 (8.0%) [1.0%;26.0%]	0 (0.0%) [0.0%;16.8%]	2 (4.4%) [0.5%;15.1%]	
- Infections and infestations	2 (8.0%) [1.0%;26.0%]	2 (10.0%) [1.2%;31.7%]	4 (8.9%) [2.5%;21.2%]	
- Injury, poisoning and procedural complications	4 (16.0%) [4.5%;36.1%]	7 (35.0%) [15.4%;59.2%]	11 (24.4%) [12.9%;39.5%]	
- Investigations	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Metabolism and nutrition disorders	2 (8.0%) [1.0%;26.0%]	0 (0.0%) [0.0%;16.8%]	2 (4.4%) [0.5%;15.1%]	
- Musculoskeletal and connective tissue disorders	2 (8.0%) [1.0%;26.0%]	0 (0.0%) [0.0%;16.8%]	2 (4.4%) [0.5%;15.1%]	
- Nervous system disorders	4 (16.0%) [4.5%;36.1%]	8 (40.0%) [19.1%;63.9%]	12 (26.7%) [14.6%;41.9%]	
- Reproductive system and breast disorders	1 (4.0%) [0.1%;20.4%]	0 (0.0%) [0.0%;16.8%]	1 (2.2%) [0.1%;11.8%]	

	Surgery N=16	Standard N=14	Total N=30	p-value
- Respiratory, thoracic and mediastinal disorders	5 (20.0%) [6.8%;40.7%]	0 (0.0%) [0.0%;16.8%]	5 (11.1%) [3.7%;24.1%]	
- Surgical and medical procedures	0 (0.0%) [0.0%;13.7%]	1 (5.0%) [0.1%;24.9%]	1 (2.2%) [0.1%;11.8%]	
- Vascular disorders	2 (8.0%) [1.0%;26.0%]	0 (0.0%) [0.0%;16.8%]	2 (4.4%) [0.5%;15.1%]	

*[1] = chi^2-Test

Table 9-30: Serious Adverse Events (PP)

	Surgery N=16	Standard N=14	Total N=30	p-value
Patients with				
- no SAE	8 (50.0%) [24.7%;75.3%]	1 (7.1%) [0.2%;33.9%]	9 (30.0%) [14.7%;49.4%]	0.0106 *[1]
- at least one SAE	8 (50.0%) [24.7%;75.3%]	13 (92.9%) [66.1%;99.8%]	21 (70.0%) [50.6%;85.3%]	
Number of SAEs per patient				
- 0	8 (50.0%) [24.7%;75.3%]	1 (7.1%) [0.2%;33.9%]	9 (30.0%) [14.7%;49.4%]	0.0322 *[1]
- 1	7 (43.8%) [19.8%;70.1%]	10 (71.4%) [41.9%;91.6%]	17 (56.7%) [37.4%;74.5%]	
- 2	1 (6.3%) [0.2%;30.2%]	3 (21.4%) [4.7%;50.8%]	4 (13.3%) [3.8%;30.7%]	
Total number of SAEs	9	16	25	
Severity				
- mild	1 (11.1%) [0.3%;48.2%]	1 (6.3%) [0.2%;30.2%]	2 (8.0%) [1.0%;26.0%]	0.4922 *[1]
- moderate	4 (44.4%) [13.7%;78.8%]	4 (25.0%) [7.3%;52.4%]	8 (32.0%) [14.9%;53.5%]	
- severe	4 (44.4%) [13.7%;78.8%]	11 (68.8%) [41.3%;89.0%]	15 (60.0%) [38.7%;78.9%]	
Causality				
- none	5 (55.6%) [21.2%;86.3%]	13 (81.3%) [54.4%;96.0%]	18 (72.0%) [50.6%;87.9%]	0.4208 *[1]
- unlikely	1 (11.1%) [0.3%;48.2%]	0 (0.0%) [0.0%;20.6%]	1 (4.0%) [0.1%;20.4%]	
- assumed	1 (11.1%) [0.3%;48.2%]	1 (6.3%) [0.2%;30.2%]	2 (8.0%) [1.0%;26.0%]	
- certain	2 (22.2%) [2.8%;60.0%]	2 (12.5%) [1.6%;38.3%]	4 (16.0%) [4.5%;36.1%]	
Outcome				
- fatal	3 (33.3%) [7.5%;70.1%]	8 (50.0%) [24.7%;75.3%]	11 (44.0%) [24.4%;65.1%]	0.4203 *[1]
- non-fatal	6 (66.7%) [29.9%;92.5%]	8 (50.0%) [24.7%;75.3%]	14 (56.0%) [34.9%;75.6%]	
Preferred Term (PT)				
- missing	0	1	1	0.2116 *[1]
- Amaurosis	0 (0.0%) [0.0%;33.6%]	1 (6.7%) [0.2%;31.9%]	1 (4.2%) [0.1%;21.1%]	
- Brain compression	0 (0.0%) [0.0%;33.6%]	2 (13.3%) [1.7%;40.5%]	2 (8.3%) [1.0%;27.0%]	
- Brain herniation	2 (22.2%) [2.8%;60.0%]	7 (46.7%) [21.3%;73.4%]	9 (37.5%) [18.8%;59.4%]	
- Cerebral infarction	0 (0.0%) [0.0%;33.6%]	1 (6.7%) [0.2%;31.9%]	1 (4.2%) [0.1%;21.1%]	
- Cerebrospinal fluid leakage	1 (11.1%) [0.3%;48.2%]	0 (0.0%) [0.0%;21.8%]	1 (4.2%) [0.1%;21.1%]	
- Complex partial seizures	1 (11.1%) [0.3%;48.2%]	0 (0.0%) [0.0%;21.8%]	1 (4.2%) [0.1%;21.1%]	
- Convulsion	1 (11.1%) [0.3%;48.2%]	3 (20.0%) [4.3%;48.1%]	4 (16.7%) [4.7%;37.4%]	
- Grand mal convulsion	1 (11.1%) [0.3%;48.2%]	1 (6.7%) [0.2%;31.9%]	2 (8.3%) [1.0%;27.0%]	
- Impaired healing	1 (11.1%) [0.3%;48.2%]	0 (0.0%) [0.0%;21.8%]	1 (4.2%) [0.1%;21.1%]	
- Pulmonary infarction	2 (22.2%) [2.8%;60.0%]	0 (0.0%) [0.0%;21.8%]	2 (8.3%) [1.0%;27.0%]	
System Organ Class (SOC)				
- missing	0	1	1	0.1933 *[1]
- Eye disorders	0 (0.0%) [0.0%;33.6%]	1 (6.7%) [0.2%;31.9%]	1 (4.2%) [0.1%;21.1%]	

	Surgery N=16	Standard N=14	Total N=30	p-value
- General disorders and administration site conditions	1 (11.1%) [0.3%;48.2%]	0 (0.0%) [0.0%;21.8%]	1 (4.2%) [0.1%;21.1%]	
- Injury, poisoning and procedural complications	3 (33.3%) [7.5%;70.1%]	7 (46.7%) [21.3%;73.4%]	10 (41.7%) [22.1%;63.4%]	
- Nervous system disorders	3 (33.3%) [7.5%;70.1%]	7 (46.7%) [21.3%;73.4%]	10 (41.7%) [22.1%;63.4%]	
- Respiratory, thoracic and mediastinal disorders	2 (22.2%) [2.8%;60.0%]	0 (0.0%) [0.0%;21.8%]	2 (8.3%) [1.0%;27.0%]	

*[1] = chi^2-Test

Listing 9-1: Reported Adverse Events

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
101	Standard	Day 1	Infekt unklarer Genese	Infection	Infections and infestations	no	17/02/2004	NA:NA	27/02/2004	NA:NA	ongoing	mild	assumed	in keinem wahrscheinl. Zus.-hang mit Infarktspezif. Behandlung, jedoch Intubation etc.
		6 Months	epileptischer Anfall	Convulsion	Nervous system disorders	yes	13/08/2004	10:00	13/08/2004	12:00	ended	moderate	none	stationaere Aufnahme u. antiepileptische Therapie bis zum 18.8.2004, dann nach Hause entlassen
		1 Year	Epileptischer Anfall	Convulsion	Nervous system disorders	yes	14/12/2004	00:00	17/12/2004	00:00	ended	moderate	none	einmaliges Ereignis
102	Surgery	Day 30	Hyponatriaemie	Hyponatraemia	Metabolism and nutrition disorders	no	07/05/2004	15:00	09/05/2004	09:00	ended	mild	none	
103	Standard	Day 1	Hirndruckzeichen, Einklemmungszeichen	Brain compression	Nervous system disorders	yes	21/05/2004	00:00	26/05/2004	10:30	ongoing	severe	none	Tod
		Day 7	Tod, transforaminale Herniation	Brain herniation	Injury, poisoning and procedural complications	yes	25/05/2004	10:30	25/05/2004	10:30		severe	none	Verlegung zur Organentnahme in die Chirurg. Klinik
104	Surgery	Day 30	Mamma-Aufbauplastik 22.5.04, li Mamille nekrose, Nekroseektomie erforderlich	Breast necrosis	Reproductive system and breast disorders	no	03/06/2004	NA:NA	09/06/2004	NA:NA	ongoing	mild	none	
			Hypokaliaemie 2,7 mmol/l	Hypokalaemia	Metabolism and nutrition disorders	no	15/06/2004	NA:NA	17/06/2004	10:00	ended	mild	none	
			Bronchialinfekt	Bronchial infection	Infections and infestations	no	24/05/2004	NK:NK	03/06/2004	NK:NK	ended	mild	none	
			Harnwegsinfekt	Urinary tract infection	Infections and infestations	no	01/06/2004	NK:NK	03/06/2004	NK:NK	ended	mild	none	

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
105	Standard	Day 7	Tod	Brain herniation	Injury, poisoning and procedural complications	yes	06/06/2004	11:17	06/06/2004	11:17		severe	none	
106	Surgery	6 Months	Tod durch Lungenembolie nach Reimplantation des Knochendeckels	Pulmonary infarction	Respiratory, thoracic and mediastinal disorders	yes	02/12/2004	12:00	02/12/2004	12:00		severe	assumed	verstorben trotz intensiv medizinischer Maximaltherapie
108	Surgery	1 Year	epiletischer Anfall, stationaerer Aufenthalt 5 Tage	Convulsion	Nervous system disorders	yes	24/09/2005	12:00	24/09/2005	12:05	ended	mild	none	guter Verlauf, 5 Tage stat. Aufnahme
110	Standard	Day 7	Hirndruck mit Einklemmung und Tod	Brain herniation	Injury, poisoning and procedural complications	yes	08/12/2004	00:00	08/12/2004	10:00		severe	none	Unkontrollierbarer Hirndruck, verstorben
111	Standard	Day 7	Hirndruckanstieg	Brain compression	Nervous system disorders	no	25/02/2005	00:00			ongoing	moderate	none	
		6 Months	Grand mal Anfall	Grand mal convulsion	Nervous system disorders	yes	15/08/2005	21:00	15/08/2005	21:10	ended	mild	none	spontanes Sistieren, keine weiteren Anfaelle bisher, stationaere Behandlung und Aufsaettigung mit Carbamazepin
112	Standard	1 Year	symptomatischer Krampfanfall	Convulsion	Nervous system disorders	yes	16/01/2006	12:00	24/01/2006	12:00	ended	severe	none	
113	Standard	Day 1	Hirndruck	Brain compression	Nervous system disorders	yes	31/03/2005	00:00	01/04/2005	15:10	ongoing	severe	none	anhaltend, nicht behandelbar
		Day 7	Herniation	Brain herniation	Injury, poisoning and procedural complications	yes	01/04/2005	15:10	01/04/2005	15:10		severe	none	anhaltend
114	Standard	1 Year	Anlage eines Schrittmachers	Cardiac pacemaker insertion	Surgical and medical procedures	no	26/04/2005	NK:NK	29/04/2005	NK:NK	ended	moderate	none	Nachtrag innerh. der 30 Tage-Untersuchung
115	Surgery	Day 7	Hirndruck	Brain compression	Nervous system disorders	no	27/05/2005	00:00	28/05/2005	12:40	ongoing	severe	none	
			Herniation	Brain herniation	Injury, poisoning and procedural complications	yes	28/05/2005	12:40	28/05/2005	12:40		severe	none	beendet
116	Surgery	Day 30	Pneumothorax links	Pneumothorax	Respiratory, thoracic and mediastinal disorders	no	21/06/2005	12:00	11/07/2005	12:00	ended	moderate	none	

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
			Pneumothorax rechts	Pneumothorax	Respiratory, thoracic and mediastinal disorders	no	28/06/2005	12:00	04/07/2005	12:00	ended	moderate	none	
			Lungenfistel	Pulmonary arteriovenous fistula	Vascular disorders	no	04/07/2005	12:00	11/07/2005	NK:NK	ended	moderate	none	
			V. a. Lungenembolie	Pulmonary infarction	Respiratory, thoracic and mediastinal disorders	no	22/06/2005	12:00	22/06/2005	NK:NK	ended	mild	none	
118	Standard	Day 7	Herniation	Brain herniation	Injury, poisoning and procedural complications	yes	14/10/2005	15:30	14/10/2005	15:30		severe	none	anhaltend
120	Surgery	Day 7	Tod durch Herniation	Brain herniation	Injury, poisoning and procedural complications	yes	18/12/2005	09:00	18/12/2005	09:00		severe	none	anhaltend
201	Standard	Day 30	Amaurosis des linken Auges, anhaltend	Amaurosis	Eye disorders	yes	18/03/2004	16:00	NK/NK/NK	NK:NK	ongoing	moderate	none	anhaltend
202	Surgery	Day 30	Wundheilungsstoerung	Impaired healing	General disorders and administration site conditions	yes	23/03/2004	NK:NK	NK/NK/NK	NK:NK	ended	moderate	certain	Wundrevision am 24.03.04/Abstrich: ..... -> Antibiose mit Ciprobay i.v.
		6 Months	generalisierte epil. Anfall	Grand mal convulsion	Nervous system disorders	yes	30/04/2004	00:00	30/04/2004	00:00	ended	moderate	none	
203	Standard	Day 7	Tod, Oedem, cerebrale Einklemmung	Brain herniation	Injury, poisoning and procedural complications	yes	30/10/2004	20:29	30/10/2004	20:30		severe	certain	
204	Surgery	Day 30	Wundheilungsstoerung mit Liquorfistel	Cerebrospinal fluid leakage	Injury, poisoning and procedural complications	yes	23/05/2005	NK:NK	22/06/2005	09:00	ended	moderate	certain	Wundrevision, Antibiotikatherapie
206	Standard	Day 7	Oedem, Einklemmung	Brain herniation	Injury, poisoning and procedural complications	yes	19/09/2005	11:05	19/09/2005	11:05		severe	certain	zunehmender Hirndruck, Anisokorie, Einklemmung
401	Surgery	Day 1	Linsenkerneinblutung	Cataract nuclear	Eye disorders	no	03/08/2005	NK:NK			ongoing	moderate	assumed	
			subgaleales Hämatom	Post procedural haematoma	Injury, poisoning and procedural complications	no	03/08/2005	09:32			ongoing	mild	assumed	
			Fieber ohne Infektquelle			no	04/08/2006	12:00	10/08/2006	14:00	ended	mild	none	

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
		6 Months	Komplex-partieller Krampf-anfall	Complex partial seizures	Nervous system disorders	yes	02/02/2006	11:28	02/02/2006	11:30	ended	moderate	none	sondern mit Mediain-farkt, antiepileptische Einstellung
501	Surgery	Day 30	back pain	Back pain	Musculoskeletal and con-nective tissue disorders	no	10/09/2004	09:00	NA/NA/NA	NA:NA	ongoing	mild	none	Therapie mit Imbun
			fever	Pyrexia	General disorders and administration site condi-tions	no	10/09/2004	16:00	13/09/2004	02:00	ended	moderate	none	
			joint pain right shoulder	Arthralgia	Musculoskeletal and con-nective tissue disorders	no	20/09/2004	NA:NA	NA/NA/NA	NA:NA	ongoing	mild	none	Therapie mit Imbun
			hypertension	Secondary hypertension	Vascular disorders	no	17/09/2004	NA:NA	NA/NA/NA	NA:NA	ongoing	mild	none	Therapie mit Delix
		6 Months	Lungenembolie	Pulmonary infarction	Respiratory, thoracic and mediastinal disorders	yes	14/10/2004	16:00	21/10/2004	10:00	ended	severe	unlikely	nach Thrombolyse Umstellung der Sekun-daerpraevention auf Falithrom (Ziel INR 2-3). Rueckbildung der Beschwerden ohne Resid..... Am 21.10.04 Rueckverle-gung in das Neurologi-sche Reha-Zentrum
		1 Year	mehrere Zysten in der rechten Brust			no	NK/01/2005	NK:NK	11/03/2005	NK:NK	ongoing	mild	none	
			eine kleine Zyste in der linken Brust			no	NK/01/2005	NK:NK	11/03/2005	NK:NK	ongoing	mild	none	
			Ekzem perimamillaer rechts			no	NK/01/2005	NK:NK	11/03/2005	NK:NK	ended	mild	none	
			zunehmende Spastik am rechten Arm			no	NK/10/2004	NK:NK	06/01/2005	NK:NK	ended	moderate	none	

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
502	Standard	Day 1	stetige Zunahme des Hirndrucks	Brain compression	Nervous system disorders	yes	18/01/2005	05:24	18/01/2005	17:07	ended	severe	none	Bei Zunahme des Hirndrucks und Zeichen der Einklemmung wurde Dekompressions-OP durchgefuehrt
		Day 30	Subluxation linke Schulter	Joint dislocation	Injury, poisoning and procedural complications	no	03/02/2005	00:00			ongoing	mild	none	behandelt mit Imbun
			Harnwegsinfektion im Mikrobiolog. Befund			no	31/01/2005	NK:NK	NK/NK/NK	NK:NK	8	mild	none	
601	Surgery	Day 7	Zunahme der Infarktzone mit Hirndrucksymptomatik	Brain compression	Nervous system disorders	yes	19/09/2004	09:00	19/09/2004	15:00	ended	severe	assumed	Behandlung: Erweiterung des Knochenfensters (dies vormals zu klein), nach Rueckkehr aus OP Symptomatik verschwunden
		Day 30	Duraleck	Cerebrospinal fluid leakage	Injury, poisoning and procedural complications	no	01/10/2004	08:00	01/10/2004	14:45	ended	moderate	certain	Liquoraustritt nach Klammernentfernung, daraufhin operative Revision
			Wundheilungsstoerung mit sekundaerer Meningoenzephalitis			yes	10/10/2004	NK:NK	17/10/2004	NK:NK	ended	severe	certain	
602	Standard	Day 1	brain stern areflexion	Brain stem auditory evoked response abnormal	Investigations	no	30/09/2005	13:30	01/10/2005	09:36	ended	severe	assumed	
			maligner Mediainfarkt links	Cerebral infarction	Nervous system disorders	yes	30/09/2005	13:30	01/10/2005	09:36		severe	assumed	medikamentoese ....., Barbituratnarkose unter ICP-Kontrolle nicht .....

Pat.No.	Group	Visit	AE	PT	SOC	SAE?	Start Date	Time	End Date	Time	Outcome	Severity	Relationship	Comment
1001	Standard	6 Months	Harnwegsinfekt	Urinary tract infection	Infections and infestations	no	31/03/2005	NK:NK	NK/NK/NK	NK:NK	ended	mild	none	
		1 Year	erstmaliger GM-Anfall (Grand-Mal-Anfall) d. h. erstmaliger epileptischer Anf			yes	22/01/2006	NK:NK	01/02/2006	NK:NK	ended	moderate	none	

Listing 9-2: Reason for death

Pat.No.	Group	Random.date	Date of death	Reason for death	Comment
103	Standard	21/05/2004	25/05/2004	unkontrollierbarer Hirndruck	
105	Standard	02/06/2004	06/06/2004	unkontrollierbarer Hirndruck mit Herniation	
106	Surgery	28/06/2004	02/12/2004	Lungenembolie	
110	Standard	01/12/2004	08/12/2004	Hirndruck und Herniation	
113	Standard	30/03/2005	01/04/2005	Herniation	
115	Surgery	21/04/2005	28/05/2005	Herniation	
118	Standard	09/10/2005	14/10/2005	Herniation	
120	Surgery	14/12/2005	18/12/2005	Herniation	
203	Standard	28/10/2004	30/10/2004	Oedem, Einklemmung	
206	Standard	16/09/2005	19/09/2005	Oedem, Einklemmung	
602	Standard	29/09/2005	01/10/2005	maligner Mediainfarkt links	

Listing 9-3: Further medical findings

Pat.No.	Group	Visit	CCT/MRT	Doppler/Duplex	MRA	DSA	Others
101	Standard	6 Months	13.8.2004: subtotaler Mediainfarkt links u. Anterior-Teilinfarkt links, post-kontusioneller Substanzdefekt rechts-fronto-basal (alt)				EEG: leichte Allgemeinveraenderung, links-hemisphaerischer Herdbefund, keine epilepsietypischen Potentiale
111	Standard	6 Months	CCT am 15.8.05: Nahezu kompletter Mediainfarkt links. Keine frische Ischaemie, keine Blutung, keine Raumforderung				EEG: leichte Allgemeinveraenderung, links-hemisphaerischer Herdbefund, keine epilepsietypischen Potentiale
201	Standard	Day 30	CCT am 15.8.05: Nahezu kompletter Mediainfarkt links. Keine frische Ischaemie, keine Blutung, keine Raumforderung				CT-Angiographie: 1 CT-Verschluss links
401	Surgery	Day 30	CCT 11.8.05: leichte Resorpt. der Linsenkerneinblutung u. Galea Haematom konst.	EC voellig regelrecht. TCD M1-Verschluss li, sonst bei guten Gehallbed. o. B.	n. d.	n. d.	Transthorek. u. oesoph. Echo: Grenzwertig grosser LV, LVEF ca. 50 %. Kein ASD, keine .....thromben, keine Aortenplegies, LZ-EKG: o. B., EKG: o. B.
401	Surgery	6 Months	alter Mediainfarkt links	EC voellig regelrecht. TCD M1-Verschluss li, sonst bei guten Gehallbed. o. B.	n. d.	n. d.	Transthorek. u. oesoph. Echo: Grenzwertig grosser LV, LVEF ca. 50 %. Kein ASD, keine .....thromben, keine Aortenplegies, LZ-EKG: o. B., EKG: o. B.
501	Surgery	Day 30	9.9.04: kompletter Media-Infarkt links, keine wesentliche Mittellinienverlagerung	2.9.04: Verschluss der A. carotis interna links	n. d.	n. d.	TEE/TTE 15.9.04: kein Hinweis auf kardiale Embolequelle, 24 h: EKG: durchgehend Sinusrhythmus
502	Standard	Day 30	Infarkt im Stromgebiet der A cerebri media rechts, im Verlauf Rueckbildung der Raumforderung	keine Stenosen der hirnversorgenden Gefaesse	n. d.	n. d.	TEE keine kardiale Embolequelle; EKG kein Vorhofflimmern
601	Surgery	Day 30	keine Einblutung, Fluessigkeitsansammlung links im Trepanationsbereich, Demarkierung Media+Anteriorinfarkt	ICA Verschluss links, VA rechts im Seitenvergleich hypoplastisch, sonst o. B.	n. d.	n. d.	TEE keine kardiale Embolequelle; EKG kein Vorhofflimmern

Listing 9-4: Comments on neurological assessment

Pat.No.	Group	Visit	Finding
101	Standard	Day 1	Patient intubiert, beatmet, sediert, Pupillen isokor, LR+/+, CR rechts schwach, links pos., MER allseits schwach, Babinski bds. neg., keine Reaktion auf SR, WR+, sonst nicht beurteilbar
		Day 7	Patient intubiert, sediert, beatmet, Pupillen isokor, LR+/+, CR +/+, MER re>li, Babinski bds. neg., keine Reaktion auf SR
		Day 30	wach, kann einfache Aufforderungen befolgen. Pupillen mittelweit rund isokor, LR bds. Prompt. AFB glatt. GF nicht pruefbar. Faciale Parese re. Hemiplegie re. MER lebhaft re>li Bab. bds. neg. Koord./Sens. nicht pruefbar
		6 Months	Pat. wach, orientiert, kooperativ, globale Aphasie mit gut erhaltenem Sprachverhaeltnis, Plegie des re. Armes, Sitzen ohne Hilfe moeglich, Arm Hk 4/5, Bein 0/5, Hypo..... ges. re KH, MER re>li, Babinski re pos.
		1 Year	wie vorbeschrieben am 17.8.2004
102	Surgery	Day 1	Pat. analgosediert, DK beatmet, kein Menigismus, Pupillen eng, isokor LR+/+, CR re>li, keine Reaktion auf SR, MER li betont kein Babinski
		Day 7	Pat. wach, teilweise orientiert, teilweise kooperativ, Pupillen isokor, LR+/+, CR+/+, WR+, Babinski links pos., MER li>re, Paresen Bein links 0/5, Arm links 0-1/5, Sensibili-taetsstrg. linke KH, sonst nicht beurteilbar
		Day 30	Mundastbetonte Faziale Parese links, hypotone, armbetonte Hemiparese links, hk 2/5 Arm, 2/5 Bein, MER li>re, mittelkath., Hyp- und ..... links
		6 Months	Pat. wach, orientiert, kooperativ, faziale Parese links, keine Aphasia, Dysarthrie, hochgradige Hemiparese links, Arm 2/5, Bein 3/5, MER re>li, Babinski re pos., Stand moeglich, Gehen nur mit Hilfe, hochgradige Hypaesthesie-Anaesthesie links
		1 Year	Pat. wach, voll orientiert, deutliche faziale Parese links, keine Aphasie, geringe Dysarthrie, Hemiparese links, Arm KG 2/5, Bein KG 3/5, MER linksbetont, Babinski links pos., ausgepraegte Hypaesthesie links, Hemispastik links
103	Standard	Day 1	Pat. beatmet, komatoes, keine Reaktion auf Schmerzreize, Stumme Sohle bds., Pupillen anisokor li>re, LR-/-, CR-/-, WR-
		Day 7	tot
104	Surgery	Day 1	Patientin analgosediert, intubiert, beatmet, relaxiert. Pupillen isokor, LR+/+, CR-/-, WR-
		Day 7	Patientin wach, zu Person orientiert, sonst desorientiert, Blickpraeferenz nach rechts, Hemiplegie links, Neglect nach links, MER li>re, Babinski links pos., geringe Dy-sarthrie, komplette faziale Parese links, HN sonst regelrecht
		Day 30	Hemiparese links, Arm 0/5, Bein 2/5, distal 0/5, spast. Tonuserhoehung, visueller Neglect n. links
		6 Months	Patientin wach, vollorientiert, faziale Schwaeche links, Hemiparese links, Arm prox. 4/5, distal 0/5, Bein 4-/5, Hemihypaestehesie fuer alle Qualitaeten links, MER li>re, Babinski li pos., Hemispastic mit einsch. Myoklonie links, Gehen ohne Hilfe ca. 30-4
		1 Year	Patientin wach, vollorientiert, geringe faziale Schwaeche links, Hemiparese links, Arm 1-2/5, Bein 4/5, Hemihypaesthesie links, Gehen+Treppensteigen moeglich, MER links betont, Babinski links pos.
105	Standard	Day 1	Patientin intubiert, sediert, beatmet, relaxiert, Pupillen anisokor, li> re, LR+/+, CR-/-, WR-, Babinski -/-, (nicht beurteilbar, da relaxiert)

Pat.No.	Group	Visit	Finding
		Day 7	tot
106	Surgery	Day 1	Patient analgosediert, beatmet, komatoes, Pupillen isokor, eng, LR+/+, CR+/+, WR-, Babinski -/-, keine Reaktion auf SR
		Day 7	Patient wach, kontaktfaehig, orientiert, kooperativ, kein Meningismus, faziale Parese links (inkomplett), geringe Dysarthrie, Hemiplegie links, Anaesthesie links, sensible Neglect links, Babinski -/-, spastische Tonuserhoehung links
		Day 30	Patient wach, orientiert, kooperativ, faziale Parese links, HN-Befund sonst o. p. B., Hemipar. links KH 1-2/5, Hemihypaesthesie links, sensible Neglect n. links, Babinski -/-, MER li>re, deutlich Hemispastik links, Stand+Gang nicht moeglich
107	Surgery	Day 1	Pat. AS, komatoes, kein Meningismus, Pupillen eng isokor LR+/+ CR li>re; keine Reaktion auf SR==, MER stgl., Babinski re pos.
		Day 7	Patient wach, nimmt Blickkontakt auf, Pupillen isokor, LR+/+, kein Meningismus, CR+/+, WR+, keine Blickparese, faziale Parese rechts, hemiphlegie rechts, Zurueckziehen auf SR, Babinski re pos.
		Day 30	Patient wach, ansprechbar, geringe sprachl. Aeusserungen, Dysarthrie, kein Meningismus, faziale Parese rechts, Hemiparese rechts Arm 1/5, Bein 0/5, Babinski re pos., links neg., Sitzen moeglich, Stand und Gang nicht moeglich
		6 Months	Patient wach, teilweise orientiert, kooperativ, faziale Parese rechts, Gesichtsfeld .....nach rechts, hochgradige, armbetonte Hemiparese rechts, Arm KG 0/5, Bein KG 1-2/5, Hemihypaesthesie rechts, Hemineglect nach rechts, ausgepraegte globale Aphasie m
		1 Year	Patient wach, globale Aphasie bei teilweise erhaltenem Sprachverstaendnis, hochgradige Hemiparese rechts, Arm 0/5, Bein 2-3/5, Hemihypaesthesie rechts
108	Surgery	Day 1	Pat. komatoes, druckkontrolliert beatmet
		Day 7	Komatoes I. Grades, Pupillenwerte o. B., LR+/+, ...reflexe erhalten, ... Schmerzreiz: linke Seite KG 3-4/5, rechte Seite ob. Ext. 0/5, unt. Ext. 1-2/5, Kardiopulmonal stabil
		Day 30	Patientin wach, keine sprachliche Aeusserung, Zuwendung auf Ansprache, Imitionen von Bewegungen moeglich, jedoch keine Aufforderungen werden befolgt. Hemiplegie rechts, partieller Neglect, rechte KH wird wahrgenommen, faziale Parese rechts, Blickfolge reg
		6 Months	Patientin wach, orientiert, keine Sprachproduktion, aber gut erhaltenes Sprachverstaendnis, Hemiparese rechts, Arm proximal 3/5, distal 0/5, Bein proximal 4/5, distal 4-/5, Hemihypaesthesie rechts, taktiler Neglect nach rechts, Gehen ohne Hilfe fuer 5-10
		1 Year	Pat. wach, orientiert, keine Sprachproduktion bei gutem Sprachverstaendnis, Hemiparese rechts, armbetont, Hemihypaesthesie rechts, kein Neglect, Gehen ohne Hilfe moeglich (mit Stock)
109	Surgery	Day 1	Pat. komatoes, analgosediert, CR+/+, WR+, Babinski bds. neg., keine Reaktion auf SR
		Day 7	Patient wach, Zuwendung auf Ansprache, Aufforderungen werden nicht befolgt, keine Reaktion auf SR rechts, Plegie rechts, MER re>li, Babinski re pos., Hemi..... n. rechts
		Day 30	Patient wach, teilweise erhaltenes Sprachverstaendnis, Hemiparese rechts mit teilweise ..... des re Beines KG 1-2/5, MER re>li, Babinski re pos., Gehen u. Stehen nicht moeglich

Pat.No.	Group	Visit	Finding
		6 Months	Patient wach, fraglich orientiert, rel. gut erhaltenes Sprachverstaendnis, Hemiparese rechts armbetont, Gehen mit fremder Hilfe moeglich
		1 Year	Pat. wach, orientiert, Hemiparese rechts, gutes Sprachverstaendnis, ohne Sprachproduktion, geringe Dysarthrie bei einzelnen Worten
110	Standard	Day 1	intubiert, relaxiert, beatmet, Pupillen isokor, LR+/+, CR-/-, WR-
111	Standard	Day 1	Patient intubiert, sediert, relaxiert, beatmet, kein Meningismus, keine Reaktion auf SR, Babinski bds. neg.
		Day 7	Pat. komatoes, sediert, relaxiert, beatmet, keine Reaktion auf SR, Pupillen isokor, CR bds. pos. und schwach, WR-, CR-/-
		Day 30	Patient somnolent, Augenoeffnen auf SR, teilweise Fixieren moeglich, globale Aphasie linke KH und teilweise auf SR bewegt, rechts keine Reaktion auf SR und deckt erhoehten Muskeltonus, Babinski re pos.
		6 Months	Patient wach, freundlich zugewandt, globale Aphasie, Worte nur vereinzelnt, dann voellig verwaschen und unverstaendlich, hochgradige Hemiparese rechts, Arm KG 0/5, Bein KH 1-2/5, Hemihypaesthesie rechts, multimodaler Neglect nach rechts
112	Standard	Day 1	Intubierte, voll kontrollierter Pat., Pupillen nur leicht anisokor l>re, CR+/+, WR-, auf SR keine Reaktion, MER re>li, Bab. -/- , ICP 12 katecholaminpflichtig
		Day 7	somnolent, erweckbar, fixiert bei Blickwendung nach li, Pupillen rund isokor CR+/+, schluckt, hustet, Hemiplegie re, MER+/+, Bab +/+
		Day 30	Patientin somnolent, erweckbar, Hemiparese rechts mit beginnender Funktion im rechten Bein
		6 Months	Pat. wach, teilweise orientiert, teilweise erhaltenes Sprachverstaendnis, hochgradige Hemiparese rechts
113	Standard	Day 1	Pat. soporoes, fixierte Kopf- und Blickwendung n. rechts, Hemiplegie rechts
114	Standard	Day 1	Pat. intubiert und beatmet
		Day 7	Pat. wach, fixiert intermittierend, bedingt kontaktfaehig, global aphatisch, Pupillen isokor, LR+/+, CR+/+, HP re, MER re>li, PBZ bds, Flexion auf Schmerzreize re Seite
		Day 30	Patient wach, zur Person orietiert, globale Aphasie mit teilweise erhaltenem Sprachverstaendis und guter expressiver Sprache, Hemihypaesthesie rechts, multimodaler Neglect n. rechts, Hemiparese rechts Arm KG 0/5, Bein KG 3-4/5, MER re>li, Babinski rechts
		6 Months	Pat. wach, orientiert, armbetonte Hemiparese rechts, gutes Sprachverstaendnis, Hemihypaesthesie rechts
115	Surgery	Day 1	Patientin intubiert und beatmet
		Day 7	Patientin intubiert und beatmet
116	Surgery	Day 1	Patientin intubiert und beatmet
		Day 7	Patientin intubiert und beatmet
		6 Months	Pat. wach, orientiert, Hemiparese links, Arm plegisch, inkomlette Hemianopsie nach links
117	Surgery	Day 1	Pat. intubiert u. beatmet, Pupillen isokor, CR+/+, CR li<re, WR-, HN+, keine Reaktion auf SR, keine PBZ, Pulmo bds. frei, DG+, Abdomen weich, Cor im SR
		Day 7	Mediansyndrom re mit Hemiplegie li, Hemianosognosie, Blickwendung n. re, ... ML ....., Hemianopsie n. li, Kardiopulmonal unauffaellig
		Day 30	Pat. wach, orientiert, inkomplette Hemianopsie n. links, Hemiparese links, armbetont, Hemihypaesthesie links

Pat.No.	Group	Visit	Finding
118	Standard	Day 1	Pat. intubiert u. beatmet. Pupillen li>re, CR li-re (+), CR re<li, WR-, HR (+), keine Reaktion auf SR, keine PBZ, Pulmo bds. frei, DG (+), Cor tachycard
119	Surgery	Day 1	Pat. intub. u. beatmet, Pupillen isokor, CR+/+, CR re>li, WR-, OZR-, keine Reaktion auf SR, kein PBZ, Trep. Defekt ohne Spannung, Pulmo bds. frei, Cor im SR, DG+, Abdomen weich
		Day 7	komatoese, as, intubiert, beatmete Pat.; keine Reaktion auf SR oder Ansprache (auch keine mot. Reaktion), MER insgesamt lebhaft, links etwas gesteigert, ASR-Kl..... links, Bab. Zeichen negativ; Kardiopulmonal unauffaellig unter ..... (1-6 ml/h); kei
		Day 30	Pat. wach, weitgehend orientiert, Hemiplegie links, im Rollstuhl mobil
120	Surgery	Day 1	Pat. intubiert u. beatmet
201	Standard	Day 1	globale Aphasie, dist. Sprachprod. unverst. Laute, befolgt keine Aufforderung; Hemiparese KG 2, Abducensparese links, Facialisparese links, keine PBZ
		Day 7	Pat. wach, hochgradige sensible Aphasie, maessig motorische Aphasie => befolgt keine Aufforderung, KG 2 Hemiparese, kein Babinski Zeichen
		Day 30	Patient wach, global aphasisch, partielle Blickparese, hochgradige beinbetonte Hemiparese rechts, Gang und Stand nicht moeglich, schwere Hemihypaesthesie rechts fuer alle Qualitaeten, Dysarthrie
		6 Months	Patient wach, zu Person und Ort orientiert, zeitlich desorientiert faziale Parese rechts, globale Aphasie mit teilweise gut erhaltenem Sprachverstaendnis, Hemiparese rechts, Arm provex 5/5, distal 3-4/5, Bein 4/5, geringe Hemihypaesthesie rechts, MER re>l
		1 Year	Pat. wach, orientiert, voll orientiert, geringe faziale Parese rechts, KG Bein rechts 4/5, Arm 4/5, Hemihypaesthesie rechts, MER re>li
202	Surgery	Day 1	Blickwendung nach links, partielle Hemianopsie, Hemiparese KG 2 re, PBZ re, auf SR werden Augen geoeffnet; nimmt li Blickkontakt
		Day 7	Pat. wach, kontaktfaehig, befolgt verzoegert Aufforderungen; partielle Hemianopsie re, KG 3 HP re; leicht-maessige Hemihypaesthesie re, MER re gesteigert, PBZ re, Neglect nach re
		6 Months	Pat. wach, orientiert, kooperativ, hochgr. Hemiparese rechts, Arm 0-2/5, Bein 3-4/5, Gehen mit Hilfe moeglich, faziale Par. rechts, Hemihypaesthesie rechts, Hemispastik, armbetont rechts, deutliche Aphasie, geringer Neglect n. rechts
		1 Year	Patientin wach, allseits orientiert, Hemiparese rechts, Arm KG 1-2/5, Bein KG 3-4/5, distal betont, Hemihypaesthesie rechts, faziale Parese rechts, geringe Dysarthrie, Broca-betonte globale Aphasie
203	Standard	Day 1	hochgrad. Hemiparese re; globale Aphasie
204	Surgery	Day 1	hochgradige Hemiparese, Aphasie
		Day 7	hochgradige Hemiparese, Aphasie
		Day 30	noch ausgepraegte Hemiparese
		6 Months	Patientin wach, orientiert, gutes Sprachverstaendnis bei eingeschraenkter Sprachproduktion, Hemiparese rechts, armbetont, Gehen ohne Hilfe nicht moeglich
205	Surgery	Day 1	hochgradige Hemiparese li; Neglect
		Day 7	hochgradige Hemiparese

Pat.No.	Group	Visit	Finding
		Day 30	Pat. wach, orientiert, keine Aphasie, Hemiparese links, HG 1-2/5, Hemihypaesthesie links, Gang+Stand nicht moelich
		6 Months	Pat. wach, orientiert, arm-betonte Hemiparese links, geringe Hemihypaesthesie, inkompl. Hemianopsie n. links
206	Standard	Day 1	Patient analgosediert, Osmotherapie bei erhoehtem Hirndruck
401	Surgery	Day 1	postop. i.....genes Koma
		Day 7	s NIHSS
		Day 30	wach, einzelne Worte, versteht gut; weiter hochgrad. Hemiparese rechts, Armfunktion gebessert (Mess.... prox.)
		6 Months	Pat. wach, orientiert, geringe Sprachstoerung, Hemiparese rechts, armbetont, Gehen ohne Hilfe moeglich
501	Surgery	Day 1	wach, Blickparese nach rechts, zusaetzlich divergente Bulbi mit Adduktionsschwaeche rechts, Facialisparese, globale Aphasie, dysarth....., keine Spontanbewegung der rechten Extr....., Babinski-Zeichen rechts, reagiert rechts nur auf starke Schmerzreize,
		Day 7	Pat. wach, keine Meningismus, divergente Bulbi, Lichtreaktion prompt, keine Blickparese, Facialisparese rechts, Hemiplegie rechts, Babinski-Zeichen rechts, Hemihypaesthesie rechts, kein Neglect, globale Aphasie nur einzelner verwirrten Silben
		Day 30	Pat. wach, Adduktionsschwaeche des rechen Auges (vorbestehend), dadurch divergente Bulbi, keine Blickparese, keine Gesichtsfeldeinschraenkung, visueller Neglect rechts, Fazialisparese (neutral) rechts, Dysarthrie, schwere motorische Aphasie, kann nur einz
		6 Months	wach, orientiert, faziale Parese, Arm plegisch, Bein KG 3-4/5, Hemihypaesthesie, taktiler Neglect, Gehen am Stock moeglich, kontinent
		1 Year	siehe Vorbefund vom 2.3.05
502	Standard	Day 1	Patientin sediert und beatmet, Pupillenreaktion bei rechts groesser Pupille als links bds nicht ausloesbar, schlaffer Muskeltonus
		Day 7	Pat. intubiert, flach analgosediert, Pupillenreaktion +/+, Bulbi leicht divergent, Plegie der linken Extremitaeten lediglich Strecken des li Armes , Strecken des re Armes und Anspannen der Muskeln des re Beines mit angedeuteter Fluchtreaktion
		Day 30	Pat. wach, orientiert, Wortfluessigkeit einschraenkt, Dysarthrie, Sprachverstaendnis erhalten, Pupillen weit isokor, LP prompt, keine Blickparese, Gesichtsfeldeinschraenkung links, visueller Neglect, Facialisparese li, Hemiphlegie links, Hypaesthesie/alge
		6 Months	Patientin wach, orientiert, keine Aphasie, geringe Dysarthrie, geringe Hemianopsie n. links, Neglect nach links, Hemiparese links, armbetont, KG Arm 0/5, Bein 3/5
		1 Year	Patientin wach, Befund wie vorbeschrieben am 10.7.2005, ausser: keine Dysarthrie, Funktion in linker Schulter vorhanden
601	Surgery	Day 7	Pat. wach, befolgt keine Kommandos, globale Aphasie, obere und untere Extremitaet li gezielte Bewegungen mit voller Kraft re plegisch
		6 Months	Patientin wach, zusammenhangslose Laute, kein Sprachverstaendnis, hochgradige, armbetonte Hemiparese rechts, Arm KG 0/5, Bein KG 2/5, Hemihypaesthesie rechts, Hemineglect nach rechts
		1 Year	Hemiparese rechts, Arm 1/5, Bein 2-3/5, teilweise Sprachverstaendnis vorhanden, sonst keine Aenderung zum Vorbefund vom 17.3.2005
602	Standard	Day 1	Pat. analgesodiert kontrolliert beatmet seit ca 13:30 (29.9.), Hirnstammreflexe sind ausgefallen, P.... bds ....., weil CR (.....reflex) bds ausgefallen, ...reflex negativ
1001	Standard	Day 1	Hemiplegie links, wach, ausgepraegtes Neglect, kontaktaufnahme gut moeglich, Pat. reagiert adaequat auf Fragen

Pat.No.	Group	Visit	Finding
		Day 7	weitgehend unveraendert, wach, hemipar.....
		Day 30	telefonisch mit der behandelnden Reha-Klinik (Godeshoehe, Bonn) (Dr. Meier-Bartock): Besserung des Neglects, jetzt nur noch Arm stark betroffen, beginnende Bewegung im Bein (Hueftbeugung/Beugung im Sprunggelenk)
		6 Months	Patientin wach, orientiert, Hemiparese links, beinbetont, Arm KG 1-2/5, Bein KG 3-4/5, Hemihypaesthesie links, faziale Parese links

Listing 9-5: Comments on progression and treatment

Pat.No.	Group	Visit	Progression and Treatment
102	Surgery	6 Months	Beinschmerzen durch Spastik, ertraeglich, intermittierend, noch behandlungsbeduerftig aus Sicht des Patienten
108	Surgery	Day 1	weiterhin intub. u. beatmet
		Day 7	komplikationslos
119	Surgery	Day 7	keine Besonderheiten
202	Surgery	Day 1	post-OP extubation
204	Surgery	Day 1	Schmerztherapie
		Day 7	lokale Revision
		Day 30	Wundrevision, Antibiotikum Therapie
205	Surgery	Day 1	Schmerztherapie => Besserung
206	Standard	Day 1	Patient bekommt Osmotherapie, ist analgosediert
401	Surgery	Day 1	Linsenkerneinblutung u. subgaleales Haematom
		Day 7	Stggl-Einblutung, Kompress. iprilat. Seitenventrikel
		6 Months	Pat. wach, orientiert, geringe Sprachstoerung, Hemiparese rechts, armbetont, Gehen ohne Hilfe moeglich
501	Surgery	Day 7	komplikationslos
		Day 30	Schmerzen rechte Schulter, hypertensive Blutdruckwerte, sonst komplikationsfreier Verlauf, 16.9.04: Verlegung in das Neurologische Reha-Zentrum in Greifswald
502	Standard	Day 1	Trotz max. antioedematoeser Therapie zunehmender Hirndruck und Zeichen der Einklemmung. Am Tag 1 wurde als schwere Protokollverletzung Dekompressions-OP durchgefuehrt
		Day 7	Nach Dekompressions-OP komplikationsloser Verlauf, Patientin wird antioedematoes behandelt und ist intubiert und noch enalgosediert
		Day 30	Tracheostoma am 9.2. entfernt, PEG liegt noch, nimmt schon oral weiche Vollkost auf. Sprachverstaendnis erhalten, spricht weitgehend fluessig. Plavix, Nexium, Imbun 2x 800 (.....) Mono-Embolex, Bifeteral; Nachtrag: 1.3.05 PEG entfernt

Pat.No.	Group	Visit	Progression and Treatment
601	Surgery	Day 1	Revision der Hemikraniektomie, da Knochenfenster zu klein und Patientin war Vigilanzgemindert mit Anisocoria
		Day 30	Pat. hatte ein Duraleck, welches 2mal revidiert wurde
		6 Months	Knochendeckel noch nicht reimplantiert
1001	Standard	Day 1	keine Komplikationen, keine wesentliche Befundaenderung

Listing 9-6: Other comments

Pat.No.	Group	Visit	CRF-Page	Comment
117	Surgery	Day 1	5	intub./beatmet
118	Standard	Day 1	5	intub./beatmet
119	Surgery	Day 1	5	intubiert u. beatmet
401	Surgery	Day 1	5	tief sediert, intubiert, wird als Null gezaehlt
			6	tief sediert, intubiert, wird als Null gezaehlt
		Day 30	20	zwischenzeitlich kein Kontroll-CT in Rehaklinik, insofern kann Blutungsresorption nicht bildgebend beurteilt werden
602	Standard	Day 1	7	nicht erfolgt bei zu erwartendes RF und schlechte Prognose
1001	Standard	Day 1	7	Infarktgroesse: 90% bis kompletter Mediainfarkt

9.2 References

1. Heinsius T, Bogousslavsky J, Van Melle G. *Large infarcts in the middle cerebral artery territory. Etiology and outcome patterns.* Neurology 1998;59:341-350
2. Hacke W, Schwab S, Horn M, Spranger M, DeGeorgia M, von Kummer R. *„Malignant" middle cerebral artery infarction. Clinical course and prognostic signs.* Arch Neurol 1996;53:309-315
3. Berrouschot J, Sterker M, Bettin S, Koster J, Schneider D. *Mortality of space-occupying (malignant) middle cerebral artery infarction under conservative intensive care*. Intensive Care Med 1998;24:620-623
4. Wijdicks EFM, Diringer MN. *Middle cerebral artery territory infarction and early brain swelling: progression and effect of age on outcome.* Mayo Clin Proc 1998;73:829-836
5. Bereczki D, Liu M, do Parado GF, Fekete I. *Mannitol for acute stroke.* Cochrane Database Syst Rev 2004;CD001153
6. Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. *Glycerol for acute stroke.* Cochrane Database Syst Rev 2000;CD000096
7. Hofmeijer J, van der Worp HB, Kappelle LJ. *Treatment of space-occupying cerebral infarction*. Crit Care Med 2003;31:617-625
8. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W. *Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke.* Stroke 1998;29:1550-1555
9. Schwarz S, Georgiadis D, Aschoff A, Schwab S. *Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke.* Stroke 2002;33:497-501
10. Schwab S, Spranger M, Schwarz S, Hacke W. Barbiturate coma in severe hemispheric stroke: useful or obsolete? Neurology 1997;48:1608-1613
11. Wirtz CR, Steiner T, Aschoff A, Schwab S, Schnippering H, Steiner HH, Hacke W, Kunze S. Hemicraniectomy with dural augmentation in medically uncontrollable hemispheric infarction. Neurosurgery Focus 1997;2:1-4
12. Schwab S, Rieke K, Aschoff A, Albert F, von Kummer R, Hacke W. *Hemicraniectomy in space-occupying hemispheric infarction: useful early intervention or desperate activism?* Cerebrovasc Dis 1996;6:325-329

13. Morley NC, Berge E, Cruz-Flores S, Whittle IR. *Surgical decompression for cerebral oedema in acute ischaemic stroke.* Cochrane Database Syst Rev 2002;3:CD003435
14. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. *Early hemicranectomy in patients with complete middle cerebral artery infarction.* Stroke 1998;29:1888-1893
15. Cho DY, Chen TC, Lee HC. *Ultra-early decompressive craniectomy for malignant middle cerebral artery infarction.* Surg Neurol 2003;60:227-232
16. Gupta R, Connolly ES, Mayer S, Elkind MS. *Hemicraniectomy for massive middle cerebral artery territory infarction.* A systemiatic review. Stroke 2004;35:539-543
17. Frank JI, Krieger D, Chyatte D. *Hemicraniectomy and durotomy upon deterioration from massive hemispheric infarction: A proposed multicenter, prospective, randomized study*. Stroke 1999;30:243
18. Frank JI. *HeADDFIRST Preliminary results.* Presented at the 55th Annual AAN Meeting in Honolulu, Hawaii, April 3rd, 2003
19. Hofmeijer J, Amelink GJ, Algra A, van Gijn J, Macleod MR, Kappelle LJ, van der Worp HB; HAMLET investigators. *Hemicraniectomy after middle cerebral artery infarction with life-threatening Edema trial (HAMLET). Protocol for a randomised controlled trial of decompressive surgery in space-occupying hemispheric infarction.* Trials. 2006 Sep 11;7:29.
20. Vahedi K, Vicaut E, Mateo J, Kurtz A, Orabi M, Guichard JP, Boutron C, Couvreur G, Rouanet F, Touzé E, Guillon B, Carpentier A, Yelnik A, George B, Payen D, Bousser MG; DECIMAL Investigators. *Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial).* Stroke 2007; 38:2506-17.
21. Jüttler E, Schwab S, Schmiedek P, Unterberg A, Hennerici M, Woitzik J, Witte S, Jenetzky E, Hacke W; DESTINY Study Group. *Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial.* Stroke. 2007 Sep;38(9):2518-25
22. *Major ongoing stroke trials.* Stroke 2006;37:e18-e26
23. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, 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 Neurol. 2007 Mar;6(3):215-22.

24. Thom T, Haase N, Rosamond W, Howard V, Rumsfeld J, Manolio T, Zheng Z-J, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC, Hong Y, Members of the Statistics Committee and Stroke Statistics Subcommittee, Adams R, Friday F, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V, Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P: *Heart Disease and Stroke Statistics - 2006 Update; A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee*. Circulation Feb. 2006; 113: e85 - e151; published online before print January 11 2006, doi:10.1161/CIRCULATIONAHA.105.171600 http://circ.ahajournals.org/cgi/reprint/113/6/e85
25. Fuchs EC, Muller-Busch C, Amtenbrink V: *Prognosis and long-term prognosis of epidural haematoma (a study of 83 patients).* Rehabilitation (Stuttg). 1975 May; 14(2): 82-87.
26. EMEA: *Points to consider on clinical investigation on medicinal products for the treatment of acute stroke*. 20.1.2005; CPMP/EWP/560/98; http://www.emea.eu.int/pdfs/human/ewp/056098en.pdf
27. Whitehead J, Brunier H. The PEST project, University of Reading 1989. The design and analysis of sequential clinical trials. In: Wiley. 1997. Planning and Evaluation of Sequential Trials
28. Mahoney GI, Barthel DW. Functional evaluation. The Barthel Index. MD State Med J 1965;14:61-65
29. Rankin J. Cerebral vascular accidents in people over the age of 60: II. Prognosis. Scott Med J 1957;2:200-215
30. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW; *Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators. NXY-059 for acute ischemic stroke.* N Engl J Med 2006;354: 588-600
31. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J: *Interobserver agreement for the assessment of handicap in stroke patients.* Stroke. 1988 May;19(5):604-7.
32. Wilson JT, Hareendran A, Grant M, Baird T, Schulz UG, Muir KW, Bone I.: *Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin Scale.* Stroke. 2002 Sep;33(9):2243-6.

33. Wilson JT, Hareendran A, Hendry A, Potter J, Bone I, Muir KW. *Reliability of the modified Rankin Scale across multiple raters: benefits of a structured interview.* Stroke. 2005 Apr;36(4):777-81.
34. Shinohara Y, Minematsu K, Amano T, Ohashi Y: *Modified Rankin Scale with Expanded Guidance Scheme and Interview Questionnaire: Interrater Agreement and Reproducibility of Assessment.* Cerebrovascular Diseases 2006;21(4):271-278

9.3 Study Protocol

(see separate document)

9.4 Case Report Form

(see separate document)

9.5 Statistical Analysis Plan

(see separate document)