Neurocrit Care (2019) 30:S79–S86
https://doi.org/10.1007/s12028-019-00727-2

NEUROCRITICAL CARE SOCIETY

SPECIAL ARTICLE

Common Data Elements for Unruptured Intracranial Aneurysm and Subarachnoid Hemorrhage Clinical Research: Recommendations from the Working Group on Long-Term Therapies

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Abstract

Objectives: The goal for the long-term therapies (LTT) working group (WG) of the Unruptured Intracranial Aneurysm (UIA) and Subarachnoid Hemorrhage (SAH) common data elements (CDEs) was to develop a comprehensive set of CDEs, data definitions, case report forms, and guidelines for use in UIA and SAH LTT 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 other neurological disease-specific CDEs already developed and available for use by research investigators.

Methods: The eight LTT WG members comprised international UIA, and SAH experts reviewed existing NINDS CDEs and instruments, created new elements when needed, and provided recommendations for future LTT clinical research. The recommendations were compiled, internally reviewed by the all UIA and SAH WGs and steering committee members. The NINDS CDE team also reviewed the final version before posting the SAH Version 1.0 CDE recommendations on the NINDS CDE website.

Results: The NINDS UIA and SAH LTT 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 subcommittee members discussed and reviewed various parameters, outcomes, and endpoints in UIA and SAH LTT studies. The following meetings with WG members, the LTT WG's recommendations are incorporated into the disease/injury-related events, assessments and examinations, and treatment/intervention data domains.

Conclusions: Noting gaps in the literature regarding medication and rehabilitation parameters in UIA and SAH clinical studies, the current CDE recommendations aim to arouse interest to explore the impact of medication and

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Unruptured Intracranial Aneurysm and SAH CDE project investigators are listed in the "Appendix".

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rehabilitation treatments and therapies and encourage the convergence of LTT clinical study parameters to develop a harmonized standard.

Keywords: Common data elements, Clinical research, Subarachnoid Hemorrhage, Cerebral aneurysm, Rehabilitation, Medication, Outcome, Endpoint, Long-term therapy

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. They are intended to be dynamic and may evolve over time. 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. The goals are to disseminate standards, create easily accessible tools, encourage focused and simplified data collection, and improve data quality in clinical researches.

The Unruptured Intracranial Aneurysm (UIA) and Subarachnoid Hemorrhage (SAH) CDEs are the 22nd set of disease/disorder-focused recommendations developed by the NINDS and the first to be completed as a joint project between NINDS and the National Library of Medicine. CDEs are available on the NINDS CDE website (www.commondataelements.ninds.nih.gov) and the NIH CDE repository (www.nlm.nih.gov/cde). This paper reviews the process and recommendations by the long-term therapies (LTT) working group regarding the current status, gap, and future directions in clinical researches on LTT in UIA and SAH.

Methods

The UIA and SAH CDE project was conceived and planned in late 2014. The LTT working group (WG) was formed in early 2015 and composed of clinical research investigators from different specialties including neurology, neurosurgery, neuroradiology, neurorehabilitation, neuropsychology, and pharmacology. WG members reviewed the literature, discussed, drafted, reviewed, and deliberated with consensus upon the CDE recommendations regarding LTT of UIA and SAH CDE between 2015 and 2016. The UIA and SAH CDEs were available for public review on the NINDS CDE website between January 31, 2017, and March 17, 2017. Stakeholders and professional societies in different parts of the world were invited for comment before first CDE generation finalization and release.

CDEs are classified as general core or by disease [1]. General core refers to data elements that are required for all NINDS-funded studies. Disease-specific CDEs are positioned as core, supplemental–highly recommended, supplemental, and exploratory, depending on the current and perceived future research best practice [1]. Core CDEs are data elements that collect essential information applicable to any UIA and SAH research study. Supplemental–highly recommended CDEs are data elements that are essential based on certain conditions or study types in clinical research studies in UIA and SAH. Supplemental CDEs are optional data elements that are commonly collected in clinical research studies and whose relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or type of research involved. Exploratory CDEs are data elements that require further validation, and potentially fill current gaps in the core and supplemental–highly recommended CDEs.

Results

The LTT WG communicated with the subject characteristics WG, UIAs WG, and outcomes and endpoints WG to ensure that key CDEs were included in the respective WG CDEs. The LTT WG recommended one supplemental case report form (CRF) and 16 exploratory instruments CDEs. The LTT did not identify additional core or supplemental–highly recommended CDEs (Table 1).

Medications

A review of the literature found that medications were not uniformly documented in UIA and SAH LTT clinical study publications. Studies of long-term outcomes were observational or follow-up for acute therapy. The WG also found an emerging theme in the long-term medical therapies for UIA [2].

Medications also reflect on medical comorbidities, interventional treatment on UIA, and acute therapy of SAH. Antiepileptic therapy is indicated for SAH patients that develop seizures. Antiepileptic therapy has known adverse effects and is associated with worse cognitive and functional outcomes [3]. Also, there may be potential drug interaction between long-term medical therapy and antiepileptic therapy. To complicate the matter, some guidelines recommend against the use of phenytoin following SAH but consider other antiepileptics, such as levetiracetam, acceptable [4]. Non-uniformity

Table 1 SAH long-term therapies working group 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	Assessments and Examinations	General and Motor	Exploratory
Arm Motor Abilities Test	Assessments and Examinations	General and Motor	Exploratory
Berg Balance Scale	Assessments and Examinations	General and Motor	Exploratory
Chelsea Critical Care Physical Assessment Tool	Assessments and Examinations	General and Motor	Exploratory
DEMMI: Elements	Assessments and Examinations	Hospital Care/Management	Exploratory
Fugl-Meyer Assessment	Assessments and Examinations	General and Motor	Exploratory
Functional Ambulation Categories	Assessments and Examinations	General and Motor	Exploratory
Functional Gait Assessment	Assessments and Examinations	General and Motor	Exploratory
Functional Independence Measure	Assessments and Examinations	General and Motor	Exploratory
London Handicap Scale	Assessments and Examinations	Hospital Care/Management	Exploratory
Mobilizing ICU Patients Safety Assessment	Assessments and Examinations	Hospital/Care Management	Exploratory
Overall Measurement Schema for ICU Acquired Weakness and Related Conditions	Assessments and Examinations	Hospital/Care Management	Exploratory
Physical Function ICU Test	Assessments and Examinations	General and Motor	Exploratory
PUMP Plus	Assessments and Examinations	General and Motor	Exploratory
Reintegration to Normal Living	Assessment and Examinations	Hospital/Care Management	Exploratory
Rivermead Mobility Index	Assessments and Examinations	General and Motor	Exploratory

CDE common data elements, *CRF* case report form, *DEMMI* de Morton Mobility Index, *ICU* intensive care unit, *PUMP* Progressive Upright Mobility Protocol

would ideally be documented in a systemic manner. The WG developed the Discharge Medications CRF recommended it as supplemental and endorses this CRF to be included in all relevant studies.

An area that requires special attention is that of medication administration in patients undergoing endovascular treatment with flow diverters. The latter treatment has matured over the past decade as an established modality of interventional treatment for UIA [5]. Flow diverter treatment typically requires 6–12 months of antiplatelet treatment including aspirin. Aspirin treatment has recently been shown to decrease aneurysm rupture risk in animal experiments and human epidemiological studies [6]. The exact molecular mechanisms and inflammatory mediators that ultimately cause aneurysm rupture are still uncertain, and inflammatory enzymes cyclooxygenase-1 and cyclooxygenase-2 which catalyze prostaglandin synthesis from arachnoid acid are thought to be important components in the pathogenesis of aneurysm rupture [2]. Effect of flow diverter treatment to prevent aneurysm rupture should therefore take into account possible effects of aspirin and other antiplatelets in future study design. Also, effect of aspirin in on UIA should be further investigated in randomized controlled clinical trials. Current data in small case series do not observe a significant increase in the risk of aneurysm rupture among patients receiving systemic anticoagulation and therefore anticoagulation is not contraindicated in the presence of UCA [7]. Given the strong evidence of beneficial effect of anticoagulation in patients with atrial fibrillation, more and more patients with UIA would be out on warfarin or other novel oral anticoagulants. Practically, whether anticoagulation increases the risk of UIA rupture is a question that commonly enters patient consultation and is considered in clinical decision-making process. To have a clearer idea of what happens in patients requiring systemic anticoagulation and harboring UIA, CDEs to record these medications are of paramount importance.

As hypertension is a known factor for UIA growth and rupture [8], it seems logical to treat hypertension in people with UIA, not only for the purpose of reducing the risk of rupture, but also to reduce the risk of cardiovascular disease in general [2]. Older patients with atherosclerosis have been shown to have a different pattern of UIAs [9]. Interestingly, a retrospective observational study suggested that diabetes was the only factor in older patients ($\geq$65 years of age) that related to signs of instability in aneurysm wall [10]. Whether particular type of diabetic medications or glycemic control make a difference would be of interest to study in

future observational studies. In a Japanese multihospital case–control study, the use of statin was associated with UIA rupture after adjustment for potential confounders [11]. Therefore, it would be of interest to document statin use in future long-term therapies for UIA.

Another important reason to look at medications is to observe any disease-modifying effects for vascular death. In a cohort of 1,765 survivors at 3 months after SAH, the risk of death was 8.7% (95% CI 7.3–10.1); within 5 years, 17.9% (95% CI 16.1–19.9); within 10 years, 29.5% (95% CI 27.3–31.8); within 15 years; and within 20 years, 43.6% (95% CI 41.2–46.1) [12]. Overall, the standardized mortality rate was doubled for all-cause death and vascular death.

Cognitive Dysfunction, Neuropsychiatric Problems, and Quality of Life

Cognitive dysfunctions are common and diverse after SAH. A 2010 systemic review revealed cognitive deficits in memory, executive function, and language after SAH [13]. The contributions from diffuse brain damage and secondary complications such as vasospasm and elevated intracranial pressure remained to be understood. In fact, at 1 year after SAH, prevalence of severe deficit in each individual cognitive domain occurs in up to 15%. Besides, 13% of the SAH patients had severe deficits in two or more cognitive domains which were associated with unfavorable outcome (modified Rankin Scale 3–5) and dependent instrumental activity of daily living (Lawton Instrumental Activity of Daily Living < 15) [14]. The overall rate of cognitive dysfunction (from mild cognitive impairment to dementia) was 73% at 3 months after SAH and was a good discriminant for neurological and instrumental activity of daily living outcomes [15].

The medical literature related to treatment and cognitive dysfunction after SAH have centered on aneurysm treatment with microsurgical clipping and endovascular coiling. [16] Medical treatment of cognitive impairment has been understudied. Wong et al. [17] carried out a pilot study of 12-week course of Rivastigmine, a selective carbamate-derived reversible acetylcholinesterase and butyrylcholinesterase inhibitor, in 20 SAH patients with cognitive dysfunction 1 year after SAH. The patients showed improvement in assessments using cognitive subscale of Alzheimer disease assessment scale, functional assessment battery, and Rivermead behavioral memory test. However, the improvement was not correlated with baseline cholinergic dysfunction. Another medical treatment of interest for cognitive dysfunction after SAH is statins. One experimental study had suggested that statin administration could reduce cognitive dysfunction in a murine SAH model [18]. However, a recent case control study in humans did not show any beneficial effect on cognitive dysfunction after SAH with a 3-week course of Simvastatin [19].

Health-related quality of life has recently been suggested as a supplement to the traditional neurological outcome measures from the patient's perspective according to the World Health Organization model, and may capture the effects of other factors such as posttraumatic stress disorder and neuroendocrine dysfunction [20]. Using a generic quality of life scale (Short Form-36), 42.9% of the patients had a deteriorated quality of life after 4 months, and that the most affected dimension was the Physical Role [21]. Disease-specific quality of life scale is more sensitive to the disabling effect of disease such as stroke. In that respect, stroke-specific quality of life scale (SSQOL) had been validated for application in SAH [22, 23]. In the Dutch validation study, SSQOL scores showed significant correlations with Cognitive Failure Questionnaire, Life-Satisfaction-9, and Hospital Anxiety and Depression Scale [22]. In the Chinese validation study, SSQOL scores showed significant correlations with Chinese Lawton Instrumental Activity of Daily Living Scale, Short Form-36 physical health and mental health component scores, and Geriatric Depression Scale score [23].

In UIA, challenges remain on finding the most beneficial and cost-effective management paradigm. A postal questionnaire study found that UIA patients had a reduced quality of life but reduction in quality of life is not improved with aneurysm treatment [24]. The effect of long-term therapies on quality of life and psychological outcome would be important to address.

Rehabilitation Outcomes

Hospital length of stay is a common metric of excellence in health care and not surprisingly there is a drive to reduce length of stay for SAH episodes [25]. For example, in a US study, the mean length of stay is 14 days and the total hospital costs per SAH patient is US$269,000 [25]. There is a significant potential for immobility after SAH, which places these patients at a high risk for cognitive, neuromuscular, psychological, and functional deterioration. An early mobilization program is a key to prevent complications and facilitate discharge. A number of factors need to be considered in implementing an early mobilization program, which includes the effect of positional change and blood pressure, the time from admission to initiation of mobilization, and the type and intensity of exercise [26]. It is noted that SAH patients typically require 5.4 ± 4.2 days to participate in out of bed activity and 10.7 ± 6.2 days to walk more than 50 feet [27]. The healthcare resource utilization is typically higher among SAH patients than ischemic

stroke and intracerebral hemorrhage patients [28]. Future randomized controlled trials are needed to examine the benefits of early mobilization after SAH and should identify the type and intensity of the activities performed during early mobilization [26].

Rehabilitation is a key to achieve functional independence among SAH patients. While SAH patients typically are admitted to the hospital with a lower functional level, they make larger improvement in functional independence measure (FIM) as compared to ischemic stroke and intracerebral hemorrhage patients. SAH patients have significantly better odds for obtaining moderate level of functional independence, not only in activities of daily living and stair walking, but also in comprehension and expression [29]. Severe SAH patients have also made functional gains with inpatient rehabilitation. In a previous study of poor grade SAH, FIM scores reached a mean of 91 after a course of inpatient rehabilitation [30]. However, return to work and cognitive dysfunction remain a major problem among SAH patients after discharge from inpatient rehabilitation [31]. Despite improvement in organized rehabilitation care [32], the resulting social and vocational disability hindering work reentry, home, and community function should not be neglected. The presence of hydrocephalus, delayed cerebral infarction, old age, and poor admission neurological grade negatively impacted on functional outcome. It is essential that the rehabilitation professional be aware of these potential sequelae, as they have significant impact on recovery and reintegration [33]. Personality changes have been found to be a great hindrance to functional social reintegration [34].

There has not been a clear regimen of rehabilitation programs for SAH patients. In the literature, rehabilitation programs for SAH patients are included in rehabilitation programs for traumatic brain injury, ischemic stroke, and intracerebral hemorrhage patients. A further understanding of these program parameters and their effects on rehabilitation outcomes is needed. Other than the functional independence measures, the LTT WG noted a gap in the literature in these traditional rehabilitation progress indicators. The list of progress indicators the LTT WG selected from the stroke rehabilitation literature aim to provide a platform to document progress in SAH patient rehabilitation, and allow cross comparisons with the stroke population. As such these CDEs are classified as Exploratory.

Discussion

Randomized clinical trials have tested many medical therapies for SAH, but none have been successful other than oral nimodipine. There are numerous explanations for the failure of these trials, including ineffective interventions, inadequate sample size, treatment side effects, and insensitive or inappropriate outcome measures [35]. To address these issues, the Subarachnoid Hemorrhage International Trialists (SAHIT) data repository that catalogs individual patient data from multiple clinical trials and observational databases of SAH patients was established. The primary aim of the SAHIT data repository is to provide a unique resource for prognostic analysis and for studies aimed at optimizing the design and analysis of phase III trials in aneurysmal SAH [35]. The problems with merging SAHIT data were related to lack of common definitions and coding of variables, differences in the outcome scales used, and times of assessment [36]. The SAHIT consortium suggested that the way forward would include CDEs, outcomes analysis, and to prioritize research questions, among others [36]. The importance of CDEs in SAH research is again highlighted.

The commonly neglected effect of the use of medications in LTT is emphasized by the WG. Medications can be used as surrogate markers for comorbid disease, disease severity, and management practice variation. The direct and indirect effects of medication use and compliance on trial treatment outcomes are often overlooked and misunderstood.

A multidisciplinary consensus building approach can be impactful in guiding research and development. In 2010, a consensus-built proposal based on literature review suggested that in observational studies and clinical trials aiming to investigate strategies to prevent delayed cerebral ischemia, the two main outcome measures should be: (1) cerebral infarction identified on computed tomography or magnetic resonance imaging or proven at autopsy, after exclusion of procedure-related infarctions; and (2) functional outcome [37]. Most subsequent research studies on delayed cerebral ischemia are reported accordingly, which enables a more meaningful comparison and pooling of results.

It must be emphasized that the development process of the SAH CDEs is dynamic. Therefore, some of the rehabilitation CDEs classified as Exploratory may become supplemental CDEs, with the availability of reliability and validity data in future SAH studies. The approach in selecting these SAH CDEs has been inclusive and the aim is to be supportive in the development of rehabilitation studies with a SAH focus. The WG hope that in a few years' time the literature will be able to support a clearer framework to guide SAH rehabilitation studies.

Conclusions

We noted a gap in the literature regarding medication and rehabilitation therapeutic parameters in UIA and SAH clinical studies. With the current CDE recommendations, we aim to arouse the interest to explore the impact of medication and rehabilitation and encourage the convergence of LTT clinical studies parameters to develop a harmonization standard.

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Acknowledgements

The views expressed here are those of the authors and do not represent those of the National Institutes of Health (NIH), the National Institute of Neurological Disorders and Stroke (NINDS) or the US Government.

Authors' contributions

GKCW, JJD, and JT were involved in protocol development, and manuscript writing/editing was done by DHR, JB, CO, YBR, and AS. 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.

Source of support

Logistical support for this project was provided in part through NIH Contract HHSN271201200034C, the Intramural Research Program of the NIH, NLM, The Neurocritical Care Society and the CHI Baylor St Luke's Medical Center in Houston, TX. The development of the NINDS SAH CDEs was made possible thanks to the great investment of time and effort of WG members and the members of the NINDS CDE Project and NLM CDE project teams participating from 2015 to 2017.

Conflict of interest

Dr Wong has nothing to disclose. Dr Daly has nothing to disclose. Dr Rhoney has nothing to disclose. Dr Broderick has nothing to disclose. Dr Roos reports and Minor shareholder of start-up Nico-Lab, a company aiming at improving stroke care through AI-supported neuroimaging assessment. Dr Ogilvy reports Data Safety Monitoring Board of Medtronic, Inc. Dr. Siddiqui reports personal fees from Amnis Therapeutics, BlinkTBI, Inc, Buffalo Technology Partners, Inc., Cardinal Consultants, LLC, Cerebrotech Medical Systems, Inc, Cognition Medical, Endostream Medical, Ltd, Imperative Care, International Medical Distribution Partners, Neurovascular Diagnostics, Inc., Q'Apel Medical, Inc., Rebound Therapeutics Corp., Rist Neurovascular, Inc., Serenity Medical, Inc., Silk Road Medical, StimMed, Synchron, Three Rivers Medical, Inc., Viseon Spine, Inc.Ð personal fees from Amnis Therapeutics, Boston Scientific, Canon Medical Systems USA, Inc., Cerebrotech Medical Systems, Inc., Cerenovus, Corindus, Inc., Endostream Medical, Ltd, Guidepoint Global Consulting, Imperative Care, Integra, Medtronic, MicroVention, Northwest University—DSMB Chair for HEAT Trial, Penumbra, Q'Apel Medical, Inc., Rapid Medical, Rebound Therapeutics Corp., Serenity Medical, Inc., Silk Road Medical, StimMed, Stryker, Three Rivers Medical, Inc., VasSol, W.L. Gore & AssociatesÐ personal fees from Cerenovus LARGE Trial and ARISE II Trial; Medtronic SWIFT PRIME and SWIFT DIRECT Trials; MicroVention FRED Trial & CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial;Ð outside the submitted work.

Ethical approval/informed consent

The UIA and SAH CDEs project adhered to ethical guidelines.

Appendix: UIA and SAH WORKING GROUP MEMBERS

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Publisher's Note

Published online: 10 May 2019

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