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SPECIAL ARTICLE

Common Data Elements for Unruptured Intracranial Aneurysms and Subarachnoid Hemorrhage Clinical Research: A National Institute for Neurological Disorders and Stroke and National Library of Medicine Project

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Abstract

Objectives: The goal for this project was to develop a comprehensive set of common data elements (CDEs), data definitions, case report forms and guidelines for use in unruptured intracranial aneurysm (UIA) and subarachnoid hemorrhage (SAH) clinical research, as part of a new joint effort between the National Institute of Neurological Disorders and Stroke (NINDS) and the National Library of Medicine of the US National Institutes of Health. These UIA and SAH CDEs will join several other neurological disease-specific CDEs that have already been developed and are available for use by research investigators.

Methods: A Working Group (WG) divided into eight sub-groups and a Steering Committee comprised of international UIA and SAH experts reviewed existing NINDS CDEs and instruments, created new elements when needed and provided recommendations for UIA and SAH clinical research. The recommendations were compiled, internally reviewed by the entire UIA and SAH WG and posted online for 6 weeks for external public comments. The UIA and SAH WG and the NINDS CDE team reviewed the final version before posting the SAH Version 1.0 CDE recommendations.

Results: The NINDS UIA and SAH CDEs and supporting documents are publicly available on the NINDS CDE (https://www.commondataelements.ninds.nih.gov/#page=Default) and NIH Repository (https://cde.nlm.nih.gov/home) websites. The recommendations are organized into domains including Participant Characteristics and Outcomes and Endpoints.

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Conclusion: Dissemination and widespread use of CDEs can facilitate UIA and SAH clinical research and clinical trial design, data sharing, and analyses of observational retrospective and prospective data. It is vital to maintain an international and multidisciplinary collaboration to ensure that these CDEs are implemented and updated when new information becomes available.

Keywords: Subarachnoid hemorrhage, Unruptured intracranial aneurysms, Common data elements, Clinical trials, Observational studies, Outcomes

Introduction

In 2005, the National Institute of Neurological Disorders and Stroke (NINDS) initiated the development of common data elements (CDEs) to assist NINDS-funded investigators in collecting neuroscientific clinical trial research data in a standard and consistent fashion [1]. The CDEs are content standards that can be applied to various data collection models and are intended to be dynamic and may evolve over time [1, 2]. CDEs are the foundation for interoperability among data systems and are a subset of the universe of all data elements. The CDEs are not a database—rather they are a collection of metadata and data standards. To date, the NINDS CDE project has collected metadata with data standards that identify common definitions and standardized case report forms (CRFs) and instruments for 24 neurological diseases and disorders [3–7]. All NINDS CDEs are available on both the NINDS CDE website (www.commondataelements.ninds.nih.gov) and the NIH CDE repository (www.nlm.nih.gov/cde). The goals of the NINDS CDE Project are to:

- Disseminate standards for the collection of data from participants enrolled in studies of neurological diseases.
- Create easily accessible tools for investigators in collecting study data. These tools should be especially helpful to new investigators and others working with limited budgets.
- Encourage focused and simplified data collection to reduce burden on investigators and practice-based clinicians to facilitate their participation in clinical research.
- Improve data quality while controlling cost by providing uniform data descriptions and tools across NINDS-funded clinical studies [1].

The benefits and advantages of establishing CDEs include the standardization of definitions of events or variables considered important for specific neurological disorders; efficient construction of study databases by providing elements for CRFs; facilitation of adoption and validation of clinical outcomes measures most relevant for the particular disease being studied; and more homogenous reporting of clinical study results that can be understood across the world.

It has been estimated that approximately 3% of the adult global population harbors an unruptured intracranial aneurysm (UIA) [8–18]. The increased availability and usage of high-quality imaging have led to a higher detection rate of these lesions. UIAs can follow one or more of the following clinical courses: remain clinically asymptomatic; present with focal neurological deficits from local mass effect or ischemia; or they may rupture. A ruptured intracranial aneurysm is the most common cause of spontaneous subarachnoid hemorrhage (SAH), which is a subset of stroke that carries high case fatality and morbidity and can affect the central nervous system and many other systemic organs [8, 9]. Spontaneous SAH accounts for about 2–5% of all strokes and has a global incidence of 1.6 per 100,000 person-years [10–13]. The incidence of SAH increases with age, commonly affecting individuals between 40 and 60 years of age, and is 1.5 times higher in women older than 75, compared to men [14]. The average case fatality for SAH is about 50% with 30–50% of survivors remaining dependent [15, 16]. Despite its low incidence, SAH has a socioeconomic burden comparable to that of ischemic stroke, primarily due to disease severity, resulting in early loss of productive life-years, and significant costs [12, 17]. One of the major limitations in UIA and SAH research is the lack of standardized definitions and CRFs to be able to compare results across observational studies and randomized controlled trials. Thus, investigators are limited in their efforts to reduce the uncertainty regarding the appropriate management of patients with UIA and also management of complications from SAH.

The UIA and SAH CDE project was a unique pilot project between NINDS and the National Library of Medicine (NLM) to develop CDEs by the UIA and SAH work group (WG) members. These WGs were comprised of an international and multidisciplinary group of subject matter experts. The overarching goal for this project was to develop a comprehensive set of CDEs with data

definitions, CRFs and guidelines for use in UIA and SAH clinical research. These UIA and SAH CDEs will join several other neurological disease-specific CDEs that have already been developed and are available for use by research investigators. The NINDS UIA and SAH CDEs and supporting documents are publicly available on the NINDS CDE [19] and NIH CDE Repository websites [20]. This paper reviews the process by which the UIA and SAH WG developed CDEs with review by curators of the NINDS and NLM CDE teams, and incorporated subsequent public comments prior to their release on the websites.

Methods

Development of NINDS CDEs for UIA and SAH

The UIA and SAH CDE project began in August 2014 as part of the larger NINDS CDE effort. The two co-Chairs (JIS and RLM) of the UIA and SAH CDE WG met with the NINDS representative during an initial teleconference on August 30, 2014, where the first outline of the development process was discussed, including plans for the joint venture between NINDS and NLM, which had not been previously done for other disease CDEs. Subsequently, a Steering Committee (SC) comprised of seventeen international and multi-professional UIA and SAH investigators was convened. This group included clinicians, clinical researchers, and clinical trial experts to oversee the effort. A second teleconference was organized on September 30, 2014, and the SC agreed by consensus to divide the project into eight domain-specific WGs: (1) subject characteristics; (2) assessments and examinations; (3) hospital course and acute therapies; (4) biospecimens and biomarkers; (5) imaging; (6) long-term therapies; (7) unruptured intracranial aneurysms; and (8) outcomes and endpoints. Two SC members were appointed as co-Chairs for each WG, and an average of six to eight UIA and SAH experts were selected and invited to join each WG. The domains were chosen with the understanding that the process would likely unveil important areas that would require further consideration. As such, the Hospital Course and Acute Therapies WG was subsequently expanded due to the complexity of medical and surgical interventions that SAH patients require in the acute phase. The initial face-to-face meeting for the entire WG was held during the International Stroke Conference in Nashville, TN in February 2015. During this meeting, WG membership was finalized and training on the use and navigation of the NLM CDE repository website was provided. One member from each WG was also designated as a "superuser" of the NLM website, responsible for facilitating the process of selecting and uploading CDEs to the NLM website. The initial task for each WG was to perform an extensive review of CDEs from other neurological diseases [3–7, 21, 22]. WG members then selected and classified their chosen CDEs by consensus from 03/01/2015 to 03/31/2017. Further prospective observational studies and clinical trials on SAH were reviewed to derive a comprehensive list of variables for assessments and clinical exam that were not previously described by other disease CDE recommendations. Variables pertaining to UIA and SAH research were selected based on use in prior UIA and SAH studies, and their reliability and validity in wide patient populations. The collected variables were discussed via teleconferences and electronic correspondence. Variables not relevant to UIA and SAH research were excluded. There was a second face-to-face meeting during the International Stroke Conference in Los Angeles in February 2016 where all WGs shared their progress and further discussions and refinement of the CDEs took place. The third and final face-to-face meeting took place during the Fourth Neurocritical Care Research Conference in Houston, TX in May 2016 where further agreement by consensus took place and the process for selection of the CDEs to be released to the public was decided. Following an internal review of all recommendations by all WG members, the CDEs were made available for public review on the NINDS CDE website from January 31 through March 17, 2017, and were released in April 2017 as version 1.0. In addition to what has been described, it is important to point out that the WGs worked closely with the NINDS CDE Team and the NLM CDE Team throughout the entire process. These teams provided valuable input and helped organize the final classification of the UIA and SAH CDEs.

Terminology of the NINDS CDEs

Consistent with guidance across the NINDS CDE project, the WG was also charged with classifying each of the recommended UIA and SAH CDEs and instrument recommendations as "Core", "Supplemental" or "Exploratory" according to the following standard definitions:

1. Disease Core CDE: A data element that collects essential information applicable to any UIA and SAH research study. The NINDS and their appointed WGs assign the "Core" classification based on the current clinical research best practices. 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 UIA and SAH study.
2. Supplemental—Highly Recommended: A data element, which is essential based on certain conditions or study types in clinical research studies in UIA and SAH. In most cases, these have been used and

validated in UIA and SAH. These data elements are strongly recommended for the disease condition, study type or design.
3. Supplemental: A data element, which is commonly collected in clinical research studies but whose relevance depends upon the UIA and SAH study design (i.e., clinical trial, cohort study, etc.) or type of research involved.
4. 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. They are reasonable to use with the understanding that limited study has been done in UIA and SAH.

Results

WG Process

As mentioned above, WG members selected and classified the CDEs by consensus from 03/01/2015 to 03/31/2017. Each of the WGs proceeded with slightly different approaches, which were largely dependent on the status of existing data standards and elements. For example, the Subject Characteristics WG's purview had the most overlap with other clinical conditions and neurological diseases, and thus, they started with and selected data elements from many existing individual CDEs and recommended adding several items that were most appropriate for UIA and SAH studies. The Hospital Course and Acute Therapies WG recommended mostly new CDEs that were not previously available and are specific for SAH studies. The Biospecimens and Biomarkers WG focused their work on protocols for collection, storage, and analysis of samples for SAH studies. The UIAs WG developed entirely new CDEs for two thirds of their recommendations as there was very little in the way of established outcome measures or guidelines for use in UIA and SAH studies. In addition, they constructed a classification for intracranial aneurysm morphology.

The two co-Chairs for each WG, worked in close cooperation with the NINDS and NLM CDE project staff to initially collect potential CDEs, measures, and tools for discussion in the group. In regular WG teleconferences (usually monthly), members were assigned subdomains in their area of expertise for which they researched existing outcome measures and tools for evidence of validity, reliability and acceptance in the community. Once the initial recommendations were made, WGs decided by consensus which elements to include and how they should be classified. All procedural or cross-WG questions or concerns were brought up for review by the full SC.

SAH Domains and WG Recommendations

The UIA and SAH CDE Version 1.0 release includes over 1000 distinct CDEs, many of which are compiled into template CRFs. A total of 28 CDEs were classified as "Core" and 50 items were classified as "Supplemental—Highly Recommended". The other items were classified as either "Supplemental" or "Exploratory". The summary list and breakdown of all the recommended CDEs and instruments by WG domain and classification is provided in Tables 1–7. A summary of each WG's recommendations is presented below. A more detailed description of the process for each WG is outlined in separate manuscripts in this issue of Neurocritical Care [23–30].

Subject Characteristics

This WG identified factors relevant to the characteristics regarding participants or subjects involved in research on UIAs and SAH [23]. Each factor was quantified using at least one CDE for which a definition and standard of measurement is described. Recommendations are based on standard terms defined by the United States Census Bureau, on CDEs previously defined for Stroke, Epilepsy and Traumatic Brain Injuries, on literature, and on expert opinion of the WG. The "Participant/Subject characteristics" domain has been defined by 192 CDEs divided in 7 template CRFs: Demographics (8 CDEs), Social status (8 CDEs), Behavioral status (22 CDEs), Family and medical history (144 CDEs), Pregnancy and perinatal history (8 CDEs), History data source reliability (3 CDEs) and Prior functional status (3 CDEs). The UIA and SAH project is characterized by 6 core elements, all classified in the "Participant/Subject characteristics" domain. Four exploratory elements out of the 39 for UIA and SAH overall are in the "Participant/Subject characteristics" domain, and all remaining 182 CDEs in the "Participant/Subject characteristics" domain are classified as highly recommended supplemental elements (Table 1).

Assessments and Examinations

The recommended Assessments and Clinical Exam variables have been collated from numerous potentially useful scales, histories, clinical presentation, and laboratory and other tests (Table 2). The WG identified 248 variables for the Assessments and Clinical Exam domain. Only the World Federation of Neurological Societies (WFNS) grading scale was classified as "Core", and the Glasgow Coma Scale (GCS) was classified as "Supplemental—Highly Recommended". All other Assessments and Clinical Exam variables were categorized as "Supplemental". Several randomized controlled trials have used the WFNS score which compresses the GCS into five grades, with the addition of a fourth axis (focal

Table 1 Subject characteristics WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Behavioral History CRF	Participant history and family history	General health history	Core: Date history taken; current tobacco use; past tobacco use; Supplemental—Highly Recommended: type(s) of tobacco used; number of cigarettes smoked per day; current drinker; past drinker; alcohol—how often; current drug use; regular aerobic exercise
Demographics CRF	Participant characteristics	Demographics	Core: Gender; genotypic sex; birth date; ethnicity; race category Supplemental—Highly Recommended: Intracranial aneurysm ethnicity; country of residence; zip code (1st three digits); social security number
Family History CRF	Participant history and family history	General health history	Core: Date history taken; stroke indicator; Brain aneurysm indicator; SAH indicator; coronary artery disease indicator
History Data Source and Reliability CRF	Participant history and family history	General health history	Core: Data source; reasons data not obtained from participant
Medical History CRF	Participant history and family history	General health history	Core: Date history taken; body system categories; Stroke history indicator; UIA history indicator Supplemental—Highly Recommended: TIA history indicator; AVM history indicator
Pregnancy and Perinatal History CRF	Participant history and family history	General health history	Exploratory
Prior Functional Status CRF	Participant history and family history	General health history	Core: Date information collected Supplemental—Highly Recommended: Modified Rankin Scale Score
Social Status CRF	Participant characteristics	Social status	Exploratory
Mini-Mental State Examination	Outcomes and endpoints	Emotional and cognitive status	Exploratory

AVM arteriovenous malformation, *CDEs* common data elements, *CRF* case report form, *SAH* subarachnoid hemorrhage, *TIA* transient ischemic attack, *UIA* unruptured intracranial aneurysm, *WG* Working Group

neurological deficit) to differentiate grades 2 and 3 [31–33]. The primary advantages of the WFNS over other scales are that it uses objective terminology and grades each of its axes separately [34]. A systemic review of 11 studies showed that the WFNS was one of the most commonly used variables for clinical prediction models [35], however this study lacked external validation. This issue was addressed in pooled analysis from the Subarachnoid Hemorrhage International Trialists data [36], which used the WFNS as one of the core measures in its predictive model. This model was validated internally and externally and showed AUC of 0.80–0.81 to predict functional outcome and 0.76–0.78 to predict mortality. The WFNS also has the advantage of ease of use and low inter- and intra-observer variability [37].

Biospecimens and Biomarkers

A systematic review of UIA and SAH biomarkers was performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [26]. The WG's recommendations focused on harmonization of (1) target cellular and molecular biomarkers for future investigation in SAH, (2) standardization of best-practice procedures in biospecimen and biomarker studies, and (3) experimental method reporting requirements to facilitate meta-analyses and future validation of putative biomarkers. The WG found that no cellular or molecular biomarkers have been validated for inclusion as "core" recommendation. Fifty-four studies met inclusion criteria and generated 33 supplemental and emerging biomarker targets. Core recommendations include best-practice protocols for biospecimen collection and handling as well as standardized reporting guidelines to capture the

Table 2 Assessments and examinations WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Aneurysm History CRF	Disease/injury related events	History of disease/injury event	Supplemental
Clinical Presentation CRF	Disease/injury related events	History of disease/injury event	Core: WFNS Supplemental—Highly Recommended: Glasgow Coma Scale
Laboratory Tests CRF	Assessments and examinations	Laboratory tests and biospecimens/biomarkers	Supplemental
Prehospital and Emergency Status CRF	Disease/injury related events	History of disease/injury event	Supplemental
SAH Grading CRF	Disease/injury related events	Classification	Supplemental
SAH Neurological Exam CRF	Assessments and examinations	Physical/neurological examination	Supplemental
Vital Signs and Acute Physiological Measurements CRF	Assessments and examinations	Vital signs and other body measures	Supplemental
Galveston Orientation and Amnesia Test (GOAT) NOC	Outcomes and endpoints	Emotional and cognitive status	Supplemental
Los Angeles Motor Scale (LAMS) NOC	Outcomes and endpoints	Functional outcomes	Supplemental
Neurobehavioral Symptom Inventory (NSI) NOC	Outcomes and endpoints	Neurological outcomes	Supplemental
NIH Stroke Scale (NIHSS) NOC	Outcomes and endpoints	Neurological outcomes	Supplemental

CDEs common data elements, *CRF* case report form, *SAH* subarachnoid hemorrhage, *WFNS* World Federation of Neurological Societies, *WG* Working Group

heterogeneity and variabilities in experimental methodologies and biomarker analyses platforms.

Hospital Course and Acute Therapies

Most of the recommended CDEs have been newly developed by the WG [25]. The Hospital Course and Acute therapies CDEs were selected and prioritized through a consensus-building process. The concept CDEs were discussed and refined during several Skype meetings, telephone conferences, and e-mail interaction. Because of the complexity of hospital care and acute therapies given to SAH patients, this WG was further divided into 2 sub-groups: Subgroup-1, whose members were tasked with developing CDEs for the following topics: Surgical Procedures and Interventions, Rescue Therapies, Neurological Complications, intensive care unit (ICU) Therapies; and Subgroup-2, whose members were tasked with developing CDEs for the following topics: Prior and Concomitant Medications, EEG, Invasive Brain Monitoring, Medical Complications, Palliative Comfort Care and End of Life Issues, Discharge Status (Table 3). The category of Surgical Procedures and Interventions contains CDE's regarding the treatment (surgical or endovascular) of target intracranial aneurysms (either ruptured or unruptured) and details regarding the procedure. The category of Neurological Complications includes CDEs describing global cerebral edema, herniation syndromes, re-bleeding, hydrocephalus, delayed cerebral edema (DCI), seizures and meningitis/ventriculitis. The category of Rescue Therapies pertains to treatments for DCI and cerebral vasospasm administered as either intra-arterial chemical agent or mechanical balloon angioplasty, including potential complications of these procedures. The category of ICU therapies refers to CDEs for interventions that routinely occur in the ICU setting and include hemodynamic management, temperature management, glucose control, (invasive) mechanical ventilation and the use of osmotherapy.

Imaging

The WG reviewed previously established CDEs from other entities, adapted for the purpose of the UIA and SAH CDE project and also proposed to all subcommittee members for review via e-mail. All CDEs, the CDE definitions, and classifications were reviewed by the two co-Chairs. Following a final round of review and agreement by each subcommittee member, CRFs were developed (Table 4) [27]. A total of 85 CDEs on imaging for UIA and SAH, including 55 previously established CDEs from other neurological diseases, three 3 previously established CDEs, which were modified for the purpose of the UIA and SAH CDE project, as well as 27 new CDEs were established. Forty CDEs were organized into template CRFs for 'parenchymal imaging', forty-one CDEs to 'modalities', and forty-eight CDEs to 'angiography'.

Table 3 Hospital course and acute therapies WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Cardiac MRI	Assessments and examinations	Imaging diagnostics	Supplemental
Discharge Status	Disease/injury related events	Discharge information	Supplemental
Echocardiogram	Assessments and examinations	Imaging diagnostics	Supplemental
Echocardiogram II	Assessments and examinations	Imaging diagnostics	Supplemental
Electrocardiogram	Assessments and examinations	Non-imaging diagnostics	Supplemental
Holter Exam	Assessments and examinations	Non-imaging diagnostics	Supplemental
ICU Therapies	Treatment/intervention data	Therapies	Supplemental
Imaging	Assessments and examinations	Imaging diagnostics	Core: Brain imaging assessment result
Intracranial Pressure (ICP) Monitoring	Assessments and examinations	Vital signs and other body measures	Supplemental
Neurological Complications	Assessments and examinations	Physical/neurological examination	Supplemental—Highly Recommended: Re-bleeding indicator; Clinical deterioration/cerebral infarction from delayed cerebral ischemia (DCI); clinical deterioration due to DCI; cerebral infarction due to DCI
Palliative/Comfort Care Issues	Treatment/intervention data	Therapies	Supplemental
Rescue Therapy	Treatment/intervention data	Therapies	Supplemental
Surgical/Procedural Interventions	Treatment/intervention data	Surgeries and other Procedures	Core: Surgical intervention indicator; endovascular intervention indicator Supplemental—Highly Recommended: Vessel repaired type; Day of intervention from SAH ictus
Vital Signs and Blood Gases	Assessments and examinations	Vital signs and other body measures	Supplemental

CDEs common data elements, *CRF* case report form, *ICU* intensive care unit, *MRI* magnetic resonance imaging, *SAH* subarachnoid hemorrhage, *WG* Working Group

Long-Term Therapies (LTT)

The WG communicated with the Subject Characteristics WG, Unruptured Intracranial Aneurysms WG, and Outcomes and Endpoints WG to ensure that key CDEs were included in their respective WG domains [24]. The LTT WG recommendations include one Supplemental CRF and 16 Exploratory instrument CDEs. The LTT WG did not identify additional Core or Supplemental—Highly Recommended CDEs (Table 5). The WG members noted that medications have not been uniformly documented in UIA and SAH clinical study publications and therefore recommended a Medications CRF and classified its CDEs as Supplemental. The group also found that most publications on long-term outcomes are observational or follow-up for acute therapy, and there is also an emerging theme in the long-term medical therapies for UIA.

Unruptured Intracranial Aneurysms

The WG compiled 91 CDEs, of which 69 were newly created and 22 were reused from existing CDEs. The CDEs were assigned to eight subcategories and then classified eight into core, 23 into supplemental highly recommended, 25 into supplemental and 35 into exploratory elements (Table 6) [29]. Additionally, the WG developed and agreed on a novel classification for aneurysm morphology. The CDEs recommendations were divided into eight categories: demographics, reason of medical consult and diagnosis, clinical symptoms and assessment at baseline, risk factors, concomitant medications, concomitant diseases, radiological findings as well as management of unruptured aneurysms.

Outcomes and Endpoints

The WG made recommendations for 60 CDEs, derived from a broad pool of potentially useful scales, instruments and endpoints (Table 7) [30]. None were 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 (GOS) score, and GOS-extended were classified as Supplemental. All other Outcomes and Endpoints recommendations were categorized as "Exploratory". The WG proposed outcome assessment at 3 months and again at 12 months for studies interested in long-term outcomes. In addition, the

Table 4 Imaging WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Electroencephalogram CDEs	Assessments and examinations	Non-imaging diagnostics	Supplemental
Imaging Modalities CRF	Assessments and examinations	Imaging diagnostics	Core: Imaging modality used Supplemental—Highly Recommended: Imaging date and time collected; scan purpose; modified Fisher Scale grade; presence of subdural hematoma; presence of arteriovenous malformation
Parenchymal Imaging CRF	Assessments and examinations	Imaging diagnostics	Core: Imaging modality used Supplemental—Highly Recommended: imaging date and time collected; scan purpose; sequences acquired and slice thickness; CTA source image use; IVH presence; Graeb IVH scale result; volume of IVH; presence of SAH; type of subdural hematoma; presence of hydrocephalus; presence of arteriovenous malformation
Vessel Imaging Angiography CRF	Assessments and examinations	Imaging diagnostics	Core: Imaging modality used; arterial findings, cause and symptomology Supplemental—Highly Recommended: Imaging date and time collected; scan purpose; type of MRA; type of CTA; confidence level of venous findings; anatomic location of aneurysm; aneurysm location; dome size; neck size; largest height/largest neck diameter; occlusion percentage of aneurysm; Raymond-Roy occlusion classification

CDEs common data elements, *CRF* case report form, *CTA* CT angiography, *IVH* intraventricular hemorrhage, *MRA* magnetic resonance imaging, *SAH* subarachnoid hemorrhage, *WG* Working Group

WG gave recommendations for standardized dichotomization of outcome scales.

Discussion

Implications and Use of the NINDS CDEs for UIA and SAH

The NINDS CDEs for UIA and SAH (Version 1.0) include over 1000 data elements unique to UIA and SAH. Whereas many of these were created de novo, some of the UIA and SAH CDEs were taken from already available sets that are also used across other domains and diseases. Dissemination and widespread use of CDEs can facilitate UIA and SAH clinical research and trial design, data sharing and analyses of observational retrospective and prospective data, and meta-analyses based on individual patient data.

The UIA and SAH CDEs are intended to be a resource to facilitate developing, designing and writing protocols for any clinical studies related to UIA and SAH. The CRFs and instruments recommended are available on the NINDS CDE website, and the guidelines and recommendations provided with each of the domains should be consulted to help select and apply the relevant items for certain project. CRFs are modifiable and may be downloaded and used without any charge, while links provide contact information to obtain necessary permissions or licenses required for copyrighted instruments, if needed. CRFs can be assembled to accommodate a wide range of study designs, while maintaining the selected format, permissible values and nomenclature for each unique element intact and consistent to enable useful data sharing. It is important to note that recommended copyrighted instruments may not be altered without requesting the necessary permission from the copyright holders.

NINDS CDE SAH Website

An introduction to the UIA and SAH CDE project can be found on the SAH page of the NINDS CDE website (http://www.commondataelements.ninds.nih.gov/SAH.aspx#tab=Data_Standards). New users should begin with the resources in the "Learn" tab, which provides a project

Table 5 Long-term therapies WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Discharge Medications CRF	Disease/injury related events	Discharge information	Supplemental
Action Research Arm Test	Outcomes and endpoints	Functional outcomes	Exploratory
Arm Motor Abilities Test	Outcomes and endpoints	Functional outcomes	Exploratory
Berg Balance Scale	Outcomes and endpoints	Functional outcomes	Exploratory
Chelsea Critical Care Physical Assessment Tool	Outcomes and endpoints	Functional outcomes	Exploratory
de Morton Mobility Index (DEMMI): Elements	Outcomes and endpoints	Functional outcomes	Exploratory
Fugl-Meyer Assessment	Outcomes and endpoints	Functional outcomes	Exploratory
Functional Ambulation Categories	Outcomes and endpoints	Functional outcomes	Exploratory
Functional Gait Assessment	Outcomes and endpoints	Functional outcomes	Exploratory
Functional Independence Measure	Outcomes and endpoints	Functional outcomes	Exploratory
London Handicap Scale	Outcomes and endpoints	Activities of daily living/performance	Exploratory
Mobilizing ICU Patients Safety Assessment	Assessments and examinations	Physical/neurological examination	Exploratory
Overall Measurement Schema for ICU Acquired Weakness and Related Conditions	Assessments and examinations	Physical/neurological examination	Exploratory
Physical Function ICU Test	Outcomes and endpoints	Functional outcomes	Exploratory
Progressive Upright Mobility Protocol (PUMP) Plus	Outcomes and endpoints	Functional outcomes	Exploratory
Reintegration to Normal Living	Outcomes and endpoints	Activities of daily living/performance	Exploratory
Rivermead Mobility Index	Outcomes and endpoints	Functional outcomes	Exploratory

CDEs common data elements, *CRF* case report form, *ICU* intensive care unit, *WG* Working Group

overview, instructions, glossary, references and more. The WG recommended CRFs and corresponding guidelines are listed in alphabetical order in each section, and the underlying data element information ("CDE Details", containing the CDE IDs, definitions, permissible values, etc.) or copyright instrument information can be downloaded from the adjacent location. Finally, tabs at the top of the main page can be used to search the CDE or CRF data base and to build custom forms for specific study use.

Issues Unique to SAH

SAH patients are often critically ill and their in-hospital management is very complex [8–10]. In addition, SAH survivors require close follow-up and specific interventions to prevent further events or complications. There are currently very few interventions that have been shown to be efficacious at improving long-term clinical outcomes in SAH [8–10]. Several therapeutic clinical trials have reported negative results and comparison across those studies have been difficult partly due to the variability of data collection tools and definitions. Prior to this project there were no agreed upon CDEs standards. The WG considered that the non-uniformity is one of the reasons hindering the reporting of data in the literature and therefore CDE recommendations are important for the development of future registries and clinical trials. The overall perception among clinical researchers is that the development of UIA and SAH CDEs is a step in the right direction.

While the benefits of using the WG consensus approach to develop CDE recommendations are clear, there are also potential limitations of both the process and outcome. Like the other CDEs groups, the recommendations presented are clearly based on the current knowledge, experience, and perceptions related to UIA and SAH and developed by a subset of all UIA and SAH clinical research experts [3]. The group identified many variables, outcome scales, and metrics that measured similar qualities of outcome. In absence of studies addressing the question regarding which outcome metric is best in the setting of SAH, some of the decisions for or against an outcome scale had to be made based on "expert opinion" of members of the WG. We hope that the selected CDEs will be approved and used by clinicians and researchers in the field.

Table 6 Unruptured intracranial aneurysm WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Demographics UIA CRF	Participant characteristics	Demographics	Core: Age value Supplemental—Highly Recommended: Sex participant or subject genotype type
Baseline Assessment CRF	Assessments and examinations	Physical/neurological examination	Supplemental
Concomitant Diseases CRF	Assessments and examinations	Physical/neurological examination	Supplemental—Highly Recommended: History/current diagnosis of autosomal-dominant polycystic kidney disease
Concomitant Medications CRF	Treatment/intervention data	Drugs	Supplemental & Exploratory elements
Consult/Diagnosis CRF	Disease/injury related events	Classification	Supplemental
Management CRF	Treatment/intervention data	Therapies	Supplemental and Exploratory elements
Radiological Findings CRF	Assessments and examinations	Imaging diagnostics	Core: Maximum diameter; height; width; morphology type for each UIA Supplemental—Highly Recommended: Imaging modality; number of UIA; aneurysm laterality; neck measurement; aspect ratio; size ratio; bottle neck factor; shape type; diameter growth from last imaging indicator; growth in diameter since last imaging measurement; time since last imaging; de novo formation of aneurysm since last imaging
Risk factors CRF	Participant history and family history	General health history	Core: Hypertension history; current and past tobacco use; age started and stopped tobacco use Supplemental—Highly Recommended: Family history of UIA; family history of SAH due to UIA; family member with history of SAH; prior history of SAH due to UIA; autosomal-dominant polycystic kidney disease indicator; intracranial aneurysm pertinent ethnicity; blood pressure; average number of cigarettes smoked per day; number of pack-years of smoking; alcoholic drinks per day; six or more drinks consumption

CDEs common data elements, *CRF* case report form, *SAH* subarachnoid hemorrhage, *UIA* unruptured intracranial aneurysm, *WG* Working Group

Unanswered Questions and Research Gaps

The NINDS UIA and SAH CDEs are meant to serve as a valuable resource to all researchers in the field. Therefore, it must be understood that to remain relevant and reliable the CDEs need to be updated periodically. It is vital to maintain an international and multidisciplinary collaboration to ensure that these CDEs are implemented and updated when new information becomes available. Furthermore, researchers and the community must be proactive and provide feedback to the NINDS CDE Project team regarding items that are particularly useful and should be considered for more widespread use, as well as those that should be refined or removed. Any researcher or member of the public can and should provide feedback by visiting the UIA and SAH CDE project website and clicking the "Feedback and Suggestions" tab.

During WG discussions many issues were considered as relevant and in need for further research and development. For example, WGs entertained the need for homogenous definitions of intracranial aneurysm morphology, anatomical sites, measurements, and hemodynamic parameters based on modern imaging analysis. WGs also considered that further research

Table 7 Outcomes and endpoints WG recommendations

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Aneurysm Reperfusion and Rerupture CRF	Treatment/intervention data	Surgeries and other procedures	Exploratory
Cranial Nerve Function CRF	Assessments and examinations	Physical/neurological examination	Exploratory
Death CRF	Outcomes and endpoints	Endpoints	Supplemental
Disease Burden CRF	Outcomes and endpoints	Quality of life	Exploratory
Headache Pain CRF	Disease/injury related events	History of disease/injury event	Exploratory
Home Time CRF	Outcomes and endpoints	Family and environment	Exploratory
Return to Work CRF	Outcomes and endpoints	Quality of life	Exploratory
Shunt Dependency CRF	Outcomes and endpoints	Neurological outcomes	Exploratory
Barthel Index	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Beck Anxiety Inventory	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Beck Depression Inventory	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Boston Naming Test	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Brief Symptom Inventory-18	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Center for Epidemiologic Studies Depression Rating Scale	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Clinician-Administered PTSD Scale	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Color-Word Interference Test of the Delis-Kaplan Executive Function System	Outcomes and endpoints	Neuropsychological impairment	Exploratory
Computerized Test of Attentional Performance (TAP 2.3)—Alertness subtest	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Computerized Test of Attentional Performance (TAP 2.3)—Divided Attention subtest	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Computerized Test of Attentional Performance (TAP 2.3)—Go/NoGo subtest	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Computerized Test of Attentional Performance (TAP 2.3)—Neglect subtest	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Digit Span Subtest of the WAIS-IV	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Euro-QoL 5 Dimension Questionnaire	Outcomes and endpoints	Quality of life	Exploratory
Five Point Test	Outcomes and endpoints	Neuropsychological impairment	Exploratory
Frontal Systems Behavioral Scale	Outcomes and endpoints	Behavioral function	Exploratory
Generalized Anxiety Disorder-7	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Glasgow Outcomes Scale	Outcomes and endpoints	Activities of daily living and performance	Supplemental
Glasgow Outcome Scale-Extended	Outcomes and endpoints	Activities of daily living and performance	Supplemental
Grooved Pegboard Test	Outcomes and endpoints	Neuropsychological impairment	Exploratory
Hospital Anxiety and Depression Scale	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Impact of Event Scale	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Modified Rankin Scale	Outcomes and endpoints	Activities of daily living and performance	Supplemental—Highly Recommended
Montreal Cognitive Assessment	Outcomes and endpoints	Emotional and cognitive status	Supplemental—Highly Recommended

Table 7 (continued)

Instrument/Scale/CRF name Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs	Domain	Subdomain	Classification (e.g., Core, Supplemental—Highly Recommended, Supplemental, Exploratory)
Multidimensional Assessment of Fatigue	Outcomes and endpoints	Activities of daily living and performance	Exploratory
Neuro-QoL	NIH resources; outcomes and endpoints	NIH resources; quality of life	Exploratory
Neuropsychiatric Inventory Questionnaire	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Patient Health Questionnaire-9	Outcomes and endpoints	Emotional and cognitive status	Exploratory
PROMIS	NIH resources; outcomes and endpoints	NIH resources; activities of daily living and performance	Exploratory
PTSD Checklist-Civilian	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Rey Auditory Verbal Learning Test	Outcomes and endpoints	Neuropsychological impairment	Exploratory
Rey–Osterrieth Complex Figure Test	Outcomes and endpoints	Neuropsychological impairment	Exploratory: Copy trial for visuoperception; Delayed trial for memory
Short-Form 36	Outcomes and endpoints	Quality of life	Exploratory
Short-Form Health Survey 12	Outcomes and Endpoints	Quality of life	Exploratory
Similarities Subtest of the WAIS-IV	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Standardized Link's Probe	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Stroke Impact Scale version 3.0	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Stroke-Specific Quality of Life Scale	Outcomes and endpoints	Quality of life	Exploratory
Telephone Interview for Cognitive Status	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Token Test	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Trail Making Test Parts A and B	Outcomes and endpoints	Neuropsychological impairment	Exploratory: Trail Making Test Part A (Cognitive Speed) Trail Making Test Part B (Executive Function)
Utrecht Scale for Evaluation of Rehabilitation-Participation	Outcomes and endpoints	Quality of life	Exploratory
Visual Span Forward (WISC)	Outcomes and endpoints	Emotional and cognitive status	Exploratory
Written Verbal Fluency Test	Outcomes and endpoints	Emotional and cognitive status	Exploratory

CDEs common data elements, *CRF* case report form, *NIH* National Institutes of Health, *PROMIS* Patient Reported Outcome Measurement Information System, *PTSD* post-traumatic stress disorder, *QoL* quality of life, *SAH* subarachnoid hemorrhage, *WAIS* Wechsler Adult Intelligence Scale, *WG* Working Group, *WISC* Wechsler Intelligence Scale for Children

and development was needed in intracranial aneurysm morphology and definition of risk factors. Furthermore, several variables remain to be further validated and determined such as the prehospital assessment scales and the use of the NIH Stroke Scale in SAH. Moreover, an area that lacks solid scientific evidence pertains to in-hospital management of SAH patients. Many ICU therapies remain uncertain: hemodynamic and fluid management; rescue therapies; fever and glucose control; and impact of osmotherapy to mention but a few. Lastly, the WGs also discussed further areas for research regarding surgical and endovascular treatments of ruptured intracranial aneurysms: further development of outcome measures for surgical and endovascular aneurysm treatment; transfusion consequences during the perioperative period; and complication rates associated with ruptured aneurysm treatment.

Conclusions

The NINDS CDEs for UIA and SAH clinical research provide a comprehensive resource for investigators, including common standards and tools, variable names, range checks, permissible values, and standard definitions for use across UIA and SAH studies. Eight WGs and a Steering Committee comprised of international UIA and SAH experts reviewed existing NINDS CDEs and instruments, created new elements when needed and provided recommendations for UIA and SAH clinical research. The recommendations were compiled, internally reviewed by the UIA and SAH Working Groups, and posted online for 6 weeks for external public comments. The UIA and SAH

CDE WGs have volunteered their expertise and time to identify a catalogue of CDEs, included informed guidance documents and recommendations for their use, and have assembled and included relevant references that can be used when designing a broad range clinical studies and trials for UIA and SAH. Investigators interested in seeking NINDS funding for UIA and SAH clinical research are strongly encouraged to use the recommended CDEs. Dissemination and widespread use of CDEs can facilitate UIA and SAH clinical research and trial design, data sharing and analyses of observational retrospective and prospective data. It is vital to maintain an international and multidisciplinary collaboration to ensure that these CDEs are implemented and updated when new information becomes available.

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Authors' Contribution
JIS, MK, and RLM: protocol development, and manuscript writing/editing; SA-H, RDB, ALdOM, CPD, NE, EK, PDL, SAM, AM, GR, DR, MS, JT, MDIV, and GKCW: manuscript writing/editing. The corresponding author confirms that authorship requirements have been met, the final manuscript was approved by all authors. The UIA and SAH CDEs project adhered to ethical guidelines.

Compliance with Ethical Standards

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Conflict of interest
Dr Suarez reports being President of the Neurocritical Care Society, a member of the Editorial Board of Stroke Journal, and Chair of the DSMB for the INTREPID Study sponsored by BARD, outside of the submitted work. Dr Mayer reports having received personal consulting fees from Edge Therapeutics and Idorsia Pharmaceuticals outside of the submitted work. Dr Macdonald reports personal fees from Edge Therapeutics, and grants from Brain Aneurysm Foundation, outside the submitted work. Dr Amin-Hanjani, has nothing to disclose. Dr Stienen reports grants from Fujirebio Europe, and Actelion/Idorsia, outside of the submitted work. Dr Keller, Dr Vergouwen, Dr LeRoux, Dr Morita, Dr Brown, Dr Torner, Dr Rinkel, Dr Wong, Dr Rufennacht, Dr LeRoux, Dr de Oliveira Manoel, Ms Sheikh: has nothing to disclose.

Ethical Approval/Informed Consent
This project did not involve patient contact or review of patient-related information and thus it was not considered human research.

Appendix: UIA and SAH Working Group Members

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