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Measuring the Impact of Delayed Cerebral Ischemia on Neuropsychological Outcome After Aneurysmal Subarachnoid Hemorrhage—Protocol of a Swiss Nationwide Observational Study (MoCA–DCI Study)

BACKGROUND: The exact relationship between delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH) and neuropsychological impairment remains unknown, as previous studies lacked a baseline examination after aneurysm occlusion but before the DCI-period. Neuropsychological evaluation of acutely ill patients is often applied in a busy intensive care unit (ICU), where distraction represents a bias to the obtained results.
OBJECTIVE: To evaluate the relationship between DCI and neuropsychological outcome after aSAH by comparing the Montreal Cognitive Assessment (MoCA) results in aSAH patients with and without DCI at 3 mo with a baseline examination before the DCI-period (part 1). To determine the reliability of the MoCA, when applied in an ICU setting (part 2).
METHODS: Prospective, multicenter, and observational study performed at all Swiss neurovascular centers. For part 1, n = 240 consecutive aSAH patients and for part 2, n = 50 patients with acute brain injury are recruited.
EXPECTED OUTCOMES: Part 1: Effect size of the relationship between DCI and neuropsychological outcome (MoCA). Part 2: Reliability measures for the MoCA.
DISCUSSION: The institutional review boards approved this study on July 4, 2017 under case number BASEC 2017-00103. After completion, the results will be offered to an international scientific journal for peer-reviewed publication. This study determines the exact impact of DCI on the neuropsychological outcome after aSAH, unbiased by confounding factors such as early brain injury or patient-specific characteristics. The study provides unique insights in the neuropsychological state of patients in the early period after aSAH.

KEY WORDS: Delayed cerebral ischemia, Cognitive disorders, Montreal Cognitive Assessment, Outcome, Reliability, Stroke, Subarachnoid hemorrhage

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GENERAL INFORMATION

Protocol Title: Measuring the impact of delayed cerebral ischemia on neuropsychological outcome after aneurysmal subarachnoid hemorrhage – protocol of a Swiss nationwide observational study (MoCA–DCI study)
Protocol Identifying Number: BASEC 2017-00103
Registration Date: July 4th, 2017

ABBREVIATIONS: aSAH, aneurysmal subarachnoid hemorrhage; **ASPECTS,** Alberta Stroke Program Early CT Score; **DCI,** delayed cerebral ischemia; **HRQoL,** Health-Related Quality of Life; **ICC,** intraclass correlation coefficient; **ICU,** busy intensive care unit; **PI,** principle investigator; **MoCA,** Montreal Cognitive Assessment; **NIHSS,** National Institute of Health Stroke Score; **NPD,** neuropsychological deficits

Supplemental digital content is available for this article at www.neurosurgery-online.com.

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RATIONALE AND BACKGROUND INFORMATION

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with high mortality and morbidity.[1] Early brain injury is typically attributed to the severity of the initial or re-bleeding, acute hydrocephalus, or results from aneurysm occlusion.[2] The subacute phase after aSAH is characterized by delayed cerebral ischemia (DCI),[3,4,5,1] with higher incidence in patients with early brain injury.[6-9]

DCI is among the most important predictors of neurological morbidity and the dominating risk factor for mortality in patients surviving initial aneurysm repair.[2,10] However, survival rates are improved in modern neurosurgical patient care and functional aspects of the clinical outcome become increasingly important.[11,12] DCI has recently been identified to be an important predictor of neuropsychological deficits (NPD),[13,14] but the exact role of DCI needs to be confirmed by further investigations. Previous studies were always subject to methodological weaknesses, as no study ever used a baseline evaluation before DCI onset, and were therefore subject to confounding by early brain injury.

The Montreal Cognitive Assessment (MoCA) is a short but comprehensive instrument,[15,16] incorporated into the Swiss national standard on neuropsychological outcome assessment[11,17] and "highly recommended" by the National Institute of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE) group.[18] Despite its use in aSAH patients, its validity and reliability has only been demonstrated for Parkinson's disease or dementia.[19,20] Besides, the MoCA is often applied in the busy intensive care unit (ICU), while it remains largely unknown whether the distraction in such an environment influences the results.

STUDY GOALS AND OBJECTIVES

This study aims to determine the exact impact of DCI on the neuropsychological outcome, as measured by the in-subject difference of the MoCA before and after the DCI-period (= Δ-MoCA) in patients with or without DCI (Figure 1).

1. $H_0$1: There is no difference in Δ-MoCA between patients with and without DCI.

In addition, the study determines the MoCA's test–retest, as well as its reliability in an ICU setting (Figure 2).

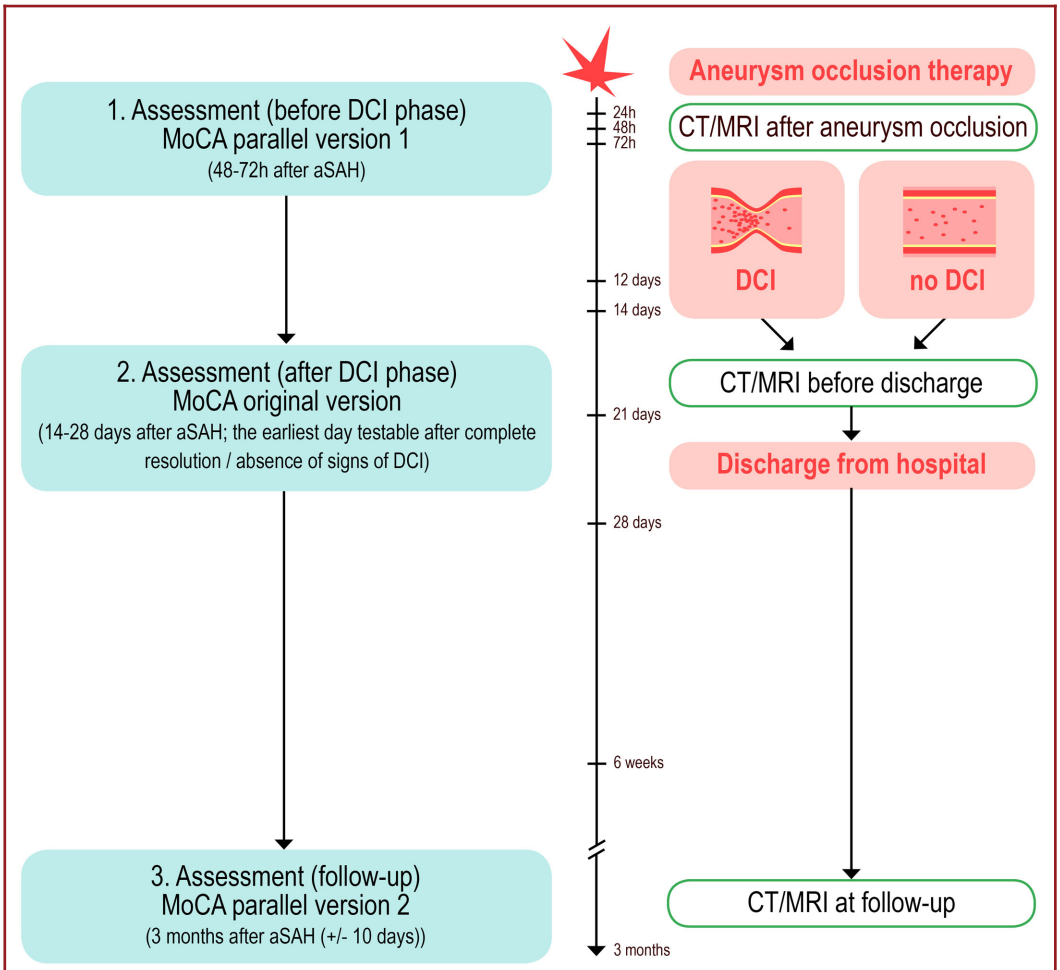

FIGURE 1. *Illustration of part 1 of the study. After initial treatment of the ruptured aneurysm, eligible patients undergo the first assessment with the MoCA before the DCI phase. Then, some patients will experience DCI over the next days, whereas others will not. After termination of the DCI phase, all patients undergo the second assessment and a third assessment at 3 mo after the hemorrhage (follow-up). The difference between the MoCA before and after the DCI-period or at follow-up can be compared in the group of patients that suffer vs the group of patients that does not suffer from DCI.*

2. $H_0 2$: The MoCA assessment on the ICU does not result in worse results, compared to the office.
3. $H_0 3$: The test–retest reliability of the MoCA is high.

STUDY DESIGN

Part 1 is set up as a prospective nationwide multicenter observational cohort study on aSAH patients, conducted at all Swiss neurosurgical departments that treat aSAH patients (Table 1).

Part 2 of the study is performed at the main site only, including patients with acute brain injury that are clinically stable and transferable without risk, as proxy for aSAH patients (Table 2). The rational for this is that aSAH patients cannot be randomly assigned to assessment on the (busy) ICU or the (quiet) office, as bed rest, careful control of hemodynamics, oxygenation, and temperature are recommended up to day 14 to minimize the risk for DCI.

METHODOLOGY

The study will be reported according to the STROBE guidelines.[21]

Eligibility Criteria

For part 1 of the study, adult aSAH patients of at least 18 yr of age who fulfill all of the following inclusion criteria:

- Consent of the patient or consent of patient's next of kin (plus consent of an independent physician if patient is unable to consent)

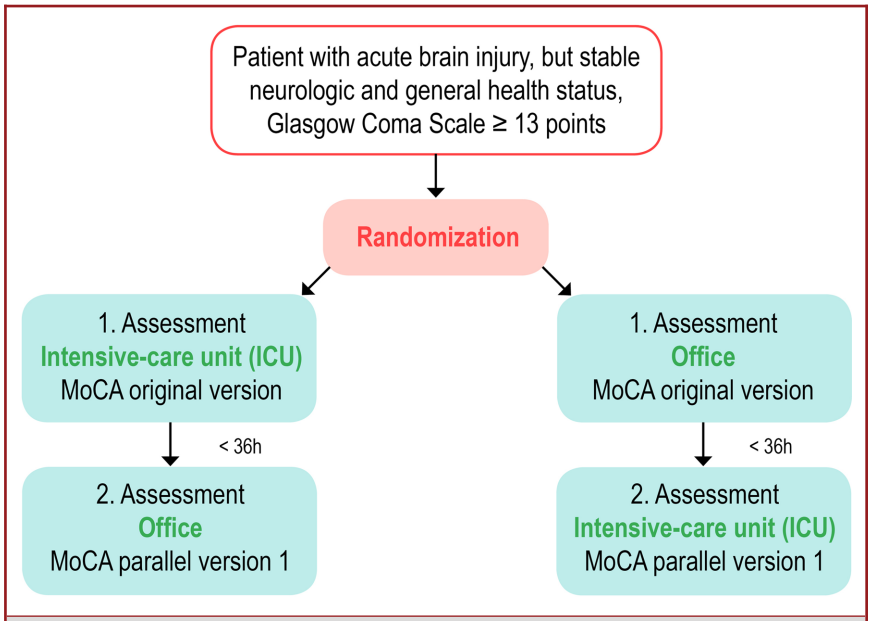

FIGURE 2. *Algorithm of part 2 of the study, performed on patients with acute brain injury. Patients are randomized to either the first assessment with the MoCA on the (busy) ICU first and then in the (quiet) office, or to the first MoCA assessment in the office, followed by a second in the ICU. The time between first and second assessment is < 36 h, and the neurological condition is stable between assessments 1 and 2.*

- Time of aSAH known (IMPORTANT: at least approximated. Time of aSAH refers to the bleed that led to hospital admission; warning leaks/sentinel headache are not considered aSAH in this context)[22]
- Complete aneurysm occlusion therapy within 48 h after aSAH
- Glasgow Coma Scale (GCS) ≥13 points at time point 48 h to 72 h after aSAH
- Fluent language skills in either English, German, French, or Italian

For part 2 of the study, adult patients who suffer from acute brain injury that requires an in-patient treatment, eg, for (surgical) treatment of a brain tumor, intracranial hemorrhage, hydrocephalus, stroke, or traumatic brain injury, with stable neurological and general health status and fulfill all of the following inclusion criteria:

- Consent of the patient
- GCS ≥ 13 points
- Fluent language skills in German

The exclusion criteria for study participation are listed in **Supplemental Digital Content 1** (part 1) and **2** (part 2).

Interventions

None. Patients are treated according to local protocols that comply with recent recommendations.[10,11,23,24]

Study Groups

For part 1 of the study, assignment to 1 of 2 study groups (see below) is done at hospital discharge. Patients that experience DCI, defined as

(1) cerebral infarction identified on imaging or proven at autopsy, after exclusion of procedure-related infarctions, and
(2) clinical deterioration caused by DCI, after exclusion of other potential causes of clinical deterioration,

will be assigned to the DCI group. All other patients will be assigned to the non-DCI group (Figure 1). Definitions of clinical deterioration and cerebral infarction attributable to DCI follow the current gold standards.[4,5]

Primary Outcome and Follow-Up

The proportion of patients with or without DCI who show worsening on the MoCA 3 mo after the ictus, as compared to before the DCI phase by at least 2 points (= minimum clinically important difference [MCID]).[20,25]

Secondary Outcomes

Neuropsychology/MoCA

- Proportion of patients with or without DCI that show worsening on the MoCA 14 to 28 d after the ictus, as compared to before the DCI phase by at least 2 points[20,25]

TABLE 1. Visit Schedule for the First Part of the Study on aSAH Patients

	Before DCI phase	After DCI phase	Follow-up
Visit	1	2	3
Time scale	48 to 72 h after aSAH	14 to 28 d after aSAH; earliest day after resolution of DCI; absence of any signs of CVS/DCI	3 mo ± 10 d
Patient information and consent	X[A]		
Inclusion/Exclusion criteria	X[A]		
Demographics and medical history	X[B]		
Physical examination			
• GCS	X[B]	X[B]	X[B]
• NIHSS	X[B]	X[B]	X[B]
• mRS	X[A]*	X[B]	X[B]
• DCI		X[B]	
Radiological examination[+]			
• ASPECTS	X[A]	X[A]	X[A]
Treatment and hospital course			
• Complications		X[B]	
• Treatment details		X[B]	
Neuropsychological examination			
• MoCA	X[A]	X[B]	X[B]
• EuroQol (EQ5D)	X[A]*		X[B]
• Home time			X[A]
• Shunt-dependency			X[B]
Sampling of biological material	None	None	None
Serious (adverse) events	X[A]	X[A]	X[A]

[A]Recorded explicitly for study purpose.
[B]Usually recorded for patient care.
*Estimation of pre-aSAH mRS and pre-aSAH EuroQol.
[+]All CT-scans are performed for patient care; no CT-scans are performed explicitly for study purpose.

- Absolute difference in the MoCA score between 48 to 72 h after aSAH and at 3 mo after aSAH in patients that develop and those that do not develop DCI
- Absolute difference in the MoCA score between 48 to 72 h after aSAH and at 14 to 28 d after aSAH in patients that develop and those that do not develop DCI
- Absolute results of the MoCA at 48 to 72 h, 14 to 28 d, and 3 mo in patients that develop and those that do not develop DCI
- Reliability of the MoCA when tested in the ICU unit, as compared to testing in the office setting (Part 2)
- Test–retest reliability of the MoCA (Part 2)
- Correlation of the MoCA at 48 to 72 h with the Alberta Stroke Program Early CT Score (ASPECTS)[26] for ischemic lesions on the CT-scan/MRI at 24 to 72 h after aSAH
- Correlation of the MoCA at 14 to 28 d with the ASPECTS[26] at 12 to 21 d
- Correlation of the MoCA at 3 mo with the ASPECTS[26] at 6 wk to 3 mo

Death/Disability

- Mortality at 3 mo in patients that develop and those that do not develop DCI
- Distribution of modified Rankin scale (mRS) at 3 mo in patients that develop and those that do not develop DCI
- Dependency (= mRS 4 and 5) at 3 mo in patients that develop and those that do not develop DCI
- Home time at 3 mo in patients that develop and those that do not develop DCI[27]

Health-Related Quality of Life (HRQoL)

- HRQoL (Euro-Qol [EQ5D]) at 3 mo in patients that develop and those that do not develop DCI

For tertiary and other outcomes of interest, see **Supplemental Digital Content 3**.

DISCUSSION

The exact impact of DCI on the neuropsychological outcome remains unknown today. Previous studies have reported strong relationships,[13,14,28] but those were likely biased by early brain injury. Even with statistical adjustment can the true association between DCI and neuropsychological outcome only be roughly estimated. It is possible to obtain more robust estimates by use of

TABLE 2. Visit Schedule for the Second Part of the Study on Patients with Acute Brain Injury

	First assessment	Second assessment
Visit	1	2
Time scale	No specific time required	Within 36 h after first assessment
Inclusion/Exclusion criteria	X[A]	
Demographics and medical history	X[B]	
Neuropsychological examination		
• GCS	X[B]	
• NIHSS	X[B]	
• mRS	X[B]	
• MoCA	X[A]	X[A]
• EuroQol	X[A]	
• Random number generation	X[A]	X[A]
Sampling of biological material	None	None
Serious (adverse) events	X[A]	X[A]

[A]Recorded explicitly for study purpose.
[B]Usually recorded for patient care.

a baseline examination before onset of the DCI phase, however. The time window 48 to 72 h after the hemorrhage, when the aneurysm is secured, is sometimes referred to as "honeymoon period", as patients can often be extubated and neuropsychologically assessed. DCI rarely occurs before day 3 or after day 14, but manifests to the maximum between days 5 and 14.[10] Assessing the neuropsychological status is thus possible both before and after the studied condition (DCI), enabling determination of its accurate relationship in a causal fashion. This convenient situation is similar to neuropsychological testing before and after elective brain surgery for eg, the removal of a neoplastic lesion, whereas eg, in traumatic brain injury research usually no neuropsychological testing before the injury is possible.

The chosen study methodology also has weaknesses. We will not be able to include many poor-grade aSAH patients into the study, as they can or should not awake from sedation for the initial assessment before the DCI-period. Of note, the study protocol does not exclude patients with high WFNS grades per se. Patients graded poor at admission due to a reversible condition (eg, hydrocephalus or space-occupying hematoma) can be included, if meeting the inclusion criteria at 48 to 72 h. In addition, other factors that may influence the neuropsychological outcome and occur in parallel to DCI (eg, chronic hydrocephalus, infection, or other medical complications) can potentially bias the results. Those factors are prospectively collected and will be statistically adjusted for. The fact that for part 2 we chose patients with acute brain injury as substitute raises question, as to whether the findings are applicable to aSAH patients. We hope that this heterogeneous group of patients, many of them having experienced stroke, hydrocephalus and recent brain surgery, will resemble well the typical aSAH patient population. In any case, the final results will have to be interpreted within these limitations.

TRIAL STATUS

The study started recruiting patients on July 20, 2017 and is currently conducted in 7 of the 8 specified centers (all, except for Kantonsspital Aarau).

SAFETY CONSIDERATIONS

Due to the observational design of the study there are no safety concerns. Adverse events, such as clinical deterioration at time of neuropsychological assessment, are recorded and reported, however.

FOLLOW-UP

Participating patients are followed for 3 mo after aSAH.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data are hosted by the Clinical Trials Center (CTC), University of Zurich. Electronic case report forms are implemented. All data are stored on a server in a dedicated database. A role concept with personal passwords (site investigator, statistician, monitor, administrator, etc) regulates permission.

Supplemental Digital Content 4 outlines the variable definitions, consistent with the NIH/NINDS CDE project for "Unruptured Cerebral Aneurysms and Subarachnoid Hemorrhage".[18]

Handling of Missing Data

All efforts first concentrate on avoiding and minimizing the chance of missing data, including regular data reviews.

Contingency plans foresee home visits and collaboration with the rehabilitation clinics. Patients who die or cannot be evaluated (as in poor clinical condition) and in whom for this reason no MoCA at follow-up can be obtained will be considered to have cognitive impairment (MoCA = 0 points). Sensitivity analyses will be performed.

If missing data are still present:

1. First, mechanisms of missing data are assessed. If the data are deemed missing at random, and there is < 10% to 15% of patients with time point missing data, case deletion will be used (and additional patients will be recruited).
2. Second, if the missing data mechanism is not at random,[29] multiple imputation will be performed.

For the second part of the study, only patients with complete datasets will be analyzed.

Determination of Sample Size

There is no data available on the change in MoCA in the early period after aSAH. When estimating that 70% of patients with DCI and 40% of patients without DCI will worsen by 2 points on the MoCA,[20,25] n = 42 patients per group are required to detect a statistically significant effect with a power of 80% and alpha set at 0.05. In order to allow for statistical adjustment, 60 patients with DCI should be included. Given that 25% of the total aSAH population suffers from DCI,[1,4,5] the study will need to include n = 240 patients.

There is no data available in the literature allowing estimating the required sample size for part 2. Including n = 50 subjects in total (thus, 25 randomized in each study arm) is considered sufficient.

Methods Used to Minimize Bias

Part 2 uses a computerized randomization process to distribute patients to initial testing in the ICU or office. The same randomization process allocates patients to either the original version or official parallel version 1 of the MoCA.

The neuropsychological assessment at 14 to 28 d and 3 mo will be performed by a professional neuropsychologist, blinded for the study group allocation of the patient (DCI-group or non-DCI group).

The primary outcome might be influenced by the following factors that are therefore prospectively recorded and, if unequally distributed, statistically adjusted for: patient age and sex, WFNS score, hydrocephalus, aneurysm occlusion therapy, prophylactic nimodipine[7], induced hypertension (rescue therapy I), chemical vessel dilatation (rescue therapy II), balloon dilatation (rescue therapy III), infection, pulmonary or cardiac complications.

Primary Analysis

A decrease of the MoCA by at least 2 points at 3 mo post-aSAH, as compared to the baseline examination, will be calculated for patients with and those without DCI.[20,25] Logistic regression will be used to calculate the odds ratio and 95% confidence intervals to estimate the effect size of DCI on the neuropsychological outcome. Multivariable analysis will adjust for the mentioned confounding factors.

Secondary Analyses—Part 1

For secondary analyses, MoCA results will be expressed as raw values, but also standardized for age, sex, and education based on Swiss normative values.

The significance of the absolute group difference (Δ-MoCA) between patients with and without DCI can be calculated using rank-sum tests. The proportion of patients with and without DCI who show cognitive impairment (MoCA < 26)[13] can be analyzed using logistic regression.

The MCID of the MoCA will be determined with mRS, GCS, and National Institute of Health Stroke Score (NIHSS) scores as anchors by the average change, minimum detectable change, and the change difference approach.[30]

Secondary Analyses—Part 2

For reliability measures, official parallel MoCA versions are used in order to prevent from learning effects and to reduce false reliability. We will estimate 3 key effects: sequence (S), period (P), and location (L) of testing.

To estimate the effect size of *S*, the mean difference of sequence 1 (ICU first): $(A = A_1 - A_2)$ is compared to the mean difference of sequence 2 (Office first): $(B = B_1 - B_2)$ and tested using an unpaired *t*-test. For the null hypothesis to be true, $\tilde{A} = \tilde{B}$.

To estimate the effect size of *P*, the average of the differences for all patients in both sequences is calculated:

$$P = (A_1 - A_2 + B_1 - B_2)/2$$

For the null hypothesis to be true, $\tilde{P} = 0$.

To estimate the effect size of *L*, the difference between Office MoCA (O) and ICU MoCA (I) is measured:

$$L = O_1 - I_2 + O_2 - I_1)/2$$

For the null hypothesis to be true, $\tilde{L} = 0$.

Because each patient serves as his/her own control, demographic/patient level variables are treated as fixed effects.

The clinical relevance of Δ-MoCA will be appraised referring to the reported MCID.[20,25]

The intraclass correlation coefficient (ICC) of repeated MoCA will be interpreted according to Cichetti with ICC < 0.40 (poor), 0.40 to 0.59 (fair), 0.60 to 0.74 (good), and 0.75 to 1.00 (excellent).[31]

Statistical significance is defined as *P*-value < .05.

QUALITY ASSURANCE

All source data are accessible for monitoring, audits, and inspections. Authorities have the right to perform inspections, and the sponsoring institution has the right to perform on-site

auditing. Monitoring for each site will be performed at study initiation and before the results are to be analyzed as follows: completeness of documents, adherence to the study protocol and data quality entered into the eCRFs for the first patient, as well at least every fifth included patient. Progress of patient inclusion and data completeness is checked continuously, at least once every 2 wk.

EXPECTED OUTCOMES OF THE STUDY

Part 1: Effect size of the relationship between DCI and neuropsychological impairment (MoCA). If DCI was to be confirmed as major driver of NPD, future research should focus even more on the effective prevention and treatment of this potentially modifiable condition. On the contrary, if the association between DCI and neuropsychological impairment was less strong than expected, funding could better be spent on, eg, the prevention of early re-bleeding or less invasive aneurysm occlusion techniques, among others.[2]

Part 2: Reliability measures for the MoCA. Early neuropsychological evaluation finds entry into the management of a broad variety of acute central nervous system disorders nowadays,[32,33] and studying a heterogeneous patient sample allows for generalizing the results to the wider neurosurgical population.

DURATION OF THE PROJECT

Recruitment is expected to be complete by the end of July 2019.

PROJECT MANAGEMENT

At each site, the principle investigator (PI) is responsible for patient inclusion, quality of data collection, and adhesion to the protocol. The PI is supported by the sponsor and the coordinating study leader.

ETHICS

The study protocol has been approved by all IRBs on July 4th, 2017 (BASEC 2017-00103) and registered with the ClinicalTrials.gov identifier: NCT03032471. All patients and/or next-of-kin will give written informed consent.

Disclosures

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Supplemental Digital Content 1. Exclusion criteria for part 1 of the study.
Supplemental Digital Content 2. Exclusion criteria for part 2 of the study.
Supplemental Digital Content 3. Tertiary and other outcomes of interest.
Supplemental Digital Content 4. Variables of the "MoCA–DCI study" that are collected, together with their definitions.