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Ethics Along the Continuum of Research Involving Persons with Disorders of Consciousness

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Abstract

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Interest in disorders of consciousness (DoC) has grown substantially over the past decade and has illuminated the importance of improving understanding of DoC biology; care needs (use of monitoring, performance of interventions, and provision of emotional support); treatment options to promote recovery; and outcome prediction. Exploration of these topics requires awareness of numerous ethics considerations related to rights and resources. The Curing Coma Campaign Ethics Working Group used its expertise in neurocritical care, neuropalliative care, neuroethics, neuroscience, philosophy, and research to formulate an informal review of ethics considerations along the continuum of research involving persons with DoC related to the following: (1) study design; (2) comparison of risks versus benefits; (3) selection of inclusion and exclusion criteria; (4) screening, recruitment, and enrollment; (5) consent; (6) data protection; (7) disclosure of results to surrogates and/or legally authorized representatives; (8) translation of research into practice; (9) identification and management of conflicts of interest; (10) equity and resource availability; and (11) inclusion of minors with DoC in research. Awareness of these ethics considerations when planning and performing research involving persons with DoC will ensure that the participant rights are respected while maximizing the impact and meaningfulness of the research, interpretation of outcomes, and communication of results.

Keywords

Coma; Research; Ethics; Disorders of consciousness

Introduction

Research involving persons with disorders of consciousness (DoC) has grown substantially over the past decade. The Neurocritical Care Society created the Curing Coma Campaign (CCC) to facilitate a collaborative, coordinated, multidisciplinary, international approach to this endeavor. The CCC elucidated priorities for research about DoC at the 2021 National Institutes of Health Symposium [1]. These included the need for an enhanced understanding of DoC biology; care needs (use of monitoring, performance of interventions, and provision of communication and emotional support to surrogates and/or legally authorized representatives and families, hereafter referred to as surrogates); treatment options to promote recovery; and neuroprognostication (Table 1).

Research involving persons with DoC requires recognition of ethics considerations. A critical evaluation of ethics considerations in research involving persons with DoC previously explored the topics of autonomy and respect for persons, balance of risks versus benefits, disclosure of results, and justice and equity [2]. In this article, members of the CCC Ethics Working Group identify ethics considerations along the continuum of research involving persons with DoC from study conception and design to translation of research into practice. The process of identification of ethics considerations was based on informal review of the literature and personal expertise in neurocritical care, neuropalliative care, neuroethics, neuroscience, philosophy, and research. The ethics considerations described in this article focus on the following components of the continuum of research: (1) study design; (2) comparison of risks versus benefits; (3) selection of inclusion and exclusion criteria; (4) screening, recruitment, and enrollment; (5) consent; (6) data protection; (7)

disclosure of results to surrogates; (8) translation of research into practice; (9) identification and management of conflicts of interest (COI); (10) equity and resource availability; and (11) inclusion of minors with DoC in research (Table 2).

Study Design

The design of a study that involves persons with DoC requires consideration of the needs of individual persons with DoC and their surrogates; the clinical team involved in their care; and the broader community of persons with, and who recovered from, DoC and their surrogates.

Safeguarding the ethical integrity of research involving persons with DoC begins with the formulation of a study design that includes (1) identification of the relevant background and aims; (2) establishment of methodology, procedures, and operational framework to test a research hypothesis, generate evidence, and report results; and (3) selection of relevant, person-centered outcomes and end points [3, 4, 5, 6]. Study designs may be translational, observational, or interventional and may aim to generate evidence pertaining to DoC biology, care, recovery, or neuroprognostication [1, 7, 8]. The most appropriate study design depends on the nature and scope of the research question, feasibility, safety, condition prevalence, preliminary data, funding, and regulatory constraints. Study design and execution should be guided by principles of respect for persons, beneficence, nonmaleficence, and justice, which have been codified in the Declaration of Helsinki by the World Medical Association, the International Ethical Guidelines for Health-Related Research Involving Humans by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, the Convention on Human Rights and Biomedicine by the Council of Europe, the Belmont Report by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the United States, and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans in Canada [9, 10, 11, 12, 13].

The general ethos and principles governing responsible study design are amplified in the context of research involving persons with DoC because these individuals meet the Declaration of Helsinki's definition of "vulnerable persons"; persons with DoC "have an increased likelihood of being wronged or of incurring additional harm" [9]. Persons with DoC lack decision-making capacity and cannot reliably report on their condition, so they are at heightened risk for overuse and underuse of life-sustaining treatment and unintended harms or exploitation [2, 14, 15, 16, 17]. Protecting the welfare and rights of vulnerable persons while fostering scientific and clinical goals necessitates careful and preemptive consideration of appropriate study design with minimization of risks and supplementation of first-person consent with surrogate consent through use of substituted judgment and assessment of best interests, or use of alternative consent models, as described below [8, 9, 18, 19]. There should be attention to equipoise and the avoidance of a therapeutic misconception when using diagnostic methods or treatments that are still under evaluation [20]. It is ideal to continue life-sustaining treatment throughout the duration of a study involving persons with DoC to mitigate risk of bias, but study design must account for the potential for goals-of-care to change during the course of a study. The decision to withdraw

life-sustaining treatment from a person with DoC enrolled in a study could be considered an outcome and/or end point or require withdrawal of consent or termination of participation.

In light of the challenges of including persons with DoC in research, unique study design adaptations should be considered to safeguard adherence to ethical norms (Table 3) [21, 22, 23, 24, 25, 26, 27].

Risks and Benefits

Maximizing benefits and minimizing risks of participation in research is pivotal to operationalizing the principles of beneficence and nonmaleficence, oriented toward a holistic concept of individual wellbeing. Risks and benefits to persons with DoC for participation in research addressing some of the priorities identified at the Second CCC National Institutes of Health Symposium “Challenging the Future of Research for Coma and Disorders of Consciousness” are analyzed in Table 1 [1]. The ethical risk–benefit assessment is contingent on study focus and design. If there is neither therapeutic intent nor direct benefits of participation in a study for a given person with DoC (as is the case with many studies on the biology of DoC and neuroprognostication studies that do not involve disclosure of results to surrogates or clinicians), the risks and burdens have to remain minimal, consistent with the widely respected consensus in research ethics [11, 28]. However, these studies could benefit future persons with DoC and may even indirectly benefit research participants themselves in the future.

Regardless of whether persons with DoC participate in research, it is important to recognize that neuroprognostication and outcome can be altered by nihilism and the self-fulfilling prophecy that nothing can or should be done for this population. Participation in research may diminish this risk, but it could also lead to a paradoxical increase in uncertainty, raising more questions than answers, or promotion of unrealistic hope, inappropriate delay of withholding or withdrawing life-sustaining treatment, or escalation of commitment.

In interventional research involving persons with DoC, the epistemological problem arises that, because of a lack of functional communication, risks and benefits have to be identified and evaluated by others on behalf of potential participants based on observed behavior, indicators from diagnostic investigations, and societally accepted objective criteria for wellbeing as well as the beliefs of surrogates based on the knowledge of the participant before injury [29]. However, in contrast with other conditions of impaired communication, such as aphasia or locked-in syndrome, for example, for a person with DoC, it is necessary to ask if wellbeing is contingent on consciousness, and weigh the impact of the potential for recovery of consciousness or identification of covert consciousness [30]. If wellbeing is understood to be an experiential state of positive emotions, thoughts, and attitudes, and consciousness is regarded as a necessary condition for wellbeing, then the risk–benefit assessment for *irreversibly unconscious* persons to participate in research would be net neutral, although there could be potential benefits to other persons with DoC. However, it is not yet possible to know with certainty *which* persons with DoC have irreversible loss of consciousness, which have covert consciousness, and which have the potential for recovery; that is the point of much of the research involving persons with DoC. As such, the risk–

benefit assessment should be study specific, taking into consideration additional individual criteria such as life expectancy, comorbid medical conditions, suffering, experiential and critical interests, and social participation [2]. The potential risks and benefits of augmented awareness differ for each person with DoC, and although recovery is generally considered favorable, augmentation of awareness is not clearly always in the best interest of a person with DoC; it could lead to both psychological and somatic pain and distress related to changes in cognition and functional status, as well other systemic illness or injuries. There are no certainties about the state of wellbeing present with an increase of awareness (the paradox of recovery, a.k.a. the self-awareness paradox) [31, 32]. Lastly, it is necessary to recognize that there is variability in cultural and religious perspectives and values pertaining to the role of consciousness in the contours of personhood and in what makes life worth living [33, 34].

Selection of Inclusion and Exclusion Criteria

Selection of inclusion and exclusion criteria for participants for DoC research requires consideration of DoC pathology, Acuity of injury (duration of time between the injury that led to development of DoC and research enrollment), severity of injury (as determined via a consistent approach to neurobehavioral ± emerging neuroimaging and electrophysiology evaluation), confounding conditions that could impact results, and goals of care (Table 4). Inclusion and exclusion criteria should address each of these characteristics rather than relying on admission trends during the study period. Overall, it is necessary to balance the desire for power and generalizability of research findings with the need for a granular understanding of variability based on DoC pathology, acuity of injury, and severity of injury. However, it is important to recognize that even among a cohort of persons with DoC with the same pathological condition, acuity of injury, and severity of injury, there are differences in lesion location, distribution, and size, which can impact the results of research on DoC biology, care, recovery, or neuroprognostication.

Research involving persons with DoC due to the most common pathologies (stroke, traumatic brain injury, and hypoxic-ischemic brain injury) has the potential to be robust and impactful [35]. However, it is imperative for research involving persons with DoC to include participants with multifactorial or less common causes of DoC, including toxic-metabolic disturbances, neuroinfectious diseases, autoimmune encephalitis, status epilepticus, and other conditions [36, 37]. Targeted selection of participants with a specific condition in an individual study enhances the potential impact of results, but studies that include (and compare) persons with DoC due to all causes are also needed.

Consideration of the acuity of injury when formulating inclusion and exclusion criteria necessitates recognition that inclusion of participants with a specific duration of time since development of DoC and research enrollment improves homogeneity of a study cohort, but it is also beneficial to include (and compare) persons with varying durations of DoC. When specifying a duration of time since development of DoC, it is more precise to use a given timeframe in days/weeks/months rather than relying on vague terms like “acute,” “subacute,” or “chronic” or focusing on time since admission to a given clinical setting (e.g., a rehabilitation center). This is important, particularly in interventional studies, because the

potential for spontaneous neurobehavioral fluctuations and recovery could interfere with interpretation of results.

In addition to addressing DoC pathology and acuity of injury, inclusion and exclusion criteria should incorporate severity of injury. A consistent approach should be employed to assess severity of injury based on neurobehavioral ± emerging neuroimaging and electrophysiology evaluation. When using neurobehavioral evaluation to determine eligibility, it is ideal to use a detailed metric, such as the Coma Recovery Scale-Revised, rather than a more superficial assessment such as the Glasgow Coma Scale [38, 39].

Inclusion and exclusion criteria should also address reversible confounding conditions that could impact results. Some examples of conditions to consider include the effects of drugs, metabolic derangements, or hemodynamic status.

Finally, goals of care should be considered in the selection of inclusion and exclusion criteria. Persons with DoC should not be included in research if participation would, or may, conflict with their wishes and values.

Screening, Recruitment, and Enrollment

After identification of the inclusion and exclusion criteria, it is necessary to screen persons with DoC for potential recruitment and enrollment. The principles of justice and equity would ideally allow all persons with DoC to be screened for inclusion in research, but geographic, resource, and socioeconomic constraints unfortunately prevent some persons with DoC from having access to opportunities to participate in research [40]. During screening and recruitment, it is important to consider ways to optimize the diversity of persons with DoC enrolled in research studies, despite existing constraints, without compromising study efficiency and power.

During enrollment, surrogates may need to provide demographic or subjective information on behalf of a person with DoC, such as their medical, neurological, and mental health history and their prior wishes (if any) about quality of life. Caution is needed when interpreting this information and comparing it to data provided by conscious individuals who are capable of communicating responses themselves [41, 42]. The enrollment process requires surrogates to be educated about the research and given the opportunity to decide freely (voluntarily) to consent to allow a person with DoC to participate, as discussed in detail below [43]. Although the focus of recruitment and enrollment should be on the interests of the person with DoC, surrogates also need support during recruitment, enrollment, and the entire course of the research study.

Consent

Voluntary informed consent, which addresses the risks, benefits, and alternatives to participation in a research study, is the anchor to recruitment and enrollment for most empirical human study participant research. It facilitates ethical and legal legitimacy and upholds the principle of respect for persons as reflected in autonomous decision making [11, 44]. The foundational criteria for decision-making capacity are the ability to understand,

appreciate, reason, and communicate a choice. Because persons with DoC often lack functional communication, and thus decision-making capacity, surrogates are typically asked to consent to participation in research on their behalf [45, 46]. National/regional regulations dictate a hierarchy for selection of a designated surrogate decision-maker for persons with DoC [9]. Surrogates must use substituted judgment and consider the preferences and best interests of the person with DoC to decide whether to consent on their behalf. Although the person with DoC is not autonomously consenting themselves, this process still emphasizes respect for persons, particularly when the object of the research is to identify covert consciousness or restore the ability to participate in decision making [47, 48, 49]. Conflict between surrogates about participation in research should be escalated to site (and central, if present) research regulatory and/or legal personnel and the principal investigator.

Unfortunately, persons with DoC do not always have surrogates to make decisions on their behalf, which could preclude them from participating in research that requires surrogate consent. Additionally, decision making about participation in research could be burdensome for surrogates. Because of this, use of alternative consent models for research involving persons with DoC warrants consideration. These include a “mosaic model” of consensus consent by the participant, as able, their surrogate, clinician, investigator, and a lay participant advocate; deferred consent with retrospective debriefing; and community consultation based on ascertainment of the values of recovered persons with DoC and other key stakeholders [2, 21]. Under select circumstances (which vary by country), it may be feasible to waive consent [50]. In the future, there may be an opportunity for persons with decision-making capacity to complete advance research directives that would apply if they lost decisionmaking capacity about their willingness to participate in therapeutic research, nontherapeutic research, and research with more than minimal risks and burdens [51, 52].

Over the course of a study involving persons with DoC, it is possible that some level of decision-making capacity and ability to communicate could develop spontaneously or via therapeutic intervention [49, 53]. Covert consciousness may also be identified, and communication can be enhanced, such as through a brain-computer interface. In these circumstances, it may be possible to ultimately facilitate appropriate evaluation of capacity to provide informed assent or consent to ongoing participation in the study, and maybe even, at least hypothetically, obtain informed consent through speech or language-generating devices or even neuroimaging [54, 55, 56]. Of course, as evaluation of capacity can be difficult even in persons who are awake and verbal, this would be extra challenging in the setting of DoC. Further, factors other than cognition can impact decision-making capacity such that a mental health assessment would also need to be incorporated in the evaluation [56].

Finally, even after consent is obtained, surrogates (or persons with DoC themselves, if they regain decisionmaking capacity) have the right to withdraw their consent at any point, as do all research participants who can consent.

Data Protection

Like other neuropsychiatric research, research involving persons with DoC requires collection of brain data from neurobehavioral evaluation, high-resolution neuroimaging, and electrophysiology studies. With the rapid advent and evolution of implantable neurotechnologies, including intracortical microarrays, deep brain stimulation, and other neural interfaces, data sets are likely to ultimately include increasingly rich information about individual brains at an unprecedented scale and resolution [57, 58, 59, 60, 61, 62, 63, 64, 65, 66]. Data collection, storage, and sharing must be done responsibly to protect autonomy, privacy, and dignity, particularly because persons with DoC are generally unaware that they are enrolled in a research study. The consent form should clearly indicate the way in which data are being protected and the potential ways in which data could be used, as information about the brain could be applicable to spheres outside of research and clinical care for persons with DoC such as criminal justice, finance, and politics [56, 67]. Because of this, some consider human brain data to be more sensitive than other types of data, as it "contains information about the organ of the mind and thus, to a certain extent, also about the mind itself," [67] which therefore may pertain to the core of the participant's identity [56].

Although in most cases persons with DoC, or their surrogates, likely would not be interested in tracking usage of their data, data stewardship systems could be implemented to allow them to monitor data usage, optimizing trust in the protection and responsible use of data. Efforts to build protected repositories to securely archive data are underway, along with development of innovative federated data access methods [68, 69, 70, 71, 72, 73, 74, 75]. However, approaches to brain data governance and standardization remain nascent. Clinicians, researchers, and institutional review boards (IRBs) need to play a growing role in informing these approaches and crafting ethical standards for data protection and management. Collaboration among experts in ethics, data security, neuroscience, and information technology will be beneficial to reach these goals [56].

Disclosure of Results to Surrogates

Although the disclosure of clinical findings to a patient or their surrogate is inherent to routine clinical care, this is not straightforward in a research relationship. The United States Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections recommends a presumption in favor of offering research participants, or their surrogates, the option to be informed about individual research results [76]. The National Academies of Sciences, Engineering, and Medicine also supports disclosure of individual research results when they are clinically actionable, valid, and reliable [77]. However, in the context of research involving persons with DoC, disclosure of findings that may impact understanding of neuroprognostication can potentially lead to the self-fulfilling prophecy by influencing treatment decisions, so it may be problematic to disclose results to surrogates [78]. Based on the above considerations and the values of reciprocity and transparency, decision making about disclosure of both results and incidental findings should occur during study design with input from ethicists and the IRB.

There are no established best practices for disclosure of evaluations for covert consciousness to surrogates. However, it has been suggested that the process should mirror disclosure of results of evaluations for Alzheimer disease: predisclosure education to temper expectations; assessment of willingness to learn results and personal implications of positive or negative findings; use of evidence-based language; and translation of technical details [79]. It is important to recognize and explain to surrogates that although lack of identification of covert consciousness can be disappointing, this does not rule out subsequent recovery, the presence of covert consciousness undetected by the methodology employed, or the willingness of a participant to cooperate with a volitional task [80, 81]. Negative findings must be interpreted with great caution in the context of studies aimed at detecting covert consciousness where substantial false negative rates, even among healthy participants, can preclude distinction between true negative and false negative results [16, 82].

On the other hand, detection of covert consciousness can lead to heightened expectations and potential moral distress due to the absence of an efficient means to facilitate consistent communication or provide further therapeutic benefit. These concerns may not be actualized in reality, though, as qualitative interviews of surrogates of persons with DoC demonstrate that they remained optimistic about the potential for recovery regardless of the results of evaluations for covert consciousness [29]. The suggested explanation for this is that while clinicians rely on concrete measurable signs of awareness to evaluate consciousness, surrogates focus on their perceived relationship with a person with DoC when assessing their current state and expectations for the future [83].

Translation of Research into Practice

Translation of research involving persons with DoC into practice requires validation of findings; demonstration of benefit to persons with DoC and/or the networks of people who care for them; and buy-in from clinicians, hospital administrators, regulatory bodies, and insurance companies. Semistructured interviews of neuroimaging researchers, ethicists, lawyers, and clinicians identified concerns about translation of research involving persons with DoC into practice related to reproducibility and consistency of the signals detected, not only within a single person but also across persons with different injuries, different hemodynamics, and different medical histories [84, 85]. Validation of research findings through large, randomized-controlled studies is essential prior to translation to clinical practice as a vast amount of data from persons with DoC is needed to optimize understanding of what the data mean, how it can be optimally used, and the ideal time to use it relative to brain injury.

In addition to the need for trust in the validity of data from research involving persons with DoC prior to translation of research into practice, there is a need for evidence that the data can benefit persons with DoC and/or the networks of people who care for them. Examples of these benefits could include identification of covert consciousness, recovery of consciousness, facilitation of communication, development of ability to express interests and preferences, improvement in quality-of-life, clarification of neuroprognostication, or disposition to a rehabilitation facility. Clinicians must be able to clearly explain to surrogates

what the research results showed and the benefits and risks of incorporating this data, intervention, or procedure into clinical practice.

Translation of research into practice can be a slow process and may be subject to resource access, reimbursement limitations, or other barriers. For example, although the American and European Academies of Neurology recommend use of advanced neuroimaging and neurophysiology tools in the clinical diagnosis and prognosis of some persons with DoC, access and use are inconsistent [38, 86, 87]. This may create moral distress for both clinicians and surrogates. Efforts to bridge these gaps are needed. One potential means to accomplish this is through partnership with disability advocacy groups and dissemination of "relevant, understandable actionable recovery science findings to the general public" [88].

Conflicts of interest

Researchers may have a variety of relationships with companies that develop medications and devices related to the care of, or research involving persons with DoC, which could lead to COI (a conflict between their private interests and official responsibilities). Because the population of persons with DoC is rather small and the number of researchers as well as companies that produce specific tools for this population are also limited, the likelihood for COI may be higher than in other areas of medicine. There are many forms of COI including personal or surrogate financial compensation, stock ownership, research support, institutional financial support, gifts, or promise of personal success. Although data on COI for research involving persons with DoC are not available, industry-related COI are prevalent among authors based in the United States in high-impact neurology journals [89].

These COI can bias researchers in study design, participant selection, recruitment and enrollment, consent, formulation of results, dissemination of findings, and translation of research into practice. In fact, both the rhetoric to describe results and the conclusions themselves of industry and pharmaceutical company funded neurology research may differ from nonfunded research [90]. This cannot be addressed through dissociation between researchers and industry and pharmaceutical companies because this would severely limit discovery [91]. Rather, all members of the team performing research involving persons with DoC must adhere to the guidance written by relevant professional organizations (e.g., the American Academy of Neurology and American Academy of Neurological Surgery) on management of COI [92, 93]. Researchers must self-identify and disclose all forms of COI to funding organizations, IRBs, persons with DoC and/or their surrogates, and peer review journals [94]. Further, they are responsible for determining ways to prevent, or at least mitigate, the effect of COI on research [95]. COI may be mitigated via self-recusal or required removal of individuals with identified COI from certain activities or decision-making tasks or staged involvement by investigators with step-back roles as the work evolves [96]. A more extreme way to address COI is through restriction, or prohibition, of participation in a research study whereby participation in the study requires termination of any conflicting financial relationships or roles.

Equity and Resource Availability

Persons with DoC should ideally all have opportunities to participate in research on novel technology and treatments that offer the hope of improving outcomes. Unfortunately, research involving persons with DoC is largely restricted to resource-rich settings and specialized referral centers, precluding broad participation and leading to selection bias [97]. This is particularly problematic as, compared with high-income countries, low-income and middle-income countries have a higher incidence of acute traumatic brain injury, yet these countries have shortages of resources, expertise, and postacute care services [98]. As much as possible, the importance of equity and justice should be considered when developing study design and participant selection criteria for clinical trials involving persons with DoC, but this must be facilitated without compromising ethical or data integrity of the research [1]. To successfully do this, barriers to research involving persons with DoC in resource-limited settings must be addressed. These include resource availability, expertise, information technology, time constraints, funding, challenges obtaining ethical approval, and early withdrawal of life-sustaining treatment [88, 99]. Research on novel technologies for persons with DoC must also consider cost, sustainability, ability to scale, and ease of implementation. The impact of language barriers on both participation in and benefit from research also must be considered, and a multilingual approach should be employed. Finally, guidelines that guard against overuse of novel technologies for persons with DoC and subsequent drain on the health care economy need to be considered to maintain equity and justice at the time of translation of research into practice.

Inclusion of Minors with DoC in Research

Results from studies involving adults with DoC cannot be extrapolated to minors due to differences in premorbid neurodevelopment, cognitive and functional status, medication metabolism, neuroplasticity, and recovery trajectories. Investigation into DoC biology, care needs, treatment options to promote recovery, and neuroprognostication for minors with DoC is desperately needed, but there are unique ethics considerations associated with inclusion of minors with DoC in research [98, 100, 101].

First, in developing the study design, it is necessary to recognize that there is a lack of standardized diagnostic assessment tools with adequate sensitivity and specificity to evaluate minors with DoC. For example, a formalized designation for the minimally conscious state does not exist in children [101]. Use of existing diagnostic categories to assess minors risks inappropriate conclusions about the consciousness state of an individual child and may overestimate or underestimate the prevalence of DoC. Many studies report either survival or favorable versus unfavorable outcomes based on gross functional neurologic scales [102]. Distinguishing between different levels of consciousness requires evaluation for alertness, awareness, and responsiveness in developmentally appropriate ways, but this can be complicated. Infants and younger minors may not have developed sufficient skills for visual tracking, purposeful motor movements, or command following before their injury. Use of assessment tools that are not based on behavior alone could improve the accuracy of diagnosis of DoC in minors.

Similarly, evaluation of recovery from DoC is complicated by neuroplasticity and the variability of developmental trajectories in minors. Timing of recovery can differ between adults and minors and between minors of different ages. Further, recovery from brain injury for minors with DoC is unique in that it requires not just return to premorbid baseline, but continuation of cognitive and social development. Neuroprognostication in this population must be considered separate from that for adults [1]. Additional data on neuroimaging, neurophysiology, and biomarker correlation with recovery in minors with DoC are needed [98, 103].

Selection of inclusion and exclusion criteria for research involving minors with DoC requires awareness that the causes of brain injuries that result in DoC differ between minors and adults. In addition to traumatic and hypoxic-ischemic brain injuries, minors may have perinatal insults or chromosomal, metabolic, degenerative, or other congenital disorders [104]. These insults can coexist; for example, a person with an underlying chromosomal disorder can suffer a cardiac arrest, making neuroprognostication more challenging than in the setting of hypoxic-ischemic brain injury in a previously healthy person. Research involving minors with DoC must assess for discrete phenotypic features and recovery trajectories.

Finally, although the recruitment, enrollment, and consent process for participation in research is similar for both minors and adults with DoC, given neither have the capacity to consent for themselves, this can be especially complicated for minors if there is concern for child abuse [105].

Conclusions

Persons with DoC, their surrogates, clinicians, and neuroscience researchers can all benefit from the coordinated efforts of the CCC to (1) expand our understanding of the biology of DoC; (2) ascertain the best interventions to address the care needs and enhance person-centered care of persons with DoC and their surrogates; and (3) develop techniques to improve identification of covert consciousness, facilitate communication, promote recovery of consciousness, and provide more accurate neuroprognostication [1]. Central to this progress is adherence to the ethics considerations reviewed here when planning and performing research involving persons with DoC. Awareness of the ethical issues attendant to this critical research enterprise will help ensure that participant rights are respected while maximizing the possibility for discovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Examples of potential benefits and risks to participants in research involving persons with disorders of consciousness (DoC)

Study focus [1]	Potential benefits to participants in research involving persons with DoC (dependent on study design)	Potential risks to participants in research involving persons with DoC (dependent on study design)[a]
DoC biology		
Differentiation of clinical subtypes of DoC based on presence or absence of responsiveness, environmental connectedness, and Interaction	(1) Evidence of covert consciousness could impact neuroprognostication, Illuminate capacities for awareness and interaction that evade bedside detection, be beneficial to goals of care and discharge decision making (2) Evidence of covert consciousness could facilitate communication	(1) Minor risk of discomfort with neurobehavioral evaluation (2) Minor risks associated with neurolmaglng[b] and neurophysiology[c] studies (3) Potential for erroneous differentiation, which could unduly affect decision making about goals of care and treatment
Identification of connections between structural brain injury and functional consequences	(1) Improved understanding ofthe Impact of injury and etiology of symptoms/funotional impairment (2) Better informed prognosis and potential interventions for treatment	Minor risks associated with neuroimaging[b] and neurophysiology[c] studies
Development of understanding ofthe relationship between the microenvironment ofthe brain (genetic, cellular, molecular, neurotransmitter, microcircuits) and function	No direct benefit	Methodology-dependent (minor risks associated with neuroimaging[b] and neurophysiology[c] studies, bloodwork, or cerebrospinal fluid collection)
Care of persons with DoC		
Establishment of global incidence, prevalence, and etiology of DoC and the impact of current practices on outcome	No direct benefit	No direct risk
Identification of variations in care of persons with DoC	No direct benefit	No direct risk
Assessment of resource availability and cost of care for persons with DoC	No direct benefit	No direct risks
Establishment of best practices for assessment, monitoring, treatment, and care transitions	(1) Improvement In care (2) Reduction In symptom burden	No direct risks
Treatment options to promote recovery from DoC		
Development of Interventions (chemical, electromagnetic, mechanical, regenerative, sensory) that promote recovery of consciousness via repair or retraining of brain circuits	(1) Recovery of or Improvement in consciousness state (2) Restoration of ability to communicate preferences (3) Potentially improved wellbeing	(1) Risks inherent to the specific Intervention (2) Recovery of consciousness could lead to suffering if distressing symptoms are inadequately managed or if care approach is discordant with the person's goals
Development and Implementation of communication tools for persons with DoC	(1) Facilitation of communication (2) Improved quallty-of-llfe	(1) Risks inherent to the specific technology (2) Facilitation of communication could have adverse effects if output is unreliable
Neuroprognostication for persons with DoC		
Assessment of correlation between neurobehavioral evaluation and outcome	No direct benefit	(1) Minor risk of discomfort with neurobehavioral evaluation (2) Uncertainty (3) Inappropriate delay of withholding/withdrawing life-sustaining treatment or escalation of commitment
Assessment of correlation between neuroimaging findings and outcome	No direct benefit	(1) Minor risks associated with neuroimaging[b] (2) Uncertainty

Study focus [1]	Potential benefits to participants in research involving persons with DoC (dependent on study design)	Potential risks to participants in research involving persons with DoC (dependent on study design)[a]
		(3) Inappropriate delay of withholding/withdrawing life-sustaining treatment or escalation of commitment
Assessment of correlation between neurophysiology and outcome	No direct benefit	(1) Minor risks associated with neurophysiology[c] studies (2) Uncertainty (3) Inappropriate delay of wlthholdlng/wlthdrawlng life-sustaining treatment or escalation of commitment
Assessment of correlation between blomarkers and outcome	No direct benefit	(1) Minor risks associated with blood or cerebrospinal fluid collection (2) Uncertainty (3) Inappropriate delay of wlthholdlng/wlthdrawlng life-sustaining treatment or escalation of commitment
Development of effective communication strategies with decision making support	Improved goals-of-care discussions and discharge decision making	Inappropriate delay of wlthholdlng/wlthdrawlng life-sustaining treatment or escalation of commitment

[a]The potential for loss of privacy is a ubiquitous risk associated with human study participant research, but this is particularly notable in research involving persons with DoC given participants with covert consciousness have no control over the time or subject matter of any communication with them and the data obtained from research may be inherent to the core of the participant's identity

[b]Neuroimaging studies could lead to anxiety, claustrophobia, discomfort, aspiration, hemodynamic instability related to transport, allergic reaction or renal failure (if contrast is administered), radiation exposure, and adverse effects of sedatives/narcotics/paralytics (if administered)

[c]Neurophysiology studies could lead to discomfort, skin damage from leads, seizures (if stimulation is provided), and adverse effects of sedatives/narcotics/paralytics (if administered)

Table 2

Summary of ethics considerations along the continuum of research involving persons with disorders of consciousness (DoC)

Consideration	Key points
Study design	(1) Adhere to the principles of respect for persons, beneficence and justice (2) Be cognizant that persons with DoC are (a) unable to reliably report on their condition or independently consent to participation in research and (b) at heightened risk of overuse or underuse of life- sustaining treatment, unintended harms and exploitation (3) Adapt the study design to safeguard ethical participation (Table 3)
Comparison of risks vs. benefits	(1) Maximize benefits and minimize risks to individual persons with DoC (2) Weigh the impact of the potential for recovery of consciousness or identification of covert consciousness for individual persons with DoC (3) Consider life expectancy, comorbid medical conditions, suffering, experiential and critical interests, and social participation when evaluating the potential impact to individual persons with DoC of participation in research (4) Recognize the variability in cultural perspectives and specific values pertaining to the role of consciousness in the contours of personhood and what makes life worth living
Selection of inclusion and exclusion criteria	(1) Consider both generalizability of research findings and the potential impact of results when identifying inclusion/exclusion criteria (2) Take the following factors into account when identifying inclusion/exclusion criteria: (a) pathology,(b) severity of injury (as determined through a consistent approach to neurobehavioral evaluation), and (c) injury acuity (duration of time between the injury that led to development of a DoC and research enrollment in days/weeks/months)
Screening, recruitment, and enrollment	(1) Aim to optimize the diversity of persons with DoC enrolled in research studies (2) Recognize that the principles of justice and equity would ideally allow all persons with DoC to participate in research, but geographic, resource, and socioeconomic constraints prevent some persons with DoC from participation in research
Consent	(1) Recognize the special vulnerability of both persons with DoC and surrogates (2) Facilitate consent via surrogate use of substituted judgment (3) Consider alternatives to surrogate consent including consensus consent, deferred consent, community consultation, waiver of consent and use of advance research directives (4) Evaluate persons with DoC for acquisition of decision-making capacity and the ability to assent or consent to ongoing participation in research (5) Inform surrogates (and persons with DoC, if able) that they have the right to withdraw their consent at any point
Data protection	(1) Ensure responsible collection, storage, and sharing of brain data to protect autonomy and privacy (2) Use data stewardship systems to allow persons with DoC and their surrogates to track data usage
Disclosure of results to surrogates	(1) Formulate disclosure plans during study design with input from ethicists and the institutional review board (2) Educate surrogates and assess their willingness to learn results and the implications the results will have for them (3) Ensure surrogates understand that both negative and positive results should be interpreted with caution
Translation of research into practice	(1) Validate research findings through large randomized-controlled studies (2) Demonstrate benefit of data/interventions/procedures to persons with DoC and/or the networks of people who care for them (3) Obtain buy-in regarding the importance of translating research into practice from (a) clinicians, (b) hospital administrators, (c) regulatory bodies, and (d) insurance companies (4) Partner with disability advocacy groups to overcome barriers to translation of research into practice including resource access or reimbursement
Identification and management of COI	(1) Identify and disclose COI to sponsors, institutional review boards, surrogates, and journals (2) Mitigate COI through restriction of participation
Equity and resource availability	Consider the principles of equity and justice during study design and participant selection
Inclusion of minors with DoC in research	Recognize that minors with DoC have different causes for their brain injuries and should be assessed with dedicated tools distinct from adults

COI conflicts of interest

Table 3

Study design adaptations to safeguard ethical participation for persons with disorders of consciousness

Adaptation	Explanation
Use of a central institutional review board for multisite studies	Use of a central institutional review board for multisite studies ensures continuity in approach; minimizes startup delays, inefficiencies, and inconsistencies; and decreases confusion and complexity
Integration of mosaic decision making in study recruitment and enrollment	Assign a patient advocate to guide decision making in lieu of conventional surrogate decision making
Operationalization of informed consent as an ongoing, iterative process	While informed consent is initially obtained through a conventional surrogate decision-maker or mosaic decision making, participants are regularly evaluated for reemerging consciousness and agency involving decisional capacity over the course of the study
Implementation of adaptive designs	Incorporate outcome data into the study design to update treatment allocation probabilities to give participants a better chance of receiving a treatment that appears superior
Use of sequential stopping rules	Establish boundaries to determine circumstances under which recruitment will be terminated
Identification of poststudy obligations and follow-up	Provide a clear explanation of access to investigational agents poststudy and the management of and communication about study results

Table 4

Considerations for formulating inclusion and exclusion criteria for research involving persons with disorders of consciousness (DoC)

Consideration	Explanation
DoC pathology	Decide whether the study objective would best be achieved via inclusion of a broad range of pathologies (with the intent to make generalizations about all persons with DoC) or a single pathology/small number of pathologies (with the intent to produce more focused results and/or identify similarities/differences across a small number pathologies)
Acuity of injury	Decide whether the study objective would best be achieved via inclusion of a broad duration of DoC (with the intent to make generalizations about all persons with DoC and/or make comparisons based on duration of DoC) or a finite timeframe of DoC (specified in days/weeks/months with the intent to produce more focused results)
Severity of injury	Use a consistent approach to neurobehavioral ± emerging neuroimaging/electrophysiology evaluation (ideally incorporating a detailed assessment such as the Coma Recovery Scale-Revised)
Confounding conditions	Consider the potential impact of reversible confounding conditions such as drugs, metabolic derangements, or hemodynamic status on study results
Goals of care	Exclude persons with DoC whose wishes and values would conflict with participation in the study