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Common Data Element for Disorders of Consciousness: Recommendations
from the Working Group on Therapeutic Interventions

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Abstract

Background. Over the past thirty years, there have been significant advances in the understanding of the mechanisms associated with loss and recovery of consciousness following severe brain injury. This work has provided a strong grounding for the development of novel restorative therapeutic interventions. While all interventions are aimed at modulating, and thereby restoring, brain function, the landscape of existing interventions encompasses a very wide scope of techniques and protocols. Despite vigorous research efforts, few approaches have been assessed with rigorous, high-quality, randomized controlled trials. As a growing number of exploratory interventions emerge, it is paramount to develop standardized approaches to reporting results. The successful evaluation of novel interventions depends on implementation of shared nomenclature and infrastructure. To address this gap, the Neurocritical Care Society's Curing Coma Campaign convened nine working groups and charged them with developing Common Data Elements (CDEs). Here, we report the work of the Therapeutic Interventions Working Group.

Methods. The Working Group reviewed existing CDEs relevant to therapeutic interventions within the NIH National Institute of Neurological Disorders and Stroke (NINDS) database and reviewed the literature for assessing key areas of research in the intervention space. CDEs were then proposed, iteratively discussed and reviewed, classified, and organized in a Case Report Form.

Results. We developed a unified CRF, including CDEs and key design elements (KDE; i.e., methodological or protocol parameters), divided into five sections: (i) patient information; (ii)

general study information; (iii) behavioral interventions; (iv) pharmacological interventions; and (v) device interventions.

Conclusion. The newly created CRF enhances systematization of future work by proposing a portfolio of measures that should be collected in the development and implementation of studies assessing novel interventions intended to increase the level of consciousness or rate of recovery of consciousness in patients with DoC

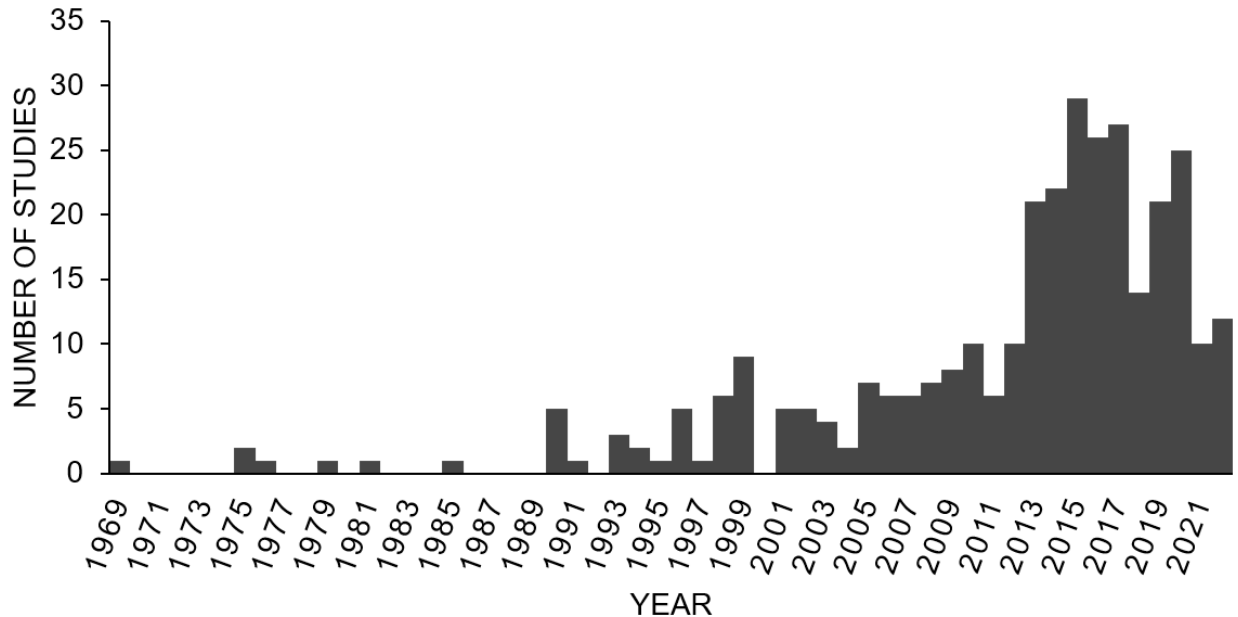
Keywords: Common Data Elements; Disorders of Consciousness; Coma; Vegetative State; Minimally Conscious State, Therapeutic Interventions

Introduction

Over the past three decades, there has been tremendous scientific progress in the understanding [1, 2] and clinical management [3-5] of patients with a disorder of consciousness (DoC), such as Coma, Vegetative State (VS; also referred to as Unresponsive Wakefulness Syndrome), and Minimally Conscious State (MCS). In parallel, there has been a steady growth in the exploration of potential therapeutic interventions aimed at increasing arousal, restoring consciousness, and cognitive function in DoC patients [6-8]. The importance of this effort has been recently highlighted in the Proceedings of the Curing Coma Campaign (CCC) Scientific Advisory Council Meetings [9, 10], an initiative of the Neurocritical Care Society (NCS). One of the central aspects of the “grand challenge” of curing coma is the development of treatments for promoting recovery of consciousness.

As described in greater depth elsewhere [7, 8], there is a growing volume of research exploring different neuromodulatory approaches aimed at hastening recovery, or improving the level of consciousness, in patients with DoC, including pharmacological (e.g., amantadine, zolpidem), electromagnetic (e.g., transcranial direct current stimulation [tDCS], deep brain stimulation [DBS]), sensory (e.g., vestibular, auditory), mechanical (e.g., low-intensity transcranial focused ultrasound [tFUS]), and regenerative (e.g., stem cell, neurogenesis) techniques. As shown in Figure 1, the number of yearly studies looking at therapeutic interventions for patients with a DoC has been steadily increasing since the 1990s. To date, less than a handful of interventions, mainly pharmacological and electromagnetic, have been assessed with high-quality randomized controlled trials [8]. Indeed, according to a recent analysis by the CCC [6], the advancement of therapeutic interventions for DoC is hampered by a number of shortcomings, including the paucity of robustly designed clinical trials, as well as the lack of a

unifying conceptual framework for evaluating therapeutic mechanisms of action, and the absence of biomarkers that can be leveraged for selecting patients likely to be responsive to a treatment and for capturing small (e.g., subclinical) effects in early-phase trials. Lack of randomized



controlled trials is also observed in pediatric DoC [11].

Figure 1. Yearly number of publications, between 1969 and 2022, assessing potential interventions for DoC patients. Data obtained from PubMed search (with the following search term: (disorders of consciousness, coma, vegetative state, minimally conscious state) AND (Therapy/Broad[filter])), integrated with all relevant, non-duplicate, references from recent expert reviews [6-8].

Despite vigorous research, there is a notable absence of well-defined common data elements (CDE) for DoC [12], unlike interventions in other fields such as stroke, traumatic brain injury, and subarachnoid hemorrhage, among others [13-17].

To address this gap, the Neurocritical Care Society's Curing Coma Campaign [18] launched a Common Data Elements (CDE) initiative for DoC in 2020. The CCC convened 10 Working Groups (WG) to create CDEs for harmonization of data elements across a broad spectrum of research domains. Among these, the Therapeutic Interventions WG was tasked with establishing a framework for standardizing future clinical studies aimed at assessing novel therapeutic interventions for DoC patients.

We present the first version of the CDE recommendations of the Therapeutic Interventions WG.

Methods

CDE Development WG Organization and Meetings

We convened a 7-member Working Group of specialists in DoC, combining expertise from several complementary backgrounds including neurocritical care and rehabilitation medicine, bioengineering, clinical psychology, physical therapy, pediatric brain injury, and basic and translational neuroscience. The group met online, monthly, from 2021 to 2023. Leveraging each member's background and prior work in the context of interventions for DoC patients, three subgroups of at least two members were created to address CDEs relevant to behavioral, pharmacological, and device-based interventions, respectively. The work of the subgroups was then evaluated and discussed by the full WG to reach consensus.

Process for Selecting CDEs

Each subgroup began by reviewing existing CDEs relevant to therapeutic interventions (in the category of behavioral, pharmacological, device-based neuromodulation) within the NIH National Institute of Neurological Disorders and Stroke (NINDS) database (available at

<http://commondataelements.ninds.gov>). Potentially relevant CDEs were initially reviewed in the “All”, “Acute Hospitalization”, “msTBI: Rehabilitation”, and “Stroke” diseases, in the “Drugs”, “Therapies”, “Surgeries and other procedures” categories. Existing CRFs reviewed included “Antithrombotics and Risk Factors Controlling Medications”, “ER/Admission Therapeutic Procedures”, “Intraoperative Management”, “Lifestyle Modification Therapies”, “Post-Discharge Outpatient Treatment”, “Prior and concomitant medications”, “Protocol Deviations”, “Rehabilitation Therapies”, “SAH Surgical/Procedural Interventions”, “Stroke Surgical and Procedural Interventions”, “Study Therapies Compliance”, “Surgical and Therapeutic Procedures”, “Therapy Intensity Level”, and “Thrombolytic/Reperfusion Therapies”.

CDE Classification

As agreed across all Working Groups of the *Curing Coma Campaign* CDE initiative, new CDEs were assigned, by consensus opinion within each WG, to one of four categories, in line with the previous NINDS CDE initiatives [13-17]. The designation of “disease core” was used to indicate CDEs which are required to be collected for all DoC studies. CDEs are designated as “basic” when they are strongly recommended (but not required) for all DoC studies. “Supplemental” indicates CDEs that are appropriate for use in a specific study context (e.g., therapeutic interventions, epidemiological). Finally, “exploratory” CDEs are items that can be considered for inclusion, in a specific study context, but require further study or validation before routine use. In addition to CDEs, the CCC initiative recognized that in certain study contexts, particularly for the purposes of data harmonization, it is appropriate to also collect “Key Design Elements (KDEs)” in addition to CDEs. While a CDE is meant to capture the *type* of datum that

is acquired in a study (e.g., a score on a specific subscale of an outcome instrument), a KDE is meant capture *how* that datum is acquired (e.g., a methodological or protocol parameter).

Applicability of CDEs

It should be highlighted that the CDEs recommended by the Therapeutic Intervention WG have a specific domain of applicability. First, by the very nature of the WG, which is focused only on a subset of potential studies in the context of DoC patients (i.e., intervention studies), the Therapeutic Interventions CRFs only include “supplemental” and “exploratory” CDEs as well as KDEs. “Disease core” and “basic” CDEs, which are, respectively, required and strongly recommended for *all* DoC studies, can be found elsewhere (see the CRF cover-page, in the Appendix). Second, the present CDEs are applicable to patients who, at the time of enrollment, fulfill established international criteria for a DoC diagnosis [3-5], including coma, vegetative state, and minimally conscious state. With respect to the two latter diagnostic categories, the CDEs can be applied equally at the acute and chronic time-point. Importantly, the present CRF is applicable to interventions *specifically* aimed at enhancing a patient’s level of or rate of recovery of consciousness, as opposed to interventions aimed at mitigating any of the comorbidities often seen in this patient cohort (e.g., spasticity). Finally, it should also be recognized that the present CRF was developed mostly on data from studies in adult cohorts. As discussed further in the limitations and opportunities section, below, the degree of applicability of each CDE and KDE to pediatric DoC studies should be evaluated on a case-by-case basis.

Ethics statement

No new data were collected or analyzed for this work; therefore there was no need for informed consent or approval from an Institutional Review Board.

Description of selected CDEs***Common CDEs across intervention types***

The therapeutic intervention CRF is divided into 5 main sections. The first two include patient information and general study information. These first two sections are applicable to all intervention studies in DoC and focus on broad information including the type of intervention being studied, the setting of the study, the delivery of the intervention as well as important information concerning whether, and to what degree, condition assignment is blinded. This latter information is very important in the context of clinical trials since published literature does suggest that open-label studies have a tendency for over-estimating intervention effect sizes [19-22].

The remaining three sections of the CRF are specific to the type of intervention being studied. Following a recent gap analysis [6], and in light of the expertise represented in the WG, interventions were categorized as behavioral, pharmacological, and device-based. Behavioral interventions refer mainly to interventions involving sensory stimulation of the patient while pharmacological interventions and device interventions focus on pharmacological compounds and technology-based interventions, respectively. The device intervention portion of the CRF focuses on neuromodulatory devices directly targeting brain tissue, such as transcranial magnetic stimulation and transcranial electric stimulation, and devices exerting indirect neuromodulatory effects, such as tilt-table.

CDEs for Behavioral Interventions

In order to gain an understanding of the types of behavioral interventions that are most frequently studied in the context of DoC patients, we conducted a search in the PubMed database to identify all existing evidence on this topic. Search terms included: psychostimulation and sleep therapy, physiotherapy and physical therapy, occupational therapy, oromotor and speech therapy, music therapy, cognitive rehabilitation, and associated disciplines. The group concluded somatosensory stimulation is the only behavior intervention with sufficient consensus and standardization. Elements are also provided for the description of therapeutic “active ingredients” beyond the somatosensory stimulations listed in the present version of the CDEs, for future tool expansion.

CDEs for Pharmacological Interventions

In order to create CDEs applicable to as broad a spectrum of pharmacological interventions respecting the minimum acceptable data limitations described above (i.e., aimed at enhancing one’s level of consciousness, applicable to patients currently in a DoC), the subgroup focused on elements characterizing the active ingredient of the intervention as well as the details of its dosage and administration. As pharmacological interventions occur in the acute, subacute, and chronic phases of DoC, the subgroup focused on CDEs that would apply across timepoints of the disease.

CDEs for Device-Based Interventions

The gamut of interventions currently applied in DoC was based on expert reviews by members of the WG [7, 8] as well as a recent gap analysis performed by the CCC initiative [6]. In the CRF, interventions were classified based on their mechanisms of action, including

electromagnetic (e.g., Deep Brain Stimulation, DBS; Spinal Cord Stimulation, SCS; Peripheral Nerve Stimulation, PNS; Transcranial Magnetic Stimulation, TMS; transcranial Electrical Stimulation, tES), mechanical (e.g., transcranial focused ultrasound, tFUS; mobilization devices, such as tilt-table), optical (e.g., infrared light therapy), and other (e.g., brain-computer interfaces; virtual reality).

Dissemination of CDEs for DoC

Version 1.0 of the proposed interventions CDEs for DoC patients has been released as a collection of eight Case Report Forms. The CRFs can be accessed at this link: <https://zenodo.org/record/8172359>. To ensure comprehensive input, the CDEs underwent a two-month public feedback phase from October to November 2022. This feedback phase was promoted at the 2022 annual Neurocritical Care Society meeting and through Twitter. Valuable input was received from the public, which was then incorporated into the final versions of the CRFs. The feedback primarily focused on the style and formatting of the CRFs and did not recommend any specific changes related to content. Ongoing feedback and suggestions for modifying the CDEs are welcome and can be submitted via email to cde.curingcoma@gmail.com. The Work Group will evaluate any proposed edits or additions to the current list of CDEs as needed. Updated versions of the CRFs will be published on the Zenodo website with new version numbers. As relevant new evidence emerges, the Work Group will ensure prompt distribution of any modified CDEs using online scientific portals.

Limitations and opportunities

Creating CDEs is a key aspect of systematizing and promoting the use of evidence-based measures in the study of disease. Developing such a portfolio of elements, however, poses multiple challenges.

At the general level, a key aspect of CDEs is that they provide an ordered set of measures classified along a graded scale ranging from “basic” (also referred to as “general core”), which implies a data element that collects essential information that is *required* for any study, to “exploratory,” which implies that a data element *can* be used but still lacks substantial validation. This one-dimensional gradation, however, confounds several distinct axes of evaluation, including a measure’s validity, its ease of use, and the breadth of its desired application. A measure’s validity is typically dependent on the existence of well characterized psychometric properties (e.g., how well does it capture the hypothetical construct of interest). Ideally, the better the characterization of a measure’s psychometric properties, the stronger the recommendation for its use. Similarly, the simpler a measure is to deploy in its intended context, the stronger it should be recommended. In contrast with these two principles, however, determining whether a measure is relevant in a specific context does not depend on either its ease of use or its validation. A measure could, for example, be very well validated and simple to use but only applicable to a specific study context (e.g., therapeutic interventions). Despite well-validated characterization and ease of use, such a CDE might not be relevant to other study types (e.g., demographic studies) and should thus not be *required* in all studies (i.e., classified as “basic” or “disease core”). As this example shows, compressing measures of quality and the notion of breadth of desired applicability into a single dimension obfuscates the multidimensional characteristic of CDEs and calls for a more sophisticated classification system.

At the specific level of therapeutic interventions, there are a number of related limitations that are not found in other CDE domains. While there has been substantial progress in identifying and predicting recovery of consciousness in patients with acute brain injury, there is still considerable work to be done in standardizing definitions of coma and prolonged DoC. Recovery from coma has many stages, of which the natural history will depend on the mechanism of brain injury, patient-related factors, environment-related factors, and support networks. Across this temporal continuum, the focus of care and the measured outcomes will change; for example, in a comatose patient with traumatic brain injury, acute ICU level interventions may focus on raised intracranial pressure, while subacute interventions may focus on awakening, and chronic interventions may focus on specific cognitive domains. Before we can define CDEs for therapeutic interventions in DoC, it is critical to define when acute brain injury becomes a DoC and if early interventions, for example in the acute phase, should be captured. Further work is required to understand the natural history of coma in the absence of confounding by withdrawal of life sustaining therapy. We support a broad definition of DoC to include comatose patients in the acute setting, allowing for evaluation of neuroprotective pharmacologic interventions. Intervention CDEs should be binned by the phase of care (acute, subacute, chronic) and by the goal of treatments (neuroprotective agent, stimulant therapy, disease specific therapy, neuromodulation).

CDEs that capture patient prognostic characteristics (e.g., disease severity, demographic factors, comorbidities) and outcome domains (e.g., functional independence, psychological distress, social participation) are likely to be of enduring interest as covariates in studies on a wide variety of topics and as indices of the impact of disease and/or treatment, respectively. Dissimilar to measurement CDEs (e.g., outcome questionnaires), where quality is mainly

predicated on empirical determination of the psychometric profile of a measure, the validation of intervention CDEs is bound by very different factors. While pharmacologic interventions are limited by temporal dimensions (phase of care) and goal of treatment, non-pharmacologic interventions are more complex. Device interventions have several parameters that need to be set by the study team (e.g., in the context of transcranial ultrasound: site of stimulation, pulse repetition frequency, duty cycle, intensity of each pulsation; [23]). However, at this stage in the progress of the field, the study of the relevance and relative efficacy of different parameters and sets of parameterizations is typically itself the objective of empirical investigations. A similar concern applies to behavioral interventions (e.g., in the context of sensory stimulation: emotional valence, personally relevant).

The issues above thus suggest that, while other CDEs are likely to be of use in all phases of research, from early exploratory to more definitive confirmatory studies, treatment CDEs may be of greatest use during the mid-phase of a program of research. At the early stages of research, when a novel intervention is first being proposed, standardization is not feasible and there is insufficient data to support a new CDE. At the late stages of research, when definitive efficacy studies have identified the active ingredients of a treatment and most effective dose, a CDE could finally be developed, however adoption would already be expected as these parameters are widely accepted. At this stage, perhaps, CDEs could remain relevant in the context of meta-analytic and comparative (e.g., non-inferiority) studies. In the mid-phase of development of an intervention, however, there are likely to be multiple investigators studying an overlapping class of treatments in varied ways. At this time point, CDEs can help systematize the research approaches and ensure that all investigators measure the same “potential” active ingredients in order to allow a more efficient meta-analytic path towards consensus. For these reasons, as this WG has done, CDEs for

treatment research cannot be selected on the basis of “psychometric rigor” (since this would imply that the efficacy research has been completed) but rather on the need to bring systematization to a meaningful volume of treatment research. This also suggests that the landscape of DoC intervention research should be revisited periodically for new critical masses of treatment research requiring new CDEs. While there is substantial consensus on CDEs for pharmacologic treatment, expert opinion was used in the current effort to identify behavioral and device treatments with sufficient critical mass and variation to warrant CDEs. In the future, it would be useful to develop formal criteria relating to the volume of research in a given treatment area and the degree of variation in its reporting, for identifying the need for new CDEs.

Finally, it is important to note that most of the extant literature addressing interventions in DoC focuses on adults. In pediatric DoC, the use of pharmacological interventions has been growing over the past few years. Nonetheless, dosage is poorly documented and is highly variable, often weight-based, and prescription hesitancy is observed, especially in patients of preschool age or younger [24]. Only case series are available to appraise the association of Amantadine with timing of awakening; and there is insufficient data published on Zolpidem to assess its utility in pediatric DoC [24]. Beyond these two drugs, for all other pharmacological interventions there only exist, at best, one single case report each. Behavioral interventions have been applied in children, mostly consisting of multisensory stimulation protocols, with or without assistive technology. Early patients’ mobilization and physiotherapy are also applied, but constraints may exist in the use of robotic assistive devices, due to the need of hardware downsizing, and forces and torques reduction [11]. It is reasonable to apply the CDEs developed on the basis of work in adult patients to pediatric populations, however, our WG recommends that each research team evaluate applicability on a case-by-case basis.

Conclusions

The CDEs proposed by this WG are aimed at supporting the development of novel restorative interventions for patients with a DoC. These CDEs should form the initial basis for the systematization of a rapidly growing investigational effort. As the field matures, and some of the difficulties discussed above find resolutions, we expect the CDEs to also develop, in continued support of consistency in data capturing and recording across studies as well as to facilitate comparison and aggregation of results across studies.

References

1. Lippi AI, Cain J, Spindler LRB, Gorska UJ, Toker D, Hudson AE, et al. Mechanisms Underlying Disorders of Consciousness: Bridging Gaps to Move Toward an Integrated Translational Science. *Neurocrit Care*. 2021;35(Suppl 1):37-54.
2. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Comprehensive Systematic Review Update Summary: Disorders of Consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Arch Phys Med Rehabil*. 2018;99(9):1710-9.
3. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Practice Guideline Update Recommendations Summary: Disorders of Consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. *Arch Phys Med Rehabil*. 2018;99(9):1699-709.
4. Kondziella D, Bender A, Diserens K, van Erp W, Estraneo A, Formisano R, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741-56.
5. Royal College of Physicians. Prolonged Disorders of consciousness following sudden onset brain injury: national clinical guidelines. London: RCP. 2020.

6. Edlow BL, Sanz LRD, Polizzotto L, Pouratian N, Rolston JD, Snider SB, et al. Therapies to Restore Consciousness in Patients with Severe Brain Injuries: A Gap Analysis and Future Directions. *Neurocrit Care*. 2021;35(Suppl 1):68-85.
7. Schnakers C, Monti MM. Disorders of consciousness after severe brain injury: therapeutic options. *Curr Opin Neurol*. 2017;30(6):573-9.
8. Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O. Therapeutic interventions in patients with prolonged disorders of consciousness. *Lancet Neurol*. 2019;18(6):600-14.
9. Claassen J, Akbari Y, Alexander S, Bader MK, Bell K, Bleck TP, et al. Proceedings of the First Curing Coma Campaign NIH Symposium: Challenging the Future of Research for Coma and Disorders of Consciousness. *Neurocrit Care*. 2021;35(Suppl 1):4-23.
10. Mainali S, Aiyagari V, Alexander S, Bodien Y, Boerwinkle V, Boly M, et al. Proceedings of the Second Curing Coma Campaign NIH Symposium: Challenging the Future of Research for Coma and Disorders of Consciousness. *Neurocrit Care*. 2022;37(1):326-50.
11. Irzan H, Pozzi M, Chikhladze N, Cebanu S, Tadevosyan A, Calcii C, et al. Emerging Treatments for Disorders of Consciousness in Paediatric Age. *Brain Sci*. 2022;12(2).
12. Olson DM, Hemphill JC, 3rd, Curing Coma C, its Executive C. The Curing Coma Campaign: Challenging the Paradigm for Disorders of Consciousness. *Neurocrit Care*. 2021;35(Suppl 1):1-3.
13. Esterlitz J, Ala'i S, Feldman R, Joseph K, Sheikh M, Moy CS, et al. A common data language for clinical research studies: five (5) new disease recommendations from the national institute of neurological disorders and stroke, national institutes of health common data elements project. *Trials*. 2017;18.

14. Grinnon ST, Miller K, Marler JR, Lu Y, Stout A, Odenkirchen J, et al. National Institute of Neurological Disorders and Stroke Common Data Element Project - approach and methods. *Clin Trials*. 2012;9(3):322-9.
15. Odenkirchen J, Kaufmann P, Hunegs L, Stout A. National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Common Data Element (CDE) Project: Using the NINDS CDEs in Research Projects. *Neurotherapeutics*. 2012;9(3):675.
16. Wong GKC, Daly JJ, Rhoney DH, Broderick J, Ogilvy C, Roos YB, et al. Common Data Elements for Unruptured Intracranial Aneurysm and Subarachnoid Hemorrhage Clinical Research: Recommendations from the Working Group on Long-Term Therapies. *Neurocrit Care*. 2019;30(Suppl 1):79-86.
17. de Oliveira Manoel AL, van der Jagt M, Amin-Hanjani S, Bambakidis NC, Brophy GM, Bulsara K, et al. Common Data Elements for Unruptured Intracranial Aneurysms and Aneurysmal Subarachnoid Hemorrhage: Recommendations from the Working Group on Hospital Course and Acute Therapies-Proposal of a Multidisciplinary Research Group. *Neurocrit Care*. 2019;30(Suppl 1):36-45.
18. Provencio JJ, Hemphill JC, Claassen J, Edlow BL, Helbok R, Vespa PM, et al. The Curing Coma Campaign: Framing Initial Scientific Challenges-Proceedings of the First Curing Coma Campaign Scientific Advisory Council Meeting. *Neurocrit Care*. 2020;33(1):1-12.
19. Juni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ*. 2001;323(7303):42-6.
20. Balk EM, Bonis PA, Moskowitz H, Schmid CH, Ioannidis JP, Wang C, et al. Correlation of quality measures with estimates of treatment effect in meta-analyses of randomized controlled trials. *JAMA*. 2002;287(22):2973-82.

21. Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can J Surg.* 2010;53(5):345-8.
22. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273(5):408-12.
23. Spivak NM, Sanguinetti JL, Monti MM. Focusing in on the Future of Focused Ultrasound as a Translational Tool. *Brain Sci.* 2022;12(2).
24. Molteni E, Canas LDS, Briand MM, Estraneo A, Font CC, Formisano R, et al. Scoping Review on the Diagnosis, Prognosis, and Treatment of Pediatric Disorders of Consciousness. *Neurology.* 2023;101(6):e581-e93.

Figures legend

Figure 1. *Yearly number of publications, between 1969 and 2022, assessing potential interventions for DoC patients.* Data obtained from PubMed search (with the following search term: (disorders of consciousness, coma, vegetative state, minimally conscious state) AND (Therapy/Broad[filter])), integrated with all relevant, non-duplicate, references from recent expert reviews [6-8].