Randomized controlled trials in adult traumatic brain injury: A systematic review on the use and reporting of clinical outcome assessments

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Abstract

As part of efforts to improve study design, the use of outcome measures in randomized controlled trials (RCTs) in traumatic brain injury (TBI) is receiving increasing attention. This review aimed to assess how clinical outcome assessments (COAs) have been used and reported in RCTs in adult TBI. Systematic literature searches were conducted to identify medium to large (n ≥ 100) acute and post-acute TBI trials published since 2000. Data were extracted independently by two reviewers using a set of structured templates. Items from the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement and CONSORT patient-reported outcomes (PRO) extension were used to evaluate reporting quality of COAs. Glasgow Outcome Scale/Extended (GOS/GOSE) data were extracted using a checklist developed specifically for the review. A total of 126 separate COAs were identified in 58 studies. The findings demonstrate heterogeneity in the use of TBI outcomes, limiting comparisons and meta-analyses of RCT findings. The GOS/GOSE was included in 39 studies, but implemented in a variety of ways, which may not be equivalent. Multidimensional outcomes were used in 30 studies, and these were relatively more common in rehabilitation settings. The use of PROs was limited, especially in acute study settings. Quality of reporting was variable, and key information concerning COAs was often omitted, making it difficult to know how precisely outcomes were assessed. Consistency across studies would be increased and future meta-analyses facilitated by (a) using common data elements recommendations for TBI outcomes and (b) following CONSORT guidelines when publishing RCTs.

Key words: clinical outcome assessments; systematic review; randomized controlled trials; traumatic brain injury; multidimensional outcomes

Introduction

There is increasing awareness of the importance of clinical outcome assessments (COAs) in evaluating health care interventions.[1] Furthermore, in clinical research, there is recent emphasis both on standardizing data collection, and on multidimensional outcome assessment including the patient's perspective.[2] In recognition of the central role of outcomes in clinical studies, the US Food and Drugs Administration (FDA) has implemented a qualification program for COAs.[3] The terminology developed to describe COAs is outlined in a Task Force report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[1] and summarized in Table 1. The ISPOR report recommends that COAs should be targeted to clinical treatments; that is, in randomized controlled trials (RCTs), selected COAs should be specifically chosen to determine whether there is a treatment benefit on the intended aspect of patient functioning or feeling (i.e., the concept of interest). The COAs selected should also be of clinical value to patients, in that they should measure meaningful aspects of health that affect daily living.[1]

In traumatic brain injury (TBI) research, there is currently a drive towards standardizing data collection using a common set of measures which can be used to provide a multidimensional description of outcome.[4-9] At its simplest, multidimensional assessment means going beyond using a single endpoint to include two or more outcome domains. Multiple outcome domains are relevant to TBI, including global functional outcome, cognition, health-related quality of life, TBI symptoms, and psychological status.[4, 7, 8, 10] Current common data elements (CDEs) recommendations for TBI outcomes include clinician-reported outcomes (clinROs), patient-reported outcomes (PROs), and performance outcomes (PerfOs).[4] The CDE outcomes for TBI comprise one *core* measure of global functioning, the GOSE, as well as a variety of *basic* and

supplemental outcome measures, which can be used across all TBI study types.[4] Use of common outcomes promotes meta-analyses and provides a potential opportunity for pooling data for secondary analysis; it is particularly desirable in medium to large scale studies where the information collected may form a valuable legacy for use in the future.[11]

Measures of global functional outcome, such as the Glasgow Outcome Scale (GOS) and its extended version, the Glasgow Outcome Scale-Extended (GOSE), have often been used alone as the primary endpoint in trials of treatments for moderate to severe TBI.[12-15] However, the GOS/GOSE has been criticized for being insensitive to subtle changes in functioning.[7, 8, 12, 14-18] In addition, the GOS/GOSE may be collected in a variety of different ways, potentially yielding results that are not comparable. There is currently no systematic overview of how COAs have been used in clinical trials in TBI. Furthermore, the extent to which previous TBI trials have used a multidimensional set of outcomes, or a single measure of global functional outcome such as the GOS/GOSE, is unclear, and warrants investigation.

Transparency and completeness in the reporting of RCTs is essential to inform clinical decision-making. However, the reporting quality of COAs in TBI trials has not specifically been evaluated. A review by Lu et al (2015) used the Consolidated Standards of Reporting Trials (CONSORT) statement[19] to evaluate whether the reporting quality of methodological characteristics in adult TBI trials has improved over time.[20] Although reporting has improved over time in line with developments in the CONSORT reporting guidelines, Lu et al (2015) concluded that there remains a need for increased transparency in the reporting of clinical trial methodologies in adult TBI. Incomplete reporting makes it difficult to assess the methodological rigour of RCTs and hinders 'risk of bias' assessments. Sub-optimal reporting

of outcomes in clinical trials is also problematic because it interferes with the interpretation of findings, and ultimately, limits their ability to inform clinical practice guidelines.

The current systematic review focuses on medium to large scale RCTs in adults with TBI published from 2000 onwards. The review had two main objectives: (1) To document patterns of use of COAs; and (2) To evaluate quality of reporting of COAs using COA-specific items from the CONSORT 2010 checklist, CONSORT PRO extension, and other COA-relevant reporting criteria.

Methods

Search Strategy

Systematic online literature searches were conducted between October 2015 and May 2017 to identify RCTs investigating the effectiveness of acute and post-acute treatments, interventions, and management strategies in adult TBI. The following online databases were searched: PubMed, CINAHL Complete, and PsychInfo. PubMed and CINAHL Complete were searched using the MeSH terms “brain injuries” (exact subject) AND “randomised controlled trial/randomized controlled trial" (title/abstract). PsychInfo was searched using the terms "traumatic brain injury" (DE subjects [exact]) AND "randomized controlled trial/randomised controlled trial" (AB Abstract). Two clinical trials registries, www.clinicaltrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched using the MeSH term "brain injuries" and condition "traumatic brain injury." A hand search was conducted by searching the reference lists of two recent systematic reviews of RCTs in TBI.[13, 20] If a single study had more than one publication, linked papers were included in the review and evaluated as one publication.

The references retrieved from the database search were imported to the Covidence system,[21] where the titles and abstracts were screened independently by two authors according to the following inclusion and exclusion criteria:

Inclusion Criteria

1. Clinical trials investigating acute or post-acute treatments, interventions, or management strategies for TBI
2. Adult participants (predominantly aged 16 and over)
3. Articles published from 2000 to the present
4. Articles published in academic journals
5. Articles published in English
6. Medium scale (n = 100-500) and large scale studies (n>500)

Exclusion Criteria

1. Small scale studies (n< 100)
2. Feasibility studies, pilot studies, study protocols, progress reports
3. Retrospective analyses of previously published RCTs

Data Extraction

Data extraction was carried out independently by two authors. Quality was ensured by randomly selecting 5 studies, piloting data extraction for these studies, and refining the process where necessary before proceeding. Further quality control measures were implemented by completing data extraction in sets of 10, and by discussing and resolving any discrepancies that occurred, until data extraction was complete.

Study characteristics

The following information relating to general study characteristics was extracted: sample size (i.e., number randomized); study size (medium/large); participant age (overall mean/median age, age range); TBI severity (mild/moderate/severe); setting (acute/post-acute); participation sites (single/multicentre); intervention characteristics/type of study; treatment benefit; treatment mechanism; hypothesis; primary COA(s); secondary COA(s); time point of primary interest; time point of secondary interest; follow-up rate.

Risk of Bias

Selection bias has been found to influence RCT outcomes and is a central measure of study quality. Therefore, risk of selection bias was assessed using two key domains from the Cochrane Risk of Bias Tool: random sequence generation and allocation concealment. Risk of bias was categorized as high, low, or unclear (if insufficient information was provided), in line with Cochrane Collaboration definitions.[22] This approach is consistent with that used in a recent scoping review of RCTs in moderate-to-severe TBI.[13]

Patterns of use of COAs

Frequency counts were made to identify: (1) How many COAs were used; (2) Which assessments were used most often; (3) How many studies used multidimensional outcomes (i.e., use of two or more measures covering different assessment domains as defined in the CDEs); and (4) Which type of COA was used most commonly in each setting (i.e., clinRO, PRO, perfO, obsRO), both for primary outcomes and for outcomes that were used in any capacity (including primary outcomes, secondary outcomes, and combined outcomes). Combined

outcomes consist of two or more component outcome measures which are combined into a single endpoint,[23, 24] or analyzed jointly using a global test.[25, 26]

Quality of reporting of COAs

A checklist was developed to assess the reporting quality of COAs. The checklist was based on COA-relevant items from the CONSORT PRO extension,[27] CONSORT 2010 Statement,[19] and other additional COA-relevant reporting criteria. The CONSORT PRO extension provides guidance on how to describe patient-reported outcomes (PRO). However, as this review is concerned with COAs more generally, items from the CONSORT checklists were evaluated for all four types of COA (i.e., clinRO, PRO, perfO, obsRO). Some additional COA-relevant items were added, and some of the CONSORT checklist items were expanded for the purposes of this review (see Table 3 in Results for details).

Glasgow Outcome Scale

Patterns of use and quality of reporting were evaluated for the GOS/GOSE using a checklist which was developed specifically for this review. The checklist was used to assess the following items: (1) Whether the GOS/GOSE was used as a primary outcome, secondary outcome, or not at all; (2) Method of assessment (i.e., clinician assessed, structured interview, or postal questionnaire); (3) Whether extracranial injuries were included in the rating; (4) Method of dealing with severe pre-existing disability; (5) Method of contact for assessment (i.e., face-to-face, telephone, or postal); (6) Source of information (i.e., patient, proxy respondent, or other sources); (7) Method of assigning final rating (i.e., researcher rating or central review); (8) Whether the assessor was trained; (9) Whether scores were

dichotomized; and (10) Whether ordinal analysis methods were used (including analysis of ranked data, sliding dichotomy, and proportional odds ratio methods).

Statistical analysis

The results were summarized descriptively using frequencies (i.e. number of studies) and percentages (i.e. proportion of studies) for each of the items of interest. The data were analyzed using Microsoft Excel®.

Results

Study selection process

The online literature search yielded a total of 1861 references. The hand search revealed an additional 6 articles which met the inclusion criteria for the review. After removing duplicates, a total of 1137 separate references were left to be screened. Of these references, 1025 were excluded. The remaining 113 full-text articles were assessed for eligibility. Fifty-five of the full-text articles were excluded, leaving a total of 58 studies to be included in the review. The study selection process is detailed in Figure 1.

Study characteristics

The general characteristics of the studies are presented in Supplementary Table 1. Key study characteristics are summarised in Table 2. Most of the studies were conducted in acute settings (n = 38), and most were medium sized (n = 51). Almost half of the studies were conducted with patients with severe TBI (n = 27), most studies were multicentre (n = 38), and most had follow-up rates of 90% or better (n = 41). Six months post-injury was the most popular time point of primary interest (n = 31).

Risk of Bias

Risk of selection bias for each study is presented in Supplementary Table 1. Figure 2 shows that random sequence generation was rated as low risk of bias in 42 studies (27 acute; 15 post-acute), unclear risk of bias in 15 studies (11 acute; 4 post-acute), and high risk of bias in 1 post-acute study. Allocation concealment was rated as low risk of bias in 39 studies (25 acute; 14 post-acute), unclear risk of bias in 18 studies (12 acute; 6 post-acute), and high risk of bias in 1 acute study.

Patterns of use of COAs

A total of 126 separate COAs were identified within the 58 studies. The full list of COAs by type, study setting, and frequency of use are listed in Supplementary Table 2. Twenty-six (21%) of the COAs were used exclusively in acute studies, 82 (65%) were used exclusively in post-acute studies, and 18 (14%) were used across both study settings. Figure 3 shows that the ten most commonly used COAs were the GOS, GOSE, Disability Rating Scale (DSR), Trail Making Test Parts A & B (TMT A&B), SF-36, Controlled Oral Word Association Test (COWAT), Functional Independence Measure (FIM), Selective Reminding Test (SRT), Galveston Orientation and Amnesia Test (GOAT), and Rivermead Post-Concussion Questionnaire (RPQ). Of these 10 COAs, the 3 most frequently used were the GOS (21 studies), GOSE (21 studies), and DRS (12 studies). The GOS was used exclusively in the acute studies, whereas the GOSE was used in 16 of the acute studies and 5 of the post-acute studies. The DRS was used in 8 of the acute studies and 4 of the post-acute studies.

A total of 30 studies used multidimensional outcomes (12 acute studies, 18 post-acute studies. Twenty-four of the studies with multidimensional outcomes reported individual

outcome measures; 5 studies used a composite multidimensional outcome; and 1 study used a global test to create a multidimensional outcome, i.e., the TBI Clinical Trials Network Core Battery.[25, 26]

The COAs were classified according to whether they were clinROs, PROs, perfOs, or obsROs. Supplementary Table 3 shows the number and proportion of studies that used each type of COA, both as a primary outcome, and in any capacity (i.e., as a primary outcome, secondary outcome, or as part of a composite outcome). Overall, clinROs were the most popular type of COA: they were used mostly in acute settings, and accounted for 54% of acute study primary outcomes. PROs were used rarely in acute settings, but they were used more commonly in post-acute settings. Overall, a total of 20 studies used more than one type of COA (9 acute studies; 11 post-acute studies). For primary outcomes, 10 studies used more than one type of COA (3 acute studies; 7 post-acute studies).

Quality of reporting of COAs

Reporting quality of COAs was assessed across the 58 studies. The number and percentage of studies that met each quality criterion is reported in Table 3. Each article was assessed according to whether the individual quality criteria were met. For cases where the information was unclear, or partially met, the criterion was rated as unmet. Reporting of primary and secondary outcome measures was assessed separately for checklist item 4. The numbers and percentages for each criterion are adjusted accordingly for sub-groups (see Table 3Legend).

Reporting of COAs was variable across the quality criteria. The checklist items that were reported most completely include: (2a) Treatment benefit defined (95% of all studies); (4i) Timing of follow up for primary outcomes stated (98% of all studies); (7) Baseline COA data provided, if collected (100% of the 20 applicable studies); (8) Numbers analysed for COA results stated (98% of all studies); (10c) Implications for clinical practice discussed (100% of all studies); (11) COA data interpreted in relation to clinical outcomes, including survival data, where relevant (100% of all studies). Reporting varied between acute and post-acute studies, and primary outcomes were generally reported more completely than secondary outcomes, especially in the post-acute studies. Reporting quality varied across criteria for checklist item 4: Overall, the proportion of studies meeting the criteria ranged from 6% for 'Number of assessors stated for secondary outcomes,' to 98% for 'Timing of follow-up for primary outcomes stated.' The following checklist items were least complete: (3) COA hypothesis stated and relevant domains defined, if applicable (57% of all studies); (9a) Effect size reported (53% of all studies); (9aii) For binary outcomes, absolute effect size stated (28% of applicable studies); (9b) Confidence intervals (or other measures of precision) reported (57% of all studies); (10a) COA-specific limitations discussed (36% of all studies); and (10b) Implications for generalizability discussed (41% of all studies).

Glasgow Outcome Scale

The GOS/GOSE was the most commonly used COA overall. The scale was used in 39 of the 58 studies (67%). Figure 4 shows how often the scale was used as a baseline measure, primary outcome, secondary outcome, or as part of a composite outcome. The scale was used in its original 5-point format (GOS) in 21 studies (GOS guided interview = 20 studies; GOS postal questionnaire = 1 study), and in its extended format (GOSE) in 21 studies (GOSE questionnaire

= 3 studies; GOSE structured interview = 18 studies). It was used as a primary outcome in 29 studies (GOS = 19 studies, GOSE structured interview = 8 studies, GOSE questionnaire = 1 study). It was used as a secondary outcome in 7 studies (GOS = 3 studies, GOSE structured interview = 3 studies, GOSE questionnaire = 1 study): 3 of these studies used the GOS as a primary outcome as well as the GOSE questionnaire as a secondary outcome. The GOSE structured interview was used as part of a composite in 5 studies, and as a baseline measure in 2 studies.

Table 4 displays the patterns of use and completeness of reporting in the 39 studies that used the GOS or GOSE. Clinician assessed/guided interviews were used in 46% of the studies (17 acute studies; 1 post-acute studies), while structured interviews were used in 44% of the studies (13 acute studies; 4 post-acute studies), and postal questionnaires were the primary assessment in 10% of the studies (4 acute studies; no post-acute studies). None of the articles stated whether extracranial injuries were included in the ratings, and 90% (35 studies) did not state the methods used to deal with pre-existing severe disability. Around half of the articles did not state the primary method of contact (18 acute studies; 2 post acute studies), and 64% (23 acute studies; 2 post-acute studies) did not report the source of information/respondent. Final ratings were assigned by the researcher in 87% of the studies (29 acute studies; 5 post-acute studies), and by central review in 13% of the studies (all 5 were acute studies). Most articles (69%) did not state whether the outcome assessor was trained (22 acute studies; 5 post-acute studies). GOS/GOSE scores were dichotomized in 59% of the studies (all 23 were acute studies), while ordinal analysis methods were used in 38% of the studies (12 acute studies; 3 post-acute studies).

Discussion

This review aimed to evaluate how clinical outcome assessments (COAs) have been used and reported in RCTs in adult TBI from 2000 onwards. A total of 58 clinical trials were assessed according to key study characteristics, risk of selection bias, patterns of use of COAs, and reporting quality of COAs. The included articles demonstrate that the majority of RCTs that fit criteria were medium in size (i.e., n=100-500), and most studies investigated acute hospital treatments for moderate and severe TBI.

A wide range of COAs were used across the included studies, and there were differences in the use of outcomes depending on the setting in which the RCT was conducted. A greater range of COAs were used in the post-acute studies, and there was little commonality between acute and post-acute settings. The most popular COAs were measures of global functional outcome, including the GOS, GOSE, and DRS. However, most of the COAs were used infrequently (i.e., in 1 to 3 studies). Considerable variability therefore exists in the use of outcome measures in TBI trials, especially in post-acute settings, making it challenging to link acute and post-acute studies.[5] The frequent use of the GOS/GOSE in the reviewed studies is not surprising and is consistent with the subsequent CDE recommendations for TBI.[4] Nevertheless, the GOS/GOSE has not been used universally in TBI clinical trials. The introduction of outcome CDEs for TBI should help to reduce variability in the assessments used in RCTs. However, it is notable that since first proposed,[6] the number of outcome CDEs has grown, and compartmentalisation of different areas of TBI assessment remains.

As multidimensional outcome assessment is increasingly important in the field of TBI, the GOS/GOSE is now recognised to be insufficient on its own as an outcome measure.[7, 8, 16]

Despite this, around half of the reviewed studies used a single outcome: most of these were acute studies, and the GOS/GOSE was the most frequently used endpoint. Around half of the studies used multidimensional outcomes: most of the post-acute studies used multidimensional outcomes, whereas a minority of the acute studies used multidimensional outcomes. Most studies with multidimensional outcomes used separate COAs to measure multiple outcome domains, and composite multidimensional outcomes were relatively uncommon. While ClinROs such as the GOS/GOSE were common in the acute studies, PROs were used rarely in these studies. Regulators have encouraged the use of PROs,[28] but these assessments have not proven popular in TBI, perhaps because they are not as closely linked to the neural substrate as functional outcome measures.[25] The findings from the review demonstrate that multidimensional outcomes are not used universally in TBI trials. Moreover, multidimensional outcomes are more commonly used in clinical trials in rehabilitation settings, perhaps due to treatments that are more clearly targeted to behavioural change and designed to tap into multiple outcome domains.

The overall reporting quality of COAs was variable across the reviewed studies, suggesting that reporting is sub-optimal in TBI trials. Most articles provided a sufficient background and rationale for the outcomes. Furthermore, the criteria relating to timing of follow-ups, participant numbers, baseline outcomes data, implications for clinical practice, and interpretation of clinical outcomes, were consistently well met across the studies. Overall, the most incompletely reported aspects included COA hypotheses, effect sizes and confidence intervals, COA-specific limitations, and implications for generalizability. Some key differences were identified between the acute and post-acute studies. Although acute studies were relatively better at explaining treatment mechanisms, more attention was paid to outcomes

in rehabilitation settings (i.e., hypotheses were stated more clearly, primary outcomes were defined more fully, and COA-specific limitations and implications for generalizability were more likely to be discussed). In the acute studies, there was often a lack of rationale for the choice of endpoint, possibly because pharmaceutical trials in acute TBI tend to be motivated by animal studies and there is a substantial gap between the behavioural measures typically used in laboratory work and the COAs used in human studies (i.e., GOS/GOSE). In future clinical trials, investigators should therefore ensure that outcomes are well defined and carefully selected to capture treatment benefit on specific aspects of the patient's functioning or feeling.[1]

Despite the wide use of the GOS/GOSE, certain aspects were reported particularly poorly across the studies. None of the included articles reported whether extracranial injuries were included in the GOS/GOSE ratings, and most studies provided no information about the method used to deal with pre-existing severe disability. Around two thirds of the articles did not state who the respondent was (i.e., the TBI patient or a proxy informant), or whether the outcome assessor was trained. Furthermore, around half of the articles did not provide sufficient information about the primary method of contact for GOS/GOSE assessments (i.e., face-to-face contact, telephone contact, postal questionnaire). In contrast, reporting of GOS/GOSE scoring and analysis methods was relatively complete, the method of assigning final ratings was clear in all of the articles, and it was apparent in most studies if the GOS/GOSE scores were dichotomized or if ordinal analysis methods were used.

Transparent reporting of how the GOS/GOSE is used and analysed is important in RCTs because variability in methods of data collection and scoring may influence study findings.

Important issues to consider when assigning outcome on the GOS/GOSE include the influence of extracranial injury, pre-existing disability, and source of information (i.e., TBI patient or proxy informant).[29] Inter-rater variability is another important issue when assigning outcome and interviewer training is required to achieve high levels of agreement between assessors.[30] Extracranial concomitant injury can have an effect on functional outcome.[31, 32] However, the original description of the structured interview for the GOSE noted that the scale did not distinguish the effects of brain injury from the effects of concomitant injuries to other parts of the body: investigators needed to decide whether to include or exclude extracranial injuries in the overall rating of disability.[29] Both approaches have been used in RCTs, with some trials including extracranial injuries in the assessment (e.g. the Dexanabinol Trial),[33] and others excluding the influence of non-brain injuries (e.g. PROTECT III).[34] This represents a substantial difference in the way that outcome assessments have been conducted, and one that should be documented in future trial reports.

Previous studies suggest that the GOSE postal questionnaire and structured telephone interview can be used as a reliable means of assigning functional outcome in the absence of face-to-face contact.[35, 36] Nevertheless, robust comparisons between these different methods of GOSE data collection have not been made. The GOSE questionnaire is increasingly used in TBI trials.[37-40] However, as impaired self-awareness can affect TBI patients' ability to provide an accurate self-report,[41] the GOSE questionnaire may not be appropriate in all contexts. Disagreements between GOSE questionnaires and GOSE interviews may occur if postal questionnaires are self-completed by patients who lack insight into their own functional limitations,[36] and investigators should take this into consideration when deciding which method of GOSE data collection to use in future TBI studies.

This review provides information about the patterns of use and reporting quality of outcomes in adult TBI trials published from the year 2000 onwards. However, it is important to note that the review has limitations. As changes in the use and reporting of COAs were not examined over time, the impact of the CDE recommendations for common outcome measures in TBI,[4, 6] and the CONSORT guidelines for RCT reporting,[19, 27] on clinical trials in TBI is unknown. Furthermore, as the review was restricted to medium and large scale RCTs (i.e., n≥100), the findings may have differed if smaller scale RCTs had been included. The inclusion criteria may have been biased against post-acute studies, as these are often smaller in scale than acute TBI studies.

Conclusion

This review demonstrates shortcomings in the use of COAs in adult TBI trials to date and highlights the issue of incomplete reporting of outcomes in these studies. Heterogeneity in the use of clinical trial endpoints is problematic because it interferes with meta-analyses of trial findings and makes it difficult to pool data for secondary analyses. Incomplete reporting of outcomes is also problematic because it limits the transparency of RCT findings and compromises their clinical applicability. To address the issues raised in this review, future studies in adult TBI should follow CDE outcomes recommendations to increase consistency in the use of COAs and facilitate future meta-analyses.[4] Future RCTs in adult TBI should also adhere to CONSORT guidelines to ensure transparency in the reporting of outcomes and contribute to the development of clinical guidelines.[19, 27] As the GOSE is currently recommended as the core COA within multidimensional outcome assessments in TBI,[4, 7, 8] further research into how it is used is now warranted and its associations with other outcome domains should be ascertained.

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Table 1: Types of COA

Type of COA	**Definition***
Clinician-reported outcome (ClinRO)	A type of COA in which a member of the investigator team is the rater. The investigator's professional training is relied upon to judge what rating or score will be reported
Patient-reported outcome (PRO)	A COA in which the report comes directly from the patient. The patients' responses to questions about their health condition are recorded without amendment or interpretation by anyone else.
Performance Outcome (PerfO)	A COA in which the patient is assessed by performing a defined task that is quantified in a specified way. Although a member of the investigator team may administer the PerfO task and monitor the patient's performance, the investigator does not apply judgment to quantify the performance.
Observer-reported outcome (ObsRO)	A COA in which observations can be made, appraised, and recorded by a person other than the patient who does not require specialized professional training. The rating is nonetheless influenced by the perspective of the observer.

*Definitions taken from Walton et al (2015)

Table 2: Key study characteristics

	Number (%) of RCTs		
	Acute (n = 38)	**Post-acute (n = 20)**	**Overall (n = 58)**
Sample size			
100-500 (medium)	31 (81%)	20 (100%)	51 (88%)
>500 (large)	7 (19%)	0 (0%)	7 (12%)
TBI Severity (GCS score)			
13-15 (mild)	1 (2%)	6 (30%)	7 (12%)
9-12 (moderate)	0 (0%)	0 (0%)	0 (0%)
3-8 (severe)	25 (66%)	2 (10%)	27 (46%)
3-15 (all severities)	3 (8%)	4 (20%)	7 (12%)
9-15 (mild/moderate)	0 (0%)	1 (5%)	1 (2%)
3-12 (moderate/severe)	9 (24%)	7 (35%)	16 (28%)
Participation Centres			
Single Centre	14 (37%)	6 (30%)	20 (34%)
Multicentre	24 (63%)	14 (70%)	38 (66%)
Time point of primary interest			
<6-months post-injury	5 (13%)	3 (15%)	8 (14%)
6-months post-injury	29 (77%)	2 (10%)	31 (53%)
1-year post-injury	0 (0%)	4 (20%)	4 (7%)
>1-year post-injury	1 (2%)	8 (40%)	9 (16%)
Other	3 (8%)	3 (15%)	6 (10%)

Follow-up rate			
≥90%	32 (84%)	9 (45%)	41 (71%)
80-89%	2 (6%)	7 (35%)	9 (16%)
70-79%	1 (2%)	2 (10%)	3 (5%)
<70%	1 (2%)	2 (10%)	3 (5%)
Not stated	2 (6%)	0 (0%)	2 (3%)

Table 3: Quality of reporting of COAs

Quality Criterion	Number (% of RCTs) meeting criterion		
	Acute (n = 38)	**Post-acute (n=20)**	**All studies (n = 58)**
1. COA identified in abstract as a primary/ secondary outcome	28 (74%)	17 (85%)	45 (78%)
2. Background and rationale for COA provided			
a. Treatment benefit defined*	35 (92%)	20 (100%)	55 (95%)
b. Explanation of treatment mechanism*	34 (89%)	12 (60%)	46 (79%)
3. COA hypothesis stated and relevant domains defined, if applicable	16 (42%)	17 (85%)	33 (57%)
4. Completely defined pre-specified ◊primary outcomes			
a. Validity & reliability described or source citation given	25 (71%)	18 (90%)	43 (78%)
b. Who assessed outcomes stated	24 (69%)	18 (90%)	42 (76%)
c. Number of assessors stated*	4 (11%)	5 (25%)	9 (16%)
d. Whether assessors were blind is clear	29 (83%)	18 (90%)	47 (85%)
e. Native language with validated translation*	13 (37%)	16 (80%)	29 (53%)
f. Methods of contact stated, e.g., telephone/postal/face-to-face	17 (49%)	16 (80%)	33 (60%)
g. Respondent stated (e.g., patient/proxy, other sources)	15 (43%)	19 (95%)	34 (62%)
h. Whether respondent was blind stated*	16 (46%)	11 (55%)	27 (49%)
i. Timing of follow-up stated	35 (100%)	19 (95%)	54 (98%)
4. Completely defined pre-specified ◊◊secondary outcomes			
a. Validity & reliability described or source citation given	10 (63%)	11 (65%)	21 (64%)
b. Who assessed outcomes stated	11 (69%)	10 (59%)	21 (64%)
c. Number of assessors stated*	1 (6%)	1 (6%)	2 (6%)
d. Whether assessors were blind is clear	16 (100%)	12 (71%)	28 (48%)
e. Native language with validated translation*	7 (44%)	10 (59%)	17 (52%)

f. Methods of contact stated, e.g., telephone/postal/face-to-face	6 (38%)	9 (53%)	15 (45%)
g. Respondent stated (e.g., patient/proxy, other sources)	8 (50%)	11 (65%)	19 (58%)
h. Whether respondent was blind stated*	11 (69%)	9 (53%)	20 (61%)
i. Timing of follow-up stated	16 (100%)	12 (71%)	28 (85%)
5. Statistical approaches for dealing with missing data are explicitly stated	26 (68%)	19 (95%)	45 (78%)
6. Number of participants at baseline and subsequent time points given	30 (79%)	19 (95%)	49 (85%)
7. ᐞBaseline COA data provided, if collected	3 (100%)	17 (100%)	20 (100%)
8. Numbers analysed for COA results stated	38 (100%)	19 (95%)	57 (98%)
9. For each primary and secondary outcome, results for each group provided			
a. Effect size reported	22 (58%)	9 (45%)	31 (53%)
i. For binary outcomes, ᐞᐞrelative effect size stated	19 (79%)	1 (100%)	20 (80%)
ii. For binary outcomes, ᐞᐞabsolute effect size stated	7 (29%)	0 (0%)	7 (28%)
b. Confidence intervals (or other measures of precision) reported	27 (71%)	6 (30%)	33 (57%)
10a. COA-specific limitations discussed	6 (16%)	15 (75%)	21 (36%)
10b. Implications for generalizability discussed	10 (26%)	14 (70%)	24 (41%)
10c. Implications for clinical practice discussed	38 (100%)	20 (100%)	58 (100%)
11. COA data interpreted in relation to clinical outcomes, including survival data, where relevant	38 (100%)	20 (100%)	58 (100%)

*Expanded items developed for this review are marked with asterisks

◊Applicable in 55 studies (35 acute studies; 20 post-acute studies)

◊◊Applicable in 33 studies (16 acute studies; 17 post-acute studies)

[Δ]Applicable in 20 studies (3 acute studies; 17 post-acute studies)

[ΔΔ]Applicable in 25 studies (24 acute studies; 1 post-acute studies)

Table 4: GOS/GOSE patterns of use and completeness of reporting

	Acute (34 studies)	Post-acute (5 studies)	Totals* (39 studies)
Method of assessment			
a. Clinician assessed/guided interview	17	1	18 (46%)
b. Structured interview	13	4	17 (44%)
c. Questionnaire	4	0	4 (10%)
Extracranial injuries included in rating			
a. Not stated	34	5	39 (100%)
Method of dealing with pre-existing severe disability			
a. Patients with pre-existing SD excluded	4	0	4 (10%)
b. Not stated	30	5	35 (90%)
Primary method of contact			
a. Face-to-face interview	3	0	3 (8%)
b. Telephone interview	6	1	7 (17%)
c. Postal questionnaire	3	0	3 (8%)
d. Face-to-face clinical assessment	1	0	1 (3%)
e. Face-to-face or telephone interview	2	2	4 (10%)
f. Postal questionnaire, telephone interview, or face-to-face interview	1	0	1 (3%)
g. Not stated	18	2	20 (51%)
Source of information/respondent			
a. Patient alone	2	3	5 (13%)
b. Proxy alone	0	0	0 (0%)
c. Patient and proxy	1	0	1 (3%)
d. Patient or proxy	8	0	8 (20%)
f. Not stated	23	2	25 (64%)

Method of assigning final rating a. Researcher b. Central review	29 5	5 0	34 (87%) 5 (13%)
Outcome assessor is trained a. Yes b. Not stated	12 22	0 5	12 (31%) 27 (69%)
Scores are dichotomized a. Yes b. No c. Not stated	23 11 0	0 4 1	23 (59%) 15 (38%) 1 (3%)
Ordinal analysis methods used a. Yes b. No	12 22	3 2	15 (38%) 24 (62%)

*Data are number (%) of the 39 studies that used the GOS/GOSE

Figure 1: Systematic review study selection process

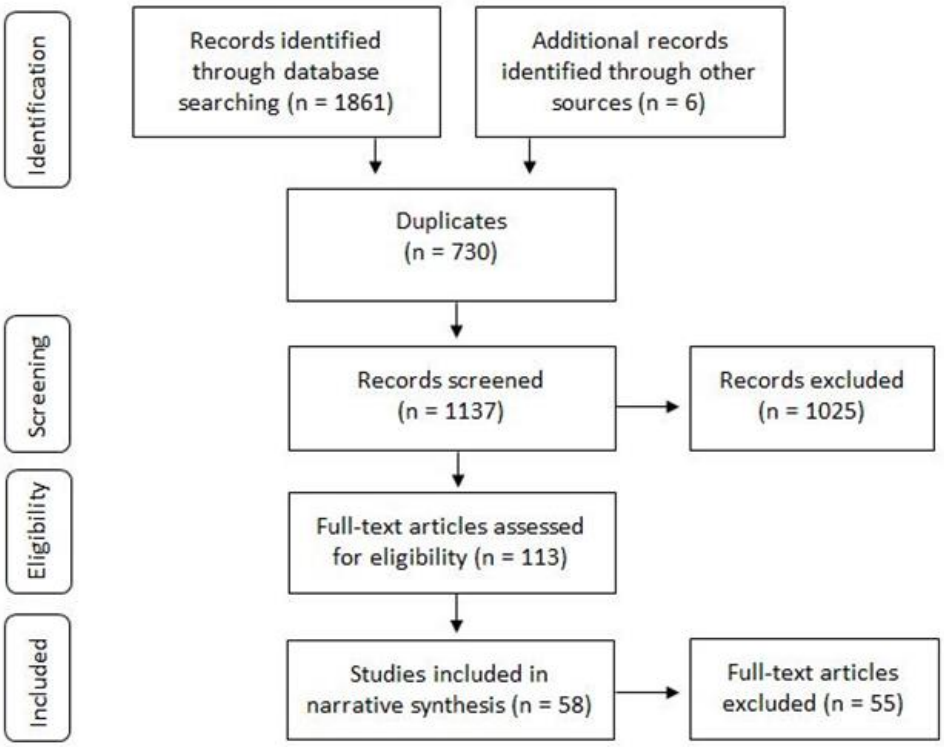


Figure 2: Risk of Bias for Allocation Concealment (AC) and Random Sequence Generation (RSG)

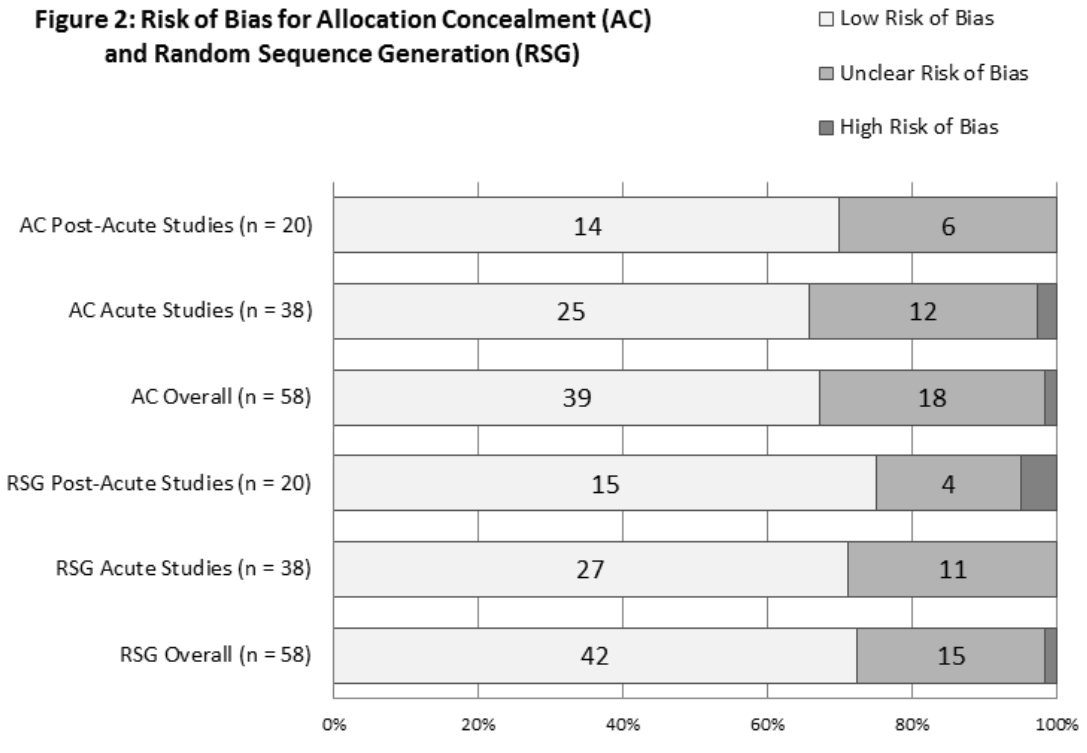


Figure 3: Most commonly used COAs

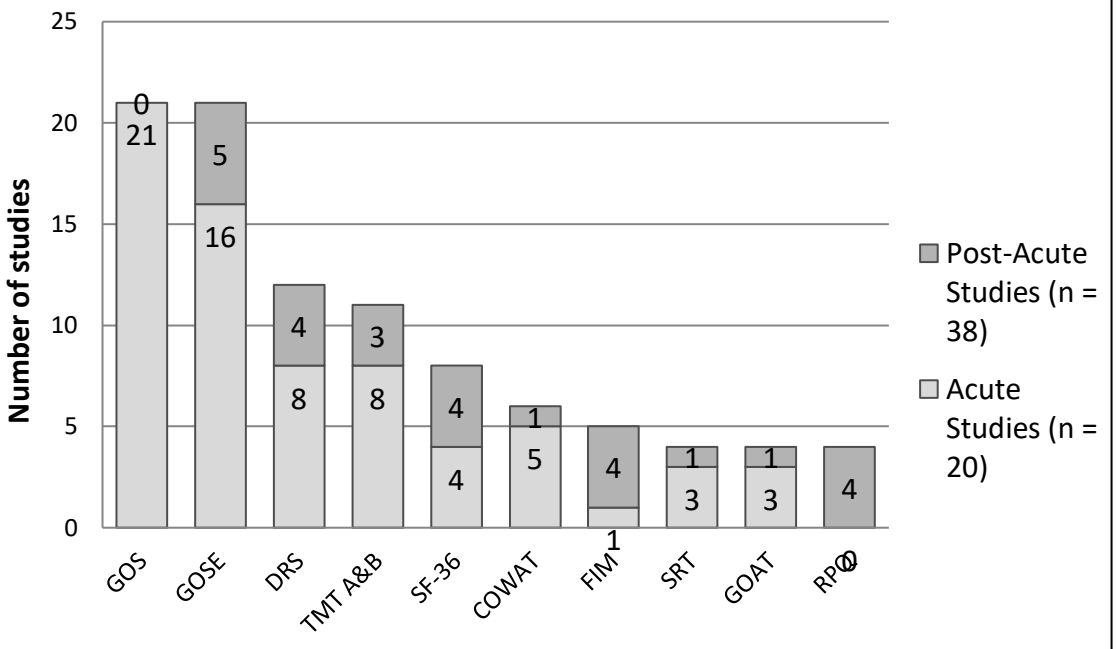
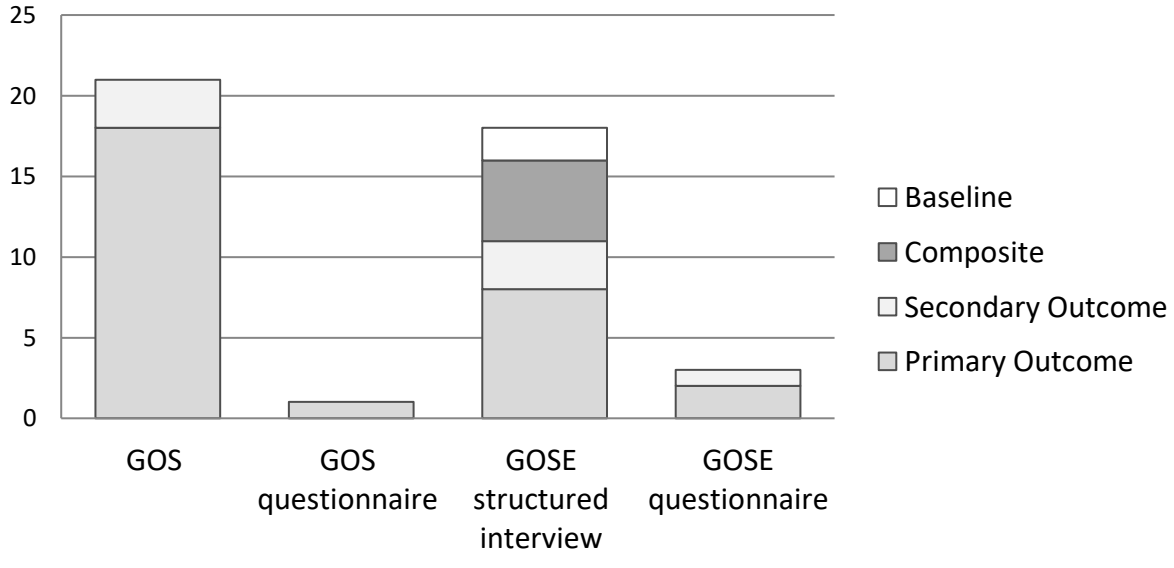


Figure 4: GOS/GOSE patterns of use for the original 5-point GOS rating, postal questionnaires for GOS and GOSE, and the GOSE structured interview



Supplementary Table 1: General Study Characteristics and Risk of Selection Bias

General Study Characteristics								Risk of Selection Bias	
Acute drug studies (neuroprotection)									
Treatment/ Intervention	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome(s) (time point)**	**Secondary outcome(s) or other outcome measures**	**Follow-up rate**	**RSG**	**AC**
Wilsonii injecta [1]	120	33.6 (18-60)	severe	acute single centre	Glasgow Outcome Scale (GOS) (6 months)	n/a	not stated	U	U
CRASH Corticosteroid Study [2, 3]	10,008	not stated (adults)	all	acute multicentre	GOS (6 months)	n/a	97%	U	L
CRASH-2 Tranexamic Acid [4]	270	36.5 (adults)	all	acute multicentre	modified Oxford Handicap Scale (mOHS) (6 months)	n/a	100%	L	L
Intensive Insulin Therapy [5]	188	53 (range not stated)	severe	acute multicentre	GOS (90 days after ICU admission)	mortality, neurological outcome at different time points	100%	L	L
Mannitol [6]	178	29 (adults)	severe	acute single centre	GOS (6 months)	n/a	100%	L	U
Mannitol [7]	141	30 (adults)	severe	acute single centre	GOS (6 months)	n/a	100%	L	U

Valproate [8]	279	36.2 (14 and over)	moderate/ severe	acute single centre	Neuropsychological battery including Finger Tapping Test, Namewriting Test, Seashore Rhythm Test, Trail Making Test (TMT) Part A & B, Stroop Color Word Tests Parts 1 &2, Wechsler Memory Scale – Revised (WMS-R): Attention and Concentration Index, Logical Memory and Visual Reproduction, Selective Reminding Test (SRT)(recall and delayed recall), Kimura Memory for Designs Test, Wechsler Adult Intelligence Scale (WAIS) Verbal Intelligence Quotient (VIQ) and Performance Intelligence Quotient (PIQ), Controlled Oral Word Association Test (COWAT) (1/6/12 months)	n/a	1m = 87% 6m = 53% 12 m = 38%	L	L
Erythropoietin [9]	159	42.3 (15-71)	severe	acute single centre	GOS (3 months after treatment. Patients treated within 6 hours of injury)	n/a	92%	U	U

Pharmos dexanabinol trial [10]	861	32.5* (16-65)	severe	acute multicentre	Glasgow Outcome Scale - Extended (GOSE) (6 months)	Barthel Index, SF-36	98%	L	L
Erythropoietin, EPO-TBI trial [11]	606	30.5* (16-83)	moderate/ severe	acute multicentre	GOSE (6 months)	n/a	98%	L	L
Erythropoietin [12]	200	30 (range not stated)	severe	acute multicentre	GOS (GOSE) (6 months)	Disability Rating Scale (DRS)	91%	U	L
BRAIN TRIAL of Bradykinin antagonist Anatibant [13]	228	36.4 (16-65)	moderate/ severe	acute multicentre	Serious Adverse Events (15 days after injury)	GCS, Disability Rating Scale (DRS), mOHS	96%	L	L
SYNAPSE Trial of progesterone [14]	1195	34.5*(16-70)	severe	acute multicentre	GOS (6 months)	GOSE, SF-36	99%	L	L
Magnesium [15]	499	34.4 (14 and over)	moderate/ severe	acute single centre	Composite comprising 39 individual measures, including mortality, seizures, functional measures (i.e., functional status examination (FSE), GOSE, Sf-36), and cognitive tests (i.e., Weschsler Abbreviated Scale of Intelligence (WASI) Full Scale IQ, WAIS III – Processing Speed Index, SRT, Paced Auditory Serial Additional test (PASAT), TMT A&B, Finger Tapping Test,	n/a	93% neuropsych. tests = 72%	L	L

					Grooved Pegboard Test, COWAT, Stroop Test (1&2), Kimura Memory for Designs Test, Galveston Orientation and Amnesia Test (GOAT) (6 months)				
Progesterone, PROTECT III trial [16]	882	35* (adults)	moderate/ severe	acute multicentre	GOSE (6 months)	DRS	94%	L	L
Intensive insulin therapy [17]	240	45.5 (adults)	severe	acute single centre	Mortality (6 months)	GOS	97%	U	L
Traxoprodil [18]	404	31.3 (16-70)	severe	acute multicentre	GOS (6 months)	DRS, Cognitive Abilities Screening Instrument (CASI), GOSE	93%	L	U
Tranexamic acid [19]	238	34.5 (16 and over)	moderate/ severe	acute single centre	Intracranial haemorrhage (at hospital discharge)	GOS	100%	L	L
Citicoline, COBRIT trial [20]	1213	not stated (18-70)	moderate/ severe	acute multicentre	TBI clinical trials network battery (i.e., TMT A&B, GOSE, COWAT, California Verbal Learning Test (CVLT), WAIS III Processing Speed Index, and Digit Span, Stroop test (1&2)) (90 days)	n/a	82%	L	L

Hypothermia trials									
Study	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome (time point)**	**Secondary outcomes**	**Follow-up rate**	**RSG**	**AC**
Hypothermia, Eurotherm Study [21]	387	37 (legal age of consent and over)	moderate/ severe	acute multicentre	GOSE (6 months)	modified Oxford Handicap Scale (mOHS)	97%	L	L
Hypothermia [22]	392	31.5 (16-65)	severe	acute multicentre	GOS (6 months)	Neurobehavioural Rating Scale-Revised, DRS, GOAT, SRT, Rey-Osterrieth Complex Figure Test, Symbol Digit Modalities Test, TMT Part B, COWAT, Grooved Pegboard Test	96%	U	U
Hypothermia [23]	232	28.5 (16 - 45)	severe	acute multicentre	GOS (6 months)	DRS	92%	L	L
Hypothermia [24]	215	32.9 (18-45)	severe	acute multicentre	GOS (6 months)	n/a	100%	U	U
Hypothermia, B-HYPO study [25]	148	39 (15-69)	severe	acute multicentre	GOS (6 months)	n/a	99%	**L**	L

Physiology of hypothermia [26]	148	27.3 (18-64)	severe	acute single centre	Physiology & GOS (1-7 years)	GOS	unclear	U	U
Hypothermia [27]	396	42.5 (15-65)	severe	acute single centre	GOS (6 months)	n/a	100%	U	U
Surgical trials									
Study	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome (time point)**	**Secondary outcomes**	**Follow-up rate**	**RSG**	**AC**
Decompressive Craniectomy (DECRA) [28]	155	24.2* (15-59)	severe	acute multicentre	GOSE (6 months)	n/a	100%	L	L
STICH Surgical trial [29, 30]	170	48 (16-83)	all	acute multicentre	Postal GOSE (6 months)	Rankin Scale, EuroQol (EQ-5D)	99%	L	H
Decompressive Craniectomy [31]	408	33.6 (10-65)	severe	acute multicentre	GOSE (6 months)	GOSE, SF-36	98%	L	L
Standard vs limited Craniectomy [32]	486	44.5 (14-70)	severe	acute multicentre	GOS (6 months)	n/a	100%	L	L
Surgical trial of Decompression [33]	182	36.8 (14-72)	severe	acute single centre	GOS (5-60 months)	n/a	91%	U	U

Surgical trial of Craniectomy [34]	230	45.6 (range not stated)	severe	acute single centre	GOS (6 months)	n/a	100%	U	U
Other acute studies (pre-hospital intubation, osmotic therapy, technology/monitoring, bed rest)									
Study	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome (time point)**	**Secondary outcomes**	**Follow-up rate**	**RSG**	**AC**
Pre-hospital intubation [35]	312	40.7 (15 and over)	severe	acute multicentre	GOSE (6 months)	GOSE dichotomised	96%	L	L
Acute osmotic therapy. Early hypertonic fluids [36]	1331	38.9 (15 and over)	severe	acute multicentre	GOSE (6 months)	DRS	85%	L	L
Acute osmotic therapy. Pre-hospital hypertonic saline [37]	229	37.5 (18 and over)	severe	acute multicentre	GOSE (6 months)	Functional Independence Measure (FIM), Rancho Los Amigos Scale	99%	L	L
Technology/ monitoring- ICP Monitoring [38]	324	29* (13 and over)	severe	acute multicentre	Composite with 21 components including survival, GOAT, GOSE, DRS, Mini Mental Status Exam (MMSE), Spanish Verbal Learning Test, Brief VisuoSpatial Memory Test, WAIS III Digit Symbol and Symbol Search, Grooved Pegboard Test, TMT Part A, Color Trails 1&2,	n/a	92%	L	L

					COWAT, Category Fluency - Animals and Actions, PASAT (6 months)				
Technology/monitoring - CPP display [39]	157	37 (16 and over)	moderate/ severe	acute single centre	GOSE and FSE (6 months)	n/a	100%	L	L
Bed rest for mTBI [40]	107	37 (older than 15)	mild	acute single centre	16 post-traumatic complaints including cognitive, vegetative, dysthymic, and physical symptoms, SF-36 (2 weeks/3 months/6 months)	n/a	74%	L	U
Post-acute drug studies									
Study	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome (time point)**	**Secondary outcomes**	**Follow-up rate**	**RSG**	**AC**
Amantadine [41]	184	36.4 (16-65)	severe	post-acute multicentre	DRS (4 weeks after treatment. Patients recruited within 4-16 weeks of injury)	Coma Recovery Scale-Revised (CRS-R)	98%	L	L
Amantadine [42]	168	39.2 (16-75)	moderate/ severe	post-acute multicentre	Neuropsychiatric Inventory (NPI-I) most problematic item (28 days after treatment. Patients recruited at least 6 months after injury)	NPI most aberrant item, NPI distress score, Clinical Global Impressions (CGI)	94%	L	L

Armodafanil [43]	117	31.3 (18-65)	mild/ moderate	post-acute multicentre	multiple sleep latency test (MSLT), Clinical Global Impressions of Change (CGI-C) (2, 4, 8, 12 weeks. Patients recruited 1-10 years post-injury)	Epworth Sleepiness Scale (ESS), MSLT, Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global Impression of change (CGI-C)	73% to 98%	U	U
Rivastigmine [44]	157	37.1 (18-50)	all	post-acute multicentre	Cambridge Neuropsychological Test Automated Battery (CANTAB) Rapid Visual Information Processing (RVP), Hopkins Verbal Learning Test (HVLT) (12 weeks. Patients recruited at least 1 year after injury)	CANTAB (RVP, Spatial Working Memory (SWM), Paired Associates Learning (PAL) & Reaction Time (RT)), HVLT, COWAT, WAIS-III Digit Span & Letter-Number Sequencing, TMT A&B, Neurobehavioural Functioning Inventory (NFI), Beck Depression Inventory II (BDI-II), Deiner Satisfaction with Life scale, CGI-C	85%	L	L
Rivastigmine [45]	102	45.5 (18 and over)	all	post-acute single centre	Symptom Checklist 90 (SCL-90), Deiner Satisfaction with Life Scale, Cognispeed tests (i.e., simple reaction time, ten-choice reaction time, subtraction and vigilance tests). (Baseline, end of period 1, after	n/a	68%	L	L

					wash-out, after 2nd period. Patients recruited at least 1 year after injury)				
Post-acute rehabilitation/counselling studies									
Study	**n**	**Mean/ median* age, (range)**	**TBI Severity**	**Study Setting**	**Primary outcome (time point)**	**Secondary outcomes**	**Follow-up rate**	**RSG**	**AC**
Mindfulness-based cognitive therapy [46]	105	46.5 (18 and over)	all	post-acute multicentre	Beck Depression Inventory-II (Post 10-week intervention. Time since TBI not reported)	PHQ-9, SCL-90-R, Philadelphia Mindfulness Scale (PHLMS), Toronto Mindfulness Scale (TMS)	72%		
Telephone counselling [47]	171	36 (18-70)	moderate/ severe	post-acute single centre	Composite including FIM, DRS, Community Integration Questionnaire (CIQ), NFI, FSE, GOSE, SF-36, Brief Symptom Inventory (BSI), EuroQol EQ-5D,	Individual measures and composites of measures in a common outcome domain	92%	L	L

					Modified Perceived Quality of Life (PQOL) (1 year)				
Telephone counselling [48]	366	32.5 (16 and over)	mild	post-acute single centre	Two composites for post-traumatic symptoms (Head Injury Symptom Checklist and 12 functional areas) and general health (SF-12, PQOL, PHQ, major role, and community integration) (6 months)	n/a	86%		
Telephone counselling [49]	433	39 (16 and over)	moderate/ severe	post-acute multicentre	Composite including FIM, DRS, Participation with Recombined Tools - Objective (PART-O), GOSE, EuroQol EQ-5D, PQOL, Sf-12, BSI-18 (1 year)	functional composite (FIM, DRS, GOSE, PART-O, EuroQol EQ-5D), community participation, wellbeing, and vocational measures	1 year: 82% 2 year: 81%	L	L
Self-advocacy intervention [50]	257	47.9 (18 and over)	moderate/ severe	post-acute multicentre	Advocacy Behaviour Rating Scale (ABRS) (at least 1 year since injury)	n/a	84%	U	U
Early intervention for mTBI [51]	395	33 (16-60)	mild	post-acute single centre	Post-Concussion Symptoms Questionnaire (PCSQ), Life Satisfaction Questionnaire (LiSat-11), CIQ, SF-36 (1 year)	Interest Checklist, Role Checklist, Job Satisfaction Checklist	90%	L	L

CBT for depression [52]	100	45.8 (18 and over)	Complicated mild to severe	post-acute multicentre	Hamilton Depression Rating Scale (HAMD-17) & patient-reported Symptom Checklist-20 (SCL-20) (16 weeks after recruitment to study. Patients recruited within 10 years of injury)	PHQ-9, MINI International Neuropsychiatric Interview, Environmental Reward Observation Scale (EROS), Automatic Thoughts Questionnaire (ATQ), Dysfunctional Attitudes Scale (DAS), Patient Global Impression (PGI), Satisfaction with Depression Care, Working Alliance Inventory - Short Form, SF-36, Head Injury Symptom Checklist	100%	L	L
Multidisciplinary rehab for mTBI [53]	191	32 (16-60)	mild	post-acute multicentre	Rivermead Post-Concussion Questionnaire (RPQ), Rivermead Follow-up Questionnaire (RFQ), General Health Questionnaire (GHQ), neurocognitive battery (Stroop Test, Symbol-Digit Modalities Test, Paced Visual Serial Addition Task, Simple Reaction Time, Choice Reaction Time, HVLT, WAIS III Vocabulary,	n/a	89%	U	U

					WAIS III Letter-Number Sequencing, WAIS III Matrix-Reasoning (6 months)				
Early rehab for mTBI [54]	173	39.4 (15-70)	mild	post-acute multicentre	RPQ, Hospital Anxiety and Depression Scale (HADS), (3 months)	n/a	83%	**L**	L
Community-based rehab [55]	110	34.5 (16-65)	severe	post-acute single centre	Barthel Index, Brain Injury Community Rehabilitation Outcome-39 (BICRO-39) (18-40 months after allocation. No limit on duration since injury)	FIM, Functional Assessment Measure (FAM), HADS	85%	L	L
Cognitive rehab [56]	120	25.5 (range not stated)	moderate/ severe	post-acute single centre	Return to work and fitness for duty (12 months after treatment. Patients recruited within 3 months of injury)	MMSE, SRT, Trahan Continuous Visual Memory Test (TCVMT),PASAT, Wisconsin Card Sorting Test (WCST),WMS-R General Memory, Auditory Consonant Trigrams, Halsted-Reitan Neuropsychological Impairment Index, Katz Adjustment Scale	100%	L	L

Brief alcohol intervention [57]	202	35.8 (18 and over)	moderate/ severe	post-acute multicentre	Alcohol Expectancy Questionnaire III, Readiness to Change Questionnaire (3 months following treatment)		59%	U	L
Comparison of two rehab approaches [58]	360	32.5* (18 and over)	moderate/ severe	post-acute multicentre	Functional independence, return to work or school (1 year post-treatment. Patients recruited within 6 months of injury)	CVLT, WMS-R, Semantic Fluency, Lexical Fluency, TMT Part B, WCST, FIM, DRS, Present State Exam, Apathy Evaluation Scale, Neurobehavioural Rating Scale	92%	L	L
Multidisciplinary outpatient treatment for mTBI [59]	151	32* (16-55)	mild	post-acute multicentre	Number of days to sustainable RTW (1 year)	RPQ, GOSE, Patient Global Impression (PGI, HADS	RTW = 100% secondary outcomes = 83%	L	L
Telephone counselling [60]	365	29.3 (20-54)	mild	post-acute multicentre	Pittsburgh Sleep Quality Index (PSQI) (6 and 12 months post-intervention. Patients recruited within 24 months of return from service)	RPQ, BSI-18, PTSD Checklist - Military Version (PCL-M), EuroQoL (pain question), 11-point numerical rating scale (NRS-11) for pain, PHQ-9, SF-12, Sheehan Disability Scale, Alcohol use Disorders Identification Test (AUDIT-C)	6 months = 76% 12 months = 72%	L	U

Supplementary Table 1: References

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Supplementary Table 2: COAs by Type, Study Setting, and Frequency of Use

	Clinical Outcome Assessment	Type of COA	Acute	Post-Acute	No. of studies
1	Glasgow Outcome Scale (GOS)	clinRO	X		21
2	*Disability Rating Scale (DRS)	clinRO	X	X	12
3	*GOS - Extended (GOSE) structured interview	clinRO	X	X	11
4	GOSE - questionnaire	clinRO	X		10
5	*SF-36	PRO	X	X	8
6	*Trail Making Test (TMT) Part B	perfO	X	X	7
7	*Trail Making Test (TMT) Part A	perfO	X	X	6
8	*Controlled Oral Word Association Test (COWAT)	perfO	X	X	6
9	*Functional Independence Measure (FIM)	clinRO	X	X	5
10	*Selective Reminding Test (SRT)	perfO	X	X	4
11	*Galveston Orientation and Amnesia Test (GOAT)	perfO	X	X	4
12	Rivermead Post-Concussion Questionnaire (RPQ)	PRO		X	4
13	*EuroQol (EQ5D)	PRO	X	X	3
14	Clinical Global Impressions Scale	clinRO		X	3
15	*Functional Status Examination (FSE)	PRO	X	X	3
16	Grooved Pegboard Test	perfO	X		3
17	Hopkins Verbal Learning Test (HVLT)	perfO		X	3
18	Modified Oxford Handicap Scale (MOHS)	clinRO	X		3
19	Modified Perceived Quality of Life (PQOL)	PRO		X	3
20	*Paced Auditory Serial Addition Test (PASAT)	perfO	X	X	3
21	*Stroop Colour Word Test (Parts 1&2)	perfO	X	X	3
22	WAIS III Digit Span	perfO	X		3
23	Beck Depression Inventory (BDI) II	PRO		X	2
24	Brief Symptom Inventory - 18 (BSI-18)	PRO		X	2
25	Community Integration Questionnaire (CIQ)	PRO		X	2
26	California Verbal Learning Test (CVLT)	PerfO	X		2
27	Diener Satisfaction with Life Scale	PRO		X	2

28	Finger Tapping Test	perfO	X		2
29	Head Injury Symptom Checklist	PRO		X	2
30	Kimura Memory for Designs Test	perfO	X		2
31	*Mini Mental State Exam (MMSE)	perfO	X	X	2
32	*Neurobehavioural Rating Scale	clinRO	X	X	2
33	Patient Health Questionnaire (PHQ) depression	PRO		X	2
34	*Rancho Los Amigos Scale	clinRO	X	X	2
35	Return to Work (RTW)	clinRO		X	2
36	Rivermead Follow-up Questionnaire (RFQ)	PRO		X	2
37	SF-12	PRO		X	2
38	*Symbol Digit Modalities Test	perfO	X	X	2
39	WAIS III Processing Speed Index	perfO	X		2
40	WAIS III Letter-Number Sequencing	perfO		X	2
41	Wisconsin Card Sorting Test (WCST)	perfO		X	2
42	11-point numeric rating scale (NRS-11)	PRO		X	1
43	Advocacy Behaviour Rating Scale (ABRS)	clinRO		X	1
44	Alcohol Expectancy Questionnaire III	PRO		X	1
45	Alcohol Use Disorders Identification Test (AUDIT-C)	PRO		X	1
46	Apathy Evaluation Scale	PRO		X	1
47	Auditory Consonant Trigrams	perfO		X	1
48	Automatic Thoughts Questionnaire (ATQ)	PRO		X	1
49	Barthel Index	clinRO		X	1
50	Brief Symptom Inventory (BSI)	PRO		X	1
51	Brain Injury Community Rehabilitation Outcome-39 (BICRO-39)	PRO		X	1
52	Brief Visuospatial Memory Test	perfO	X		1
53	Cambridge Neuropsychological Test Automated Battery (CANTAB) Paired Associates Learning (PAL)	perfO		X	1
54	CANTAB Rapid Visual Information Processing (RVP)	perfO		X	1
55	CANTAB Reaction Time (RT)	perfO		X	1

56	CANTAB Spatial Working Memory (SWM)	perfO		X	1
57	Category Fluency - Actions	perfO	X		1
58	Category Fluency - Animals	perfO	X		1
59	Choice Reaction Time	perfO		X	1
60	Cognispeed Simple Reaction Time	perfO		X	1
61	Cognispeed Subtraction Test	perfO		X	1
62	Cognispeed Ten-Choice Reaction Time	perfO		X	1
63	Cognispeed Vigilance Test	perfO		X	1
64	Cognitive Abilities Screening Instrument (CASI)	clinRO	X		1
65	Color Trails 1	perfO	X		1
66	Color Trails 2	perfO	X		1
67	Coma Recovery Scale-Revised (CRS-R)	clinRO		X	1
68	Dysfunctional Attitudes Scale (DAS)	PRO		X	1
69	Environmental Reward Observation Scale (EROS)	PRO		X	1
70	Epworth Sleepiness Scale (ESS)	PRO		X	1
71	Finnish Traumatic Brain Injury Questionnaire (FITBIQ)	PRO		X	1
72	Functional Assessment Measure (FAM)	clinRO		X	1
73	Functional independence	clinRO		X	1
74	General Health Questionnaire (GHQ)	PRO		X	1
75	Halsted-Reitan Neuropsychological Impairment Index	perfO		X	1
76	Hamilton Depression Rating Scale (HAMD-17)	PRO		X	1
77	Hospital Anxiety and Depression Scale (HADS)	PRO		X	1
78	Interest Checklist	PRO		X	1
79	Job Satisfaction Checklist	PRO		X	1
80	Katz Adjustment Scale	PRO		X	1
81	Lexical Fluency	perfO		X	1
82	Life satisfaction questionnaire (LiSat-11)	PRO		X	1
82	Medical Outcomes Study 6-item Cognitive Functioning Scale	PRO		X	1

83	MINI International Neuropsychiatric Interview	clinRO		X	1
84	Multiple Sleep Latency Test (MSLT)	perfO		X	1
85	Namewriting Test	perfO	X		1
86	Neuropsychiatric Inventory (NPI-I) observer-rated	ObsRO		X	1
87	Neuropsychiatric Inventory (NPI-I) participant-rated	PRO		X	1
88	Occupational Gaps Questionnaire (OGQ)	PRO		X	1
89	Paced Visual Serial Addition Task	perfO		X	1
90	Participation with Recombined Tools - Objective (PART-O)	PRO		X	1
91	Patient Global Impression (PGI)	PRO		X	1
92	Patient Health Questionnaire (PHQ) panic/anxiety	PRO		X	1
93	Patient Health Questionnaire-9 (PHQ-9)	PRO		X	1
94	Philadelphia Mindfulness Scale (PHLMS)	PRO		X	1
95	Pittsburgh Sleep Quality Index (PSQI)	PRO		X	1
96	Post-Concussion Symptoms Questionnaire (PCSQ)	PRO		X	1
97	Post-traumatic Checklist - Military Version (PCL-M)	PRO		X	1
98	Present State Exam	clinRO		X	1
99	Rankin Scale	clinRO	X		1
100	Readiness to Change Questionnaire	PRO		X	1
101	Rey-Osterrieth Complex Figure Test	perfO	X		1
102	Role Checklist	PRO		X	1
103	Satisfaction with Depression Care	PRO		X	1
104	Seashore Rhythm Test	perfO	X		1
105	Semantic Fluency	perfO		X	1
106	Sheehan Disability Scale	PRO		X	1
107	Simple Reaction Time	perfO		X	1
108	Spanish Verbal Learning Test	perfO	X		1
109	Symptom Checklist (SCL-20)	PRO		X	1
110	Symptom Checklist (SCL-90)	PRO		X	1
111	TBI Work Instability Scale	PRO		X	1

112	Toronto Mindfulness Scale (TMS)	PRO		X	1
113	Trahan Continuous Visual Memory Test	perfO		X	1
114	WAIS III Digit Symbol	perfO	X		1
115	WAIS III Information and Vocabulary	perfO		X	1
116	WAIS III Vocabulary	perfO		X	1
117	WAIS Matrix-Reasoning	perfO		X	1
118	WAIS performance intelligence quotient (PIQ)	perfO	X		1
119	WAIS Verbal Intelligence Quotient (VIQ)	perfO	X		1
120	WAISIII Symbol Search	perfO	X		1
121	Weschsler Abbreviated Scale of Intelligence (WASI) Full Scale IQ	perfO	X		1
122	WMS-R - General Memory	perfO		X	1
123	WMS-R - Visual Reproduction	perfO		X	1
124	WMS-R - Attention and Concentration Index	perfO	X		1
125	WMS-R - Logical Memory and Visual Reproduction	perfO	X		1
126	Working Alliance Inventory-Short Form	PRO		X	1

*COAs used in both acute and post-acute studies are marked with an asterisk

Supplementary Table 3: RCT findings for different types of COA and study setting

Type of COA and study setting		Primary COA n(%) of RCTs*	All COAs n(%) of RCTs**
clinRO	**Acute**	30 (54%)	27 (46%)
	Post-acute	4 (7%)	1 (2%)
PRO	**Acute**	1 (2%)	1 (2%)
	Post-acute	8 (13%)	8 (14%)
PerfO	**Acute**	1 (2%)	1 (2%)
	Post-acute	1 (2%)	0 (0%)
obsRO	**Acute**	0 (0%)	0 (0%)
	Post-acute	0 (0%)	0 (0%)
More than one type of COA* **	**Acute**	3 (5%)	9 (15%)
	Post-acute	7 (15%)	11 (19%)
TOTALS		**55 (100%)**	**58 (100%)**

*Data are n(%) of the 55 studies using COAs as a primary outcome

**Data are n(%) of the 58 studies using COAs in any capacity (i.e., as a primary outcome, secondary outcome, or as part of a composite outcome)

***Includes all outcomes that comprised more than one type of COA (e.g., clinRO and PRO)