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PROTOCOL TITLE:

SPARTA 'Study on Prognosis of Acutely Ruptured intracranial Aneurysms

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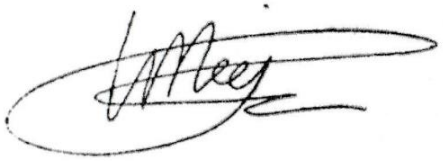
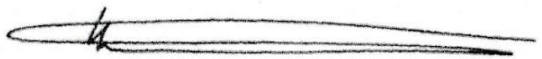
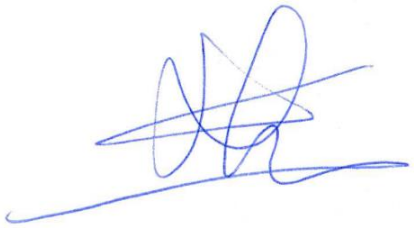
Coordinating Investigator & Principal Investigator: Dr. Wouter A. Moojen		07.12.2020
Principal Investigator: Prof. Dr. Wilco Peul		07-12-2020
Junior Investigator: Alexander Hamming		08-12-2020

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, Algemene Beoordeling en Registratie)
ADL	Activities of Daily Life
AE	Adverse Event
AR	Adverse Reaction
aSAH	Aneurysmal Subarachnoid Haemorrhage
AVG	Algemene Verordening Gegevensbescherming
AVM	Arteriovenous Malformation
BRAT	Barrow Ruptured Aneurysm Trial
CA	Competent Authority
CI	Confidence interval
CCMO	Central Committee on Research Involving Human Subjects (in Dutch: Centrale Commissie Mens-gebonden Onderzoek)

CRF	Case Report Form
CSF	Cerebrospinal Fluid
CV	Curriculum Vitae
dAVF	Dural Arteriovenous Fistula
DCI	Delayed Cerebral Ischemia
DSMB	Data Safety Monitoring Board
DCI	Delayed cerebral ischemia
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
EQ-5D	Health-related quality of life measurement instrument
ETZ	Sint-Elisabeth-TweeSteden Hospital, Tilburg
GCP	Good Clinical Practice
GOS-E	Extended version of the Glasgow Outcome Scale
HADS	Hospital Anxiety and Depression Scale
HMC	Haaglanden Medisch Centrum, the Hague

IA	Intracranial Aneurysm
IB	Investigator's Brochure
IC	Informed Consent
ISAT	International Subarachnoid Aneurysm Trial
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
LOCF	Rancho los Amigos Levels of Cognitive Functioning Scale
LUMC	Leiden University Medical Centre, Leiden
METC	Medical research ethics committee (in Dutch: Medisch Ethische Toetsing Commissie)
MOCA	Montreal Cognitive Assessment
mRs	Modified Rankin Scale
QALY	Quality Adjusted Life years

(S)AE	(Serious) Adverse Event
SAH	Subarachnoid Haemorrhage
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TICS-m	Telephone Interview for Cognitive Status
UNCH	University Neurosurgical Center Holland Leiden – The Hague
UMCG	University Medical Center Groningen, Groningen
WEB®	Woven EndoBridge®
WFNS	World Federation of Neurosurgical Societies

WMO Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Ruptured intracranial aneurysms resulting in subarachnoid haemorrhage can be treated by open surgical treatment or endovascular treatment. Despite multiple previous studies, biases and uncertainty around the best current treatment practice still exist. The resulting variation of care may result in a variable outcome. The protocol for a prospective multicentre observational study aimed at comparing the effectiveness of different treatment strategies in patients with ruptured aneurysms is presented.

Objective: The primary aim of this study is to identify the effectiveness of clipping versus coiling on functional outcome in patients presenting with a subarachnoid haemorrhage due to a ruptured intracranial aneurysm 1 year after onset of symptoms. Secondary objectives include long term functional outcome, complications, cost-effectiveness and explorative analysis of the diagnostic and prognostic value of radiological imaging.

Study design: This multi-centre study will have an observational prospective cohort design. Patient will have a follow-up of maximum 10 years.

Study population: Patients with a subarachnoid haemorrhage will be included. Patients with evident other causes and patients without diagnosis of intracranial aneurysm after six months will be excluded.

Main study parameters/endpoints: The primary endpoint is the score on the modified Rankin scale (mRs) and mortality at 1 year after the initial SAH. Secondary endpoints include mRs, MOCA, LOCF, TICS-m, EQ-5D and derived QALYs, costs from patient diaries, GOS-E, , Barthel index, and HADS.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients will receive ‘nonexperimental’ regular care during their hospital stay. For this study, health questionnaires and functional outcome will be assessed at baseline, follow-up visits and before discharge. Temporary fatigue is the only possible side-effect of completion of the questionnaires.

1. INTRODUCTION AND RATIONALE

1.1 Introduction

Spontaneous subarachnoid haemorrhage (SAH) is a life-threatening event, most frequently (around 85% of cases) caused by the rupture of an intracranial aneurysm. This intracranial aneurysm is a bulging weak area in the vessel wall of a cerebral artery, that is prone to rupture in some cases. They mostly occur on bifurcations of the large arteries near the base of the skull.

The prevalence of unruptured intracranial aneurysms in the general population is relatively high; it is estimated to be 1.8% at a mean age of 63.3 years[1,2]. Women are thought to be affected more often than men (prevalence ratio: 1.61 (confidence interval (CI): 1.02-2.54))[1,2]. The incidence of aneurysmal SAH is approximately 0.7-12 per 100.000 per year depending on the region. The incidence of SAH in The Netherlands is 8-9 per 100 000 per year and is therefore calculated to be 1500 aneurysmal SAH yearly[3–5]. The average annual incidence of SAH in the Netherlands according to the Quality Registry for Neuro Surgery (QRNS) from 2014 to 2017 is 1014 cases per year[*]. It is generally believed that 8-10% of the patients die before hospital arrival after a SAH. Mortality after aneurysmal SAH for Europe excluding northern Sweden and Finland is thought to be 44.4%[3,4,6]. The mortality rate however seems to be declining due to improved prehospital and hospitalised care[3,6]. When considering functional outcome, it is assumed that approximately a third of all patients with a SAH after ruptured intracranial aneurysm, so-called aneurysmal subarachnoid haemorrhage (aSAH) has a “good outcome” (mRs □2) [7].

A minority (around 5%) of spontaneous SAH cases are caused by other vascular lesions in the skull or spinal canal; including arteriovenous malformations (AVM) and dural arteriovenous fistulae (dAVF) with their own clinical course and treatment[8]. More frequently, no vascular lesion can be identified on initial angiographic imaging. This group of patients with angiography-negative subarachnoid haemorrhage can be split into a group with consistently good prognosis and a typical prepontine pattern of blood on CT and a group with a more diffuse pattern of blood on CT. In the first, so-called perimesencephalic subarachnoid haemorrhage, no follow-up imaging is needed[9]. They make up around 10% of all SAH patients[8]. The latter group is thought to include patients with angiographically occult aneurysms (e.g. by thrombosis of the lumen) and follow-up imaging is thought to be of value[10].

The primary treatment for ruptured intracranial aneurysms is to prevent the high-risk occurrence of early rebleeding by exclusion of the aneurysm from the circulation. Furthermore, optimal systemic supportive care including cerebrospinal fluid (CSF) drainage in case of raised intracranial pressure is needed to prevent further injury. This so-called secondary treatment is most commonly provided at intensive care or medium care units. Delayed cerebral ischemia (DCI) and hydrocephalus with raised intracranial pressure are both common and dangerous consequences of SAH, often prompting specific medical and/or surgical therapy[11]. Systemic complications including cardiac instability, hyponatremia and other metabolic dysregulation like hyperglycaemia can negatively impact the outcome and need monitoring[12–14] .

The most applied primary treatment modality is endovascular coiling of the aneurysm, which has replaced craniotomy with microsurgical clipping in the majority of cases[11]. The best but conflicting evidence for this treatment strategy comes from the results of two randomized controlled trials: the Barrow Ruptured Aneurysm Trial (BRAT) and the International Subarachnoid Hemorrhage Trial (ISAT)[15,16]. The outcomes from the ISAT trial suggest that survival is slightly but significantly superior in patients treated by endovascular coiling compared to patients treated with microsurgical clipping. ISAT included cases in which an equivalence of both coiling and clipping was assumed by the treating team before randomization[15]. Initial results from the BRAT suggested superior functional outcome for patients treated with coiling, but these did not remain significant with longer follow-up[16,17]. At one year, patients allocated to endovascular treatment had a poor outcome in 23.2% in BRAT and 23.5% in ISAT and patients assigned to clipping had a poor outcome in 33.7% and 30.9% respectively[18,19]. The implications of the BRAT trial are thought to of limited value because of crossing-over between the treatment groups, as 36% of patients assigned to the coiling arm crossed over to the clipping arm, which is a serious sign of a less effective treatment strategy by coiling[20]. Definitive occlusion is considered to be of primordial importance for long-term effectiveness of aneurysm treatment. Recanalization and regrowth of aneurysms can cause another SAH and are therefore considered a serious complication. Recanalization and regrowth of aneurysms are thought to occur more frequently after endovascular treatment (retreatment rate 20% for coiling vs. <1% clipping at 10-year BRAT follow-up for saccular aneurysms[20]), possibly necessitating retreatment. Furthermore, the results from the ISAT trial indicate significantly higher rates of rebleeding and retreatment for coiled aneurysms as compared to clipped aneurysms at ten-year follow-up (retreatment: 17.4 for coiling vs. 3.9% for clipping)[15,16,21].

Results from both studies demonstrate that the best evidence-based practice for treatment of acutely ruptured intracranial aneurysms has yet to be determined. The promising endovascular treatment, initiated in two decades ago, seems to have a high incidence of rebleeding and retreatment,

necessitating intensive outpatient radiological follow-up and therefore keeps a large proportion of treated patients unsure about their future. This uncertainty is very debilitating as the risk of a recurring bleeding incident has an impact on the patient, their family and society (loss of work).

The choice of coiling or clipping is primarily decided by the treating physician based on the aneurysm location, morphology and local and physician-bound treatment paradigms that take the clinical condition of the patient into account. Hospitals may have different treating algorithms for similar patients including endovascular techniques and microsurgical techniques, e.g. Woven Endobridge® (WEB)-devices versus clipping for middle cerebral artery aneurysms or flow diverter placement versus stent-assisted coiling for aneurysms of the proximal internal carotid artery. Aside from the treatment modality, even deciding whether to treat ruptured intracranial aneurysms immediately after presentation, to postpone treatment or to choose not to treat the causative aneurysm, especially in cases with severely affected patients (grades IV or V according to the World Federation of Neurosurgical Societies (WFNS)-grading system) is variable.

The current observational quality registry for patients who suffered a SAH in the Netherlands only collects basic information and has a follow-up time of 6 months with or without imaging follow-up. This data is insufficient to assess long-term treatment success and is not available for scientific analysis. Additionally, there is a lack of insight into the full chain-based care for these patients in the acute hospitalized and subsequent rehabilitation, nursing home or outpatient setting, and influence of the variety of treatment protocols on the outcomes. The influence of variation in provided care on clinical and functional outcomes between different medical centres in the Netherlands and abroad remains to be investigated. This high practice variation rate is a sign of low value care, considering the unknown personal and societal effect by lack of evidence and unknown of cost-effectiveness results.

The treatment of SAH patients comes with high costs (mean: €38,300,- in the first year) as suggested by a German study carried out in 2004, with worse functional outcome and younger age being major cost-driving factors[22]. This includes both direct (health insurance- and out of pocket costs) as indirect costs (productivity losses). Primary treatment choice also seems to make a difference in the cost of treatment. Coiling is associated with higher material-related costs but lower in-hospital costs and clipping is associated with higher in-hospital costs and lower treatment-related cost[23,24].

In the growing concept of value-based healthcare, a greater importance has justly been put on measuring relevant outcomes and costs for all patients. This implies a shift from providercentred outcomes, most commonly focussed on processes, to outcomes that are important to the patient[25]. The aim of this study will be to gather outcomes according to the different hierarchical tiers, primarily focusing on the first tier of the achieved or retained health status, best exemplified in the so-called functional status of the patient. The study will as well focus on the other two tiers being process of recovery and the sustainability of health[26].

According to the recommendations of the IDEAL collaboration, long-term follow-up of large parts of the population is needed to validate the findings of randomized trials[27]. Randomized study designs are cumbersome for long-term follow-up of clinical outcomes of large groups of patients, decreasing their utility for this goal. Randomisation is finally not necessary for the study of cost-effectiveness. A longitudinal prospective cohort study design with a focus on inherent variation in care might be able to identify the best current practice using this existing variation. In a similar fashion, the CENTER-TBI study was performed for traumatic brain injury starting in 2013, capitalizing on the variation inherent in treatment of traumatic brain injury patients[28].

1.2 Aim of this study

The aim of this comparative observational study is to identify the most effective existing clinical care to achieve favourable functional outcomes for patients with ruptured intracranial aneurysms.

2. OBJECTIVES

The overall objective is to identify the most effective existing clinical care to achieve favourable functional short and long-term outcomes for patients with ruptured intracranial aneurysms.

The primary objective is aimed at comparing the effectiveness of two primary treatment options: clipping and coiling at 1 year. The secondary objectives are more exploratory and aimed at; exploring the effect of clipping versus coiling on longer term outcome, exploring the effect of specific aspects of these treatment modalities and the effect of other secondary and rehabilitation interventions on short and long term outcome, assessing cost-effectiveness of different treatments and organisation of care, and improving prognostication.

2.1 Primary objective and research question

The primary objective is to determine the effect of clipping versus coiling on the functional outcome at 1 year in patients presenting with a subarachnoid haemorrhage due to a ruptured intracranial aneurysm. We hypothesize that the functional outcome of clipping is non-inferior to coiling at 1 year after treatment, but that inherent treatment differences might become apparent beyond this horizon.

2.2 Secondary objectives and research questions

Primary treatment

I. To determine the effectiveness of any kind of treatment (coiling or clipping) versus best supportive therapy on the functional outcome and mortality in aSAH at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that patients in an initially bad clinical condition do not have a better outcome after treatment will be tested.

II. To determine the effectiveness of clipping versus coiling on the functional outcome and mortality in patients presenting with aSAH at 6 months, 2, 5 and 10 years after onset of symptoms. The hypothesis that patients treated with clipping and coiling have a similar functional

2- and 5-year outcome and that patients treated with clipping have a superior functional 10-year outcome after onset of symptoms will be tested.

III. To determine the effectiveness of different timing (within 6 hours, within 24 hours, within 72 hours, within 1 week, within 2 weeks, first month) of primary aneurysm treatment in the acute setting (e.g. clipping or coiling) after aSAH on the functional outcome 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that earlier treatment is associated with better outcome will be tested.

IV. To determine the effectiveness of flow diversion and Woven EndoBridge®-devices (WEB-devices) when compared to clipping or coiling in patients presenting with aSAH at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that using flow diversion or Woven EndoBridge®-devices has a worse functional outcome when compared to clipping or coiling will be tested.

V. To compare the impact of different primary treatment timings and modalities on cognitive functioning, mood and fatigue in patients with aSAH at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that clipping has a higher negative impact on mood of at 1 and 2 years after onset of symptoms and that coiling has a higher negative impact at 5 and 10 years will be tested.

Secondary treatment

VI. To determine the effectiveness of induced hypertension and endovascular treatment of vasospasm for suspected imminent delayed cerebral ischemia after aSAH on the occurrence of DCI and functional outcome at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that that both induced hypertension and endovascular treatment of vasospasm are not effective for functional outcome, but are effective in preventing occurrence of DCI, will be tested.

VII. To determine effectiveness of early CSF drainage and the amount of drainage on functional outcome at 6 months, 1, 2, 5 and 10 years after onset of symptoms of aSAH. To determine if the amount of drainage of CSF is proportionate with the rate of rebleeds. The

hypothesis that CSF drainage is associated with a worse functional outcome and that CSF drainage is not proportionate with the rate of rebleeds will be tested.

VIII. To determine the effect of the different secondary treatment modalities on cognitive functioning, mood and fatigue in patients at 6 months, 1, 2, 5 and 10 years after onset of symptoms of aSAH. The hypothesis that patients treated with CSF drainage, induced hypertension or endovascular treatment of vasospasm have a higher negative impact on mood compared to their peers will be tested.

Rehabilitation

IX. To determine the effectiveness of different timing of mobilisation during hospitalisation in patients with aSAH on functional outcome at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that earlier mobilisation is associated with a better functional outcome will be tested.

X. To compare the effectiveness of high intensity and low intensity rehabilitation programmes on the functional outcome at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that a high intensity rehabilitation programme is associated with a better functional outcome will be tested.

XI. To determine the effectiveness of different primary treatment modalities (coiling, clipping, advanced endovascular techniques), supportive care measures and care settings, different treatments for complications (e.g. endovascular treatment or induced hypertension for suspected DCI), long-term follow-up imaging and different rehabilitation intensities on the return to independent functioning during activities of daily life (ADL) at 6 months, 1, 2, 5 and 10 years after onset of symptoms.

XII. To determine the effectiveness of different primary treatment modalities (coiling, clipping, advanced endovascular techniques), supportive care measures and care settings, different treatments for complications (e.g. endovascular treatment or induced hypertension

for suspected DCI), long-term follow-up imaging and different rehabilitation intensities on participation in society at 6 months, 1, 2, 5 and 10 years after onset of symptoms.

XIII. To determine the effect of mobilisation during hospitalisation and rehabilitation programmes on cognitive functioning, mood and fatigue in patients at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that early mobilisation and high intensity rehabilitation has a positive impact on cognitive functioning, mood and fatigue will be tested.

Follow-up and imaging

XIV. To collect and store initial CT and CT-angiography imaging data for analysis of markers (including aneurysm morphology and location) to improve prediction of complications (hydrocephalus, DCI, epilepsy, rebleeding, death), surgical outcome (recurrence, recanalization) and functional outcome at 6 months, 1, 2, 5 and 10 years after onset of symptoms. The hypothesis that imaging markers are predictive of complications and measures of outcome will be tested.

XV. To predict aneurysm recanalization, recurrence, rebleeding and retreatment using reported morphological changes on follow-up imaging. The hypothesis that aneurysm morphological changes is predictive of rebleeding will be tested.

Cost-effectiveness and organization of care

XVI. To determine cost-effectiveness of clipping versus coiling. An estimate of the costs associated with other primary treatment modalities (e.g. advanced endovascular techniques), supportive care measures and care settings, different treatments for complications (e.g. endovascular treatment or induced hypertension for suspected DCI), long-term follow-up imaging and different rehabilitation intensities will be established. The hypothesis that clipping is more cost-effective than coiling will be tested.

XVII. To determine the role of different referral area, caseload, number of care providers when considering functional outcome at 6 months, 1, 2, 5 and 10 years of follow-up after onset of symptoms caused by aSAH. The hypothesis that these factors play no role in the functional outcome will be tested.

Baseline information

XVIII. To collect high quality provider-reported and patient-reported data to differentially predict good from worse functional and clinical outcome and significant clinical events including complications (hydrocephalus, delayed cerebral ischemia, rebleeding of aneurysm, epilepsy, death). The hypothesis that these complications and measures of outcome can be predicted using subject-specific and treatment data will be tested.

3. STUDY DESIGN

3.1 Study Design

Longitudinal multicentre prospective observational cohort study.

During the period of the study, all SAH patients presenting in the study sites to the emergency department, neurology or neurosurgery departments will be screened for inclusion eligibility. Eligible patients will be included as subjects in the study. Treatment decisions and treatment methods (e.g. neurosurgical clipping or endovascular coiling for primary treatment of the aneurysm) will not be influenced by inclusion in the study. Standard care tailored to the specific patient should be provided, as is customary in the study site by the local treating team. Information on the patient characteristics and initial treatment will be gathered for subjects included in the study as baseline information.

Follow-up of the subjects during the initial 6 months after treatment will be as is required by national quality regulations, and during this time should also be tailored to the specific needs of the patient. At several of the regulated follow-up visits, study questionnaires should be completed.

After regulated follow-up visits, patients included in the study will have at least 4 more visits, at respectively 1, 2, 5 and 10 years after treatment. Other visits may be necessary for patient-specific reasons and should be documented, but are not required by the study. During these study visits, patients will complete questionnaires and the local treating team will report on the treatment and clinical findings.

The primary outcome measurement will be assessed at 1 year after inclusion of the final patient. The study will be completed at 10 year after follow-up of the last included patient.

3.2 Study Sites

To answer the research questions 5 centres from The Netherlands (n=5) will include subjects, with a possibility to expand with inclusion of subjects from the academic centres of Amsterdam, Maastricht, Rotterdam and Utrecht.

Participating centres:

- University Neurosurgical Center Holland Leiden – The Hague (UNCH), including the Leiden University Medical Centre (LUMC) in Leiden, HAGA hospital in The Hague and Haaglanden Medisch Centrum (HMC) in The Hague
- Sint-Elisabeth-TweeSteden Hospital Tilburg (ETZ)
- Isala Hospital Zwolle
- Radboud University Medical Center (Radboud UMC)
- Academic Medical Center Amsterdam (AMC)
- Maastricht University Medical Center (MUMC)
- Erasmus Medical Center (EMC)

All of these study sites will collect data from their own patients in an electronic database and centralised analysis will be performed from the main study location in Leiden – the Hague.

A steering committee will be established to include local investigators in the management aspects surrounding the study, including publication policy and for the sake of transparency.

3.3 Sample size / sample size calculation

Calculation of sample size was performed to show non-inferiority of clipping compared to coiling on 1 year outcome, analysed as the ordinal modified Rankin Scale. We assume that the rate of poor outcome after clipping and coiling is equal (31%) based on the uncertainties in previous literature regarding selection of patients and biases. The non-inferiority margin is set at 7% difference. Alpha is set to 0.05 and beta to 0.8. Using these assumptions, we require a sample size of 1100 patients. Since analyzing the full modified Rankin Scale instead of dichotomizing it decreases the required sample size by approximately 20%, we therefore require 880 patients.

3.4 Number of subjects

We will include 880 subjects (440 in each group).

3.5 Study duration

During a 4-year period the study sites will each include a maximum of 176 patients with aSAH. Patients will have a maximum follow-up of 10 years, resulting in a maximum of 14 years data collection. Inclusion of patients stops when the targeted number of 176 per study site is reached. In the event of slower recruitment, the recruitment period may be extended.

4. STUDY POPULATION

4.1 Population (base)

All patients that present primarily or after acute referral (in-patient to in-patient) to the participating centres, with a spontaneous subarachnoid haemorrhage will be screened for eligibility for this study by the treating physicians or local research nurses.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all the following criteria:

- Confirmed diagnosis of subarachnoid haemorrhage on CT-scan or lumbar puncture (in the presence of a negative CT-scan)

- Intracranial aneurysm proven within 6 months to be the cause of subarachnoid haemorrhage
- Age 18 years or over at presentation.
- Written informed consent

Written informed consent for participation in the study will be obtained from the patient or the legal representative during the admission period by the local treating team.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria on presentation to one of the participating centres or later during the clinical course will be excluded from participation in this study:

- Subarachnoid haemorrhage deemed most likely of ’perimesencephalic’ origin after consideration of history, clinical examination and radiological findings (including angiographic imaging)
- Subarachnoid haemorrhage deemed most likely of post-traumatic origin after consideration of history, clinical examination and radiological findings (including angiographic imaging)
- Diagnosis of intracerebral arteriovenous malformations or dural arteriovenous fistula.
- No diagnosis of intracranial aneurysm at 6 months after onset of symptoms.
- Not mastering the Dutch language

5. TREATMENT OF SUBJECTS

The treatment protocol for the patients included in the study is not specified by the study protocol as the study is strictly observational with current practice care.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The primary endpoint in this study is the score on the mRs at 1 year after onset of symptoms.

This will be collected through a case report form addressed to the local treating team at the 6 month and 1-year interval after onset of symptoms. The mRs will be obtained through a structured interview, either by phone or at a face-to-face assessment. Additionally, mortality before this point will be documented by the local treating team using a specific case report form.

6.1.2 Secondary study parameters/endpoints

To summarize some of the most used outcome parameters we will use the following terms:

'Functional outcome'-data set:

- mRs at 6 months, 1, 2, 5 and 10 years after onset of symptoms, as measured by completion of case report forms by local treating teams
- GOS-E at 6 months, 1, 2, 5 and 10 years after onset of symptoms, as measured by completion of case report forms by local treating teams
- Barthel index at 6 months, 1, 2, 5 and 10 years after onset of symptoms, as measured by completion of case report forms by local treating teams

'Cognitive outcome'-data set, meaning general cognitive functioning and mood/fatigue:

- TICS-M at 6 months, 1, 2, 5 and 10 years after onset as measured by completion of case report forms by local treating teams
- Hospital Anxiety and Depression Scale (HADS) at 6 months, 1, 2, 5 and 10 years after onset of symptoms by completion of questionnaires by subjects

'Quality of life and Costs'-data set:

- EQ-5D-5L at 6 months, 1, 2, 5 and 10 years after onset of symptoms, as measured by completion of questionnaires by subjects

- Estimation of societal costs by completion of a custom healthcare consumption and loss of productivity (paid and unpaid) questionnaire at 3 months, 6 months, 1 year, 2 years, 5 years and 10 years

Primary treatment

- Case report form on type of primary treatment, timing of treatment, reasoning for choice of treatment, periprocedural complications, used material and time
- Case report form on the occurrence of rebleeding and retreatment, reasoning for choice of retreatment, modality of retreatment, timing of retreatment, used material and time
- Case report form on death of subject, timing of death, suspected cause of death
- Functional outcome data set(see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

Secondary treatment

- Case report form on the occurrence of DCI and its treatment, timing of treatment, reasoning for choice of treatment, periprocedural complications, used material and time
- Case report form on the occurrence of hydrocephalus and its treatment, timing of treatment, reasoning for choice of treatment, periprocedural complications, used material and time, amount of drainage
- Case report form on the admission of patient to ICU or medium care unit, reasoning for choice of ward, modalities of vitals- and neuromonitoring on unit
- Case report form on death of subject, timing of death, suspected cause of death
- Continuous vital sign data from hospital electronic patient file
- Functional outcome data set (see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

Rehabilitation

- Case report form on the mobilisation of patient as an inpatient, and in-hospital rehabilitation, reasoning for choice of mobilisation and rehabilitation modalities and timing
- Case report form on the rehabilitation choice for patients, reasoning for choice, timing of rehabilitation and intensity of programme.
- Functional outcome data set (see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

Follow-up and imaging

- Case report form on the follow-up schedule, reasoning for the schedule, used time and imaging requested
- Case report form on aneurysm recanalization and recurrence describing aneurysm morphology, changes, clinical course before
- Initial CT and (CT-)angiography digital images and centralized analysis by blinded radiology panel
- Functional outcome data set (see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

Cost-effectiveness and organization of care

- All case report forms above, except CRF's on recanalization and death.
- Hospital specific referral area, caseload, number of care providers.
- Functional outcome data set (see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

Baseline information

- Baseline patient information case report form on common data elements
- All case report forms above

- Functional outcome data set (see above)
- Cognitive outcome data set (see above)
- Quality of life data set (see above)

6.1.3 Other study parameters (if applicable)

No other study parameters are applicable.

6.2 Randomisation, blinding and treatment allocation

Randomisation is not applicable as the study is strictly observational with current practice care. There will be no experimental treatment, no randomisation or blinding of treatment. The study compares treatments as they are indicated by the local treating team. As such, there will be no allocation of a specific treatment regimen to any patient.

6.3 Study procedures

Study procedures for inclusion in the study are the same in all study sites. The local treating physicians will obtain informed consent and treat patient according to local hospital protocol or their own clinical insight. The data collected in this study will be collected without interfering in treatment of the patient and is strictly observational, supplemented by questionnaires.

Written informed consent for participation in the study will be obtained from the patient or the legal first representative during the admission period. If no informed consent can be obtained from the subject because of his/her incompetence at the time, possibly by the effects of the SAH, consent will be obtained from the legal representative. If no legal representative is available during the admission period, consent will be assumed, and data acquisition started. The consent procedure will be attempted as soon as a legal representative is available, or the subject becomes competent. If no consent is obtained at that time of deferred consent, all obtained data will be destroyed. If a subject where the legal representative had previously given consent because of incompetence, becomes competent a new consent procedure is initiated. If no consent is obtained at that second time, acquisition of data will cease and data acquired up until then will be used for analysis. If a subject dies during data acquisition before formal consent was given, consent will be assumed and information will be given to legal representatives on how to actively withdraw their consent.

Outcomes, baseline information, treatment information and imaging data will be collected according to specified time points. The follow-up of all patients will be 10 years after inclusion. Data will be collected by the local treating physician and other appropriate treatment providers. They will fill out the questionnaires and perform the necessary tests. The data will be entered into the database directly. A data-assistant will enter the data into the database at a later point if this is not possible in some locations.

All measurements will be performed by qualified physicians or research nurses that have received training to perform the measurements. The measurements will take place during follow-up appointments, by phone, by (e-)mail and will be registered in an online environment. In cases where patients have difficulty completing the form, legal representatives or family or close caregivers can assist them in completing the form. Patients that have a lowered consciousness will be evaluated by physicians or research nurses trained to handle these specific patients. After assignment of a patient-specific study code, the data will be entered into a centralised electronic database in the different study sites by treating physicians or study nurses, according to local organisation. The masterfile containing the link between the identifiable patient data and the study code will be kept in the local study site. Process related variables and associated costs will be acquired from participating centres.

After collection of this data in the centralised database, analysis will be primarily performed by the sponsor and the coordinating researchers. Local investigators may use the data from their center for separate analyses after consensus in the steering committee.

6.3.1 Timing of data acquisition:

On baseline/admission

- Informed consent form
- Baseline information CRF
- Initial CT and (CT-)angiography digital images

Admission to a ward

- Deferred informed consent form if not yet consented
- CRF on admission

Primary treatment

- CRF on primary treatment
- If rebleeding or retreatment, fill CRF on rebleeding and retreatment

Secondary treatments

- CRF on patient mobilisation and inpatient rehabilitation
- If hydrocephalus, fill CRF on hydrocephalus
- If DCI, fill CRF on DCI

Hospital discharge

- Deferred informed consent form if not yet consented
- If death, fill CRF on death

Scheduled follow-up visits

- CRF on follow-up schedule
- If rehabilitation referral, fill CRF on rehabilitation
- If recanalization/retreatment, fill CRF on recanalization/retreatment
- If death, fill CRF on death
- At 3 months: costs questionnaire
- At 6 months: mRs, GOS-E, TICS-m, Hospital Anxiety and Depression Scale (HADS), EQ-5D , Barthel ADL index, costs questionnaire
- At 1 year: mRs, GOS-E, TICS-mHADS, EQ-5D, Barthel index, costs questionnaire
- At 2 year: mRs, GOS-E, TICS-m, HADS, EQ-5D, Barthel index, costs questionnaire
- At 5 year: mRs, GOS-E, TICS-m, HADS, EQ-5D, Barthel index, costs questionnaire
- At 10 year: mRs, GOS-E, TICS-m HADS, EQ-5D, Barthel index, costs questionnaire

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any further consequences. If the patient would like to, they are requested to complete a questionnaire on withdrawal from the study.

There is no required withdrawal of a subject unless they would like to as described above. In general, if the health of a study subject would benefit from withdrawal from the study, the local investigator should withdraw the patient from the study.

6.4.1 Replacement of individual subjects after withdrawal

Subjects who are withdrawn from the study will not be replaced.

6.4.2 Follow-up of subjects withdrawn from treatment

General category of reason for withdrawal should be completed on the case report form. After this, there is no study follow up of patients after withdrawal. Regular clinical follow up is maintained as decided by the local treating team.

6.5 Premature termination of the study

Not applicable as the study is strictly observational with current practice care.

7. SAFETY REPORTING

Aneurysmal subarachnoid haemorrhage is a life-altering event that can lead to temporary or permanent discomfort or injury and even death. This is unfortunately inherent to the disease and this study will not interfere with the clinical course of this disease by any intervention. As the study is observational in nature comparing different forms of accepted practice, it is unlikely that any events will occur that are caused by participation in the study.

Information on the course of the disease in the study subjects will be gathered in the study. As such, CRF's require local investigators to report complications of the SAH. We will not report AE's, SAE's or SUSAR's to the METC but include them in the CRF.

However, in accordance to article 10, subsection 4, of the WMO, the sponsor must suspend the study if there is enough ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

No committee regarding the safety of patients will be established as the safety is not at risk in the observational design of the study. A committee considering the correct performance of the study will be convened because of the long term run of the study and multicentric design, a socalled data safety monitoring board. The charter is attached.

8. STATISTICAL ANALYSIS

8.1 Primary study parameter

To examine effectiveness of the interventions, proportional odds logistic regression models with ordinal mRs as outcome variable will be used. This method increases statistical power when compared to reporting on a dichotomized ordinal scale. We will report the odds ratios per cut-off and an average (common) odds ratio to give insight in fulfilment of the requisites of the proportional odds model[29].

To account for the risk of confounding by indication in the observational design, correction will be performed based on the aneurysm location, morphology and current clinical patient status. Strongest predictors of outcome from literature (age, history of hypertension, WFNS grading on admission, CT blood clot burden, aneurysm location and size, treatment variables, cerebral ischemia[30–33]) will be added as covariates.

Analysis will be performed in R and in the Statistical Package for the Social Sciences (SPSS) version 21. A p-value < 0.05 will be considered statistically significant.

8.2 Secondary study parameter(-s)

As a secondary study parameter, we will analyse the between-hospital differences to correct for confounding. Conventional methods are likely unable to account for the (unmeasured) confounding in SAH, like in traumatic brain injury[34]. Therefore, the main analyses will use the between-hospital variation in treatment for determining effectiveness by comparing regional treatment strategies. This is an instrumental variable approach [34]. The instrument is treatment preference and is determined as the amount of either coiled or clipped patients of total amount of treated patients. The proportion (percentage) exposed to the intervention in each hospital (the instrument) is entered as an independent variable to the analyses. The unmeasured and measured confounding at the hospital level, for example hospitals that perform more surgery also more often perform other treatments, is overcome with a multilevel model[35]. In this model the random intercept should capture the measured and unmeasured confounders at hospital level, resulting in unbiased treatment effect estimates. The random intercept for each hospital represents the unexplained hospital effect (beyond all factors included in the model, including the instrument treatment preference).

In sensitivity analyses the instrument validity will be further explored by quantifying a priori collected data and the results of provider profiling of SPARTA and comparing these to the posthoc derived relative proportion exposed to the intervention per hospital.

Moreover, as an alternative to the IV approach of the primary analyses, the instrument is modelled as a categorical variable. Specifically, the hospitals are divided into halves, tertiles and/or quartiles based on their preference for the intervention.

As secondary analyses conventional ordinal regression analyses are planned with actual treatment as binary treatment variable and mRs as outcome variable. For aneurysm treatment effectiveness confounding will be controlled for by adding known predictors for outcome as covariates in the model.

A similar strategy will be utilized to analyse the effectiveness of clipping versus coiling on longer time intervals, the effectiveness of flow diversion and Woven EndoBridge®-devices, the effectiveness of secondary treatment modalities, timing of mobilisation and different rehabilitation programmes on the functional outcome using mRs and proportional odds regression modelling.

HADS for anxiety and depression will be analysed in a dichotomized way because of the uncertainty of abnormality in the borderline categories. total score will be analysed using a proportional odds logistic regression model as described above. Different timing of treatment will be analysed

both as a categorical variable (within 6 hours, within 24 hours, within 72 hours, within 1 week, within 2 weeks, first month) and as a continuous variable. Amount of CSF drainage daily will be analysed as a continuous variable.

Multivariate regression analysis and stepwise univariate analyses will be used for correlation of the imaging, patient specific and treatment data and outcome measurements, including occurrence of complications. Proportional odds regression modelling will be used for the analysis of recanalization and rebleeding using the reported morphological changes and occurrence of rebleeding.

Cost-effectiveness and cost-utility analysis will be performed using mRs at one year and QALY respectively. Effectiveness in QALYs, costs and cost-effectiveness ratios will be calculated. The analysis will use direct and indirect healthcare costs from both self-reported and CRFprovided data, aspiring an extensive list of the costs in- and out of hospital and productivity losses. Sensibility analyses will be performed to validate the results[36,37].

8.3 Other study parameters

Not applicable as we report no other study parameters.

8.4 Interim analysis (if applicable)

Not applicable

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (as last modified in October 2013 at the General Assembly in Brazil) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients that present to one of the participating medical centres (primarily or after referral) will be asked to participate and will be consented after being informed about the study, risks, and advantages of participation to acquire informed consent. This procedure will be done according to the protocol “Samenwerkende Topklinische Ziekenhuizen Standard Operating Procedure Informed Consent”. If an eligible patient is identified, prospective data collection will start. This will be noted in the patient file. The written consent from the patient or legal representative should be obtained during the admission period. Information will be giving both verbally and in writing. After given time for consideration, informed consent will be obtained (from the patient or from a representative). The informed consent form will be signed by both the investigator and the patient or representative and participation in the trial will be registered in the patients’ medical file. Other outcomes of the informed consent procedure will also be logged in the patients file. If a patient withdraws their consent, all data up to the moment the participant withdrew consent will be used for analysis.If informed consent cannot be obtained from the patient or legal representative before emergency treatment or if the patients is incapacitated at time of inclusion and the legal representative is not available, consent will be assumed, and data acquisition started. The consent procedure will be attempted as soon as a legal representative is available, or the subject becomes competent. If patient or legal representative refuse to participate in the study at a first moment of deferred consent, all data will be destroyed.

Some exceptions that are possible on the abovementioned procedure are discussed and a solution is chosen based on both ethical and legal considerations as well as methodological considerations (diminishing of bias). If patients die before the informed consent procedure could be discussed and there is no legally appropriate shared decision making (SDM), no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects. If patients die and there is a legally appropriate SDM, but there has been no possibility yet to discuss the informed consent procedure, no consent is necessary and patients remain included in the study as long as there is no clearly written objection in the chart from the patient against participation in scientific research projects. In both cases, the reason to deviate from the standard procedure as well as the decision that the patient remains included in the study has to be written clearly in the chart.

9.3 Objection by incapacitated subjects

This procedure will be done according to the protocol “Samenwerkende Topklinische Ziekenhuizen Standard Operating Procedure Informed Consent”. If an eligible patient is identified, prospective data collection will start. If the patient is incapacitated at time of inclusion, a representative will be informed about the study and is asked to read the information letter and sign the consent form.

In the case a patient becomes capacitated during the research, an information letter and informed consent form is provided, and informed consent of the patient is gained. If the patient refused to participate in the study, all study data will be destroyed. If a patient becomes incapacitated during the study period, informed consent will be gained again from the representative. In case the representative refused to further participate, all data up to the moment the participant became incapacitated will be used for analysis.

If a patient where the legal representative had previously given consent because of incompetence, becomes competent and refuses consent to the trial, acquisition of data will cease and data acquired up until then will be used for analysis. If a subject dies during data acquisition before formal consent was given, consent will be assumed and information will be given to legal representatives on how to actively withdraw their consent

9.4 Benefits and risks assessment, group relatedness

Patients will receive normal care during their hospital stay. For study purposes, health questionnaires and functional outcome will be assessed at follow-up. During follow-up, patients will be asked to complete several questionnaires to assess treatment success. These test and questionnaires will take approximately 2 hours to complete.

Measurements will be done in the hospital, the outpatient clinic, the rehabilitation centre, or in the patient’s home (in the case of patient reported questionnaires). Patients may experience temporary fatigue from completing questionnaires.

9.5 Compensation for injury

The sponsor/investigator has asked the ethical committee to waive the obligatory liability insurance as described in article 7 of the WMO. This is based on the strictly observational nature of the study and the low possibility of damage occurring caused by the study.

9.6 Incentives (if applicable)

Not applicable.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All data will be treated confidentially and coded and will be registered on data registration forms. Data management will be handled at the Division Neurosurgery of Leiden University Medical Center. Data will be stored in an electronic data capture and management system. Imaging data from participating centres will be stored separately in a picture archiving and communication system at the main study centre (imaging from admission and 1, 5- and 10-year follow-up). A list that contains the study participant and associated study identification code will be used to identify an individual study participant if necessary. Every study site has a specific identifier, and subjects will be assigned a study code based on an increasing number. This identification code will not be based on the participants initials or date of birth. The list that links the study identification code to the study participants will be kept on a designated partition on the hard drive of the research centre. This part will be protected by a password. People who have access to this partition are local researchers and quality monitor appointed by the principal investigator. These procedures comply with the European law: *Algemene verordening gegevensbescherming (AVG)*. All raw data will be collected and stored at the main study site, including the trial master file, investigator site file, informed consent forms, study data and imaging data. The acquired data will be stored for 15 years after the study is finished and will be used for further research if the participant has provided consent for the data to be used in further studies.

10.2 Monitoring and quality assurance

Data monitoring and quality assurance will be handled by the Department of Neurosurgery at Haaglanden Medical Center. The study will be monitored as described in the "Monitoring Plan", appendix 'Monitorplan SPARTA'. Study monitoring will be done on a yearly basis. We will monitor the informed consent forms, the investigator site file and the trial master file, as well as the data defined in the "Monitoring Plan".

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the local scientific research bureau

(Wetenschapsbureau's in the Netherlands) and METC that gave a favourable opinion in the Netherlands and other participating countries.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year as well as the local research bureau. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (premature) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The study protocol will be published online, and the study will be registered in an online trial register. After analysis of the one-year results, these will be published in a peer-reviewed journal. Similarly, also the five and ten-year results will be published. All publications using data generated by this study should be discussed and agreed upon by the investigators and sponsor. Local investigators may use the data from their center for separate analyses.

11. STRUCTURED RISK ANALYSIS

Not applicable

11.1 Potential issues of concern

Not applicable

11.2 Synthesis

Not applicable

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APPENDICES

Appendix 1: Measurements, including standardized instruments

Digital images from initial CT and CT-angiography if available

Patient questionnaires:

- Informed consent form
- Deferred informed consent form
- mRs at discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- GOS-E at discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- MOCA at discharge
- Rancho los Amigos Levels of Cognitive Functioning Scale (LOCF) at discharge,
- TICS-m at discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- Hospital Anxiety and Depression Scale (HADS) at discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- EQ-5D-5Lat discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- Barthel ADL index at discharge, 6 months, 1 year, 2 years, 5 years and 10 years
- Custom health associated cost questionnaires at discharge, 6 months, 1 year, 2 years, 5 years and 10 years

Case report forms:

- Baseline information CRF
- Admission CRF
- Primary treatment CRF
- Rebleeding CRF
- Retreatment CRF
- Mobilization and early rehabilitation CRF
- Hydrocephalus CRF

- Delayed cerebral ischemia CRF
- Death CRF
- Out of hospital rehabilitation CRF
- Follow-up CRF
- Recanalization or recurrence CRF