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SPECIAL ARTICLE

Common Data Elements for Subarachnoid Hemorrhage and Unruptured Intracranial Aneurysms: Recommendations from the Working Group on Subject Characteristics

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Abstract

Background: The National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) have been generated to standardize and define terms used by the scientific community. The widespread use of these CDEs promotes harmonized data collection in clinical research. The aim of the NINDS Unruptured Intracranial Aneurysms (UIA) and Subarachnoid Hemorrhage (SAH), and Subject Characteristics working group (WG) was to identify, define, and classify CDEs describing the characteristics of patients diagnosed with an UIA and SAH. Thus, "Participant/Subject characteristics" is a set of factors defining a population of selected individuals and allowing comparisons with a reference population and overtime.

Methods: Based on standard terms defined by the United States' Census Bureau, CDEs previously defined by several (Stroke, Epilepsy and Traumatic Brain Injury) NINDS CDE working groups literature and expert opinion of the WG, the "Participant/Subject characteristics" domain has been defined.

Results: A set of 192 CDEs divided in 7 subsections: 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) was defined. SAH is characterized by 6 core elements, all classified in the "Participant/Subject characteristics" domain. Four exploratory elements out of the 39 for SAH overall are in the "Participant/Subject characteristics" domain, and all remaining 182 CDEs in the "Participant/Subject characteristics" domain are classified as Supplemental-Highly Recommended elements.

Conclusions: These CDEs would allow the development of best practice guidelines to standardize the assessment and reporting of observations concerning UIA and SAH.

Keywords: Intracranial aneurysm, Subarachnoid Hemorrhage, Common Data Elements, Participant/Subject characteristics

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Unruptured Cerebral Aneurysms and SAH CDE Project Investigators members are listed in Appendix.

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Introduction

Intracranial aneurysm (IA) is a disease of the vascular wall corresponding to a local outpouching of the artery. Its prevalence is approximately 2–3% of the general population. IA is most commonly asymptomatic, but its rupture leads to severe brain damage or even death [1, 2]. The aim of the working group (WG) was to identify and define elements regarding the characteristics of subjects recruited in studies on patients diagnosed with unruptured intracranial aneurysm (UIA) and subarachnoid hemorrhage (SAH), to classify element as Core, Supplemental-Highly Recommended (S-HR), Supplemental and Exploratory elements for future research, and finally to develop practice guidelines to standardize the assessment and reporting of observations [3].

Common Data Elements Overview

Summary

The scope of the National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) initiative is to encourage the use of standard data elements by the research community and provide recommendations in how to use the resources; to promote harmonized data collection for clinical research, patient registry and other human subject research; and allow comparison between studies and combination of data from multiple studies and electronic health records. The aim is to better monitor health and disease management to reduce the burden of diseases on societies globally. Efforts are made to identify and define relevant elements to record data in a format that optimizes exchange of information around the world and over time.

Participant/Subject (P/S) characteristics are a set of factors defining a population of selected individuals allowing comparison with a reference population and over time. The selection of factors is driven by two requirements: (1) to monitor if studied cohorts are representative of the reference population and (2) to monitor changes over time regarding the studied population to identify trends in the disease epidemiology. A CDE describes data collected in a study and that are common to multiple data sets across different studies. There may be multiple data elements to describe a concept or a factor. The selection of specific data elements requires one to choose terms and definitions representing sets of factors that are optimally defined, widely used in a broad range of sciences and specific enough to discriminate relevant factors that could impact on research in the disease of interest and relevant to other diseases that could be associated.

Process for Selecting CDEs

For subject characteristics, the first source of information the WG used was the standards set up by the United States' Census Bureau, the US authority responsible for producing basic demographic data about the population. Based on the experience of group members previously involved in large clinical studies relevant to UIA or SAH epidemiology, some elements were added to better address the needs of the project at the global level and the areas specific to the disease. The second source of information was CDEs previously defined by other WGs involved in the NINDS efforts, such as CDEs for stroke, epilepsy, and traumatic brain injuries. The third source of information used was the literature reporting on risk factors associated with UIA and SAH. The WG has identified the most relevant factors to be recorded and agreed on the existing CDEs that could be used to create a set of new CDEs. The expert opinion of the WG members was then utilized to carefully review the elements, the definitions, relational organization, and group them in major subsections.

Distinguishing Core, Supplemental-Highly Recommended, Supplemental, and Exploratory

The NINDS CDEs are structured into a classification system based on their recommended use in general or disease-specific studies. A core element is defined as a CDE that should be used in all studies regarding UIA and SAH. A S-HR element is a CDE which is essential based on certain conditions or study types in clinical research studies. These CDEs have been used and validated in the field of UIA and SAH. The use of these CDEs is strongly recommended by the WG. A Supplemental element is a CDE which is commonly collected in clinical research studies but whose relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or the type of research. An exploratory element is a CDE 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 widespread use in clinical research studies. They are reasonable to use with the understanding that limited study has been done in the field of UIA and SAH.

The overall SAH disease has been categorized by the SAH-WG in 4 domains covering 775 CDEs: (1) P/S characteristics (192 CDEs), (2) Assessments and Examinations (481 CDEs), (3) Hospital Course and acute Therapies (77 CDEs), and (4) Outcomes and End Points (41 CDEs).

Description of Selected CDEs

The WG identified factors relevant to the characteristics of participants or subjects involved in research on IAs and SAH. Each factor is quantified using at least one CDE for which a definition and standard of measurement

is described. The high-level rationale behind the choice of factors and CDE is described below. Specific definitions, measurements tools, and references regarding each SAH CDE can be found on the weblink here: https://www.commondataelements.ninds.nih.gov/SAH.aspx#tab=Data_Standards.

The 192 CDEs for P/S characteristics have been divided into 7 subsections: 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 6 core elements characterizing SAH are classified in the P/S characteristics. Four exploratory elements out of 39 defined for SAH overall are in the P/S characteristics, and all remaining 182 CDEs described in the P/S characteristics domain were classified as highly Recommended Supplemental Elements and none as Supplemental Elements.

Demographics

The demographics category groups all CDEs regarding the origins of participants in time and location. IAs and SAH affect middle-age individuals and are associated with higher risk in women. The incidence of SAH varies geographically, with a suspected ethnic and genetic predisposition. Demographic information is therefore highly relevant in the context of UIA and SAH.

The selected core elements comply with the NINDS inclusion policy as defined in the National Institutes of Health Revitalization Act of 1993 (later amended in October 2001) and the Office of Management and Budget standards (May 2002) to facilitate compliance regarding inclusion of women and minority subjects in all clinical standards set by US law. Four relevant factors [4–24] identified by the WG have been classified as core elements:

> *"Race USA category" and "Ethnicity USA category": It is suspected that ethnicity has an impact on IA and SAH. Race and ethnicity are complex, sensitive concepts. Geographic origins are associated with particular genetic and environmental backgrounds that may be clinically relevant. A specific list of worldwide ethnicities has been developed based on the current knowledge regarding the history of population migration and gene distributions. A list of 16 relevant ethnic groups has been proposed.*
> *"Gender type": The working group conferred and affirmed that gender will be defined phenotypically or personal identification of sex versus genetically-determined.*
> *"Birth Date": The WG decided age would be determined from the date of birth and recorded date of recruitment for research. This date of recruitment could be defined as one of the following: initial diagnosis of the presences of an UIA, first symptoms due to the aneurysm, or SAH. It was recognized by all WG members as an essential element regarding the description of the demography of cohorts recruited in UIA/SAH research and an important factor to stratify a cohort according to risks and outcomes. Age is known to be strongly associated with SAH and to have impact on the management. The consensus in the P/S characteristics WG is to allow the calculation of the age of recruited subjects at each relevant milestone of life or disease by collecting "Medical history taken date and time" CDE as a Core element (see subsection 4. Family and medical history).*

The prevalence of IAs and the incidence of SAH differ from country to country, and there may be even more localized differences in epidemiology at the state or county level. Specifically, participants may be exposed to risk factors specific to their environment and local habits. Recording a precise residency location may be of sensitive nature regarding personal data protection. The WG decided that the country of residency and partial ZIP code would allow a sufficient granularity. In the existing CDEs, "country of residence name" and "ZIP partial code" were selected as exploratory elements.

To allow tracking of participants over time or prevent duplicate records if participants move, it has been suggested to collect US "Personal Social Security Number" or equivalents in other countries. Due to the sensitive nature and the possible threat to personal data protection, this CDE which had been created by the National Cancer Institute (NCI) has been classified as an exploratory element.

Social Status

The theme "social status" covers aspects describing the living environment of the participant and ability to interact with it. Dimensions such as the education level, financial resources, employment and familial structure are captured by 8 different CDEs all defined as Highly Recommended Supplemental elements.

Socioeconomic factors may influence the access to medical care and recruitment in clinical studies and may also be associated with different exposure to risk factors associated with the disease. Traditional socioeconomic factors include education, income, health, and environment [25]. The WG selected CDEs capturing information regarding education level, employment status, income, and living arrangement types. The environment of each subject is inferred using information collected regarding geographic location of residency, ethnicity, educational

level, and income. The religious background of the community in which subject lives, beliefs of subjects, and associated behavior may have an impact on health but collecting the information is sensitive and may be associated with a potential concern regarding discrimination. The WG decided that the complexity of collecting valid data on the religious background of subjects outbalanced its scientific value in the context of UIAs and SAH.

Behavioral Status

"Behavioral status" lists a set of 22 CDEs covering different aspects of subjects' behavior that were identified as potentially relevant to UIA or SAH. It defines elements to capture information of exposure to substances and physical activities. Exposition to toxic substances and drug abuse are known risk factors associated with IA formation or rupture. The impact of physical activity on UIAs and SAH is a frequently asked question, and there are many uncertainties. The 22 CDEs of this subsection have been defined as Highly Recommended Supplemental Elements.

The WG selected the existing CDEs capturing information regarding alcohol consumption, smoking and drug or substances illicit use [4–8, 10–14, 16, 18, 20, 22–35]. Two new CDE were created to capture information regarding physical activity [29, 31, 34, 36]. One CDE is the assessment of level of regular physical activity. The threshold to consider a physical activity to be significant was set at 30 min of physical activity inducing sweating. The second CDE measures the frequency of such exercise.

Family and Medical History

Family and medical history theme lists all CDEs that define elements regarding risk and confounding factors associated with UIA or SAH. The list contains 144 items, 25 previously defined by other WGs of the NINDS CDE project and 8 by members of the NCI. There were 110 new CDEs specifically created for the UIA or SAH disease.

The CDE "Medical history taken date and time" has been classified by the WG as a core element to allow the calculation of the age of recruited subjects (see Subsection 1. Demographics).

This subsection groups CDEs allowing the assessment of factors known to be associated or highly suspected to be associated with the disease initiation or progression [4, 10, 16, 35, 37, 38]. A list of diseases or conditions associated with the presence of IAs or an increased incidence of SAH has been established by the WG based on a literature review and personal experience. CDEs have been specifically created to capture the presence or absence of those factors, to assess the strength of the observation and to determine if the associations are relevant or not.

Comorbidities and associated treatments may impact on the disease progression and management [7, 8, 10–14, 16, 18, 19, 21–25, 28–30, 32–35, 37–39]. Patients with multiple diseases are often excluded from studies, poorly documented because of the complexity of their medical files or are lost during follow-up. They may be more vulnerable and underrepresented in medical studies. It is therefore relevant to monitor how patients with multiple comorbidities are represented in different cohorts. The WG selected CDEs to assess these comorbidities.

The history regarding the diagnosis of UIA or SAH in other family members directly genetically linked or not is recognized as a major factor to estimate the probability of an individual to be exposed to the disease [18, 21, 23–25, 29, 30, 33, 35]. CDEs were created to specifically assess this factor.

Pregnancy and Perinatal History

The WG recommends some information to be collected regarding pregnancy, delivery, and temporal relation with SAH. Eight CDEs have been classified in this subsection.

Women are more frequently diagnosed with UIA. Mechanisms responsible for this higher prevalence remain unknown. Association between IAs and female hormones, contraception, pregnancy, or association between SAH and delivery has been studied extensively, and observations do not yet allow drawing solid conclusions [7, 24, 34, 40]. The WG decided to define a minimum data set including information about the number of pregnancies, miscarriages, and healthy deliveries as well as dates to be able to calculate the temporal relationship between pregnancy/delivery events and UIA/SAH-related events.

History Data Source Reliability

Information regarding basic characteristics may be obtained directly as measurements (e.g., genetic exploration) or from highly reliable sources but also from interviews where information quality may be degraded by subjectivity, lack of memory, or transmission of information through multiple individuals. It is essential that the context in which the information is collected is recorded. Three CDEs have been classified in this subsection. "Data source," "History data reliability type," and "History data not obtained reason" CDEs were selected specifically to record and assess the reliability of the collected information regarding demographics, subjects' and participants' medical, familial, pregnancy, and perinatal history as well as social status, behavior, and prior function status.

Prior Function Status

The WG recommends that some information regarding the patient condition prior to the diagnosis of the disease be recorded to serve as a baseline. Three CDEs are present in this subsection, and the "modified Rankin Scale (mRS) Score" has been classified as core element.

An important socioeconomic factor is health. The most frequently and consistently used tool to assess the overall level of functional ability and state of health of subjects involved in SAH studies has been the mRS Score. To harmonize the assessment of outcomes, members of the WGs involved in the domains of Assessments and Examinations, Outcomes and End Points and P/S characteristics have defined the CDE "mRS Score " as core element.

Disability being an important outcome measurement of the impact of UIAs and SAH on health and society, the WG recommended that the CDE "Ambulatory status" just prior to the diagnosis was a relevant measurement which is easy to extrapolate or collect from the subject or relatives.

In conjunction with the CDE "Medical history taken date and time" (see Subsection 4. Family and medical history), the CDE "mRS Score" will allow the measurement of the health condition over periods of time if not the whole life of participants. This will allow the assessment and monitoring of the burden of the disease on society by measuring the overall years of life lost due to premature death or disabilities associated with the disease and management of the disease.

Next Steps/Future Work

Critical to the value of CDEs is their broad acceptance, with utilization in ongoing clinical trials and the scientific literature. Therefore, it is of utmost importance for the scientific community to embrace these efforts and commit to the use of CDEs. Once there is broad utilization of CDEs, there will be tremendous potential benefit for cross-investigational comparison and patient level data pooling. Future efforts should focus on demonstrating the value and power of the widespread use of these CDEs. Acceptance of the CDEs may be facilitated by the development of dedicated software and information platforms to collect information as well as by dissemination of their existence to the community globally in publications and during conferences. It is also possible that additional CDEs will need to be added in the future as scientific knowledge evolves.

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PB, AM, NUK, JM, SM, YM, MJHW, and RDBJr were involved in protocol development and manuscript writing/editing. The corresponding author confirms that authorship requirements have been met, the final manuscript was approved by ALL authors, and that 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
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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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