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SPECIAL ARTICLE

# Prioritization and Timing of Outcomes and Endpoints After Aneurysmal Subarachnoid Hemorrhage in Clinical Trials and Observational Studies: Proposal of a Multidisciplinary Research Group

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## Abstract

**Introduction:** In studies on aneurysmal subarachnoid hemorrhage (SAH), substantial variability exists in the use and timing of outcomes and endpoints, which complicates interpretation and comparison of results between studies. The aim of the National Institute of Health/National Institute of Neurological Disorders and Stroke/National Library of Medicine Unruptured Intracranial Aneurysm (UIA) and SAH common data elements (CDE) Project was to provide a common structure for future UIA and SAH research.

**Methods:** This article summarizes the recommendations of the UIA and SAH CDE Outcomes and Endpoints subgroup, which consisted of an international and multidisciplinary ad hoc panel of experts in clinical outcomes after SAH. Consensus recommendations were developed by review of previously published CDEs for other neurological diseases and the SAH literature. Recommendations for CDEs were classified by priority into "Core," "Supplemental—Highly Recommended," "Supplemental," and "Exploratory."

**Results:** The subgroup identified over 50 outcomes measures and template case report forms (CRFs) to be included as part of the UIA and SAH CDE recommendations. None was classified as "Core". The modified Rankin Scale score and Montreal Cognitive Assessment were considered the preferred outcomes and classified as Supplemental—Highly Recommended. Death, Glasgow Outcome Scale score, and Glasgow Outcome Scale-extended were classified as Supplemental. All other outcome measures were categorized as "Exploratory". We propose outcome assessment at 3 months and at 12 months for studies interested in long-term outcomes. We give recommendations for standardized dichotomization.

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**Conclusion:** The recommended outcome measures and CRFs have been distilled from a broad pool of potentially useful CDEs, scales, instruments, and endpoints. The adherence to these recommendations will facilitate the comparison of results across studies and meta-analyses of individual patient data.

**Keywords:** Clinical studies, Common data elements, Data coding, Data collection, Subarachnoid hemorrhage, Aneurysm, Outcomes, Endpoints, Standardization, Hemorrhagic stroke, Modified Rankin Scale, Montreal Cognitive Assessment, mRS, MoCA

## Introduction

The prognosis of patients with aneurysmal subarachnoid hemorrhage (SAH) has improved over the last decades [1, 2]. For a long time, SAH studies focused on disability. Over the last decade, it is increasingly recognized that many patients with SAH also have cognitive and emotional (neuropsychological) impairments in the long term, which decrease quality of life [3–5]. However, results of studies are often difficult to compare or pool for the following reasons: (1) more than one scale exists for measuring a similar outcome or endpoint, while it remains unclear which scale is preferred; (2) definitions of outcomes and endpoints differ between studies; (3) timing of outcome and endpoint assessment differs between studies; and (4) various cutoffs and dichotomizations are used for certain scales.

## Common Data Elements Overview

### Summary

The aim of the National Institute of Health (NIH)/National Institute of Neurological Disorders and Stroke (NINDS)/National Library of Medicine (NLM) Unruptured Intracranial Aneurysms (UIA) and SAH Common Data Elements (CDE) Project was to provide a common structure for future UIA and SAH research. This paper describes the recommendations from the SAH Outcomes and Endpoints subgroup of the overall UIA and SAH CDE Working Group (WG).

### Process for Selecting CDEs

For a description of the UIA and SAH CDE Project, we refer to the main paper of this project [6]. The Outcomes and Endpoints WG consisted of an international and multidisciplinary (neurology, neurosurgery, neurorehabilitation) ad hoc panel of experts in clinical studies and/or neuropsychological outcomes after SAH. Prior to the start of the project, all subcommittee members were trained by the NINDS and NLM CDE Teams by means of a webinar to use the NINDS CDE and NIH CDE Repository Web sites and online tools.

A consensus-building approach was used for the selection and prioritization of CDEs. Existing CDEs from traumatic brain injury [7], epilepsy [8], stroke [9], and other neurological diseases were systematically reviewed. Outcomes and endpoints considered relevant for SAH were collected in a list (February 2015–September 2015). To complete the list, observational studies and clinical trials on SAH were reviewed for potential outcome measures that were not previously described by other CDE projects (October 2015–December 2015). The collected outcome measures and CDEs were discussed by means of telephone conferences and multiple e-mail interactions. For those outcome recommendations addressing similar aspects of outcome, the subgroup decided to use the ones most appropriate for future SAH research based on the following criteria: previous use in SAH studies, reliability and validity for SAH research, and availability (in multiple languages). Outcome measures and CDEs considered less relevant or suitable were omitted to restrict their number (December 2015–January 2016). Predefined outcome measures and CDEs were critically reviewed by group members for applicability regarding SAH research, and if necessary, amendments were created. For outcome measures without previously available definition, group members created definitions. All included outcome measures and CDEs were prioritized according to a predefined classification (Table 1; February 2016–May 2016). The list of outcome recommendations was presented at the UIA and SAH CDE meeting (May 13–15, 2016, Houston, TX). Feedback received during this conference resulted in several amendments. A final list of outcome recommendations was submitted to the NINDS CDE Team by the end of June 2016. The NINDS CDE team combined the reports of all WGs to create a document with instructions for internal review. Internal review across subcommittees took place in December 2016. The recommendations were exposed to the public on the NINDS CDE Web site in January 2017 and were available for external review between January and March 2017 (Table 2).

### Classification into Core, Supplemental—Highly Recommended, Supplemental, and Exploratory Outcomes and Endpoints

In total, the Outcomes and Endpoints subgroup identified almost 60 outcome measures and template case report forms (CRFs). None were classified as "Core". The modified Rankin Scale (mRS) score and Montreal

**Table 1 Classification of outcomes and endpoints subgroup outcome measures according to the level of recommendation (*Source*: http://www.commondataelements.ninds.nih.gov)**

| Class | Meaning |
|---|---|
| Core | A data element that collects essential information applicable to any study, including either those that span across all disease and therapeutic areas or those that are specific to one disease area. The NINDS and their appointed working groups assign the "Core" classification based on the current clinical research best practices. This term applies to both the General CDEs and the Disease-specific CDEs. In each case, the Core CDEs are a small subset of the available CDEs, where it is anticipated that investigators will need to collect the Core CDEs on any type of study |
| Supplemental—highly recommended | A data element, which is essential, based on certain conditions or study types in clinical research studies. In most cases, these have been used and validated in the disease area. These data elements are strongly recommended for the specified disease condition, study type, or design |
| Supplemental | A data element, which is commonly collected in clinical research studies, but whose relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or type of research involved |
| Exploratory | A data element that requires further validation but may fill current gaps in the CDEs and/or substitute for an existing CDE once validation is complete. Such data elements show great promise but require further validation before they are ready for prime-time use in clinical research studies. They are reasonable to use, but limited study has been done in the target group |

*CDEs* Common Data Elements, *NINDS* National Institute of Neurological Disorders and Stroke

Cognitive Assessment (MoCA) were considered the preferred outcome measures and classified as Supplemental—Highly Recommended. Death CDEs, Glasgow Outcome Scale (GOS) score, and GOS-extended (GOS-E) were classified as Supplemental. All other variables were categorized as "Exploratory" variables. We recommend outcome assessment at 3 months after SAH and at 12 months for studies interested in long-term outcomes.

## Description of Selected CDEs

Below, we report the selected outcomes and endpoints measures and CRFs which have been used for SAH research, grouped according to the recommendations given by the International Classification of Functioning, Disability, and Health [10].

### Case Fatality/Survival

The CDEs on the Death CRF were classified as Supplemental. In case of death, the date should be recorded, and distinction should be made between a neurological or non-neurological cause of death. The most important causes of death after SAH are early brain injury, re-bleeding of the aneurysm, delayed cerebral ischemia, or other [2, 11].

### Disability

The scales most often used for measuring disability after SAH are as follows:

- Modified Rankin Scale [12–24],
- Glasgow Outcome Scale [20–22, 25–31],
- Glasgow Outcome Scale-Extended [23, 32].

Since many randomized trials in patients with SAH showed neutral results, it can be questioned whether these scales are somewhat insensitive to detect difference in functional outcome. However, other trials did find a difference in outcome using either the mRS [14] or the GOS [31]. The mRS shows better discriminative power than the GOS between 3 and 12 months after SAH and therefore is the preferred outcome scale [33].

- Another available scale for measuring disability is the Barthel Index: It was used in some trials [22, 23, 34] but has also been criticized for its strong ceiling effect [33].

### Impairment (Cognitive, Emotional, and Physical)

#### *Cognitive Impairment*

For measuring cognition in observational studies and clinical trials after SAH, the subgroup recommended using a screening tool. The most common screening tools are as follows:

- Montreal Cognitive Assessment [35, 36],
- Mini-Mental Status Examination [33, 37, 38],
- Telephone Interview for Cognitive Status [39].

In small studies, the MoCA is superior over the Mini-Mental Status Examination (MMSE) for SAH patients [35, 40]. It is more sensitive to SAH-associated cognitive impairment than the MMSE, making it the most attractive cognitive assessment tool for the present SAH research [5, 36, 41]. Despite its strengths, the MoCA has not been validated in SAH patients. The Telephone Interview for Cognitive Status is simple to apply and does not require a face-to-face interview, making it a decent instrument to estimate global and domain-specific cognitive function [39]. However,

**Table 2 Recommendations of the subcommittee on outcomes and endpoints**

| Name (instrument/scale/CRF) | Classification | Timing+ | References |
|---|---|---|---|
| *Case fatality/survival* | | | |
| Death CRF (including cause and time of death) | Supplemental | 3 (12) | [2] |
| *Disability* | | | |
| mRS | Supplemental—highly recommended | 3 (12) | [12–24] |
| GOS | Supplemental | 3 (12) | [20–22, 25–31] |
| GOS-E | Supplemental | 3 (12) | [23, 32] |
| DALY | Exploratory | | |
| BI | Exploratory | 3 (12) | [22, 23, 34] |
| *Cognitive impairment** | | | |
| Screening | | | |
| MoCA | Supplemental—highly recommended | 3 (12) | [5, 35, 36, 40, 41] |
| MMSE | Exploratory | 3 (12) | [33, 37, 38] |
| TICS | Exploratory | 3 (12) | [39] |
| Attention | | | |
| Computerized Test of Attentional Performance (TAP 2.3)—Subtest alertness | Exploratory | 3 (12) | [5, 44, 83, 84] |
| Computerized Test of Attentional Performance (TAP 2.3)—Subtest divided attention | Exploratory | 3 (12) | [5, 44, 83, 84] |
| Computerized Test of Attentional Performance (TAP 2.3)—Subtest Go/NoGo | Exploratory | 3 (12) | [5, 44, 83, 84] |
| Computerized Test of Attentional Performance (TAP 2.3)—Subtest neglect | Exploratory | 3 (12) | [5, 44, 83, 84] |
| Working memory | | | |
| WAIS IV—Verbal span forward | Exploratory | 3 (12) | [5, 42, 43] |
| Visuospatial short-term memory | | | |
| Visual Span Forward | Exploratory | 3 (12) | [5] |
| Executive functions | | | |
| CWIT; Stroop task—Victoria version | Exploratory | 3 (12) | [3, 5, 79, 85] |
| 5-PT | Exploratory | 3 (12) | [5, 44, 85] |
| TMT-B | Exploratory | 3 (12) | [3, 5, 35, 44, 83] |
| Written Verbal Fluency Test | Exploratory | | |
| SLP | Exploratory | 3 (12) | [5, 86] |
| Cognitive speed | | | |
| TMT-A | Exploratory | 3 (12) | [3, 5, 35, 44, 83] |
| Memory | | | |
| RAVLT | Exploratory | 3 (12) | [3, 5, 44, 56] |
| RO-CFT—Delayed recall | Exploratory | 3 (12) | [3, 5, 44] |
| Visuoperception | | | |
| RO-CFT—Copy | Exploratory | 3 (12) | [3, 5, 44] |
| Language | | | |
| Token Test | Exploratory | 3 (12) | [3, 5, 87] |
| BNT | Exploratory | 3 (12) | [3, 35, 44, 85] |
| Premorbid intelligence | | | |
| WAIS IV—Similarities | Exploratory | 3 (12) | [3, 5, 44, 79, 85] |
| Eye-hand coordination/motor speed | | | |
| Grooved Pegboard Test | Exploratory | 3 (12) | [3, 5, 35, 85] |
| Behavior | | | |
| FrSBe | Exploratory | 3 (12) | [5] |
| *Emotional Impairment* | | | |
| HADS | Exploratory | 3 (12) | [5, 42, 43, 46] |

**Table 2 (continued)**

| Name (instrument/scale/CRF) | Classification | Timing[+] | References |
|---|---|---|---|
| BAI | Exploratory | 3 (12) | |
| Generalized Anxiety Disorder (GAD-7) | Exploratory | 3 (12) | |
| BSI-18—ANX | Exploratory | 3 (12) | [3] |
| NPI-Q | Exploratory | 3 (12) | [88] |
| BDI-II | Exploratory | 3 (12) | [3, 42, 43, 48] |
| PHQ-9 | Exploratory | 3 (12) | |
| CES-D | Exploratory | 3 (12) | [89] |
| BSI-18—DEP | Exploratory | 3 (12) | [3, 90] |
| PCL—Civilian | Exploratory | 3 (12) | |
| IES | Exploratory | 3 (12) | [42, 43, 47] |
| CAPSTICS | Exploratory | 3 (12) | |
| *Physical Impairment* | | | |
| MAF | Exploratory | 3 (12) | [5, 48] |
| Headache Pain CRF | Exploratory | 3 (12) | |
| CRF | Exploratory | 3 (12) | |
| *HRQoL outcome* | | | |
| Neuro-QoL | Exploratory | 3 (12) | [60] |
| EQ-5D | Exploratory | 3 (12) | [5, 61–63] |
| SF-36 | Exploratory | 3 (12) | [23, 30, 33, 64] |
| SF-12 | Exploratory | 3 (12) | [5, 65–67] |
| SSQoL | Exploratory | 3 (12) | [45, 68–71] |
| PROMIS | Supplemental | 3 (12) | [60] |
| SIS, long version | Exploratory | 3 (12) | [22] |
| *Participation Restriction/Return To Work* | | | |
| USER-P | Exploratory | 3 (12) | [52, 80] |
| Return-to-Work CRF | Exploratory | 3 (12) | [5, 53, 54, 56–58] |
| Home time | Exploratory | 3 (12) | [59] |
| *Treatment variables* | | | |
| Shunt Dependency CRF | Exploratory | 3 (12) | |
| Aneurysm Recanalization CRF | Exploratory | 6, 18, 60, 120, (long term) | [72, 74–76] |
| Aneurysm Re-treatment and Re-rupture CRF | Exploratory | 6, 18, 60, 120, (long term) | [72, 74–76] |

*BI* Barthel Index, *BAI* Beck Anxiety Inventory, *BDI* Beck Depression Inventory, *BNT* Boston Naming Test, *BSI* Brief Symptom Inventory, *CES-D* Center for Epidemiologic Studies Depression Scale, *CAPS* Clinician-Administered PTSD Scale, *CWIT* Color–Word Interference Test, *CRF* Cranial Nerve Function, *DALY* Disability-adjusted life years, *EQ-5D* EuroQoL-5 Dimensions, *5-PT* Five-Point Test, *FrSBe* Frontal Systems Behavior Scale, *GAD-7* Generalized Anxiety Disorder, *GOS* Glasgow Outcome Scale, *GOS-E* Glasgow Outcome Scale-Extended, *HADS* Hospital Anxiety and Depression Scale, *HRQoL* Health-Related Quality of Life, *IES* Impact of Event Scale, *MMSE* Mini-Mental Status Examination, *mRS* Modified Rankin Scale, *MoCA* Montreal Cognitive Assessment, *MAF* Multidimensional Assessment of Fatigue, *NPI-Q* Neuropsychiatric Inventory Questionnaire, *Neuro-QoL* Quality of Life in Neurological Disorders, *PHQ* Patient Health Questionnaire Depression Scale, *PROMIS* Patient-Reported Outcome Measurement Information System, *PCL* Posttraumatic Stress Disorder Checklist, *RAVLT* Rey Auditory Verbal Learning Test, *RO-CFT* Rey–Osterrieth Complex Figure Test, *SF* Short-Form, *SLP* Standardized Link's Probe, *SIS* Stroke Impact Scale, *SSQoL* Stroke-Specific Quality of Life, *TICS* Telephone Interview for Cognitive Status, *TMT* Trail-Making Test, *USER-P* Utrecht Scale for Evaluation of Rehabilitation-Participation, *WAIS* Wechsler Adult Intelligence Scale

*Some of the listed instruments test more than one neuropsychological domain; for reasons of simplicity, only the major tested domain is listed

[+] In months after SAH

it is even less sensitive than the MMSE for SAH-associated cognitive impairment [37]. For studies that intend to measure cognitive functions in more detail, the domain-specific recommendations given in Table 2 reflect a selection of instruments that have been or are currently used in SAH patients, with normative data and test versions available in multiple languages [3–5, 42–44]. Of note, results of neuropsychological tests might be negatively influenced by a distracting intensive care environment if tested in the acute phase after SAH.

#### *Emotional Impairment*

Anxiety and depression are common after SAH and various instruments exist to determine the presence and severity.

- The Hospital Anxiety and Depression Scale is the most often used instrument and measures both qualities simultaneously [5, 42, 43, 45, 46].

Posttraumatic stress disorder (PTSD) has been studied most extensively using the:

- (Revised) Impact of Events Scale [42, 43, 47].

#### *Physical Impairment*

Fatigue after SAH has been studied using various diagnostic tools or single questions [48]. None of the scales has been validated for SAH patients. The subgroup proposed using the:

- Multidimensional Assessment of Fatigue as it covers different aspects of fatigue including quantity, degree, distress, impact, and timing [5].

Pain (headache) after SAH can be measured with a:

- Numeric rating scale from 0 (no pain) to 10 (worst pain).

Cranial nerve function can be affected by compression from the aneurysm, by the aneurysm occlusion treatment, or by the presence of blood in the subarachnoid space [49, 50]. For each cranial nerve and laterality, function is rated as normal or abnormal (with additional explanations given in the case of abnormality).

#### Participation Restriction/Return to Work

For frequency, restriction, and satisfaction with participation after SAH, the subgroup proposed the following validated scale as a measure of choice:

- Utrecht Scale for Evaluation of Rehabilitation-Participation [51, 52].

Data on return to work after SAH are scarce and its assessment has been heterogeneous [53–58]. Therefore, the subgroup created a:

- Return-To-Work CRF with CDEs that cover most important aspects of return to work, including detailed classification of pre- and post-SAH work type according to the International Standard Classification of Occupations, workload, responsibility, and timing [5].

A further aspect of participation and domestic life:

- Home time is defined as the duration of stay in the patient's own or relative's home over the first 90 days after stroke. It was shown that home time is associated with post-stroke disability, especially among the better recovery levels. It is reliable, less prone to inter-observer variability than grading scales, and easily understood by the public [59].

#### Health-Related Quality of Life (HRQoL) Outcome

Several scales are available for measuring quality of life, but no scale has shown superiority for SAH research:

- Quality of Life in Neurological Disorders (Neuro-QoL): It generates a standardized *T*-score, which correlates well with morbidity after SAH [60].
- EuroQoL-5 Dimensions: It is a sensitive tool to measure short- and long-term HRQoL after SAH [61–63]. Five dimensions relevant for SAH patients are scored: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. These dimensions are scored in 3 (3L) or 5 levels (5L).
- SF-36: It is a generic measure of health status and HRQoL, shows broad variability among SAH patients [33], and has been used in SAH trials before [23, 24, 30, 64].
- SF-12: This is the shorter version of SF-36. The SF-12 is more convenient to use for researchers who must restrict survey length and study large cohorts [65, 66]. The SF-12 is valid and reliable in patients with SAH and cerebral aneurysms [67].
- Stroke-Specific Quality of Life (SSQoL) scale: It has been validated in SAH patients in a both Dutch and Chinese cohort [45, 47, 68]. The minimum clinically important difference of the SSQoL total and subscores in SAH patients has been determined [69]. Traditionally, the original 49-item version is used in clinics and for research, but shorter 12-item versions have been developed and validated in SAH patients [70, 71].
- Patient-Reported Outcome Measurement Information Systems: It uses convenient Web links and measures progressive disability using standardized *T*-scores [60].
- Stroke Impact Scale: This scale has been used for the ALISAH trial [22], but other than that experience is currently limited.

### Treatment Variables

#### *Shunt Dependency*

The subgroup defined shunt dependency as clinical symptoms of hydrocephalus (at least decreased mental status) with radiographic evidence of enlarged ventricles or a high opening pressure on repeated lumbar punctures requiring the insertion of a permanent shunt or ventriculostomy for cerebrospinal fluid (CSF) diversion. The type (ventriculo-peritoneal shunt, ventriculo-atrial shunt, lumbo-peritoneal shunt, or endoscopic third ventriculostomy) and date of CSF diversion need to be recorded. A Shunt Dependency CRF was created to capture relevant CDEs.

#### *Aneurysm Recanalization After Aneurysm Treatment*

The subgroup defined aneurysm recanalization as aneurysm re-opening or increase in neck remnant after initial treatment of the ruptured aneurysm and to record the earliest date of recanalization diagnosis after completed primary treatment. The Aneurysm Recanalization CRF was created to capture this information.

#### *Aneurysm Re-treatment and Re-rupture After Aneurysm Treatment*

Aneurysm re-treatment is defined as repeated aneurysm treatment after primary treatment [72]. The date of re-treatment should be recorded. Details on the type of aneurysm re-treatment agree with treatment details of the Acute Therapies CDE subgroup and are outlined in the Aneurysm Re-treatment and Re-Rupture CRF [73].

The subgroup proposed to define re-rupture after aneurysm treatment as rupture of a previously ruptured aneurysm after primary treatment [74, 75]. Here, we do not take into account a re-rupture of an untreated aneurysm. Hemorrhages during initial or follow-up treatment are also not considered re-ruptures. The date of eventual re-rupture should be noted as indicated in the CRF.

#### *Timing of Outcome Assessment*

Since patients can show significant recovery after SAH, the studied outcome is influenced by the time interval between SAH and outcome assessment. The subgroup proposed assessing outcome 3 months after ictus for the following reasons: (1) Most patients have reached a relatively stable clinical status after 3 months. Medical and surgical complications directly related to the SAH (including CSF diversion, etc.) are rare after this time point. (2) Many patients visit an outpatient clinic approximately 3 months after ictus, which promotes reliable and standardized outcome assessment. As a result, outcome assessment for research purposes can more easily be integrated in standard medical care. In many centers, patients are only seen on indication beyond 3 months or they have recovered and do not want to return for follow-up. (3) The study duration of clinical trials will increase when outcomes need to be assessed at a later point, and therefore, a trial will become more expensive. However, for studies interested in long-term outcomes, the subgroup proposes an outcome assessment after 12 months in addition to an outcome assessment at 3 months [5]. Endpoints without a clear ceiling effect, such as recanalization, re-treatment, or re-rupture, may require a longer observation time [72, 74–76]. If studies aim to assess aneurysm recanalization at predefined time points, follow-up imaging at 6 months, 18 months, 5 years, and 10 years is recommended.

#### *Reporting of Outcome and Dichotomization*

Comparison of results between studies is difficult when the same outcome scale but a different cutoff for dichotomization is used. To decrease the risk that important information is lost, the subgroup recommends reporting outcomes on the full scale. If dichotomization is required, it should be done in a standardized way as listed in Table 3 for the mRS, GOS, and GOS-E, but with a description of the non-dichotomized outcomes in a supplement to the main article. HRQoL and neuropsychological outcomes should be reported as percent ranks or standardized *z*-/*t*-scores, meaning individual test scores adjusted for age, sex, and education using normal population benchmarks whenever possible. A five-tier scale for interpretation has been proposed before and is listed in Table 4 [4, 77, 78]. If dichotomization of neuropsychological profiles of an individual patient is required, this can easily be done by dichotomization into "impaired" (categories 1–2) and "unimpaired" (categories 3–5; Table 4).

## Limitations

Many outcome scales are available for patients with SAH. Although the Outcomes and Endpoints subgroup used a systematic approach, for many outcomes there is no gold standard or superiority of one over another. The use of a broader range of instruments is recommended, as patient outcome cannot yet be estimated accurately on

**Table 3 Recommendation for the dichotomization of neurological/functional outcomes**

| Name (instrument/scale/CRF) | Favorable outcome | Unfavorable outcome |
|---|---|---|
| mRS | 0–3 | 4–6 |
| GOS-E | 5–8 | 1–4 |
| GOS | 4–5 | 1–3 |

*GOS* Glasgow Outcome Scale, *GOS-E* Glasgow Outcome Scale-Extended, *mRS* Modified Rankin Scale

**Table 4 Interpretation and classification of neuropsychological test results, according to Lienert and Raatz [78] and Fisseni [77]**

| Category | *T*-score* | *Z*-score | Percentile rank | Deviation from the mean in SDs | Interpretation |
|---|---|---|---|---|---|
| 5 | > 70 | > 2.0 | > 98 to 100 | 2–3 SDs above the mean (or higher) | Far above average |
| | < 70 to 60 | < 2.0 to 1.0 | > 84 to 98 | 1–2 SDs above the mean | Above average |
| 4 | < 60 to 43 | < 1.0 to − 0.7 | > 24 to 84 | Within 1 SD of the mean | Average |
| 3 | < 43 to 40 | < − 0.7 to − 1.0 | > 16 to 24 | Within 1 SD of the mean | Lower average |
| 2 | < 40 to 30 | < − 1.0 to − 2.0 | > 2 to 16 | 1–2 SDs below the mean | Below average |
| 1 | < 30 | < − 2.0 | 0 to 2 | 2–3 SDs below the mean (or lower) | Far below average |

*SD* standard deviation

**T*-scores are transformations of *Z*-scores and can vary for individual tests

a single grading scale [33, 79]. In addition, the levels of recommendation do not express importance. Many relevant determinants of outcome such as anxiety, PTSD, or ability to return to work have been rated "Exploratory" because of the limited experience in previous studies. Disability strongly correlates with case severity of SAH. When impairment, participation, and HRQoL are analyzed, personal factors (personality, premorbid functioning, education level) and environmental factors (partnership, social network, etc.) play important roles [80, 81].

## Next Steps/Future Work

Future studies need to investigate which outcomes and endpoints are superior and most practical to work with. Many neuropsychological outcomes are presently assessed behind a desk, but assessments using real-life situations may be more realistic. Simulations using virtual reality tools may show promise. In an ideal situation, a single scale would be used, which incorporates all previously mentioned aspects of outcome and even integrates outcome over time. Using a single scale for different diseases also increases the comparability of impairments from various diseases. Efforts are being made in that direction [82].

## Conclusions

The preferred outcome measures are the mRS and MoCA, which were classified as Supplemental—Highly Recommended. Death CDEs, GOS score, and GOS-E were classified as Supplemental. All other outcome measures were categorized as "Exploratory". None was classified as "Core". The subgroup recommends outcome assessment at 3 months and at 12 months for studies interested in long-term outcomes. Recommendations for standardized dichotomization have been given. The recommended outcome measures and CDEs have been distilled from a broad pool of potentially useful scales, instruments, and endpoints. The adherence to these recommendations will facilitate the comparison of results across studies and meta-analyses of individual patient data.

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**Author contributions**

MNS, JV-M, TAS, DH, RLM, and MDIV wrote and edited the manuscript. The corresponding author confirms that authorship requirements have been met, the final manuscript was approved by all authors, and this manuscript has not been published elsewhere and is not under consideration by another journal. The UIA and SAH CDEs Project adhered to ethical guidelines.

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**Conflicts of interest**

Dr Macdonald reports personal fees from Edge Therapeutics and grants from Brain Aneurysm Foundation, outside the submitted work. Dr Stienen reports grants from Fujirebio Europe and Actelion/Idorsia, outside of the submitted work. Dr Vergouwen, Dr Visser-Meily, Dr Schweizer, and Dr Hänggi have nothing to disclose.

**Ethical Approval/Informed Consent**

This article does not contain any studies with human participants or animals performed by any of the authors.

## Appendix: UIA and SAH Working Group Members

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## Publisher's Note



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