Mapping outcomes for recovery of consciousness in studies from 1986 to 2020: a scoping review protocol

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ABSTRACT

Introduction Historically, heterogeneous outcome assessments have been used to measure recovery of consciousness in patients with disorders of consciousness (DoC) following traumatic brain injury (TBI), making it difficult to compare across studies. To date, however, there is no comprehensive review of clinical outcome assessments that are used in intervention studies of adults with DoC. The objective of this scoping review is to develop a comprehensive inventory of clinical outcome assessments for recovery of consciousness that have been used in clinical studies of adults with DoC following TBI.

Methods and analysis The methodological framework for this review is: (1) identify the research questions, (2) identify relevant studies, (3) select studies, (4) chart the data, (5) collate, summarise and report results and (6) consult stakeholders to drive knowledge translation. We will identify relevant studies by searching the following electronic bibliographic databases: PubMed, Scopus, EMBASE, PsycINFO and The Cochrane Library (including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Cochrane Methodology Register). Criteria for article inclusion are published in the English-language, peer-reviewed studies of interventions aimed at facilitating recovery of consciousness among adults (>18 years) with DoC following a severe TBI, published from January 1986 to December 2020. Articles meeting inclusion criteria at this stage will undergo a full text review. We will chart the data by applying the WHO International Classification of Functioning, Disability and Health framework to identify the content areas of clinical outcome assessments. To support knowledge translation efforts, we will involve clinicians and researchers experienced in TBI care throughout the project from conceptualisation of the study through dissemination of results.

Ethics and dissemination No ethical approval is required for this study as it is not determined to be human subjects research. Results will be presented at national conferences and published in peer-reviewed journals.

Trial registration number CRD42017058383.

INTRODUCTION

Rationale To date, there has been limited success in clinical trials for treatment of survivors with severe traumatic brain injury (TBI) that result in disorders of consciousness (DoC). Representing a continuum of impaired consciousness, DoC is based on a person’s ability to demonstrate arousal and/or awareness. The DoC continuum includes comatose, vegetative state/unresponsive wakefulness syndrome, minimally conscious state and emergence from the minimally conscious state. Recovery of consciousness for people with DoC following a severe TBI is uncertain and difficult to predict. Accurate measurement of recovery of consciousness for people in DoC is essential for diagnosis and prognosis as well as determining the efficacy and effectiveness of interventions. To date, there has been no review of the range of

STRENGTHS AND LIMITATIONS OF THIS STUDY

The proposed scoping review will result in a comprehensive catalogue of outcome assessments used in traumatic brain injury research aimed at facilitating recovery of consciousness among adults with disorders of consciousness (DoC).

The outcome assessments will be grouped according to the WHO International Classification of Functioning, Disability and Health domains and subdomains to identify key trends and gaps in concepts of interest.

To the authors’ knowledge, this will be the first study to identify whether the introduction of National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDEs) influenced outcome assessment reporting among studies that received federal funding in the USA.

Studies reporting US federal funding published after the introduction of NINDS CDEs may have been conducted prior to 2010 and therefore the authors may not have been strongly encouraged to use NINDS CDEs.

It is possible that our search strategy will miss relevant studies; we will mitigate this risk by searching multiple databases and manually searching review articles and meta-analyses.
Historically, measuring recovery of consciousness in clinical trials has involved a range of clinical outcome assessments measuring different concepts of interest (e.g., response to pain, awareness), making it difficult to compare results across studies.\textsuperscript{11–14} The National Institute of Neurological Disorders and Stroke (NINDS), part of the US National Institutes of Health (NIH), established a set of Common Data Elements (CDEs) for TBI in 2010 with the goal of promoting comparability across studies. TBI researchers applying for US federal funding sources including NIH, Department of Defense, Department of Veteran’s Affairs are strongly encouraged to use NINDS CDEs for outcome measures.\textsuperscript{5} The goal of the NINDS CDE project is to improve comparability across trials. Further, a data repository for TBI research was created as a result of collaboration between NIH and the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System;\textsuperscript{15} federally funded researchers may be required to submit their data to this repository in the future. This requirement provides additional incentive to use NINDS CDEs.\textsuperscript{15–17}

CDEs are categorised as core, basic or supplemental. The ‘core’ designation indicates data elements pertinent for all TBI studies. Basic CDEs are specific to studies of populations within TBI, such as ‘concussion/mild TBI’, ‘acute hospitalised’, ‘moderate/severe TBI: rehabilitation’ and ‘epidemiology’. Basic CDEs for ‘moderate/severe TBI: rehabilitation’ include, but are not limited to, pupil reactivity, death date and time, hospital discharge destination, and alteration of consciousness duration.\textsuperscript{18} Supplemental CDEs are optional and may be appropriate depending on the research question and scope.\textsuperscript{16} Only two supplemental CDEs are related to recovery of consciousness in adults: the Galveston Orientation Amnesia Test and JFK Coma Recovery Scale-Revised (CRS-R) (table 1).\textsuperscript{18}

Two studies have described the implementation of CDEs in TBI research.\textsuperscript{13,19} Yue et al described the implementation of CDEs for a multicentre prospective study and note recommendations for future data collection procedures as well as the success in transferring the data to FITBIR. Stead et al used CDEs to describe TBI patients in emergency departments and were able to compare results to several other published studies. Although the goal of the NINDS CDE project is to improve consistency and comparability across clinical studies of patients with DoC following severe TBI by encouraging more consistent use of clinical outcome assessments, there is currently no evidence to indicate whether this outcome has been achieved.

### Objective
The primary objective of this scoping review is to develop a comprehensive inventory of clinical outcome assessments in clinical trials aimed at recovery of consciousness for patients with DoC after TBI. Secondary objectives are to examine the trends in primary outcomes over time and whether reporting of NINDS CDEs increased after their introduction in 2010 in studies that received US federal funding.

### METHODS AND ANALYSIS
A scoping review is an appropriate method to achieve the stated objectives because we want to identify characteristics of clinical outcome assessments used to evaluate the recovery of consciousness following a severe TBI.\textsuperscript{20} The scoping review will be conducted based on the Arksey and O’Malley\textsuperscript{21} methodological framework that has been refined by Levac et al.\textsuperscript{22} The methodological framework for this review will include: (1) identify the research questions, (2) identify relevant studies, (3) select studies, (4) chart the data, (5) collate, summarise and report results and (6) stakeholder engagement to drive knowledge translation.\textsuperscript{21,22}

### Identify the research questions

**Primary question**

- What clinical outcome assessments have been used in published studies about recovery of consciousness for adults with severe TBI in states of disordered consciousness?

**Secondary questions**

- How have the outcomes assessments used to measure DoC in adults with severe TBI changed over time?
- Did the frequency of reporting clinical outcome assessments classified as NINDS CDEs change after their introduction in 2010 among federally funded studies in the USA?

### Table 1: Examples of Common Data Elements

<table>
<thead>
<tr>
<th>Type of CDE</th>
<th>Definition</th>
<th>Example of CDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>General core</td>
<td>Recommended for all NIH-funded studies: general</td>
<td>C00031: race expanded category</td>
</tr>
<tr>
<td>Disease-specific</td>
<td>Recommended for all NIH-funded studies: disease specific (TBI)</td>
<td>C01001: Glasgow Coma Scale (GCS)—motor response scale</td>
</tr>
<tr>
<td>Basic</td>
<td>Recommended for all TBI NIH-funded studies: specific to subspecialties (eg, epidemiology and moderate/severe: rehabilitation)</td>
<td>C07155: Disability Rating Scale Total Score</td>
</tr>
<tr>
<td>Supplememtal</td>
<td>Recommended for NIH-funded studies: specific to study design or type of research</td>
<td>C07145: JFK Coma Recovery Scale-Revised—total score</td>
</tr>
</tbody>
</table>

*Basic CDEs are comparable to supplemental-highly recommended CDEs for other diagnostic categories.

CDEs, Common Data Elements; NIH, National Institutes of Health; TBI, traumatic brain injury.
Identify relevant studies

The search strategy was developed in collaboration with a research librarian. Our search terms are broad to identify all eligible studies. These search terms encompass three primary categories: severe TBI, recovery of consciousness, and outcomes.

Search terms

An in-depth outline of the full search strategy is reported in table 2.

Information sources

We will search the following electronic bibliographic databases: PubMed, Scopus, EMBASE, PsyclINFO and The Cochrane Library (including Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Cochrane Methodology Register).

Synthesis of eligibility criteria

This review will include all published, peer-reviewed studies using an intervention/treatment to facilitate recovery of consciousness for adults (>18 years) with DoC following severe TBI (table 3).

Study design

This review will consider all designs of peer-reviewed studies including randomised control trials, observational studies, cohort studies, case–control studies, case series and case reports. Meta-analyses and review articles will be excluded.

Setting

This review will include intervention studies delivered in any setting to adults with DoC following a severe TBI. There is no restriction on the country of origin.

Participants

For a study to be included in this review, at least one participant in the study must have DoC following a severe TBI. A severe TBI resulting in DoC is defined as: (1) Glasgow Coma Scale score of 3–8 or (2) an assessment known for evaluating states of consciousness, such as the
CRS-R. Studies will be excluded if all participants were under 18 years of age, had a Diagnostic and Statistical Manual of Mental Disorders (5th edition) diagnosis of a psychiatric disorder, had brain pathologies such as Alzheimer’s Disease or non-TBI, or were conscious, alert, and oriented. All non-human studies will be excluded.

**Interventions**
Examples of interventions to be included are medication, nutrition, rehabilitation therapy, non-invasive brain stimulation and surgery. Studies will be excluded if the purpose of the intervention/treatment provided was not described as facilitating recovery of consciousness.

**Select studies**
Following the search, each identified article will be uploaded to Endnote, a reference management system. Duplicate articles will be removed. Titles and abstracts will be screened by two independent reviewers to assess whether articles meet inclusion criteria (table 4). If studies are meta-analyses or reviews that are relevant to the research question, we will search the reference list. Articles that are included by the screening process will undergo a full text review. Two independent reviewers will read the full text articles to make a final determination of inclusion. Articles that do not meet inclusion criteria at this stage will be excluded from the final sample, with rationale documented. Discrepancies about inclusion of articles will be resolved through further discussion and/or input by a third reviewer.

**Chart the data**
Data will be extracted from included articles by independent reviewers using a uniform data extraction tool developed for the study. A sample data extraction table is shown in box 1. Reviewers will use the Scottish Intercollegiate Guideline Network (SIGN) rating form to evaluate study quality. Consistent with the SIGN protocol, case study designs will not be evaluated for quality; other studies’ methodological quality will be rated as high, acceptable, low or unacceptable-reject. For each included article, data extraction will include details about the year of publication, funding source, study aims, study design, number of participants (including number lost to follow-up), recruitment, study completion rate, demographics (age, injury severity, days postinjury) of participants, clinical setting, specific intervention (including control conditions, if applicable), primary and secondary outcomes, timing and location of outcomes.

**Collate, summarise and report information**
Data analysis
We will transfer information from the data extraction forms into STATA14 to complete descriptive analyses. We will categorise studies based on sample size and report this information. We will also categorise studies into five groups (high, acceptable, low, unacceptable-reject or not rated) based on quality rating using SIGN criteria. We will examine whether sample size or quality rating biases results regarding frequency of clinical outcome assessment as well as utilisation of CDEs.
Conceptual framework and key concepts
WHO International Classification of Functioning, Disability and Health

Clinical outcome assessments will be categorised based on the WHO International Classification of Functioning, Disability and Health (ICF) framework using relevant concept of interest. This framework has two major components: functioning and disability which includes the domains of body function, body structure, and activities and participation that impact an individual’s daily life; and contextual factors which includes the domains of personal factors and environmental factors. Environmental factors consider the ‘physical, social and attitudinal environment in which people live and conduct their lives’. Personal factors include age, gender and education; we will not apply this domain in classifying outcome assessments since these generally represent covariates rather than outcomes/endpoints.

Clinical outcome assessments will first be categorised into one of the four relevant WHO ICF domains (body structures, body functions, activities and participation, environmental factors) based on the concept of interest they are intended to measure. These categorisations will be mutually exclusive in that each outcome assessment will only be assigned to one domain. ICF domains can be further classified into subdomains. We will also assign each outcome assessment to a relevant subdomain. Should an outcome assessment not fit into a WHO ICF domain, we will create an ‘Other’ domain. Once all outcome assessments are categorised into a domain, we will thematically analyse the outcome assessments in the ‘Other’ domain to determine if a new domain is needed. For example, previous literature argues for the inclusion of quality of life as a domain.

Common Data Elements
We will categorise outcome assessments as to whether they are an NINDS CDE for moderate/severe TBI. We will test the significance of the introduction for CDEs on outcome reporting before and after 2010 using a χ² test.

Presentation of results
Results will be presented via detailed quantitative and narrative summaries. First, we will present the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) flow diagram demonstrating the inclusion of studies, including how many articles were retrieved from each database. We will also create an outcome map table that categorises outcome assessments by WHO ICF domain and subdomain. We will create two figures to display (1) the frequency of WHO ICF subdomains to show the gaps in the concepts of interest that outcome assessments address by domain and (2) the number and percent of studies that received US federal funding by year to show the proportion that used a CDE as a primary outcome. In addition, we will present a 2×2 table of CDE status and whether the publication was pre/post the introduction of CDEs.
study title
Year
Funding source

**Inclusion/exclusion criteria**

Is the paper relevant to our research question, “What are the content areas of outcomes related to recovery of consciousness that have been used in clinical trials and/or intervention studies for adults with severe traumatic brain injury (TBI) in disorders of consciousness (DoC)?” (i.e., there are outcome measures for people in DoC following an intervention)

Inclusion criteria:

⇒ Adults (>18 years) with primary diagnosis of severe TBI.
⇒ Identified brain injury is noted to be severe by Glasgow Coma Scale of 8 or less.
⇒ At least one of the study participants are in DoC following a TBI.
⇒ Addressed outcome related to recovery of consciousness.
⇒ Written in English.

Exclusion criteria:

⇒ People with documented history of psychiatric illness (DSM criteria), and/or organic brain syndrome such as Alzheimer’s disease.
⇒ All study participants are fully conscious.
⇒ All study participants are <18 years of age.
⇒ Study participants include non-traumatic brain injury only.

**Study details**

Study design
Sample/number of participants: include sample size and diagnoses (i.e., DoC following TBI, stroke, anoxia)
Sample/demographics: age, injury severity, days postinjury (if reported)

Sample: the study’s inclusion criteria
Sample: the study’s exclusion criteria

**Data collection procedures**

Intervention characteristics (intervention(s), control condition(s), duration and protocol information)

Primary outcome measure
Context of use for primary outcome measure

End point measure
Secondary outcome measures
Were outcome measures transformed? (Yes/No)

Timing of outcome measures

**Results**

Observed sample
Number of excluded participants
Number of participants lost to follow-up
Primary outcome (mean, proportion, other effect size index)
Statistical analyses (description of groups, comparison of groups)

Key findings

**Complete SIGN Quality Rating Based on Study Design**

REFERENCES


