# Global functional outcome in traumatic brain injury: Use in clinical trials, approaches to data collection, and role in multi-dimensional outcome assessment

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A thesis submitted for the degree of Doctor of Philosophy

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**May 2019**

## General Abstract

Traumatic brain injury (TBI) affects multiple aspects of health and daily functioning. However, TBI researchers whose primary interest is in the acute care setting have often used single measures of global functional outcome, such as the Glasgow Outcome Scale (GOS), to provide an overall assessment of recovery at follow-up, and have not routinely incorporated measures that capture the multi-dimensional impact of TBI. CENTER-TBI is part of an international initiative towards standardizing and refining outcome assessment in TBI. The aim of this initiative is to promote the use of common measures to provide a multi-dimensional description of TBI outcomes in a range of study contexts. This thesis uses data collected for CENTER-TBI to examine two main issues of relevance to outcome assessment in adult TBI: (1) methods of collecting information about global functional outcome; and (2) implementation of multi-dimensional approaches to outcome assessment in TBI. The systematic review in Chapter 2 examines the patterns of use and reporting quality of outcome measures in clinical trials in adult TBI. The findings from the review demonstrate heterogeneity in the use of outcome measures, limited use of multi-dimensional outcomes, and highlight the issue of incomplete reporting of outcomes in these studies, providing the impetus for the studies in Chapters 4, 5 and 6. Chapters 4 and 5 compare outcomes assigned using clinician ratings and patient reports on the extended GOS (GOSE). The two GOSE approaches were found to be broadly equivalent indicating that, in this context, patient reports generally provide information that is comparable to that obtained via clinician-rated interviews. Chapter 5 demonstrates that the GOSE has significant, but modest, associations with prognostic factors and other outcome measures. The role of the GOSE in implementing multi-dimensional outcome assessment is considered in Chapter 6. Chapter 6 demonstrates that the applicability of individual outcome assessments is strongly driven by level of disability. Thus, a tailored approach to outcome assessment is needed. The studies in this thesis indicate that mixed modes of GOSE data collection can be used to maximise follow-ups in studies with pragmatic constraints. Furthermore, outcome measures need to be carefully selected to capture the multi-dimensional impact of TBI across the spectrum of recovery. The findings have implications for further CENTER-TBI analyses, for selecting outcome measures in future prospective studies, and for pooling data for secondary analyses.

## Acknowledgements

This thesis is presented with sincere thanks to my supervisors Prof. Lindsay Wilson and Dr. Jonathan Rhodes for believing in me and providing the opportunity for me to be involved in the CENTER-TBI project. I am particularly grateful to Lindsay Wilson for his guidance, support, and encouragement throughout my PhD project: his knowledge, experience, and expertise in TBI research is invaluable. I am also grateful to Jonathan Rhodes for providing a vital link with clinical staff and patients and for his feedback on my thesis. I would also like to thank the research staff at the Wellcome Trust Clinical Research Facility at the Western General Hospital for recruiting patients and facilitating data collection throughout this project. A big thank you to the clinical staff working in NHS Lothian and other health boards who helped me organize follow-up visits, and to the patients and their families for taking part in this research. I appreciate the time and effort spent by everyone mentioned above for making this project a success.

I also wish to express my gratitude to the CENTER-TBI investigators and participants (listed in Appendix 1) for their hard work, dedication, and expertise. Special thanks to Prof. Andrew Maas and Prof. David Menon for doing an excellent job co-ordinating the CENTER-TBI project. I am very fortunate to be part of this innovative project and I gratefully acknowledge the funding received for this PhD from the European Commission 7$^{th}$ Framework Programme CENTER-TBI (602150).

Last but not least, thank you to my family, friends, fellow PhD students, and staff working at the University of Stirling for supporting me throughout this project.

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## List of abbreviations

| | |
|---|---|
| AIS | Abbreviated Injury Scale |
| ASA | American Society of Anaesthesiologists |
| AST | Attention Switching Task |
| CANTAB | Cambridge Neuropsychological Test Automated Battery |
| CDE | Common Data Elements |
| CDISC | Clinical Data Interchange Standards Consortium |
| CENTER-TBI | Collaborative European NeuroTrauma Effectiveness Research in TBI |
| CER | Comparative Effectiveness Research |
| COA | Clinical Outcome Assessment |
| COI | Concept of Interest |
| COU | Context of Use |
| CONSORT | Consolidated Standards of Reporting Trials |
| COWAT | Controlled Oral Word Association Test |
| ClinRO | Clinician-Reported Outcome |
| CRASH | Corticosteroid Randomization After Significant Head Injury |
| CRS-R | JFK Coma Recovery Scale - Revised |
| CT | Computerized Tomography |
| DRS | Disability Rating Scale |
| ER | Emergency Room |
| FDA | Food and Drug Administration |
| FIM | Functional Independence Measure |
| GAD-7 | Generalised Anxiety Disorder 7 |
| GCS | Glasgow Coma Scale |

| | |
|---|---|
| GOAT | Galveston Orientation and Amnesia Test |
| GOS | Glasgow Outcome Scale |
| GOSE | Glasgow Outcome Scale – Extended |
| GR | Good Recovery |
| HRQoL | Health Related Quality of Life |
| ICU | Intensive Care Unit |
| IMPACT | International Mission for Prognosis and Clinical Trial |
| INCF | International Neuroinformatics Coordinating Facility |
| InTBIR | International Initiative for TBI Research |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| ISS | Injury Severity Score |
| MCS | Mental Component Summary |
| MD | Moderate Disability |
| MRI | Magnetic Resonance Imaging |
| NINDS | National Institute of Neurological Disorders and Stroke |
| PCL-5 | Post Traumatic Stress Disorder Checklist |
| PAL | Paired Associates Learning |
| PCS | Physical Component Summary |
| PerfO | Performance Outcome |
| PHQ-9 | Patient Health Questionnaire 9 |
| PRO | Patient-Reported Outcome |
| PTA | Post-Traumatic Amnesia |
| PTSD | Post-Traumatic Stress Disorder |
| ObsRO | Observer-Reported Outcome |

| | |
|---|---|
| QOLIBRI | Quality of Life after Brain Injury Scale |
| QOLIBRI-OS | QOLIBRI Overall Scale |
| RAVLT | Rey Auditory Verbal Learning Test |
| RCT | Randomized Controlled Trial |
| RPQ | Rivermead Post-concussion Questionnaire |
| RTI | Reaction Time |
| RVP | Rapid Visual Information Processing |
| SD | Severe Disability |
| SF-36v2 | 36-Item Short Form Survey - Version 2 |
| SOC | Stockings of Cambridge |
| SRT | Selective Reminding Test |
| TBI | Traumatic Brain Injury |
| TMT | Trail Making Test |
| TRACK-TBI | Transforming Research And Clinical Knowledge in TBI |
| TUG | Timed up & Go |

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# CHAPTER 1

## Rationale and aims of the thesis

The impetus for this thesis comes from developments in three broad areas of research: (1) The drive towards harmonizing data collection in TBI studies; (2) Advances in outcomes research; and (3) Recommendations for multi-dimensional approaches to outcome assessment in TBI. Current progress in these areas of research will be evaluated in this chapter. The aims of the thesis will also be outlined.

## 1.1. Rationale for this research

### 1.1.1. *Harmonizing data collection in TBI research*

In the last decade, there has been a global drive towards the harmonization of data collection in TBI research (Yue et al., 2013). Current initiatives which aim to promote streamlined approaches to clinical data collection include the Clinical Data Interchange Standards Consortium (CDISC) (Clinical Data Interchange Standards Consortium, 2015); National Institute of Neurological Disorders and Stroke (NINDS) Common Data Elements (CDE) project (Hicks et al., 2013; Wilde et al., 2010); and International Initiative for TBI Research (InTBIR) (Tosetti et al., 2013). CDISC aims to harmonize data collection in a wide range of therapeutic areas, including TBI (Clinical Data Interchange Standards Consortium, 2015). More specifically, the NINDS CDE project aims to develop common data standards in a range of neurological research contexts, including TBI (Thurmond et al., 2010). Consistent with these two broad data standardization initiatives, InTBIR was set up in 2011 to tackle the global burden of TBI through international collaboration, data sharing, and adherence to CDE recommendations for data collection in TBI studies (Tosetti et al., 2013).

An overarching aspiration of InTBIR is to promote joint analyses of data where this yields advantages, for example, in comparative effectiveness research (CER), prognostic studies, or genomics, where large sample sizes are needed (Tosetti et al., 2013). A number of CER studies have been initiated as part of InTBIR, the largest of which are Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) in the US (Yue et al., 2013) and Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) in Europe (Maas, Menon, et al., 2015). TRACK-TBI and CENTER-TBI were set up in parallel and both projects have the aim of validating the applicability of the CDEs for TBI. CENTER-TBI was launched in 2013 and patients were recruited between December 2014 and December 2017 via 65 sites across 18 countries in Europe. It includes a core study of 4509 patients, as well as a registry providing basic observational data on 22,782 patients presenting to the sites involved. The project comprises a total of 22 work packages which cover a number of research strands,

including CER, neuro-informatics, biomarkers, magnetic resonance imaging, genetic associations, and outcomes. This PhD is part of the outcomes strand of CENTER-TBI.

### 1.1.2. *Advances in outcomes research*

Outcomes research is a broad field of investigation, which aims to improve the quality of health care by developing a better understanding of the end results of clinical practice (Jefford, Stockler, & Tattersall, 2003). Current developments in outcomes research are underpinned by the patient-centred model of health care and place emphasis upon outcomes that are important to the patient, such as functional status, participation in major life roles, and quality of life (Sacristan, 2013). In 2009, the US Food and Drug Administration (FDA) provided guidance for the use of patient-reported outcomes (PRO) in medical product labelling (U.S. Food & Drug Administration, 2009). Furthermore, in 2015, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force for Emerging Good Practices in Outcomes Research published a report that is consistent with the FDA's guidance, in which the conceptual foundations for Clinical Outcome Assessments (COAs), including PROs, are presented (Walton et al., 2015). ISPOR definitions (Eremenco et al., 2014; Walton et al., 2015) for the concepts of relevance to this thesis are presented in Tables 1.1 and 1.2.

### *1.1.3. Multi-dimensional outcome assessment in TBI*

TBI is a heterogeneous condition, which has been defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (Menon et al., 2010). It can affect multiple aspects of health and daily life. Thus, a single outcome measure is insufficient to describe the overall burden of disability from TBI, and there is currently a drive towards the use of multi-dimensional approaches to the measurement of TBI outcomes (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). The aim of multi-dimensional outcome assessment is to capture changes in specific areas of health and daily life using measures that reflect the outcome domains of relevance to TBI, such as cognitive, physical, and psychosocial functioning (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, & McCrea, 2017). The concept of multi-dimensional

outcome assessment is poorly defined, and there is currently no consensus about which outcome domains are key. Nevertheless, it is logical to consider outcomes to be multi-dimensional if they include two or more assessments that capture two or more outcome domains.

Table 1.1: ISPOR Task Force key concepts and definitions

| **Concept** | **Definition** |
|---|---|
| Clinical Outcome Assessment (COA) | "A clinical assessment instrument that is used as the measure of patient outcome in a clinical trial. There are four types: patient-reported outcomes (PRO), clinician-reported outcomes (ClinRO), observer-reported outcomes (ObsRO), and performance outcomes (PerfO)." |
| Concept of Interest (COI) | "The concept that the outcome assessment is intended to measure. The COI may be identical to the selected meaningful aspect of feeling or function. Frequently, however, the COI is a simplified form or component of a feeling or function that is not an inherently meaningful feeling or function of a patient's typical life, that is, not a complete meaningful health aspect, but thought to be indirectly well related to a meaningful health aspect." |
| Context of Use (COU) | "A description of the specifics of the study design, how the COA is used within the study, and result interpretation….The COU can affect whether the outcome assessment measurement of the COI is adequately related to the intended meaningful health aspect, as well as the measurement properties of the outcome assessment such as reliability and ability to detect change." |
| Treatment Benefit | "A favourable effect on a meaningful aspect of how patients feel or function in their life, or on survival. It is an effect on an aspect of health affected by the disease that is an alteration in feeling or functioning, about which the patient cares that it is affected, and has a preference that it does not become worse, improves, or is prevented. The aspect of feeling or functions affected by the therapy should be what occurs in the patient's usual (typical) life." |
| Mode of data collection | "Outcome assessments can be designed for more than one mode or method of administration. There are options for 1) who administers the outcome assessment, for example, self-administration, an otherwise untrained person, or a trained professional, and 2) how it is administered, for example, visual versus auditory, face-to-face versus by telephone, and electronic versus non-electronic." |

Table 1.2: ISPOR Task Force definitions for different types of COA

| **Concept** | **Definition** |
|---|---|
| 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." |
| 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. All ClinROs are COAs, but all COAs are not ClinROs." |
| 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." |
| 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." |

In acute care settings, TBI outcomes were traditionally based on ClinROs, such as the interviews for the Glasgow Outcome Scale (GOS) as a 5-point scale or 8-point scale (Jennett & Bond, 1975; Jennett, Snoek, Bond, & Brooks, 1981). However, other types of outcome measure, including PROs, are increasingly being incorporated in TBI studies (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). Current CDE recommendations for adult TBI are multi-dimensional and include one *core* measure, the GOSE, as well as a set of *basic* and *supplemental* measures, which can be used in specific study settings (Hicks et al., 2013). Examples of different types of COAs included in the CDE outcome measures for TBI (Hicks et al., 2013; Wilde et al., 2010) are presented in Table 1.3.

The CDEs for TBI were first selected in 2010 (Wilde et al., 2010), and subsequently updated in 2013 (Hicks et al., 2013) to broaden their clinical utility and incorporate outcomes which are

relevant in specific contexts of use (i.e., paediatric TBI, adult TBI, epidemiology, acute hospital, moderate-to-severe TBI rehabilitation, mild TBI/concussion) (National Institute of Neurological Disorders and Stroke, 2018b). Selection of the CDEs is an evolving process (Grinnon et al., 2012), and as the original proposals were derived from clinical practice and based on expert consensus alone, research is needed to inform future refinements (Maas et al., 2011). In particular, the outcome measures used in TBI studies need to be validated and the applicability of multi-dimensional approaches to outcome assessment needs to be evaluated in different contexts of use. Large-scale studies, such as CENTER-TBI (Maas, Menon, et al., 2015), provide an opportunity to do this. However, implementation of the CDEs is not a straightforward process, and researchers may need to compromise on the outcome measures that are selected.

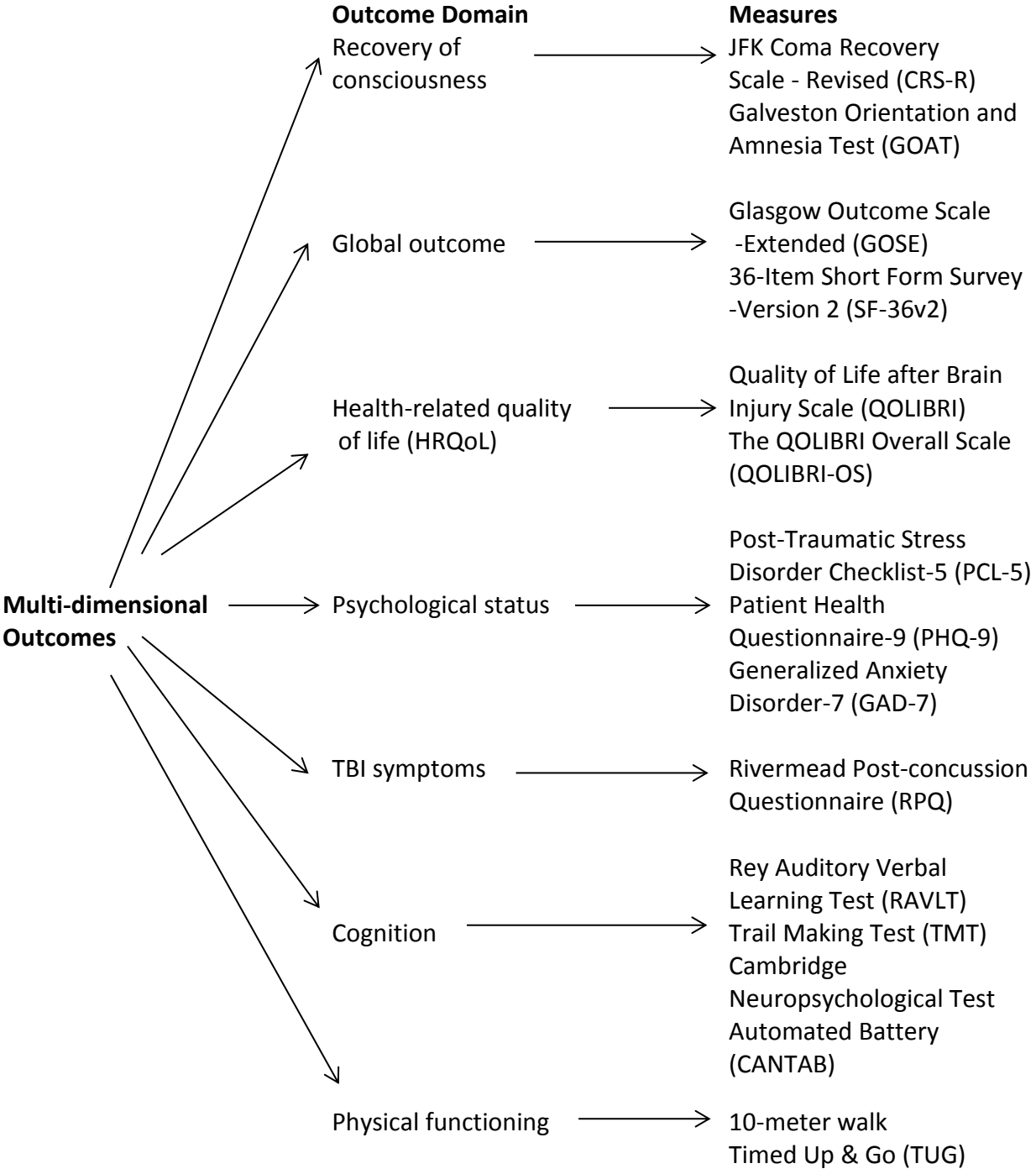
CENTER-TBI used a multi-dimensional set of outcome measures, based on the CDEs (Maas, Menon, et al., 2015; Maas et al., 2017). However, certain CENTER-TBI measures are not included in the current CDE recommendations. A number of challenges were encountered when selecting the CENTER-TBI outcome measures: some instruments could not be used due to copyright issues, while others were cost prohibitive, or could not be translated into the required languages for an international population (Burton, 2017; Maas et al., 2017).

Table 1.3: Types of COA included in the NINDS CDEs for TBI

| **Type of COA** | **Example NINDS CDE outcome measures** |
|---|---|
| PRO | Short Form-36 Medical Outcome Study (SF-36)<br>Rivermead Post-concussion Questionnaire (RPQ) |
| ClinRO | Glasgow Outcome Scale - Extended (GOSE) |
| ObsRO | Not included |
| PerfO | Trail Making Test (TMT)<br>Rey Auditory Verbal Learning Test (RAVLT) |

Figure 1.1 is a schematic diagram of multi-dimensional outcome assessment in TBI, adapted from (Maas et al., 2017), showing the outcome domains and individual measures used in CENTER-TBI.

Figure 1.1: Multi-dimensional assessment of TBI outcome



## 1.2. Aims of thesis

A number of aims were outlined for CENTER-TBI during the project planning phase. Furthermore, a manual for data access, study plan proposals, and publication requests was created, and researchers were responsible for submitting study proposals for acceptance by the CENTER-TBI Management Committee. The CENTER-TBI project aims were defined during the planning phase, however studies for particular work streams were not fully specified at this stage. Thus, during project implementation there was scope to develop specific research questions and methods for the studies presented in this thesis. The studies in this thesis were developed in the first year of the PhD and put forward to the CENTER-TBI Management Committee in three separate study proposals. The approved proposals are listed on the CENTER-TBI website and are titled and numbered as follows: Agreement between approaches for rating the GOSE in CENTER-TBI (75); The GOSE as a clinician-reported or patient-reported outcome (76); and Relation of GOSE level of disability to data quality and validity of outcomes in adult TBI (77).

The CENTER-TBI work plan was ambitious with respect to the collection of outcomes. Data collection for the CENTER-TBI follow-ups was therefore done in a pragmatic and flexible way (Maas et al., 2015). The GOSE could be completed as a structured interview and/or respondent-completed questionnaire. Furthermore, at follow-up, investigators considered whether specific outcome measures were appropriate for use with individual patients, and assessments were attempted if patients were judged to be capable of completing them. The pragmatic way in which outcomes were collected for CENTER-TBI provided an opportunity to examine two main issues of relevance to observational TBI studies: (1) the comparability of different approaches to measuring global functional outcome on the GOSE; and (2) the usability of individual outcome measures across the spectrum of recovery after TBI. These issues were selected for investigation in this thesis because they were consistent with the CENTER-TBI objectives, and because both issues can potentially result in biased study findings (e.g., information collected via the GOSE structured interview and GOSE questionnaire might not be equivalent, and TBI patients can be difficult to follow-up in longitudinal studies, potentially

resulting in selective attrition of patients with particular characteristics (Corrigan et al., 2003; Krellman et al., 2014)).

There is limited research concerning the comparability of clinician ratings and patient reports on the GOSE. Furthermore, the usability of individual outcome measures across the spectrum of disability after TBI has not been examined in the context of TBI research. In light of this, the studies presented in this thesis were designed to investigate the measurement of global functional outcome and consider the implementation of multi-dimensional outcome assessment in different contexts of use. The ISPOR Task Force framework for COAs was used to investigate the usability of ClinROs (i.e., structured interviews), PROs (i.e., questionnaires), and PerfOs (i.e., cognitive and functional mobility assessments) in TBI, and assessments were considered to be multi-dimensional if they measured two or more outcome domains.

This thesis has three broad aims:

1. To assess how COAs, including the GOS/GOSE, have been used and reported in acute and post-acute clinical trials in TBI, and to consider the extent to which multi-dimensional outcome assessment has been implemented in these studies
2. To compare clinician ratings and respondent reports of global functional outcome in TBI, by:
    - Exploring whether information obtained via the GOSE structured interview provides added value over the GOSE questionnaire
    - Examining how the GOSE structured interview and GOSE questionnaire relate to prognostic factors and other outcome measures
3. To examine the usability of multi-dimensional outcome measures in relation to level of functional recovery after TBI

# CHAPTER 2

## Randomized controlled trials in adult traumatic brain injury: A systematic review on the use and reporting of clinical outcome assessments[1]

[1]**This chapter has been published:** Horton, L., Rhodes, J. & Wilson, L. (2018). Randomized controlled trials in adult traumatic brain injury: A systematic review on the use and reporting of clinical outcome assessments. *Journal of Neurotrauma*. 35: 2005-2014.

This chapter is a systematic review on the patterns of use and reporting quality of COAs in clinical trials in adult TBI. The findings from this review demonstrate the need for increased consistency and improved reporting of outcome measures in TBI trials. The findings also highlight the limited use of multi-dimensional outcome assessment in published RCTs, especially in acute study settings.

## 2.1. 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 ($n \geq 100$) 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. Multi-dimensional 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.

## 2.2. Introduction

There is increasing awareness of the importance of clinical outcome assessments (COAs) in evaluating health care interventions (Walton et al., 2015). Furthermore, in clinical research, there is increasing emphasis both on standardizing data collection, and on multi-dimensional outcome assessment including the patient's perspective (Sheehan et al., 2016). In recognition of the central role of outcomes in clinical studies, the US Food and Drug Administration (FDA) has implemented a qualification program for COAs (U.S. Food & Drug Administration, 2014). The terminology developed to describe COAs is outlined in a Task Force report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (Walton et al., 2015) and summarized in Chapter 1 of this thesis (see Tables 1.1 & 1.2). 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 (Walton et al., 2015).

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 multi-dimensional description of outcome (Clinical Data Interchange Standards Consortium, 2015; Hicks et al., 2013; Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017; Tosetti et al., 2013; Wilde et al., 2010). At its simplest, multi-dimensional 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, health-related quality of life, psychological status, TBI symptoms, cognition, and physical functioning (Hicks et al., 2013; Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). Current common data elements (CDEs) recommendations for TBI outcomes include clinician-reported outcomes (ClinROs), patient-reported outcomes (PROs), and performance outcomes (PerfOs) (Hicks et al., 2013). 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 in specific TBI study types (Hicks et al., 2013). 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 (Maas et al., 2011).

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 (Alali et al., 2015; Bragge et al., 2016; McMillan et al., 2016; Nichol et al., 2011). However, the GOS/GOSE has been criticized for being insensitive to subtle changes in functioning (Alali et al., 2015; Maas et al., 2017; McMillan et al., 2016; Menon & Maas, 2015; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017; Nichol et al., 2011; Weir et al., 2012; Wilson, Pettigrew, & Teasdale, 2000). 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 multi-dimensional 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 (Schulz, Altman, Moher, & Group, 2010) to evaluate whether the reporting quality of methodological characteristics in adult TBI trials has improved over time (Lu et al., 2015). 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.

## 2.3. Methods

### 2.3.1. *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 (Bragge et al., 2016; Lu et al., 2015). 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, (Covidence, 2017) where the titles and abstracts were screened independently by two reviewers 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 (normally 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

### 2.3.2. *Data Extraction*

Data extraction was carried out independently by two reviewers. 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.

### 2.3.3. *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.

### 2.3.4. *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 (Higgins et al., 2011). This approach is consistent with that used in a recent scoping review of RCTs in moderate-to-severe TBI (Bragge et al., 2016).

### 2.3.5. *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 multi-dimensional 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 (Freemantle, Calvert, Wood, Eastaugh, & Griffin, 2003; Temkin et al., 2007), or analyzed jointly using a global test (Bagiella et al., 2010a; Zafonte et al., 2012).

### 2.3.6. *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, (Calvert et al., 2013) CONSORT 2010 Statement, (Schulz et al., 2010) 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. Expanded items are marked with asterisks in Table 2.3.

### 2.3.7. *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 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).

### 2.3.8. *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®.

## 2.4. Results

### 2.4.1. *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 2.1.

### 2.4.2. *Study characteristics*

The general characteristics of the studies are presented in Appendix 2. Key study characteristics are summarised in Table 2.1. 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).

Figure 2.1: Systematic review study selection process

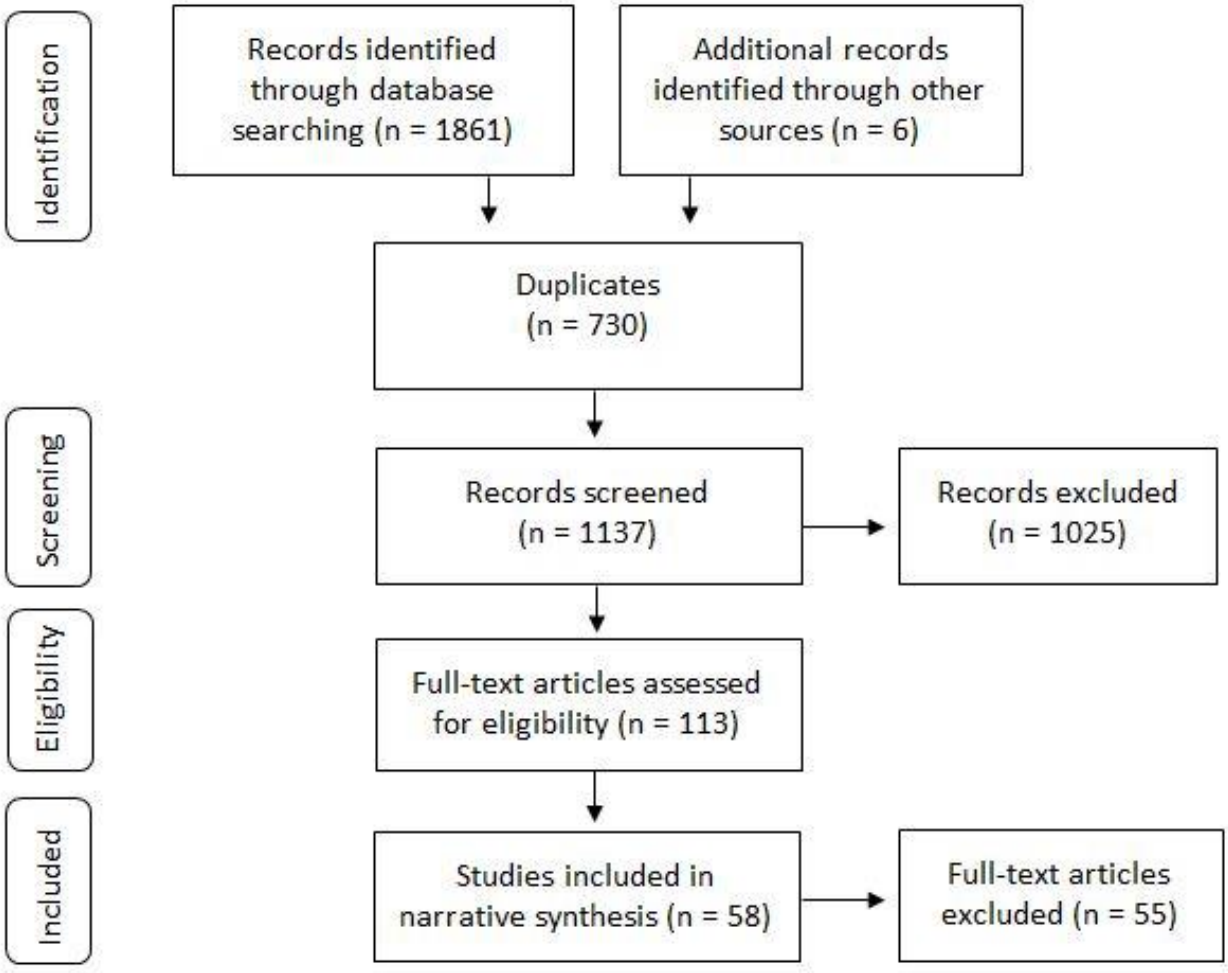


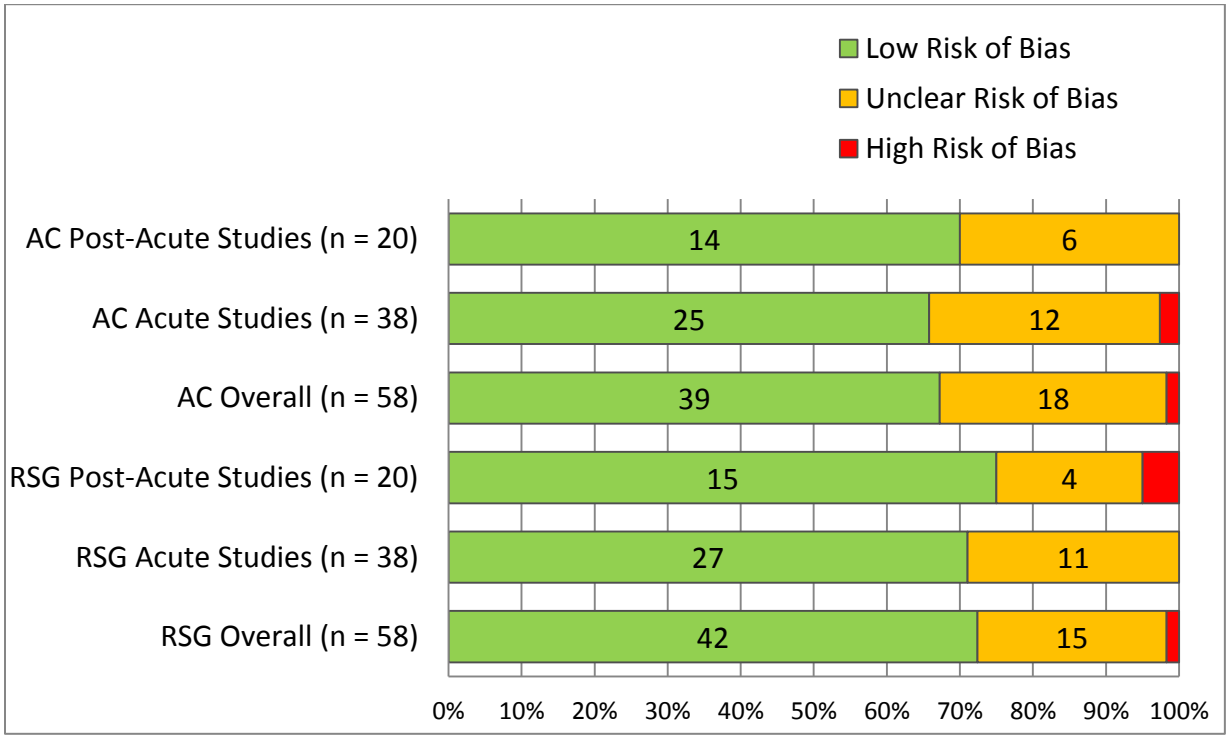
Table 2.1: Key study characteristics

| | 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%) |

### 2.4.3. *Risk of Bias*

Risk of selection bias for each study is presented in Appendix 2. Figure 2.2 shows that random sequence generation (RSG) 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 (AC) 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.

Figure 2.2: Risk of Bias for Allocation Concealment and Random Sequence Generation

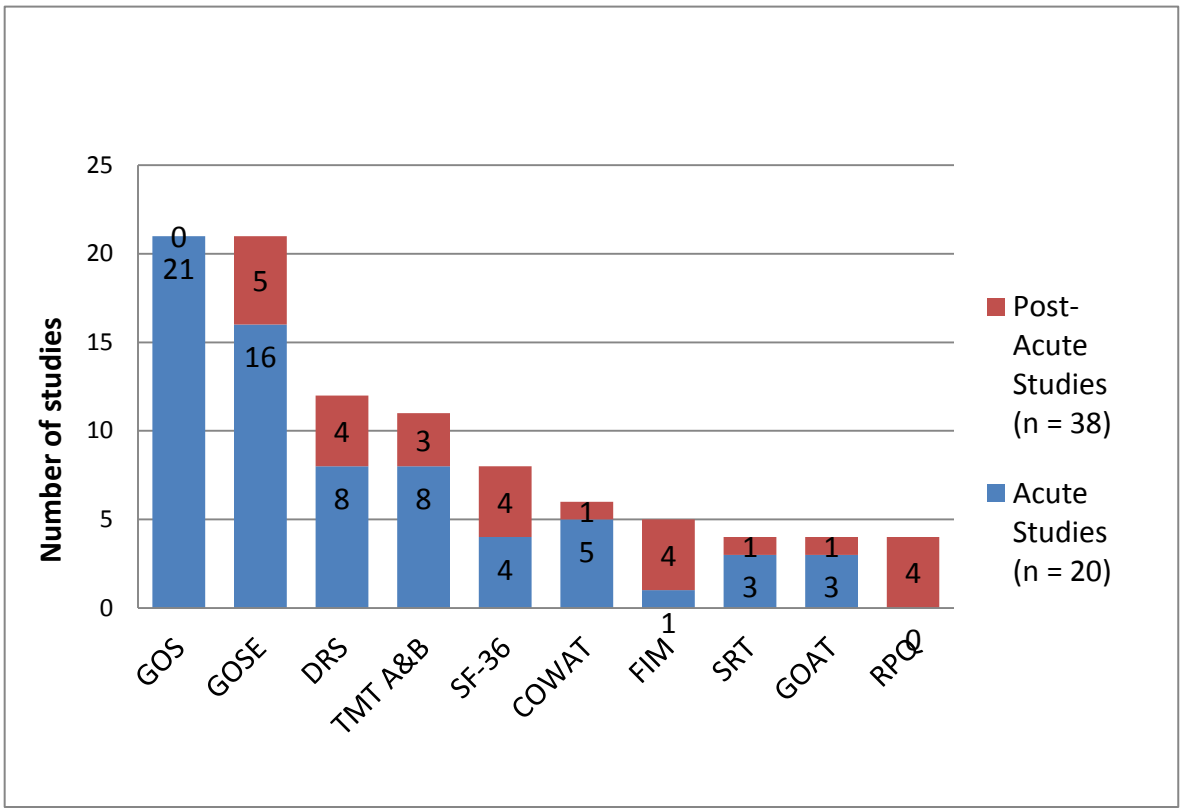



### 2.4.4. *Patterns of use of COAs*

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 Appendix 3. 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 2.3 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.

Figure 2.3: Most commonly used COAs




A total of 30 studies used multi-dimensional outcomes (12 acute studies, 18 post-acute studies). Twenty-four of the studies with multi-dimensional outcomes reported individual outcome measures; 5 studies used a composite multi-dimensional outcome; and 1 study used a

global test to create a multi-dimensional outcome, i.e., the TBI Clinical Trials Network Core Battery (Bagiella et al., 2010a; Zafonte et al., 2012).

The COAs were classified according to whether they were ClinROs, PROs, PerfOs, or ObsROs. Table 2.2 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).

Table 2.2: RCT findings for different types of COA and study setting

| **Type of COA and study setting** | | **Primary COA *n* (%) of RCTs[A]** | **All COAs *n* (%) of RCTs[B]** |
|---|---|---|---|
| **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[C]** | **Acute** | 3 (5%) | 9 (15%) |
| | **Post-acute** | 7 (15%) | 11 (19%) |
| **TOTALS** | | **55 (100%)** | **58 (100%)** |

[A]Data are *n* (%) of the 55 studies using COAs as a primary outcome
[B]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)
[C]Includes all outcomes that comprised more than one type of COA (e.g., ClinRO and PRO)

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, 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).

### 2.4.5. *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 2.3. 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 2.3 Legend).

Table 2.3 shows that 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).

Table 2.3: 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] | | | |
| 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[B] | | | |
| 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. Baseline COA data provided, if collected[C] | 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, [D]relative effect size stated | 19 (79%) | 1 (100%) | 20 (80%) |
| ii. For binary outcomes, [D]absolute 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 marked with asterisks

[A] Applicable in 55 studies (35 acute studies; 20 post-acute studies)

[B] Applicable in 33 studies (16 acute studies; 17 post-acute studies)

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

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

### 2.4.6. *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 2.4 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 format (GOS) in 21 studies (GOS guided interview = 20 studies; GOS 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 2.4 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 questionnaires were used 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).

Figure 2.4: GOS/GOSE patterns of use for the original 5-point rating, postal questionnaires for the GOS and GOSE, and the GOSE structured interview

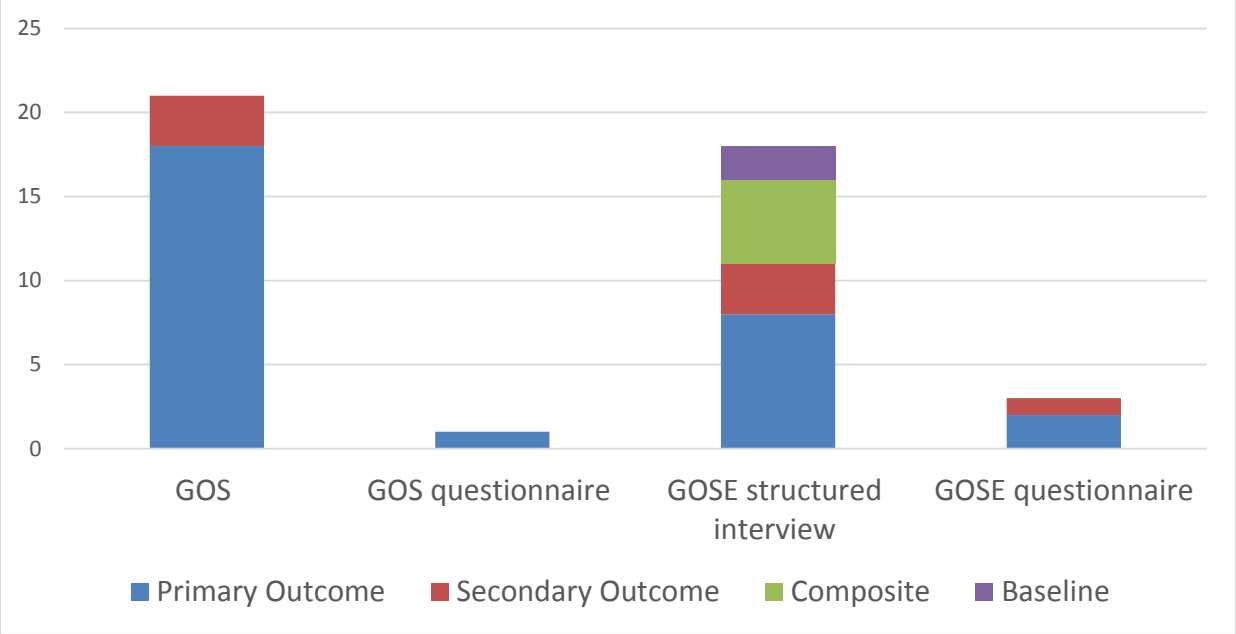


Table 2.4: GOS/GOSE patterns of use and completeness of reporting

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

*Data are number (%) of the 39 studies that used the GOS/GOSE; SD = Severe Disability

## 2.5. Discussion

This review aimed to evaluate how clinical outcome assessments (COAs) have been used and reported in RCTs in adult TBI from 2000 onwards. In total, 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 (i.e., context of use). 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 (Tosetti et al., 2013). The frequent use of the GOS/GOSE in the reviewed studies is not surprising and is consistent with the subsequent CDE recommendations for TBI (Hicks et al., 2013). 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 (Wilde et al., 2010), the number of outcome CDEs has grown, and compartmentalisation of different areas of TBI assessment remains.

As multi-dimensional 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 (Maas et al., 2017; Menon & Maas, 2015; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). 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 multi-dimensional outcomes: most of the post-acute studies

used multi-dimensional outcomes, whereas a minority of the acute studies used multi-dimensional outcomes. Most studies with multi-dimensional outcomes used separate COAs to measure multiple outcome domains, and composite multi-dimensional outcomes were relatively rare. 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 (U.S. Food & Drug Administration, 2009), 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 (Bagiella et al., 2010a). The findings from the review demonstrate that multi-dimensional outcomes are not used universally in TBI trials. Moreover, multi-dimensional outcomes are more commonly used 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 (Walton et al., 2015).

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) (Wilson, Pettigrew, & Teasdale, 1998). Inter-rater variability is another important issue when assigning outcome and interviewer training is required to achieve high levels of agreement between assessors (Wilson et al., 2007). Extracranial concomitant injury can have an effect on functional outcome (Dacey et al., 1991; Leong, Mazlan, Abd Rahim, & Ganesan, 2013). 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 (Wilson et al., 1998). Both approaches have been used in RCTs, with some trials including extracranial injuries in the assessment (e.g. the Dexanabinol Trial) (Maas et al., 2006), and others excluding the influence of non-brain

injuries (e.g. PROTECT III) (Wright et al., 2014). 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 questionnaire and structured telephone interview can be used as a reliable means of assigning functional outcome in the absence of face-to-face contact (Pettigrew, Wilson, & Teasdale, 2003; Wilson, Edwards, Fiddes, Stewart, & Teasdale, 2002). Nevertheless, robust comparisons between these different methods of GOSE data collection have not been made. The GOSE questionnaire is increasingly used in TBI trials (Andrews et al., 2015; Gregson et al., 2015; Hutchinson et al., 2017; Mendelow et al., 2015). However, as impaired self-awareness can affect TBI patients' ability to provide an accurate self-report (Prigatano, 2005b), the GOSE questionnaire may not be appropriate in all contexts. Disagreements between GOSE questionnaires and GOSE interviews may occur if questionnaires are self-completed by patients who lack insight into their own functional limitations (Wilson et al., 2002), and investigators should take this into consideration when deciding which method of GOSE data collection to use in future TBI studies.

### 2.5.1. *Limitations*

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 (Hicks et al., 2013; Wilde et al., 2010), and the CONSORT guidelines for RCT reporting (Calvert et al., 2013; Schulz et al., 2010), 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.

### 2.5.2. *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 (Hicks et al., 2013). 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 (Calvert et al., 2013; Schulz et al., 2010). As the GOSE is currently recommended as the core COA within multi-dimensional outcome assessments in TBI (Hicks et al., 2013; Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017), further research into how it is used is now warranted, and its associations with other outcome domains should also be ascertained.

# CHAPTER 3

## Multi-dimensional TBI outcomes: Research methodology

This chapter outlines the research methodology used in this thesis and provides an overview of the measures used in the studies reported in Chapters 4, 5, and 6.

## 3.1. CENTER-TBI recruitment

All patients described in this thesis were recruited to CENTER-TBI (Maas, Menon, et al., 2015). CENTER-TBI comprises a core study of 4509 TBI patients recruited between December 2014 and December 2017 via 65 sites across 18 countries in Europe, as well as a registry providing basic observational data on TBI patients presenting to sites involved in the CENTER-TBI study between December 2014 and December 2017 (*n*=22,782). Patients recruited to the CENTER-TBI core study were differentiated by clinical pathway into three strata: (1) the emergency room (ER) stratum, comprising 848 patients who were seen in the ER and discharged without being admitted to hospital; (2) the admission stratum, comprising 1523 patients who were admitted to hospital, but not to the intensive care unit (ICU); and (3) the ICU stratum, comprising 2138 patients who were admitted to ICU. Inclusion and exclusion criteria for CENTER-TBI are presented in Table 3.1.

Table 3.1: Inclusion and exclusion criteria of CENTER-TBI (Reproduced from Maas et al., 2015)

| | **Inclusion criteria** | **Exclusion criteria** |
|---|---|---|
| **CENTER-TBI core study (*n*=4509)** | Clinical diagnosis of TBI<br>Clinical indication for CT scan<br>Presentation within 24 hours of injury<br>Informed consent obtained according to local and national requirements | Severe pre-existing neurological disorder that would confound outcome assessments |
| **CENTER-TBI registry (*n*=22, 782)** | Clinical diagnosis of TBI<br>Clinical indication for CT scan | None |

## 3.2. Measures used

The sections below provide an overview of the CENTER-TBI measures and describe how they were used in this thesis. The acute measures are described in Section 3.2.1 and the outcome measures are described in Section 3.2.2.

### 3.2.1. *Acute measures*

Acute measures used in this thesis included the American Society of Anaesthesiologists' (ASA) classification of Physical Health (Dripps, 1963), Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974), CT abnormality, and Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) (Baker, O'Neill, Haddon, & Long, 1974a). These measures were collected by medical staff in the 65 acute hospitals involved in patient recruitment for CENTER-TBI. The measures are described below.

*American Society of Anaesthesiologists' (ASA) classification of Physical Health*

Pre-injury physical health status was assessed using the ASA classification of Physical Health, which categorises physical health according to severity of systemic disease (Dripps, 1963). ASA Physical Health classifications are as follows: a normal healthy patient; a patient with mild systemic disease (mild disease with no substantive functional limitation, e.g., treated hypertension); a patient with severe systemic disease (substantive functional limitations a result of disease, e.g., poorly treated diabetes, morbid obesity); a patient with a severe systemic disease that is a constant threat to life (functional limitation from severe life-threatening disease, e.g., ongoing cardiac ischemia) (American Society of Anesthesiologists, 2014; Dripps, 1963).

*Glasgow Coma Scale (GCS)*

TBI severity was classified using the GCS (Teasdale & Jennett, 1974). The GCS has three components: eye opening, best verbal response, and best motor response. Each component is assessed using a standardised approach and GCS total scores range from 3 to 15. Conventionally, GCS scores of 3-8 are classified as severe TBI, scores of 9-12 are classified as moderate TBI, and scores of 13-15 are classified as mild TBI (Teasdale et al., 2014; Teasdale, Murray, Parker, & Jennett, 1979). This thesis used baseline GCS scores which were calculated centrally by a review panel for use by CENTER-TBI investigators. The baseline GCS scores were derived using the International Mission for Prognosis And Clinical Trial (IMPACT) approach to combining scores at different time periods (Marmarou et al., 2007).

*CT Abnormality*

CT abnormality was analysed by Icometrix (Icometrix, 2019) and assessed by a central review panel according to the NINDS CDEs (Duhaime et al., 2010). In this thesis, CT abnormality indicates whether any of the following CDEs were present: mass lesion, epidural hematoma, subdural hematoma (acute), subdural hematoma (sub-acute/chronic), subdural collection mixed density, contusion, traumatic axonal injury, subarachnoid haemorrhage, intraventricular haemorrhage, midline shift or cisternal compression.

*Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS)*

The AIS was used to quantify the overall severity of injury in multiple body areas, including the head/neck, face, chest, abdomen, extremities, and external regions, while the overall severity of anatomical injuries was measured using the ISS (Baker, O'Neill, Haddon, & Long, 1974). AIS scores for each body region range from 0 (no injury); 1 (minor: no treatment needed); 2 (moderate: requires only outpatient treatment); 3 (serious: requires non-ICU hospital admission); 4 (severe: requires ICU observation and/or basic treatment); 5 (critical: requires intubation, mechanical ventilation or vasopressors for blood pressure support); to 6 (unsurvivable). The ISS ranges from 0 to 75 and the total ISS is computed by taking the three most severely injured body regions, squaring their AIS scores, and adding them together. Total ISS scores >7 are indicative of severe injury and total ISS scores >15 are indicative of major trauma (Palmer, 2007).

This thesis distinguished between injuries to the head/neck/cervical spine and injuries to other body regions. Firstly, AIS scores were used to describe the severity of head injury (composite AIS scores were calculated by combining AIS scores for the head/neck, brain, and cervical spine regions). Secondly, total ISS scores for extracranial injuries were calculated using the three worst AIS scores for peripheral body regions and excluding the head/neck/cervical spine regions. Thirdly, total ISS scores were used to describe overall injury severity.

### 3.2.2. *Outcome measures*

The CENTER-TBI outcome measures reflect the multi-dimensional impact of TBI and include measures of global functional outcome, generic and disease-specific HRQoL, psychological status, TBI symptoms, cognition, and physical functioning. For practical purposes, the outcome measures were categorised into two types: questionnaires/interviews and neuropsychological assessments. The questionnaires/interviews and neuropsychological assessments were administered at several time points after injury, including 2-3 weeks (ER stratum only); 3 months (ER, admissions & ICU strata); 6 months (ER, admissions & ICU strata); 12 months (admissions & ICU strata); and 24 months (admissions & ICU strata). Magnetic Resonance Imaging (MRI) was also used in a sub-group of CENTER-TBI study sites to characterise TBI pathology.

Table 3.2 illustrates the schedule for the CENTER-TBI outcome assessments by stratum (ER/admission/ICU), type of assessment, time point, and type of study site (i.e. MRI sites/all sites).

Table 3.2: CENTER-TBI core study outcome assessment schedule

| | | **2-3 weeks** | **3 months** | **6 months** | **12 months** | **24 months** |
|---|---|---|---|---|---|---|
| **ER** | **Neuropsychology** | MRI sites | MRI sites | All sites | | |
| | **Questionnaires** | All sites | All sites | All sites | | |
| **Admission** | **Neuropsychology** | | | All sites | MRI sites | MRI sites |
| | **Questionnaires** | | All sites | All sites | All sites | MRI sites |
| **ICU** | **Neuropsychology** | | | All sites | MRI sites | MRI sites |
| | **Questionnaires** | | All sites | All sites | All sites | MRI sites |

Due to barriers such as copyright, cost, and language restrictions, it was not possible to adhere to NINDS CDE recommendations for all CENTER-TBI outcome measures (Hicks et al., 2013; Maas, Menon, et al., 2015; Maas et al., 2017; Wilde et al., 2010). The CENTER-TBI outcome measures that are included in the CDEs for adult TBI are listed in Table 3.3.

Table 3.3: CENTER-TBI outcome measures included in NINDS CDEs for adult TBI

| **Outcome measure** | **NINDS CDE Outcome Domain** |
|---|---|
| Glasgow Outcome Scale – Extended (GOSE) | Global outcome |
| 36-item Short Form Survey – Version 2 (SF-36v2) | |
| Quality of Life After Brain Injury (QOLIBRI) | Health-related quality of life |
| Galveston Orientation and Amnesia Test (GOAT) | Recovery of consciousness |
| Rey Auditory Verbal Learning Test (RAVLT) | Neuropsychological impairment |
| Trail Making Test (TMT) | |
| Rivermead Post-Concussion Symptom Questionnaire (RPQ) | TBI-related symptoms |

CENTER-TBI is one of the largest observational studies ever to be conducted in TBI, and an international collaborative effort was required to obtain follow-ups in the 65 participating study sites. The study plan called for a total of 12,350 follow-ups employing interviews and questionnaires, and a subset of 5,850 follow-ups that required neuropsychological assessment. With over 2500 clinical, treatment and outcome variables, data collection for CENTER-TBI was complex and challenging (Burton, 2017). Outcomes were collected by trained study personnel. Methods of collecting outcomes were described in the Standard Operating Procedures manual for the project. This manual was available to investigators when data collection commenced.

The author of this thesis was responsible for obtaining follow-ups for patients recruited via NHS Lothian.

The CENTER-TBI outcome measures included in this thesis are summarised below with descriptions of how they were scored and used. The outcome measures are organised according to the CDE outcome domains (Wilde et al., 2010). All CENTER-TBI outcome measures are validated for use in research, but not all of them have been validated in the context of adult TBI.

## Global outcome

### Glasgow Outcome Scale - Extended (GOSE) structured interview and questionnaire

***Description***

The GOSE is used to measure of global functional outcome following TBI. It can be completed as a structured interview (Wilson et al., 1998) or as a self-completion questionnaire (Wilson et al., 2002).

The GOSE structured interview uses a standardised interview format to enable the assessor to objectively assign patients to the outcome category that reflects their current functional status (Wilson et al., 1998). Outcome is assigned according to: the individual's current level of independence in activities of daily living both inside and outside the home (i.e., cooking, dressing, shopping, travelling); their ability to participate in major life roles such as work, social and leisure activities, and relationships with family and friend; and whether they have returned to 'normal' life (i.e., their previous level of functioning). The GOSE structured interview can be completed face-to-face or via telephone and can be completed with the patient and/or a proxy informant such as a relative or caregiver. It is designed to be administered and scored by a researcher or clinician, and the interviewer can exercise their professional judgement, where appropriate (Wilson et al., 1998). The inter-rater and test-retest reliability for the GOSE structured interview is high (Weighted Kappa ($\kappa_w$) ranges from 0.72 to 0.92) (Pettigrew et al., 2003; Wilson et al., 1998; Wilson et al., 2007). Furthermore, the GOSE structured interview has

substantial correlations with measures of post-traumatic amnesia (rho = -0.52), disability (rho = -0.89), HRQoL (rho = 0.47 - 0.71), depression (rho = -0.64), general health (rho = -0.59), and reported head-injury symptoms and problems (rho = 0.37 to 0.69), and modest correlations with neurocognitive tests (rho = -0.19 to 0.42) (Wilson et al., 2000).

The GOSE postal questionnaire is an alternative method of collecting information about global functional outcome, which can be used on its own, or in conjunction with telephone or face-to-face contact (Wilson et al., 2002). It can be completed by the TBI patient and/or a proxy informant. It can also be completed via post or on-line, providing a means of easily and inexpensively obtaining information about outcome instead of, or in addition to, telephone or face-to-face contact. The GOSE questionnaire comprises 14 questions about the patient's independence inside and outside the home, as well as their participation in major life roles, and their return to 'normal' life. The test-retest reliability of the GOSE postal questionnaire is high ($\kappa_w = 0.98$) and it has high levels of agreement with the GOSE structured interview ($\kappa_w = 0.92$) (Wilson et al., 2002).

***Scoring***

The GOSE has eight outcome categories, ranging from worst (i.e., death) to best (i.e., upper good recovery) (see Figure 3.1). Scores are determined by identifying the area of greatest limitation, and by discounting pre-injury limitations. Scores can be assigned on the GOSE if information is missing, although some judgement may be required and confidence in the rating may decrease if items are not completed. The GOSE structured interview is usually rated by the interviewer, but it can also be scored centrally using an algorithm (Wilson et al., 1998; Wilson et al., 2007). The GOSE questionnaire can be rated using the criteria from the GOSE structured interview as a guideline, or it can be scored electronically using an algorithm (Wilson et al., 2002). The categories 'vegetative state' and 'lower severe disability' are collapsed when the GOSE questionnaire is scored, because the self-completion form does not distinguish between patients in these categories.

For CENTER-TBI, it was possible to complete the GOSE as a structured interview or questionnaire, although priority was given to the GOSE structured interview (Maas, Menon, et al., 2015). A pragmatic approach to data collection was used and the GOSE could be completed face-to-face, via telephone, or via post, either with the patient alone, with a proxy informant alone, or with the patient and a proxy together (Maas, Menon, et al., 2015). Decisions about mode of data collection were made locally on a patient-by-patient basis and were influenced by factors such as TBI severity, the patient's ability to self-report, the patient's availability for face-to-face follow-up visits, and logistic considerations (e.g., travel time). CENTER-TBI investigators were encouraged to complete both versions of the GOSE, if possible. The flexible approach to data collection was employed as a means of ensuring good follow-up rates for the study and to allow comparisons to be made between different GOSE approaches.

Composite GOSE scores were calculated centrally for the CENTER-TBI study as part of the data curation process (Wilson & Horton, 2018). The composite GOSE scores were created using the information available to maximise follow up rates. The categories of 'vegetative state' and 'lower severe disability' were collapsed when creating composite ratings and available information was used in the following order of precedence:

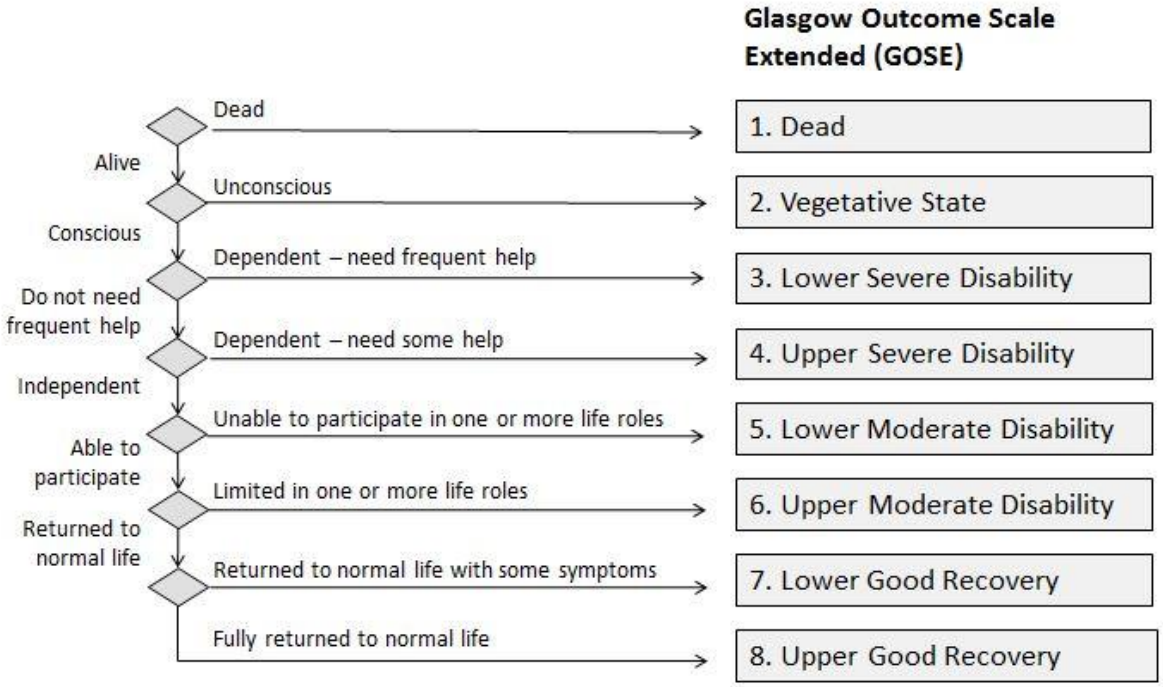
1. Central scoring of GOSE structured interview completed by investigators
2. Central scoring of respondent-completed GOSE questionnaires
3. Interviewer ratings for survivors when neither the GOSE structured interview or GOSE questionnaire was completed

***Use in this thesis***

Study 1 used the GOSE interview and GOSE questionnaire. Possible outcomes for this study ranged from 'vegetative state' to 'upper good recovery.' GOSE interviews were rated locally by trained interviewers in accordance with published guidelines (Wilson et al., 1998). The GOSE questionnaire was scored in two ways. Firstly, it was scored using the standard algorithm developed by Wilson and colleagues (Wilson et al., 2002). Secondly, it was scored using a revised algorithm (described in Chapter 4). Study 2 also used the GOSE structured interview

(rated locally by trained interviewers in accordance with published guidelines (Wilson et al., 1998)) and GOSE questionnaire (scored centrally using the standard algorithm (Wilson et al., 2002)). Possible outcomes for Study 2 ranged from 'lower severe disability' to 'upper good recovery.' Study 3 used the composite GOSE score described above. Possible outcomes for this study ranged from 'lower severe disability' to 'upper good recovery.'

Figure 3.1: GOSE: Schematic diagram of the decisions involved in assigning an outcome




**36-Item Short Form Survey - Version 2 (SF-36v2)**

***Description***

The SF-36v2 is a generic measure of health-related quality of life, which has been used across many types of health conditions (Ware & Sherbourne, 1992). It is categorised as a measure of global outcome in the NINDS CDEs. The SF-36v2 is self-completed by the patient and provides an assessment of their perceived health and wellbeing. It is the most frequently used patient-reported outcome across registered clinical trials (Scoggins & Patrick, 2009), and in TBI studies, it is the most frequently used measure of health-related quality of life (Polinder, Haagsma, van

Klaveren, Steyerberg, & van Beeck, 2015). The SF-36 has a 4-week reference period. It comprises eight domains, including Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health. HRQoL can be summarised by computing a physical component summary (PCS) score and mental component summary (MCS) score. The SF-36v2 has high levels of internal consistency in TBI (Cronbach's alpha (α) = 0.79 to 0.93) (Findler, Cantor, Haddad, Gordon, & Ashman, 2001; MacKenzie et al., 2002; von Steinbüchel et al., 2016). Furthermore, the physical health sub-scales have been found to correlate highly with the PCS score ($r$ = 0.55 to 0.83) while the mental health sub-scales correlate highly with the MCS score ($r$ = 0.68 to 0.89) (MacKenzie et al., 2002).

***Scoring***

The SF-36v2 was scored using Optum Software and norm-based scoring algorithms. Each health domain and summary component measure has a mean score of 50 and a standard deviation of 10. The minimum score for the PCS and MCS is 2 and the maximum score is 74. Higher scores indicate better health-related quality of life. The Full Missing Score Estimation (MSE) method was used to deal with missing data.

***Use in this thesis***

The SF-36v2 was used in Studies 2 and 3 to measure patient-reported HRQoL.

## Health-related quality of life (HRQoL)

### Quality of Life after Brain Injury Scale (QOLIBRI) and QOLIBRI Overall Scale (QOLIBRI-OS)

***Description***

The QOLIBRI is a TBI-specific measure of HRQoL (von Steinbüchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Sarajuuri, et al., 2010). It was developed to tap into the quality of life domains important to TBI patients, as existing generic HRQoL measures, such as the SF-36, are not designed to address condition-specific issues. The QOLIBRI is completed by the patient via

self-rating. It comprises 37 items and has 6 domains, including four 'satisfaction' scales (i.e., cognition, self, daily life and autonomy, and social relationships), and two 'bothered' scales (i.e., emotions and physical problems). The QOLIBRI has a 1-week reference period. Thus, respondents must be able to recall how they have been feeling over the week preceding assessment. The internal consistency of the QOLIBRI ranges from 0.75 ('physical problems') to 0.89 ('cognition' and 'self') (total score = 0.95) and the test-retest reliability ranges from 0.78 ('emotions') to 0.85 ('physical problems') (total score = 0.91). All sub-scales correlate with the GOSE (0.19 – 0.42), Hospital Anxiety and Depression Scale (HADS) anxiety sub-scale (-0.59), HADS Depression Scale -0.67), SF-36 PCS (0.63), and SF-36 MCS (0.61), and the QOLIBRI total score is associated more strongly with the SF-36 MCS (0.61) than the SF-36 PCS (0.49) (von Steinbüchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Formisano, et al., 2010).

The QOLIBRI-OS (von Steinbüchel et al., 2012) is the short version of the QOLIBRI comprising 6 items that cover the following domains: physical condition, cognition, emotions, daily life and autonomy, personal and social life, and current situation and future prospects. It also has a 1-week reference period. The QOLIBRI-OS has high levels of internal consistency ($\alpha = 0.86$) and test-retest reliability (0.81). Furthermore, it correlates strongly with the QOLIBRI total score ($r = 0.87$), and with the GOSE, SF-36 and HADS (r=0.54 to -0.76) (von Steinbüchel et al., 2012).

***Scoring***

Responses for the QOLIBRI and QOLIBRI-OS are recorded on a 5-point Likert-type scale ranging from 'not at all' to 'very' and then summed and converted to total scores that range from 0 to 100. Higher scores on the 'satisfaction' scale indicate better HRQoL, while higher scores on the 'bothered' scale are indicative of poorer HRQoL. The QOLIBRI has recently been mapped against the normative scoring criteria for the SF-36 to aid in the interpretation of QOLIBRI scores: QOLIBRI total scores below 60 are considered to be representative of impaired HRQoL (Wilson et al., 2017). In CENTER-TBI, prorating was used if up to one third of items were missing on the QOLIBRI and QOLIBRI-OS.

***Use in this thesis***

The QOLIBRI and QOLIBRI-OS were used in Studies 2 and 3 to measure TBI-specific, patient-reported HRQoL.

## Psychological status

### Post-Traumatic Stress Disorder Checklist-5 (PCL-5)

***Description***

The PCL-5 is a self-report inventory for measuring the severity of post-traumatic stress disorder (PTSD) symptoms (Weathers et al., 2013). The earlier version of the inventory, the PCL (Weathers, Litz, Herman, Huska, & Keane, 1993), is one of the most widely used instruments for measuring self-reported PTSD symptoms. The PCL-5 was developed in 2013 to reflect the revised diagnostic criteria for PTSD in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). It comprises 20 items and 4 sub-scales which relate to clusters B-E in the DSM-5: intrusion (5 items), avoidance (2 items), negative alterations in cognition and mood (7 items), and alterations in arousal and reactivity (6 items). The PCL-5 has a 1-month reference period and responses relate to a specific stressful event (i.e., the event which caused the TBI). The PCL-5 has been shown to have high levels of test-retest reliability ($r$ = 0.82) and internal consistency ($\alpha$ = 0.94), and is strongly associated with other measures of PTSD symptoms ($r$ = 0.84 to 0.85) and measures of anxiety and depression ($r$ = 0.40 to 0.60), when used with trauma-exposed college students (Blevins, Weathers, Davis, Witte, & Domino, 2015).

***Scoring***

Responses for each item are recorded on a 5-point Likert-type scale and include: 'not at all,' 'a little bit,' 'moderately,' 'quite a bit,' and 'extremely.' Total symptom severity scores range from 0 to 80, and higher scores reflect greater severity. Severity scores can also be calculated for each symptom cluster. Items rated as 'moderately' or higher are used to make provisional PTSD diagnoses. Cut-off scores have been generated for the PCL-5 relative to the DSM-5 diagnostic criteria for PTSD: a score of 33 has been found to be optimally efficient for detecting PTSD (Wortmann et al., 2016). In CENTER-TBI, PCL-5 scores were valid if up to 5 items were

missing. Consistent with the four DSM-5 symptom clusters for PTSD, no more than 1 missing item was permitted in items 1-5; zero missing items were permitted in items 6-7; no more than 2 missing items were permitted in items 8-14; and no more than 2 missing items were permitted in items 15-20.

***Use in this thesis***

The PCL-5 was used in Studies 2 and 3 as a self-reported measure of the severity of PTSD symptoms in TBI patients.

**Patient Health Questionnaire-9 (PHQ-9)**

***Description***

The PHQ-9 is a self-report instrument for measuring depression severity in clinical settings (Kroenke, Spitzer, & Williams, 2001). It is unidimensional and comprises 9 items which relate to each of the DSM-5 diagnostic criteria for clinical depression. It has a 2-week reference period and responses are recorded on a 4-point Likert-type scale. Respondents are required to indicate how often they have been bothered by each of the 9 listed problems. If any item is endorsed, respondents are also required to indicate how difficult the problem(s) have made it for them to work, perform activities of daily living, and get on with others. Scores for each item range from 0 (not at all), 1 (several days), 2 (more than half the days), to 3 (nearly every day). The internal consistency of the PHQ-9 has been found to be high in primary care settings ($\alpha$=0.86) (Kroenke et al., 2001). Furthermore, when used with TBI patients, the PHQ-9 has good test-retest reliability ($r$ = 0.76 & $\kappa$=0.46) and correlates strongly with other measures of depression ($r$ = 0.78-0.90), functional limitation ($r$ = 0.59), and perceived general health ($r$ = 0.40) (Fann et al., 2005).

***Scoring***

Total scores range from 0 to 27 and higher scores are indicative of greater depression severity. Scores on the PHQ-9 can be interpreted in a variety of ways. Cut-off points have been recommended for mild (5-9), moderate (10-14), moderately severe (15-19), and severe

depression (20-27) (Kroenke & Spitzer, 2002). In CENTER-TBI, the PHQ-9 was scored if up to one third of items were missing. Missing values were substituted with the mean score of non-missing items and total scores were rounded to an integer.

***Use in this thesis***

The PHQ-9 was used in Studies 2 and 3 as a self-reported measure of the severity of depression symptoms in TBI patients.

**Generalized Anxiety Disorder-7 (GAD-7)**

***Description***

The GAD-7 is a self-report instrument for measuring the severity of generalized anxiety symptoms in clinical settings (Spitzer, Kroenke, Williams, & Lowe, 2006). It is unidimensional and comprises 7-items which relate to the DSM-5 diagnostic criteria for generalised anxiety disorder. Respondents indicate how often they have been bothered by each symptom during the last 2-weeks and responses are recorded on a 4-point Likert-type scale ranging from 0 (not at all), 1 (several days), 2 (more than half the days), to 3 (nearly every day). If any item is endorsed, respondents are also required to indicate on a 4-point scale how difficult the problem(s) have made their work, activities of daily living, and relationships with others. The GAD-7 has high test-retest reliability (intraclass correlation = 0.83) and internal consistency ($\alpha$= 0.92), and increasing anxiety scores are strongly associated with functional limitations and reduced HRQoL (Spitzer et al., 2006).

***Scoring***

Total scores range from 0 to 21, with higher scores indicating greater symptom severity. The cut-off for diagnosing generalized anxiety disorder in clinical populations is 10, and cut-off points of 5, 10 and 15 can be interpreted as indicative of mild, moderate, and severe levels of anxiety in clinical and general populations (Lowe et al., 2008; Spitzer et al., 2006). In CENTER-TBI, the GAD-7 was scored if up to one third of items were missing. Missing values were

substituted with the mean score of non-missing items and total scores were rounded to an integer.

***Use in this thesis***

The GAD-7 was used in Studies 2 and 3 as a self-reported measure of the severity of anxiety symptoms in TBI patients.

## TBI symptoms

### Rivermead Post-concussion Questionnaire (RPQ)

***Description***

The RPQ is a self-report instrument which was originally developed for measuring the severity of 16 post-concussion symptoms following mild or moderate TBI, including headaches, dizziness, nausea/vomiting, noise sensitivity, sleep disturbance, fatigue, irritability, feeling depressed/tearful, feeling frustrated/impatient, forgetfulness, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness (King, Crawford, Wenden, Moss, & Wade, 1995). Respondents are required to indicate the extent to which each of the 16 symptoms has been experienced in the last 7 days, and to consider whether each symptom is more of a problem since their head injury. The RPQ also includes 2 blank spaces for respondents to report any other difficulties they are currently experiencing. The inter-rater and test re-test reliability of the RPQ is high ($r$= 0.72 to 0.91) and total scores correlate strongly with measures of social and functional outcome (0.62 to 0.83) (Eyres, Carey, Gilworth, Neumann, & Tennant, 2005; King et al., 1995).

***Scoring***

Responses are recorded using a 5-point Likert-type scale ranging from 0 (not experienced at all), 1 (no more of a problem), 2 (a mild problem), 3 (a moderate problem), to 4 (a severe problem). There is no established cut-off point for differentiating favourable and unfavourable outcomes on the RPQ. However, a threshold of at least 3 symptoms rated as a moderate or severe problem has previously been defined as being indicative of the presence of post-

concussion symptoms (Sterr, Herron, Hayward, & Montaldi, 2006). In the CENTER-TBI study, the RPQ total scores were calculated using prorating if up to one third of items were missing.

***Use in this thesis***

The RPQ was used in Studies 2 and 3 as a self-reported measure of the severity of post-concussion symptoms following TBI.

## Recovery of consciousness

### Galveston Orientation and Amnesia Test (GOAT)

***Description***

The GOAT (Levin, O'Donnell, & Grossman, 1979) is used to assess the extent to which a patient is in post-traumatic amnesia (PTA) following brain injury. PTA is a state of altered consciousness following TBI, characterised by confusion and amnesia (Marshman, Jakabek, Hennessy, Quirk, & Guazzo, 2013). The GOAT comprises 10 questions and assesses orientation for time, place, and person, as well as anterograde amnesia (the inability to recall events occurring after the injury), and retrograde amnesia (the inability to recall events occurring before the injury). The GOAT can be used as a screening test during the sub-acute phase after TBI to determine whether the patient is sufficiently oriented to undergo formal cognitive testing. The inter-rater reliability is high (0.99) and GOAT scores relate to measures of injury severity such as GCS scores and CT scans (Levin et al., 1979).

***Scoring***

GOAT scores are calculated by awarding error points for each incorrect response and subtracting the number of error points from 100. The total error score ranges from 0 to 108: therefore, total GOAT scores can range from -8 to 100. Higher scores indicate the absence of PTA, whereas lower scores reflect disorientation and amnesia. Scores between 66 and 75 are considered to be 'borderline abnormal', while scores of 75 of more indicate that the patient is no longer in PTA (Levin et al., 1979; Lezak, 2012). If items were missing from the GOAT in the CENTER-TBI study database, total scores were not calculated.

### *Use in this thesis*

The GOAT was used in the CENTER-TBI study to screen for PTA and to assess whether cognitive testing was appropriate. It was included in Study 2 as a measure of PTA.

## Neuropsychological impairment

### Rey Auditory Verbal Learning Test (RAVLT)

#### *Description*

The RAVLT is used to measure verbal memory and learning (Schmidt, 1996). It comprises a total of seven trials, during which participants are asked to recall concrete nouns from two 15-word lists (List A and List B), which are spoken aloud by the assessor. During the acquisition phase, participants are presented with the words from List A five times. Immediately after each trial, the participant is instructed to repeat as many words as they can, in any order, whether or not they have said the same words in previous trials. The fifth trial is immediately followed by a sixth trial comprising a single auditory presentation of a 15-word interference list (List B). The participant is required to repeat as many words as they can from the interference list, in any order, before being asked to recall as many words as they can remember from List A, without hearing it again. The seventh and final trial is presented after a 20-minute delay and requires the participant to recall as many words as they can from the list they heard several times. The RAVLT has adequate test-retest reliability ($r$ ~ 0.60 to 0.70), high levels of internal consistency ($\alpha$ = 0.90), and it correlates moderately with other measures of learning and memory (Strauss, Sherman, & Spreen, 2006). It has also been found to be sensitive to neuropsychological impairment in a range of conditions, including closed head injury in adults (Strauss et al., 2006).

#### *Scoring*

Performance on the RAVLT is scored by recording the number of words the participant correctly recalls for each trial. Two RAVLT summary scores were used in this thesis: (1) Total score (sum of words recalled across 5 trials), (2) 20-minute delay (number of words recalled after 20-minute delay). Normative data exist to aid the interpretation of RAVLT scores for individuals aged 16 to 89 years old (Schmidt, 1996). It is Important to note that performance on the RAVLT

declines with advancing age. However, norms for adults ages 16 to 89 range from 53.9 (6.7) to 37.1 (7.5) for the RAVLT total score, and 11.7 (2.2) to 7.0 (2.4) for the RAVLT 20-minute delay.

***Use in this thesis***

The RAVLT was used in Studies 2 and 3 as a measure of verbal memory and learning.

**Trail Making Test (TMT) Parts A & B**

***Description***

The TMT measures scanning and visuo-motor tracking, divided attention, and cognitive flexibility (Strauss et al., 2006). Part A comprises 25 consecutively numbered circles distributed randomly on a page: the participant is required to connect the numbers sequentially with lines without lifting the pencil from the paper. Part B is more demanding and comprises consecutively numbered (1-13) and lettered (A-L) circles distributed randomly on a page: the participant is required to draw lines between alternate numbers and letters in sequential order. The participant is instructed to draw the lines as quickly and accurately as possible and their performance on both parts of the test is timed. The TMT has been shown to have adequate test-retest reliability ($r$ = 0.66 to 0.94) when used with neurological groups and correlates moderately with other neuropsychological measures. The TMT is sensitive to cognitive impairment in TBI and completion times have been found to increase with greater injury severity (Strauss et al., 2006).

***Scoring***

Scoring is based on the time taken to complete each part of the test. If the participant makes an error, the assessor draws their attention to it and instructs them to correct the error as quickly as possible without stopping the timer. Performance is usually slower during Part B because it requires greater executive control and demands upon working memory. Part A is discontinued at 100 seconds and Part B is discontinued at 300 seconds.

***Use in this thesis***

The TMT was used in Studies 2 and 3 as a measure of scanning and visuo-motor tracking, divided attention, and cognitive flexibility.

**Cambridge Neuropsychological Test Automated Battery (CANTAB)**

***Description***

CANTAB was developed in 1986 by neuroscientists at Cambridge University and comprises a set of 25 computer-automated assessments of memory, attention and executive function (Cambridge Cognition Ltd, 2014). The tests are administered by a clinician or researcher using an automated touchscreen computer. Computer-based neuropsychological tests, such as the CANTAB, provide a number of advantages over traditional pencil-and-paper based cognitive assessments: CANTAB is user-friendly, requires little training, and is relatively quick and easy to administer. Standardized instruction scripts are used to ensure consistency between assessments. Data is collected automatically, resulting in increased scoring accuracy and efficiency. The difficulty of the tests is graded to permit the assessment of a broad range of cognitive abilities, and normative data is available for many of the tests to aid interpretation of the scores. The tests also use non-verbal and culture-free stimuli, making CANTAB a good choice for multicentre studies where more than one language is spoken (Levaux et al., 2007; Parsons, 2016).

***Use in this thesis***

The CANTAB tests used in this thesis include 5-choice Reaction Time (RTI), Paired Associates Learning (PAL), Attention Switching Task (AST), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVP), and Stockings of Cambridge (SOC) (outcome measures for the tests are provided in Table 3.4). Normative data is available for all of the tests, apart from the AST. The CANTAB has been used previously in the context of TBI. For example, in moderate-to-severe TBI, changes in reaction time and performance on the PAL are associated with changes in diffusion tensor imaging (Newcombe et al., 2016). Furthermore, measures of reaction time, sustained attention, and episodic memory/ new learning have been found to be sensitive to

abnormalities in the cholinergic system (e.g., basal forebrain, bilateral hippocampal formation) in patients with moderate-to-severe TBI (Salmond, Chatfield, Menon, Pickard, & Sahakian, 2005).

**5-choice Reaction Time (RTI)**

This test measures reaction and movement time. Five white circles are displayed on the screen. The participant must press down the button on the press pad until they see a yellow spot appearing inside one of the circles on the screen. When they see the yellow spot, they must let go of the button and touch the screen where they saw the yellow spot as quickly as they can. The button on the press pad must be pressed down at all times apart from when the participant touches the screen where the yellow spot appeared.

**Paired Associates Learning (PAL)**

This test measures visual episodic memory and new learning. A set of boxes are displayed on the screen: these boxes open and close in a random order to display one or more hidden patterns. During each trial, once all of the boxes have opened, the patterns are displayed one by one in the middle of the screen. The participant must then touch the box where they originally saw each pattern. If they make an error, the boxes will re-open in a random order to remind them where the patterns are located. The test is relatively easy at the start (one hidden pattern) and gets progressively more difficult until there is a total of eight hidden patterns to remember. Participants are given up to ten attempts at any stage of the test.

**Attention Switching Task (AST)**

This test measures cognitive flexibility and attention switching in accordance with changing task goals. A series of arrows are displayed on the screen. Each arrow either points to the left or the right or is located on the left or right side of the screen. Throughout the task, the arrows may point in either direction and they may appear on either side of the screen. The participant uses the left and right buttons on the press pad to respond to the direction or location of the arrows. During the first stage, the instruction “which direction” is presented on the screen: the

participant is required to press the left button if the arrow points to the left and the right button if the arrow points to the right (Rule 1). During the second stage, the instruction "which side" appears on the screen: the participant is required to press the left button if the arrow is located on the left side of the screen and the right button if it appears on the right side of the screen (Rule 2). During the third stage, both instructions are presented on the screen in a random order: here, the participant must pay attention to which rule is presented on-screen before pressing the appropriate button on the press pad. Participants are instructed to respond as quickly as possible while avoiding mistakes.

**Spatial Working Memory (SWM)**

This test measures the ability to retain and manipulate visuospatial information in working memory. A series of coloured boxes are displayed on the screen. The participant is instructed to search the box for hidden blue tokens. Using a process of elimination, the participant must search the boxes one by one and enter the tokens in an empty 'home' space at the side of the screen as they are retrieved. The test is relatively easy at the start with three boxes to search and gets progressively more difficult until there are eight boxes to search. The likelihood of search strategies becoming stereotyped is reduced by changing the colour and positioning of the boxes throughout the test.

**Rapid Visual Information Processing (RVP)**

This test measures sustained visual attention. A series of numbers are presented in a white box in the middle of the screen. The numbers are presented in a pseudo-random order, for four minutes, at a rate of 100 numbers per minute. Participants are instructed to use the press pad button to respond to three target sequences of numbers (i.e., 3-5-7, 2-4-6, and 4-6-8). Participants must press the button after the third number in the target sequence has been presented.

### Stockings of Cambridge (SOC)

This test measures spatial planning. The screen is divided vertically into two displays of coloured balls hanging in pockets. The participant must move the balls in the bottom display to match the arrangement in the top display. The test starts relatively easy and gets progressively more difficult until a minimum of 5 moves are required to solve each problem. The participant is instructed to plan their moves in advance with the aim of solving each problem in the minimum number of moves.

## Physical function

### 10-Meter Walk Test and Timed Up & Go (TUG)

#### *Description*

The 10-meter walk is a test of mobility, in which the patient is required to walk between two clearly marked points spaced 10-meters apart. The patient is timed walking 10-meters and the procedure is repeated 3 times. The TUG is another test of mobility, in which the patient is timed while they stand up from a seated position, walk to a marker on the floor 3 meters away, turn around, and walk back to the chair and sit down (Podsiadlo & Richardson, 1991).

#### *Scoring*

For the 10-meter walk test, the time is recorded for the quickest trial of three. For the TUG, the time taken to complete the test is recorded, and results are interpreted as follows; <10 = normal mobility; <20 seconds = good mobility, can go out alone, mobile without a gait aid; <30 seconds problems with mobility, cannot go outside alone, requires a gait aid.

#### *Use in this thesis*

The 10-meter walk and TUG were used in Studies 2 and 3 as measures of physical mobility.

The key characteristics of the CANTAB sub-tests are outlined below and the sub-test outcome measures used in Studies 2 and 3 are listed in Table 3.4.

Table 3.4: Outcome measures used for CANTAB sub-tests

| Test | Outcome Measures | Descriptions* |
|---|---|---|
| **RTI** | Median five-choice reaction time | The median duration between the onset of the stimulus and the release of the button. Calculated for correct, assessed trials where the stimulus could appear in any one of five locations. |
| **PAL** | Total errors (adjusted) | The number of times the subject chose the incorrect box for a stimulus on assessment problems (PALTE), plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. |
| **AST** | Median reaction latency | The median latency of response (from stimulus appearance to button press), calculated across all correct, assessed trials. |
| **SWM** | Between errors | The total number of times the subject revisits a box in which a token has previously been found in the same problem (calculated for assessed problems only). |
| **RVP** | A' (A prime) | A' (A prime) is a signal detection measure of sensitivity to the target, regardless of response tendency (on this measure 0.50 is chance while 1.00 is perfect performance). In essence, this metric is a measure of how good the subject is at detecting target sequences. |
| **SOC** | Problems solved in minimum moves | The number of times the subject has successfully completed a problem in the minimum possible number of moves. |

*****Descriptions taken from CENTER-TBI outcomes scoring manual

## 3.3. Design of the studies in this thesis

All studies presented in this thesis were cross-sectional analyses of observational data collected for CENTER-TBI. Study 1 used outcomes data collected at 3 months and 6 months after injury, while Studies 2 and 3 used outcomes data collected at 6 months after injury.

## 3.4. Ethical approval

Ethical approval was obtained for CENTER-TBI prior to the commencement of this PhD project. Informed consent was obtained according to local and national requirements, and in

cases where the patient was unable to provide informed consent upon enrolment to the study, a legally acceptable representative was identified (Maas, Menon, et al., 2015).

## 3.5. Data management

All local data for the CENTER-TBI core study were de-identified using Global Unique Personal Identification (GUPI) labels before being entered on electronic case report forms (eCRFs) managed by the QuesGen data management platform (QuesGen Systems Inc, 2016). INCF (International Neuroinformatics Coordinating Facility, 2019) was responsible for data hosting and created an informatics platform, Neurobot, to allow cleaned data to be stored and downloaded for analysis. All CENTER-TBI core study data used in this thesis were downloaded from the INCF Neurobot database (Version 1) on 8 November 2018 and saved in SPSS files.

## 3.6. Selection of study participants

### 3.6.1. *Characteristics of the CENTER-TBI study sample*

The demographic and clinical characteristics of the 4509 patients enrolled in the CENTER-TBI core study are presented in Tables 3.5 and 3.6.

Table 3.5: Demographic characteristics of the total CENTER-TBI core study sample

| | ***n* (%)** |
|---|---|
| **Age band** | |
| 0-15 | 149 (3.3%) |
| 16-25 | 726 (16.1%) |
| 26-35 | 519 (11.5%) |
| 36-45 | 554 (12.3%) |
| 46-55 | 675 (15%) |
| 56-65 | 689 (15.3%) |
| 66-75 | 636 (14.1%) |
| 76-86 | 450 (10%) |
| >86 | 111 (2.5%) |
| Median (IQR) age | 50 (30-66) |
| **Gender** | |
| Male | 3022 (67%) |
| Female | 1487 (33%) |
| **Race** | |
| Caucasian | 4158 (92.2%) |
| Other | 138 (3.1%) |
| Unknown | 213 (4.7%) |
| **Education** | |
| Primary school or less | 641 (14.2%) |
| High school | 1261 (28%) |
| Post-high school training | 696 (15.4%) |
| College/University | 968 (21.5%) |
| Unknown | 943 (20.9%) |
| **Previous employment** | |
| Working | 1946 (43.2%) |
| Not working | 362 (8%) |
| Retired | 1112 (24.7%) |
| Student/homemaker | 560 (12.4%) |
| Unknown | 529 (11.7%) |
| **Marital status** | |
| Partnered | 2070 (45.9%) |
| Previously partnered | 621 (13.8%) |
| Single/unspecified | 1384 (30.7%) |
| Unknown | 434 (9.7%) |

IQR = inter-quartile range

Table 3.6: Clinical characteristics of the total CENTER-TBI core study sample

| | ***n* (%)** |
|---|---|
| **ASA Physical Health** | |
| Healthy patient | 2501 (55.5%) |
| Mild systemic disease | 1410 (31.3%) |
| Severe/life threatening systemic disease | 462 (10.2%) |
| Unknown | 136 (3.1%) |
| **Cause of injury** | |
| Road traffic accident | 1682 (37.3%) |
| Incidental fall | 2024 (44.9%) |
| Violence/assault | 246 (5.5%) |
| Other | 436 (9.7%) |
| Unknown | 121 (2.6%) |
| **Clinical Care Pathway** | |
| Emergency Room | 848 (18.8%) |
| Admitted to hospital | 1523 (33.8%) |
| Intensive Care Unit | 2138 (47.4%) |
| **GCS Score** | |
| Mild TBI | 2955 (65.5%) |
| Moderate TBI | 389 (8.6%) |
| Severe TBI | 986 (21.9%) |
| Unknown | 179 (4%) |
| **CT abnormality** | |
| Present | 2217 (49.2%) |
| Absent | 1606 (35.6%) |
| Unknown | 686 (15.2%) |
| **Injury Severity** | |
| Median (IQR) total ISS | 16 (9-29) |
| **Head & neck injury[1]** | |
| No injury/minor injury | 712 (15.7%) |
| Moderate injury | 577 (12.8%) |
| Serious injury | 1289 (28.6%) |
| Severe injury | 788 (17.5%) |
| Critical injury | 1055 (23.4%) |
| Unsurvivable injury | 88 (2%) |
| **Non-head & neck injury[2]** | |
| No injury/mild injury | 2730 (60.5%) |
| Severe injury | 1722 (38.2%) |
| Unknown | 57 (1.3%) |

IQR = Inter-quartile range; [1]Head & neck injury = combined Abbreviated Injury Severity (AIS) score for head, neck & cervical regions; [2]Non-head & neck injury (severe injury=total Injury Severity Score (ISS) >7)

The median (IQR) age of the CENTER-TBI sample was 50 (30-66). Two-thirds of the patients were male, and most patients were Caucasian. Information about educational level was missing for one-fifth of the patients. However, around two-thirds of the sample was educated to high school level (28%) or better (37%). Information about previous employment and marital status was missing for around one-tenth of the sample. However, 43% of patients were in employment prior to injury, around one-quarter were retired, and around one-quarter were students, homemakers or not working. Almost half of the patients were partnered prior to injury, and the rest were previously partnered (14%), single/unspecified (31%), or unknown (10%).

Over half of the patients were healthy prior to injury and 31% had mild systemic disease (i.e., conditions with no functional limitations). Incidental falls were the most common cause of injury, accounting for 45% of all TBIs, while road traffic accidents accounted for 37% of TBIs. Almost half of the patients were admitted to ICU, while 34% were admitted to the hospital ward, and 19% were recruited via the ER. Two-thirds of the patients scored in the GCS 13-15 range, and CT abnormalities were present in around half of the sample. The median (IQR) total ISS score for the sample was 16 (9-29), which is above the threshold (>15) for major trauma. Almost 70% of the sample had head and neck injuries in the 'serious' or worse categories. Moreover, 38% of patients had severe injuries to non-head and neck regions.

CENTER-TBI provides up-to-date information about the demographic and clinical characteristics of TBI in Europe, and the registry data helps to improve the generalizability of the core study. The core study sample reflects the changing epidemiology of TBI in Europe, in that TBI is becoming increasingly common in elderly individuals and falls have surpassed road traffic accidents as the most common cause of injury, especially in older adults (Brazinova et al., 2016; Peeters et al., 2015).

### 3.6.2. *Participant selection process*

The studies reported in this thesis included sub-samples of CENTER-TBI patients selected from the adults who were eligible for 3-month and 6-month follow-up (i.e., surviving patients aged 16 and over, who were still enrolled in the study at 6-months after injury). Study 1 (reported in Chapter 4) included a 3-month sub-sample and a 6-month sub-sample. Patients were selected for inclusion in Study 1 if GOSE scores were in the 'vegetative state' category or better, and if the GOSE structured interview and GOSE questionnaire were completed within a 3-week interval at each time-point. Study 2 (reported in Chapter 5) included patients who were selected from the 6-month sub-sample described in Chapter 4. Patients were selected for inclusion in Study 2 if GOSE scores were in the 'lower severe disability' category or better, and if they were assessed alone, or with help from another person. Study 3 (reported in Chapter 6) included patients who were assessed using the GOSE (as a structured interview and/or questionnaire), alone or with help, at 6 months post-injury, and patients were included if GOSE scores were in the 'lower severe disability' category or better. The participant selection process for the studies reported in Chapters 4, 5, and 6 is presented in Figure 3.2.

## 3.7. Statistical analysis

*Demographics and clinical characteristics*

The demographic and clinical characteristics of the patient sub-groups selected for the studies in Chapters 4, 5 and 6 were described using frequencies and percentages for categorical variables and medians and inter-quartile ranges (IQR) for continuous variables. In Chapter 6, the study sample was compared to patients without a 6-month GOSE using independent samples t-tests for continuous variables and Chi-square ($\chi^2$) tests for categorical variables.

*Study specific analyses*

In Study 1 (reported in Chapter 4), strength of agreement between clinician rated GOSE structured interviews and respondent completed GOSE questionnaires was evaluated using the weighted kappa statistic ($\kappa_w$) for overall GOSE ratings and kappa statistic ($\kappa$) for ratings on individual GOSE sections. The Wilcoxon signed-rank test was used to test for bias on overall

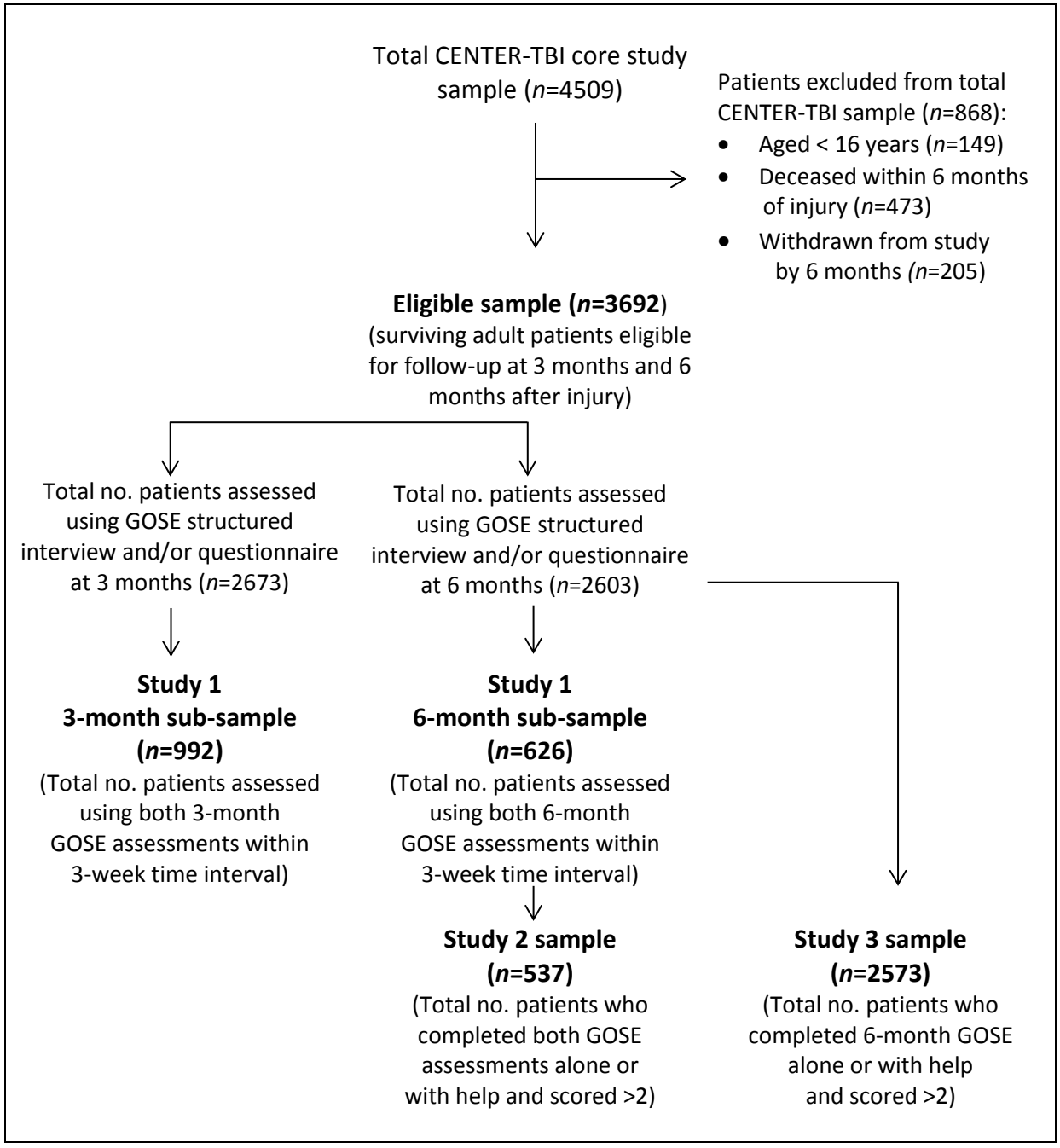
GOSE scores. McNemar's test was used to compare ratings for patients assigned to 'better' (i.e., 'moderate disability' and 'good recovery' categories) and 'worse' (i.e., 'vegetative state' and 'severe disability' categories) outcome groups. The symptoms section of the GOSE questionnaire was re-scored and agreement with the GOSE structured interview was evaluated using the Kappa statistic. Weighted Kappa was also used to explore whether clinical factors and type of respondent affected levels of agreement between overall GOSE scores. In Study 2 (reported in Chapter 5), Spearman correlations were used to examine how clinician ratings on the GOSE structured interview and patient reports on the GOSE questionnaire related to prognostic factors and other outcome domains. Steiger's tests were used to examine whether correlations for the two GOSE approaches were significantly different from each other.

In Study 3 (reported in Chapter 6), means and standard deviations (SD) were calculated for scores on the CENTER-TBI outcome measures. Patients were divided into sub-groups based on GOSE category and one-way analysis of variance (ANOVA) was used to test for differences on the outcome measures. Frequencies and percentages were used to examine outcome measure completion rates and reasons for non-completion of the RAVLT, TMT, and 10-meter walk/TUG. Floor and ceiling effects were examined for each outcome measure. Floor and ceiling ranges were generally defined as the top and bottom 10% of the range of possible scores for each outcome measure. For the CANTAB sub-tests, empirical minimum and maximum scores were defined using Tukey's rule to exclude outliers and floor and ceiling ranges were calculated as 1.5 times the interquartile range below the $25^{th}$ percentile and above the $75^{th}$ percentile. The internal consistency of the PROs was assessed using Cronbach's alpha (α).

Multiple testing is an issue in clinical research as it increases the risk of finding spurious effects (i.e., type 1 error). There is no universally accepted method for dealing with multiple testing and several methods for adjusting *p* values have been advocated, including the Bonferroni approach, which adjusts the significance level by the number of tests being performed (Bender & Lange, 2001; Feise, 2002; Sainani, 2009; Walters, 2016). To reduce the risk of type 1 errors, statistical tests were considered significant only if $p<0.01$. Bonferroni adjustment for multiple

testing was carried out where type 1 errors were considered relevant. All statistical analyses were conducted using IBM SPSS Statistics 23 using data downloaded from the INCF Neurobot database (Version 1) on 8 November 2018.

Figure 3.2: Participant selection process for the studies reported in this thesis



# CHAPTER 4

## Approaches to GOSE assignment: Comparison of clinician-rated structured interviews and respondent-completed questionnaires

The systematic review in Chapter 2 demonstrated that information for the Glasgow Outcome Scale has been collected in various ways in previous clinical trials in TBI. As different approaches to data collection may not be equivalent, the use of mixed modes of data collection in clinical studies may affect study outcomes. The study presented in this chapter compares outcomes obtained via the clinician-rated GOSE structured interview and the respondent-completed GOSE questionnaire. This study provides information about the comparability of the two GOSE approaches and explores whether information obtained via the GOSE structured interview provides added value over the GOSE questionnaire.

## 4.1. Abstract

Information for the GOSE can be collected via clinician-rated interviews or by respondent-completed questionnaires. However, there is limited evidence concerning the value that can be added when assigning global functional outcomes via clinician ratings on the GOSE structured interview. This chapter compared outcomes obtained using the GOSE structured interview and GOSE questionnaire and explored whether agreement between ratings were affected by the patient's functional level and clinical factors, such as the presence of pre-existing functional limitations, extracranial injury, and greater injury severity. The study used cross-sectional data collected for CENTER-TBI and compared GOSE assessments completed at 3 months (*n*=992) and 6 months (*n*=626) after injury. Overall GOSE scores were found to be similar at 3 months ($\kappa_w$=0.77) and 6 months ($\kappa_w$=0.82). Furthermore, at the item-level, agreement was good for sections dealing with independence in everyday activities ($\kappa$=0.70-0.79) and moderate for sections dealing with subjective aspects of functioning, such as relationships and symptoms ($\kappa$=0.43-0.51). The greatest levels of disagreement between the two approaches were found in the 'good recovery' categories, suggesting that there is some subjectivity and lower reliability in ratings of whether significant symptoms are present. Exploratory analyses revealed that ratings on the GOSE questionnaire were systematically less favourable for patients with poorer outcomes at 3 months, but not at 6 months; thus, patients with greater functional limitations may underestimate their capabilities in the first few months after TBI. Extracranial concomitant injury/illness, in combination with TBI, was found to be associated with lower levels of agreement between GOSE scores at 3 months after injury ($\kappa_w$=0.55), but not at 6 months after injury ($\kappa_w$=0.79). Taken together, these findings indicate that the two GOSE approaches are broadly comparable and suggest that respondent reports and clinician ratings on the GOSE provide similar information about level of functioning after TBI. Supplementing responses on the GOSE questionnaire with information obtained via structured interview may be useful in certain circumstances, and in CENTER-TBI the GOSE structured interview appears to offer modest added value over the GOSE questionnaire.

## 4.2. Introduction

The GOS/E is commonly used in clinical studies in TBI and is associated with high follow-up rates due to its ease of use and flexibility in administration (Horton, Rhodes, & Wilson, 2018; McMillan et al., 2016). It has undergone considerable refinement since an expanded 8-point scale was originally proposed in 1981 (Jennett et al., 1981), including the publication of structured interview guidelines for the GOSE in 1998 (Wilson et al., 1998), and the subsequent introduction of the GOSE postal questionnaire in 2002 (Wilson et al., 2002). The original open-ended approach to assigning functional outcome was criticised for its potential to result in idiosyncratic use of the scale and a lack of consistency between assessors, particularly when the expanded version was used (Anderson, Housley, Jones, Slattery, & Miller, 1993; Maas, Braakman, Schouten, Minderhoud, & van Zomeren, 1983; Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998; Wilson et al., 1998). Thus, structured interview guidelines were introduced to improve the objectivity and reliability of the instrument (Teasdale et al., 1998; Wilson et al., 1998), while the respondent-completed questionnaire was originally developed to assess outcomes more easily while avoiding investigator bias (Wilson et al., 2002). The two versions of the GOSE appear to be broadly equivalent, although existing comparisons between clinician ratings and respondent reports of global functional outcome are limited.

The GOSE questionnaire offers pragmatic advantages over the structured interview as it provides a means of collecting outcomes inexpensively and with minimal effort, especially in studies with geographically dispersed populations. The GOSE questionnaire has also been favoured in studies where blinding is not feasible and interviewer bias may be an issue, for example, in surgical TBI trials (Mendelow et al., 2005). The structured interview is nevertheless considered the optimal mode of data collection for the GOSE, as the interviewer can use their clinical judgement when assigning outcomes, and there is scope to clarify any issues or inconsistencies that may arise through discussion with the respondent (Wilson et al., 2002). The structured interview should therefore, in theory, provide considerable added value over simply using the respondent-completed questionnaire.

Previous clinical trials in TBI have collected information for the GOSE in a variety of ways, including in-person interviews, telephone interviews, and postal questionnaires (Horton et al., 2018). The GOSE has also been completed with the patient alone and/or with a proxy informant, such as a relative or caregiver (Horton et al., 2018). Studies may specify a preferred way of administering the GOSE, but employ additional data collection strategies as a means of improving follow up rates. For example, multicentre trials such as Corticosteroid Randomization After Significant Head Injury (CRASH) (Edwards et al., 2005) and Eurotherm 3235 (Andrews et al., 2015) used postal questionnaires as the primary method of assessing outcomes, and also followed up non-responders by telephone interviews, thereby combining clinician ratings with patient reports of daily functioning.

Combining data collection modes is advantageous as it can facilitate follow-ups in studies with hard-to-reach populations. However, it is important to note that measurement error can be introduced if different data collection methods lack sufficient comparability (Eremenco et al., 2014). Measurement equivalence between modes cannot always be assumed because the GOSE, like other instruments, relies on the interpretations and reports of patients, clinicians, or other observers, all of which can be influenced by human judgement or motivation (Powers et al., 2017; Walton et al., 2015). Scores on the respondent-completed GOSE questionnaire may be affected by bias as patients may have a skewed understanding of their capabilities or a lack of self-awareness, making it difficult for them to provide an accurate self report (Prigatano, 2005a, 2005b). Clinician ratings on the GOSE structured interview may also be affected by bias (Sherer, Roebuck-Spencer, & Davis, 2010), as study management processes and predictors of outcome are often not masked in observational and prognostic studies.

The CENTER-TBI study employed a non-experimental design and a flexible, pragmatic data collection approach was taken to maximise follow-ups (Maas, Menon, et al., 2015). The study plan called for a total of 12,350 follow-ups after allowing for attrition: this included 5,850 follow-ups that involved neuropsychological assessment and, therefore, face-to-face contact, and 6,500 follow-ups that required questionnaire assessments. Investigators were not masked

at follow-up. Thus, there was potential for structured interview ratings to be affected by the interviewer's prior knowledge of the patient.

Despite concerns about the equivalence of different modes of GOSE data collection, there is evidence to suggest that different approaches yield comparable information about global functional outcome after TBI. For example, in the original reliability study for the GOSE questionnaire (Wilson et al., 2002), high levels of agreement were found between the structured interview (completed via telephone) and the postal questionnaire ($n$=35, $\kappa_w$=0.92). High levels of test-retest reliability have also been found between in-person and telephone structured interviews for the GOSE ($n$=30, κw=0.92) (Pettigrew et al., 2003). Together, these studies indicate that information can reliably be collected about global functional outcome in the absence of face-to-face contact, and indicate that respondent-completed questionnaires are comparable to outcomes assigned by investigators via structured interviews.

To date, no study has explored differences between clinician ratings and respondent reports on individual sections of the GOSE. Furthermore, no study has explored whether factors known to have a confounding effect on GOSE assignment affect levels of agreement between clinician ratings and respondent reports. CENTER-TBI provides an opportunity to examine these issues. Patients may rate themselves as more, or less, capable than clinicians. Furthermore, as patient reports of subjective cognitive complaints after TBI can be unreliable (Ngwenya et al., 2018), inconsistencies may particularly occur between clinician ratings and patient reports of TBI-related symptoms. As factors such as pre-injury functional limitations, extracranial concomitant injury, epilepsy, injury severity, and source of information (i.e., patient or proxy respondent) can have an effect on the assessment of global functional outcome following TBI (Wilson et al., 2002; Wilson et al., 1998), it is also important to examine whether these factors affect levels of agreement between clinician-rated interviews and respondent-reported questionnaires.

### *4.2.1. Study aim*

The primary aim of this study was to investigate whether the GOSE structured interview provides additional information about global functional outcome after TBI by comparing clinician-ratings on the GOSE structured interview and respondent reports on the GOSE questionnaire.

### *4.2.2. Exploratory analyses*

Exploratory analyses were conducted to:

- Examine whether GOSE ratings differed for patients with 'better' outcomes (i.e., patients assigned to the 'moderate disability' and 'good recovery' categories) and 'worse' outcomes (i.e., patients assigned to the 'vegetative state' and 'severe disability' categories) and to explore potential ways of improving agreement between GOSE assessments
- Investigate whether factors known to have an effect on the assessment of global functional outcome affected levels of agreement between the GOSE structured interview and GOSE questionnaire

## 4.3. Methods

### *4.3.1. Participants*

Potentially eligible patients were enrolled in the CENTER-TBI core study (see CENTER-TBI inclusion criteria in Chapter 3).

Additional inclusion criteria for the current study were as follows:

- Adults aged 16 years and over (no upper age limit)
- All injury severities
- GOSE score ≥2 (i.e., vegetative state (VS) or better)
- The GOSE structured interview and GOSE questionnaire must be complete and scorable for each participant at 3 months and 6 months after injury
- GOSE assessments must be completed within a 3-week time interval at each time-point to avoid introducing discrepancies due to changes in functional status

### *4.3.2. Design*

The study used cross-sectional data collected for CENTER-TBI, which included pairs of GOSE assessments completed 3 months and 6 months after injury.

### *4.3.3. Measures and procedure*

The following acute measures were used (described in detail in Chapter 3):

- American Society of Anaesthesiologists' (ASA) classification of Physical Health (Dripps, 1963)
- Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974)
- CT abnormality
- Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) (Baker et al., 1974)
- Injury severity was also categorised according to clinical care pathway (i.e., emergency room (ER), admission to hospital ward (Admission), intensive care unit (ICU)).

*GOSE administration and scoring*

The study compared two main GOSE approaches used in CENTER-TBI: the clinician-rated structured interview (Wilson et al., 1998) and the respondent-reported questionnaire (Wilson et al., 2002). The GOSE is described in detail in Chapter 3. For CENTER-TBI, the GOSE was collected together with a range of other outcome measures. The overall aim was to maximize completeness of all outcome measures mandated at each follow-up. In order to maximise follow-up rates, CENTER-TBI employed a flexible and pragmatic approach to outcome assessment, i.e., GOSE interviews could be completed face-to-face or via telephone, and the GOSE could be completed with the patient and/or a proxy informant such as a relative or caregiver (Maas, Menon, et al., 2015). Individual sites therefore administered the assessment in different ways and the way in which the GOSE was used was not uniform across the study.

As data collection for the GOSE structured interview and GOSE questionnaire was not managed by independent assessors, interviewers potentially had access to information collected via the GOSE questionnaire and other assessments. Nevertheless, as the questionnaires were scored electronically by algorithm, investigators were not provided with

GOSE questionnaire ratings. As described in the CENTER-TBI study manual, investigators were expected to interview patients (or their carers/relatives), ask additional questions as needed, form a judgement about the person's ability to perform activities, resolve any ambiguities or inconsistencies, and finally assign an overall rating when completing the GOSE structured interview. Therefore, in comparison to the respondent-completed questionnaire, the structured interview had the potential to provide additional relevant information that could be used to assign outcomes.

GOSE structured interviews were rated locally by trained interviewers in accordance with published guidelines (Wilson et al., 1998). GOSE questionnaires were scored centrally by machine using the standard scoring algorithm developed by Wilson and colleagues (Wilson et al., 2002). A revised scoring algorithm, developed for this study, was also used in exploratory analyses to improve levels of agreement on the 'symptoms' section of the GOSE structured interview and GOSE questionnaire.

### *4.3.4. Statistical analysis*

*Demographics and clinical characteristics*

The demographic and clinical characteristics of the 3-month sub-sample, 6-month sub-sample, and 'eligible sample' (i.e., all adult patients who were alive and eligible for follow-up assessments at 6 months post-injury) were described using frequencies and percentages and medians and interquartile ratios (IQR) were used for continuous data (i.e., age and total ISS score).

*Agreement between GOSE scores*

Strength of agreement between the GOSE structured interview and GOSE questionnaire was evaluated in two ways:

1. Agreement between overall ratings for the two approaches was evaluated using the weighted kappa statistic ($\kappa_w$), which uses quadratic weights to penalise extreme disagreements between ratings more heavily than slight disagreements (Fleiss & Cohen,

1973), and in line with conventions for interpreting kappa: 0.01-0.20 = poor agreement; 0.21-0.40 = fair agreement; 0.41-0.60 = moderate agreement; 0.61-0.80 = good agreement; and 0.81-1.00 = very good agreement (Landis & Koch, 1977). The overall percentage agreement between scores was assessed for overall GOSE ratings and the magnitude of disagreement (i.e., number of GOSE categories) between overall GOSE scores was evaluated. The Wilcoxon signed-rank test was used to test for bias on overall GOSE scores.

2. Agreement between ratings for individual sections of the structured interview and questionnaire was evaluated using the kappa statistic ($\kappa$) (Cohen, 1960), and a kappa threshold of 0.40 was used to indicate acceptable levels of agreement (Yip, Wilber, Myrtle, & Grazman, 2001).

*Exploratory analyses*

For some analyses and in line with conventions (McMillan et al., 2016), overall GOSE scores were dichotomised into two groups, i,e., 'better' outcomes ('moderate disability' and 'good recovery') versus 'worse' outcomes ('vegetative state' and 'severe disability'), and McNemar's test was used to compare outcomes on the GOSE structured interview and GOSE questionnaire at 3 and 6-months post-injury. Potential ways of improving agreement between clinician-ratings and respondent reports were then explored by examining individual sections of the GOSE, and the 'symptoms' section of the respondent-completed questionnaire was re-scored using a revised algorithm (Wilson & Horton, 2018).

Exploratory analyses also examined whether clinical factors (i.e., pre-existing disability, extracranial injury, epilepsy, and injury severity) and type of respondent, had an impact on levels of agreement between GOSE scores at 3 and 6-months post-injury.

All statistical analyses were conducted using IBM SPSS Statistics 23. The data were downloaded from the INCF-Neurobot database on 8 November 2018 (Version 1).

## 4.4. Results

### *4.4.1. Demographics and clinical characteristics*

A total of 3692 adults were eligible for follow-up 6 months after injury. At 3 months, 1096 patients completed both versions of the GOSE: 9.5% (*n*=104) were excluded as they did so outside of the 3-week time interval. Thus, 992 patients met the inclusion criteria at the 3-month follow-up. At 6 months, 678 patients completed both versions of the GOSE: 7.7% (*n*=52) were excluded as they did so outside of the 3-week time interval. Thus, 626 patients met the inclusion criteria at the 6-month follow-up. The participant selection process for the study is detailed in Figure 4.1. Tables 4.1 and 4.2 summarise the demographic and clinical characteristics of the 3-month sub-sample, 6-month-sub-sample, and eligible sample.

The median (IQR) age was 53 years (33-66) for the 3-month sample; 51 years (31-64) for the 6-month sample; and 49 years (31-64) for the eligible sample. Around two-thirds of the patients were male and most of them were Caucasian. Most patients had high school, post-high school, or college/university education. Around half of the patients were in employment prior to injury. Furthermore, around half of the patients were partnered prior to injury. Most of the patients were healthy or had mild systemic disease (i.e., conditions with no functional limitations) prior to injury. Road traffic accidents and incidental falls were the most common causes of injury, each accounting for around 40% of the samples. Most patients were either admitted to the hospital ward or intensive care unit, and emergency room admissions accounted for around one-fifth of the samples. Around two-thirds of the patients had GCS scores of 13-15 and CT abnormalities were present in around half of the patients. Total ISS scores of 15 or more are indicative of major trauma: the median (IQR) total ISS was 16 (9-26) for the 3-month sample; 16 (8-29) for the 6-month sample; and 16 (9-26) for the eligible sample. A total of 514 (51.8%) of the 3-month sub-sample, 336 (53.7%) of the 6-month sub-sample, and 1876 (50.8%) of the eligible sample met criteria for major trauma. Around one-third of the patients in the samples sustained severe non-head and neck injuries.

Figure 4.1: Participant selection process

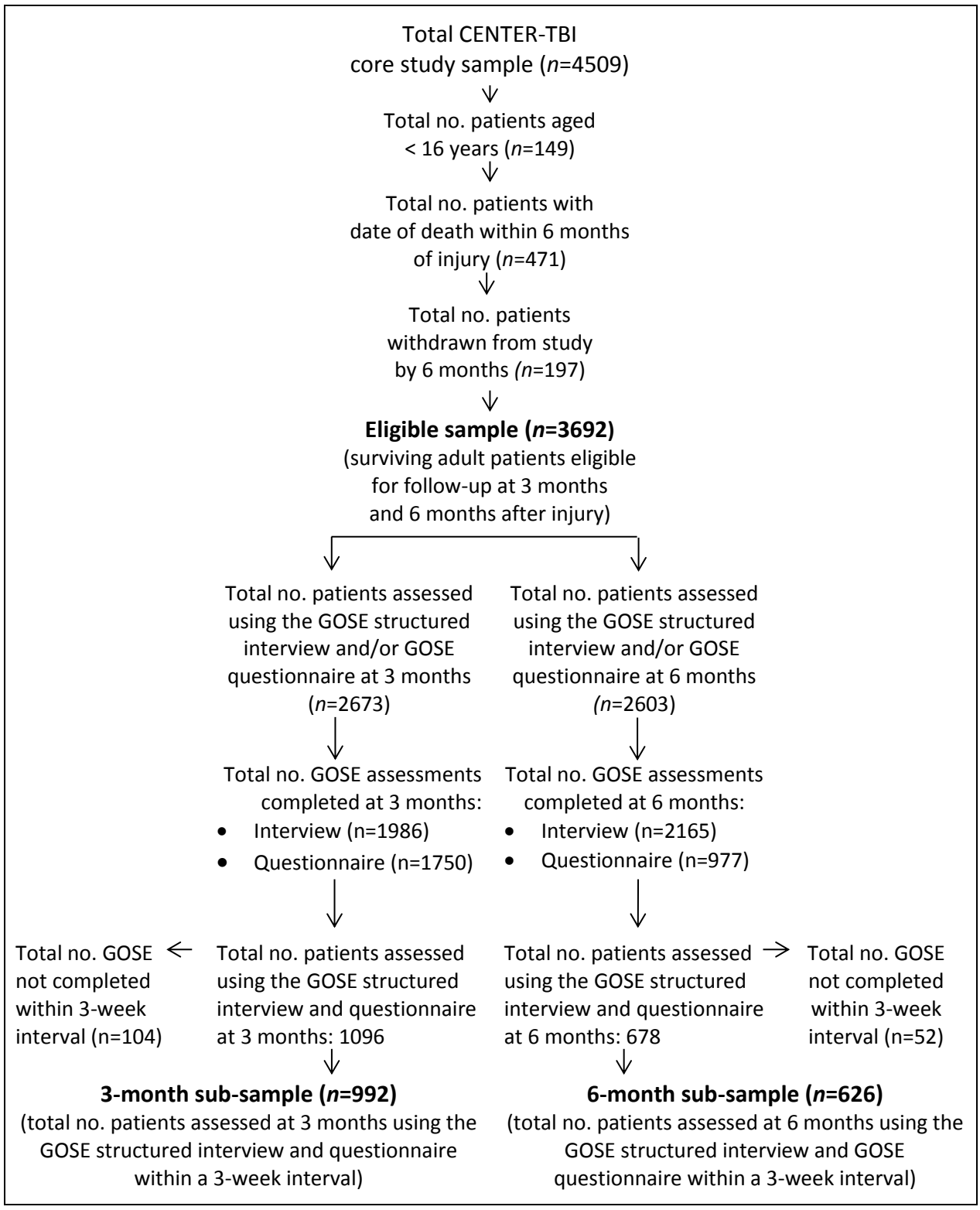


Table 4.1: Demographics for the 3 and 6-month sub-samples and eligible sample

| | 3-month sub-sample | 6-month sub-sample | Eligible sample |
|---|---|---|---|
| **Age band** | | | |
| 16-25 | 161 (16.2%) | 111 (17.7%) | 663 (18%) |
| 26-35 | 117 (11.8%) | 80 (12.8%) | 473 (12.8%) |
| 36-45 | 103 (10.4%) | 74 (11.8%) | 501 (13.6%) |
| 46-55 | 148 (14.9%) | 106 (16.9%) | 606 (16.4%) |
| 56-65 | 192 (19.4%) | 112 (17.9%) | 598 (16.2%) |
| 66-75 | 162 (16.3%) | 82 (13.1%) | 482 (13.1%) |
| 76-86 | 93 (9.4%) | 52 (8.3%) | 307 (8.3%) |
| >86 | 16 (1.6%) | 9 (1.4%) | 62 (1.7%) |
| **Gender** | | | |
| Male | 653 (65.8%) | 407 (65%) | 2487 (67.4%) |
| Female | 339 (34.2%) | 219 (35%) | 1205 (32.6%) |
| **Race** | | | |
| Caucasian | 994 (95.2%) | 604 (96.5%) | 3420 (92.6%) |
| Other | 24 (2.4%) | 12 (1.9%) | 113 (3%) |
| Unknown | 24 (2.4%) | 10 (1.6%) | 159 (4.3%) |
| **Education** | | | |
| Primary school or less | 90 (9.1%) | 65 (10.4%) | 459 (12.4%) |
| High school | 274 (27.6%) | 183(29.2%) | 1108 (30%) |
| Post-high school training | 202 (20.4%) | 101 (16.1%) | 647 (17.5%) |
| College/University | 267 (26.9%) | 145 (23.2%) | 888 (24.1%) |
| Unknown | 159 (16%) | 132 (21.1%) | 590 (16%) |
| **Previous employment** | | | |
| Working | 475 (47.9%) | 308 (49.2%) | 1805 (48.9%) |
| Not working | 71 (7.2%) | 52 (8.3%) | 317 (8.6%) |
| Retired | 256 (25.8%) | 134 (21.4%) | 828 (22.4%) |
| Student/homemaker | 112 (11.3%) | 65 (10.4%) | 409 (11.1%) |
| Unknown | 78 (7.9%) | 67 (10.7%) | 333 (9%) |
| **Marital status** | | | |
| Partnered | 522 (52.6%) | 302 (48.2%) | 1751 (47.4%) |
| Previously partnered | 132 (13.3%) | 77 (12.3%) | 520 (14.1%) |
| Single/unspecified | 283 (28.5%) | 195 (31.2%) | 1127 (30.5%) |
| Unknown | 55 (5.5%) | 52 (8.3%) | 294 (8%) |

Data are *n* (%)

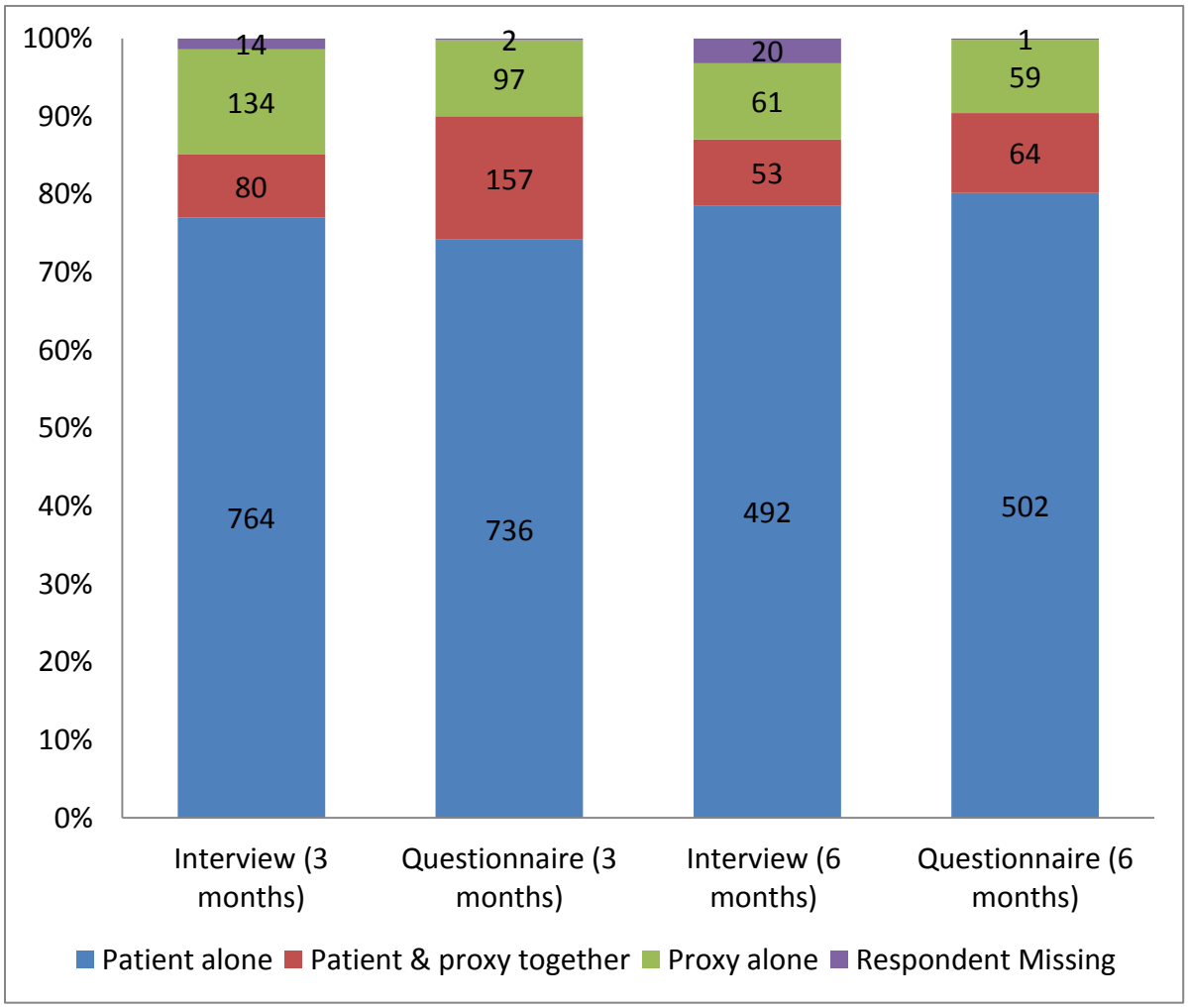
Table 4.2: Clinical characteristics of the 3 and 6-month sub-samples and eligible sample

| | 3-month sub-sample | 6-month sub-sample | Eligible Sample |
|---|---|---|---|
| **ASA Physical Health** | | | |
| Healthy patient | 591 (59.6%) | 367 (58.6%) | 2127 (57.6%) |
| Mild systemic disease | 311 (31.4%) | 194 (31%) | 1156 (31.3%) |
| Severe/life threatening systemic disease | 67 (7.5%) | 51 (8.1%) | 325 (8.8%) |
| Unknown | 10 (1%) | 14 (2.2%) | 84 (2.3%) |
| **Cause of injury** | | | |
| Road traffic accident | 405 (40.8%) | 255 (40.7%) | 1412 (38.2%) |
| Incidental fall | 423 (42.6%) | 250 (39.9%) | 1617 (43.8%) |
| Violence/assault | 67 (6.8%) | 43 (6.9%) | 208 (5.6%) |
| Other | 81 (8.2%) | 59 (9.4%) | 361 (9.8%) |
| Unknown | 14 (1.4%) | 15 (2.4%) | 94 (2.6%) |
| **Clinical Care Pathway** | | | |
| Emergency Room | 178 (17.9%) | 129 (20.6%) | 774 (21%) |
| Admitted to hospital | 376 (37.9%) | 180 (28.8%) | 1325 (35.9%) |
| Intensive Care Unit | 438 (44.2%) | 317 (50.6%) | 1593 (43.1%) |
| **GCS Score** | | | |
| 13-15 | 681 (68.6%) | 390 (62.3%) | 2623 (71%) |
| 8-12 | 93 (9.4%) | 65 (10.4%) | 285 (7.7%) |
| 3-8 | 172 (17.3%) | 134 (21.4%) | 659 (17.8%) |
| Unknown | 46 (4.6%) | 37 (5.9%) | 125 (3.4%) |
| **CT Abnormality** | | | |
| Present | 474 (47.8%) | 319 (51%) | 1745 (47.3%) |
| Absent | 357 (36%) | 232 (37.1%) | 1405 (38.1%) |
| Unknown | 161 (16.2%) | 75 (12%) | 542 (14.7%) |
| **Head & neck injury[1]** | | | |
| No injury/minor injury | 156 (16.7%) | 112 (17.9%) | 655 (17.7%) |
| Moderate injury | 113 (13.3%) | 86 (13.7%) | 521 (14.1%) |
| Serious injury | 321 (32.4%) | 144 (23%) | 1129 (30.6%) |
| Severe injury | 165 (16.6%) | 119 (19%) | 637 (17.3%) |
| Critical injury | 206 (20.8%) | 164 (26.2%) | 747 (20.2%) |
| Unsurvivable injury | 1 (0.1%) | 1 (0.2%) | 3 (0.1%) |
| **Non-head & neck injury[2]** | | | |
| No injury/mild injury | 588 (59.3%) | 390 (62.2%) | 2251 (61%) |
| Severe injury | 392 (39.5%) | 226 (36.1%) | 1389 (37.6%) |
| Unknown | 12 (1.2%) | 10 (1.6%) | 52 (1.4%) |

Data are *n* (%); [1]Head & neck injury = combined AIS score for head, neck and cervical regions
[2]Non-head & neck injury (severe injury= Total ISS >7)

Figure 4.2 shows that most GOSE assessments were completed by the patient alone (i.e., at 3-months, 77% of interviews and 74.2% of questionnaires; and at 6-months, 78.6% of interviews and 80.2% of questionnaires). A minority of assessments were completed by the patient and a proxy together (i.e., at 3-months, 8.6% of interviews and 15.8% of questionnaires; and at 6-months, 8.5% of interviews and 10.2% of questionnaires), or by a relative/caregiver alone (i.e., at 3-months, 13.5% of interviews and 9.8% of questionnaires; and at 6-months, 9.7% of interviews and 9.4% of questionnaires). Information about who responded was missing in a small number of cases.

Figure 4.2: GOSE respondent for 3-month and 6-month assessments



At 3 months, 76.7% (*n*=761) of the GOSE assessments were completed within a 1-week time window; 14.6% (*n*=145) were completed between 1 and 2-weeks apart; and 8.7% (*n*=86) were completed between 2 and 3-weeks apart. The GOSE questionnaire was completed first for 29.9% of patients (*n*=297), while the structured interview was completed first for 15.2% of patients (*n*=150). A total of 54.9% (*n*=545) of the 3-month assessments were completed on the same day.

At 6 months, 90.7% (*n*=568) of the GOSE assessments were completed within a 1-week time window; 5.6% (*n*=35) were completed within a 2-week time window; and 3.7% (*n*=23) were completed within a 3-week time window. The GOSE questionnaire was completed first for 10.8% of patients (*n*=68), while the structured interview was completed first for 12.5% of patients (*n*=78). A total of 76.7% (*n*=480) of the 6-month assessments were completed on the same day.

### *4.4.2. Agreement between GOSE scores*

*Overall GOSE ratings*

Cross-tabulations of overall GOSE ratings are displayed in Tables 4.3 (3-month follow-up) and 4.4 (6-month follow-up). $\kappa_w$ was 0.77 (CI: 0.73-0.80) for the 3-month comparison and 0.82 (CI: 0.78-0.86) for the 6-month comparison. There was perfect agreement for 52.5% of the 3-month sample (*n*=521) and 60.1% of the 6-month sample (*n*=376). Most discrepancies were within 1 GOSE category (i.e., 67.7% of disagreements in the 3-month sample, and 75.2% of disagreements in the 6-month sample). Extreme discrepancies (i.e., ≥3 GOSE categories) were uncommon, comprising 12.3% of disagreements in the 3-month sample, and 10% of disagreements in the 6-month sample. Wilcoxon signed-ranks tests indicated that GOSE scores were comparable at the 3-month follow-up (interview mean rank=219.55, questionnaire mean rank=259.29, *Z*= -1.77 *p*=0.08), but not at the 6-month follow-up (interview mean rank=123.34, questionnaire mean rank=129.77, *Z*= -4.43, *p*<0.001).

Table 4.3: Cross tabulation of overall ratings from GOSE structured interview versus overall ratings from GOSE questionnaire completed 3 months after injury

| Structured interview | Questionnaire | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Lower SD/VS** | **Upper SD** | **Lower MD** | **Upper MD** | **Lower GR** | **Upper GR** | **Totals (%)** |
| **Lower SD/VS** | **73** | 11 | 2 | 0 | 2 | 2 | 90 (9.1%) |
| **Upper SD** | 16 | **35** | 8 | 2 | 6 | 8 | 75 (7.6%) |
| **Lower MD** | 9 | 22 | **44** | 8 | 11 | 10 | 104 (10.5%) |
| **Upper MD** | 2 | 21 | 21 | **45** | 30 | 26 | 145 (14.6%) |
| **Lower GR** | 3 | 17 | 14 | 21 | **67** | 137 | 259 (26.1%) |
| **Upper GR** | 3 | 2 | 3 | 9 | 32 | **270** | 319 (32.2%) |
| **Totals (%)** | 106 (10.7%) | 108 (10.9%) | 92 (9.3%) | 85 (8.6%) | 148 (14.9%) | 453 (45.7%) | 992 (100%) |

$\kappa_w$= 0.77; 95% Confidence Intervals = 0.73-0.80; Overall level of agreement = 52.5%

Table 4.4: Cross tabulation of overall ratings from GOSE structured interview versus overall ratings from GOSE questionnaire completed 6 months after injury

| Structured interview | Questionnaire | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Lower SD/VS** | **Upper SD** | **Lower MD** | **Upper MD** | **Lower GR** | **Upper GR** | **Totals (%)** |
| **Lower SD/VS** | **54** | 3 | 0 | 0 | 1 | 1 | 59 (9.4%) |
| **Upper SD** | 3 | **15** | 1 | 3 | 3 | 5 | 30 (4.8%) |
| **Lower MD** | 0 | 11 | **51** | 4 | 4 | 6 | 76 (12.1%) |
| **Upper MD** | 1 | 7 | 15 | **34** | 17 | 15 | 89 (14.2%) |
| **Lower GR** | 1 | 5 | 4 | 13 | **51** | 92 | 166 (26.5%) |
| **Upper GR** | 0 | 1 | 1 | 4 | 18 | **182** | 206 (32.9%) |
| **Totals (%)** | 59 (9.4%) | 42 (6.7%) | 72 (11.5%) | 58 (9.3%) | 94 (15%) | 301 (48.1%) | 626 (100%) |

$\kappa_w$= 0.82; 95% Confidence Intervals = 0.78-0.86; Overall level of agreement = 60.1%

*Ratings for individual sections of the GOSE*

Levels of agreement between individual sections of the structured interview and questionnaire are displayed in Tables 4.5 (3-month sub-sample) and 4.6 (6-month sub-sample). The responses for each section of the GOSE are coded according to whether a limitation was recorded. Sections dealing with independence at home and during shopping and travel had good levels of agreement ($\kappa$=0.70-0.79), and levels of agreement for sections dealing with work and participation in social and leisure activities were generally good ($\kappa$=0.60-0.74). Subjective aspects of functioning (i.e., relationships and symptoms) had moderate levels of agreement ($\kappa$=0.43-0.51), with the symptoms section of the GOSE having the lowest levels of agreement ($\kappa$=0.43 at both time-points). Figures 4.3 and 4.4 show the percentages of patients who endorsed limitations on each section of the GOSE structured interview and GOSE questionnaire: limitations were most common in the domains of TBI-related symptoms, social and leisure activities, and work, and least common for domains pertaining to independence inside and outside the home, and relationships.

Table 4.5: Levels of agreement between individual sections of the GOSE structured interview and GOSE questionnaire completed 3 months after injury

| | **I-/Q-** | **I-/Q+** | **I+/Q-** | **I+/Q+** | **% Agreement** | **Kappa** | **SE** | **95% CI** |
|---|---|---|---|---|---|---|---|---|
| **Assistance at home** (*n*=977) | 741 | 38 | 53 | 145 | 90.7% | 0.70 | 0.03 | 0.64-0.76 |
| **Shopping** (*n*=977) | 778 | 18 | 39 | 132 | 93.1% | 0.79 | 0.03 | 0.73-0.85 |
| **Travel** (*n*=977) | 771 | 36 | 26 | 144 | 93.7% | 0.78 | 0.03 | 0.72-0.84 |
| **Work** (*n*=896) | 492 | 15 | 121 | 268 | 84.8% | 0.68 | 0.02 | 0.64-0.72 |
| **Social & leisure** (*n*=971) | 456 | 146 | 45 | 324 | 80.3% | 0.60 | 0.03 | 0.54-0.66 |
| **Relationships** (*n*=970) | 761 | 59 | 68 | 82 | 86.9% | 0.49 | 0.04 | 0.39-0.57 |
| **Symptoms** (*n*=976) | 377 | 34 | 258 | 307 | 70.1% | 0.43 | 0.03 | 0.41-0.51 |

I- = no limitation recorded on interview; I+ = limitation recorded on interview
Q- = no limitation recorded on questionnaire; Q+ = limitation recorded on questionnaire

Table 4.6: Levels of agreement between individual sections of the GOSE structured interview and GOSE questionnaire completed 6 months after injury

| | I-/Q- | I-/Q+ | I+/Q- | I+/Q+ | % Agreement | Kappa | SE | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Assistance at home** (*n*=601) | 476 | 13 | 33 | 79 | 92.3% | 0.73 | 0.04 | 0.65-0.81 |
| **Shopping** (*n*=600) | 503 | 9 | 25 | 63 | 94.3% | 0.76 | 0.04 | 0.68-0.84 |
| **Travel** (*n*=601) | 498 | 23 | 15 | 65 | 93.7% | 0.74 | 0.04 | 0.66-0.82 |
| **Work** (*n*=585) | 358 | 11 | 57 | 159 | 88.4% | 0.74 | 0.03 | 0.68-0.80 |
| **Social & leisure** (*n*=600) | 327 | 74 | 24 | 175 | 83.7% | 0.65 | 0.03 | 0.59-0.71 |
| **Relationships** (*n*=601) | 448 | 48 | 39 | 66 | 85.5% | 0.51 | 0.05 | 0.41-0.61 |
| **Symptoms** (*n*=599) | 258 | 26 | 149 | 166 | 70.8% | 0.43 | 0.03 | 0.37-0.49 |

I- = no limitation recorded on interview; I+ = limitation recorded on interview
Q- = no limitation recorded on questionnaire; Q+ = limitation recorded on questionnaire

Figure 4.3: Percentage of patients endorsing limitations in individual sections of the GOSE structured interview and GOSE questionnaire at 3 months post-injury

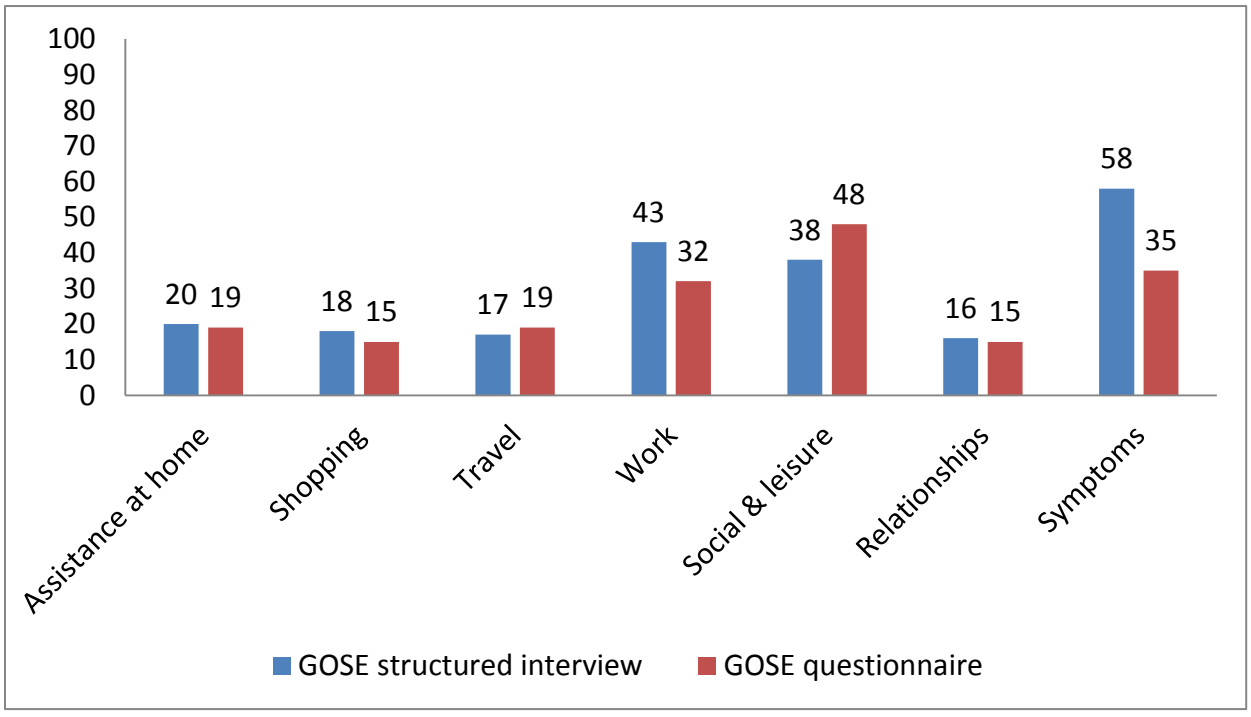
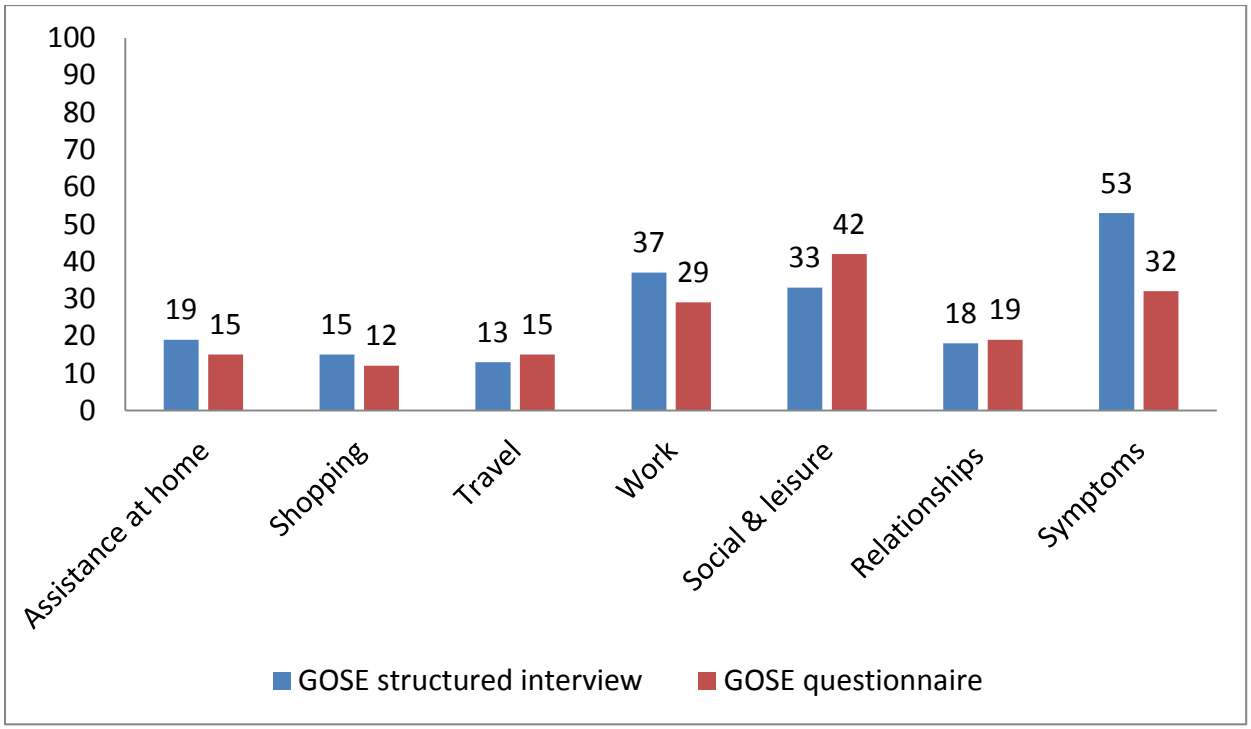


Figure 4.4: Percentage of patients endorsing limitations in individual sections of the GOSE structured interview and GOSE questionnaire at 6 months post-injury




### *4.4.3. Exploratory analyses*

*Dichotomised GOSE ratings*

Comparisons were made for patients assigned to 'better' (i.e., 'moderate disability' and 'good recovery' categories) and 'worse' (i.e., 'vegetative state' and 'severe disability' categories) outcome groups using McNemar's test. At 3 months, there was a significant difference in the proportion of patients assigned to 'better' and 'worse' outcome groups ($p$<0.001). However, at 6 months, these groups were comparable ($p$=0.08). Figures 4.5 and 4.6 show the proportions of patients assigned to the 'better' and 'worse' outcome groups at 3 and 6-months.

Figure 4.5: Dichotomised GOSE ratings at 3 months post-injury

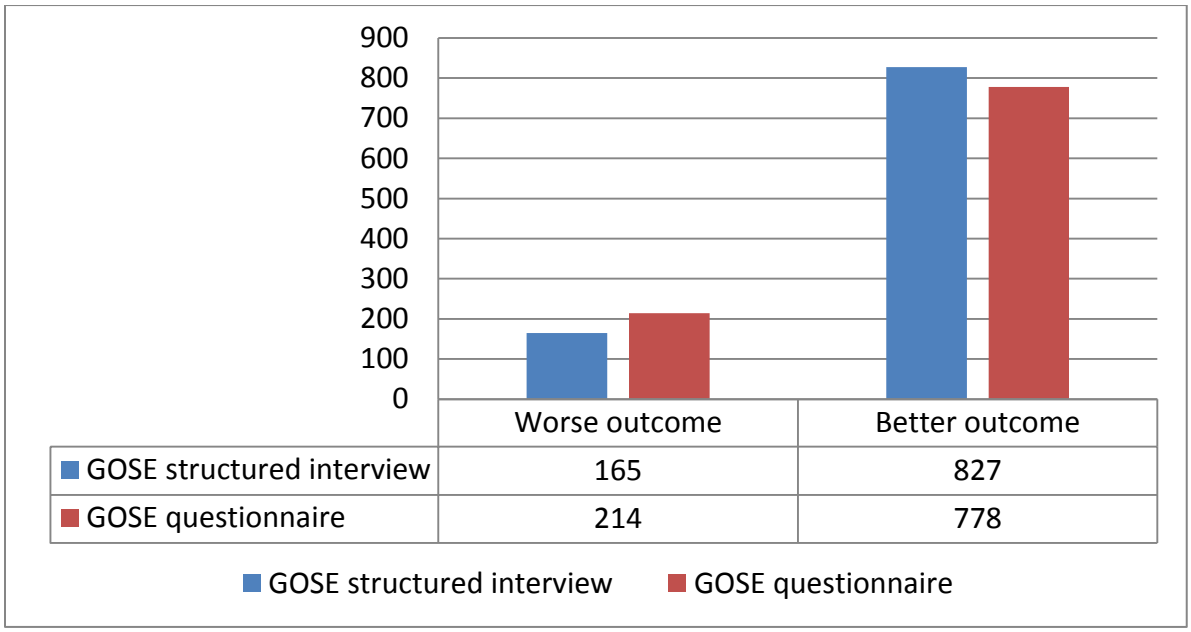
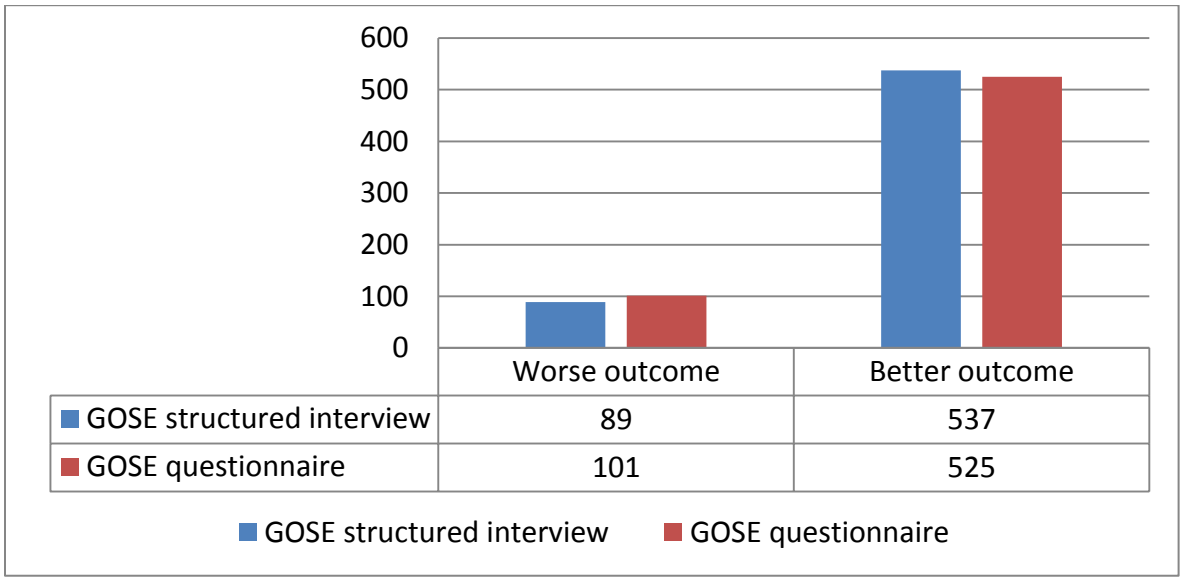



Figure 4.6: Dichotomised GOSE ratings at 6 months post-injury




*Re-scoring the GOSE questionnaire*

Limitations were endorsed most frequently on the symptoms section of the GOSE. Furthermore, the symptoms section of the scale had the lowest levels of agreement ($\kappa$=0.43 at both time-points), and symptoms were less likely to be endorsed when the GOSE questionnaire

was completed. The symptoms section of the GOSE questionnaire was therefore re-scored using a revised algorithm in which all symptoms were counted as relevant to outcome even if respondents indicated that they did not have an impact on daily functioning (Wilson & Horton, 2018). Table 4.7, and Figures 4.7 and 4.8, show that levels of agreement between the structured interview and questionnaire improved when the revised algorithm was used.

Table 4.7: Levels of agreement between GOSE structured interview and GOSE questionnaire when the symptoms section is re-scored using a revised scoring algorithm

| Symptoms | I-/Q- | I-/Q+ | I+/Q- | I+/Q+ | % Agreement | Kappa | SE | 95% CI |
|---|---|---|---|---|---|---|---|---|
| **3-months** (*n*=976) | 317 | 94 | 112 | 453 | 78.9% | 0.57 | 0.03 | 0.51-0.63 |
| **6-months** (*n*=599) | 199 | 85 | 51 | 264 | 77.3% | 0.54 | 0.03 | 0.48-0.60 |

I- = no limitation recorded on interview; I+ = limitation recorded on interview
Q- = no limitation recorded on questionnaire; Q+ = limitation recorded on questionnaire

Figure 4.7: Number of patients assigned to 'good recovery' categories at 3-months post-injury for the GOSE questionnaire (scored using the standard algorithm and revised algorithm), and the GOSE structured interview

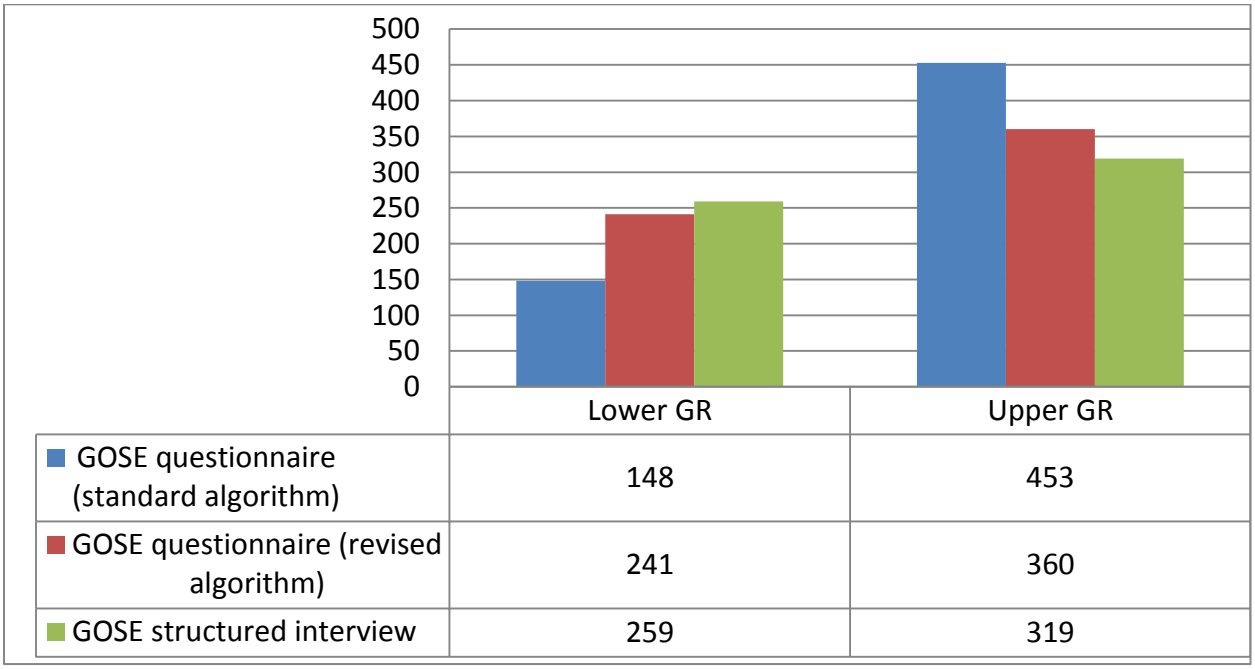
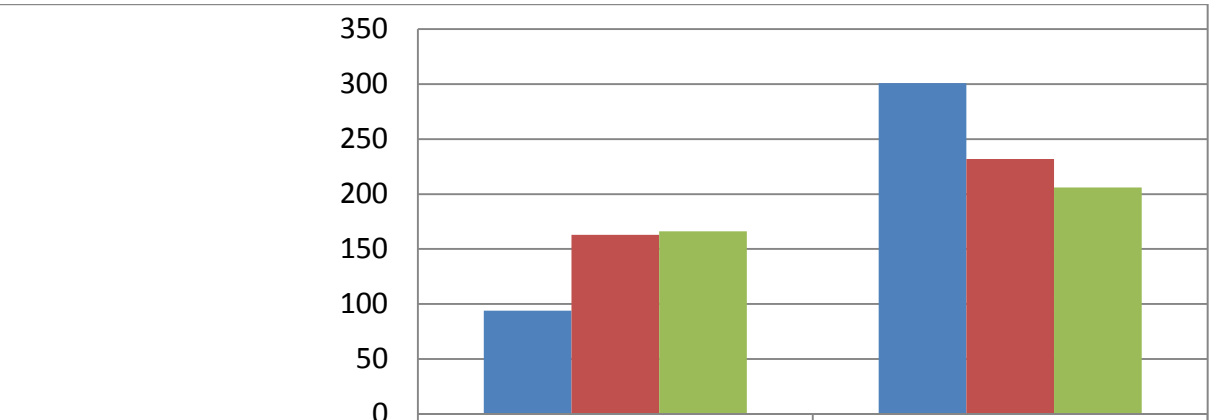


Figure 4.8: Number of patients assigned to 'good recovery' categories at 6-months post-injury for the GOSE questionnaire (scored using the standard algorithm and revised algorithm), and the GOSE structured interview




| | Lower GR | Upper GR |
|---|---|---|
| GOSE questionnaire (standard algorithm) | 94 | 301 |
| GOSE questionnaire (revised algorithm) | 163 | 232 |
| GOSE structured interview | 166 | 206 |

*Sub-group comparisons*

Comparisons were made for sub-groups of patients to examine whether pre-existing functional limitations, extracranial concomitant injury, epilepsy, injury severity, CT abnormality, and type of respondent affected levels of agreement between overall scores on the GOSE structured interview and GOSE questionnaire.

Table 4.8 shows that there was at least good agreement (i.e., $\kappa_w$>0.60) between GOSE assessments for the sub-group comparisons. However, the 3-month comparison for patients with functional limitations due to the combined effects of head injury and extracranial injury/illness showed a moderate level of agreement ($\kappa_w$=0.55, CI: 0.41-0.69).

Table 4.8: Levels of concordance between overall scores for GOSE structured interview and GOSE questionnaire for sub-groups at 3 and 6-months post-injury

| | **3-month GOSE assessments** ($\kappa_w$, 95% CIs) | **6-month GOSE assessments** ($\kappa_w$, 95% CIs) |
|---|---|---|
| **Pre-existing functional limitations** | | |
| Healthy patients/patients with mild systemic disease (no pre-existing functional limitations) | 0.78 (0.74-0.81) (*n*=902) | 0.84 (0.80-0.88) (*n*=561) |
| Patients with severe/life threatening systemic disease (pre-existing functional limitations) | 0.64 (0.49-0.80) (*n*=77) | 0.65 (0.46-0.83) (*n*=51) |
| **Extracranial concomitant injury** | | |
| No extracranial injury (outcome is the result of head injury alone) | 0.83 (0.79-0.87) (*n*=439) | 0.83 (0.77-0.88) (*n*=290) |
| Outcome is the result of head injury & extracranial injury/illness | 0.55 (0.41-0.69) (*n*=152) | 0.79 (0.67-0.91) (*n*=79) |
| Outcome is the result of extracranial injury/other illness alone | 0.73 (0.66-0.80) (*n*=247) | 0.83 (0.76-0.91) (*n*=126) |
| **Epilepsy** | | |
| Patients without epilepsy | 0.75 (0.71-0.79) (*n*=909) | 0.82 (0.77-0.86) (*n*=551) |
| Patients with epilepsy | 0.76 (0.62-0.90) (*n*=44) | 0.74 (0.57-0.92) (n=37) |
| **Injury severity** | | |
| Mild TBI (i.e., GCS=13-15) | 0.66 (0.60-0.72) (*n*=681) | 0.71 (0.63-0.79) (*n*=390) |
| Moderate TBI (i.e., GCS 9-12) | 0.73 (0.63-0.84) (*n*=93) | 0.89 (0.80-0.98) (*n*=65) |
| Severe TBI (i.e., GCS=3-8) | 0.81 (0.74-0.87) (*n*=172) | 0.86 (0.80-0.93) (*n*=134) |
| **CT Abnormality** | | |
| Present | 0.76 (0.71-0.81) (*n*=474) | 0.83 (0.78-0.88) (*n*=319) |
| Absent | 0.69 (0.60-0.78) (*n*=357) | 0.69 (0.57-0.81) (*n*=232) |
| **Type of respondent** | | |
| Patient alone or with proxy | 0.68 (0.63-0.73) (*n*=830) | 0.75 (0.69-0.80) (*n*=537) |
| Proxy informant alone | 0.82 (0.72-0.92) (*n*=85) | 0.86 (0.74-0.97) (*n*=51) |

## 4.5. Discussion

This study compared two main approaches to collecting information about global functional outcome after TBI to determine whether clinician ratings on the GOSE structured interview

provide added value over respondent reports on the GOSE questionnaire. Overall GOSE scores were found to be similar: there was perfect agreement for more than half of the patients, and where discrepancies occurred, most were slight (i.e., within 1 category). Levels of agreement for ratings on individual sections of the GOSE were also acceptable: concordance was strongest for objective aspects of functioning such as independence in activities of daily living, and weakest for subjective aspects of functioning such as TBI-symptoms and relationships. The findings indicate that outcomes obtained using the two GOSE approaches are broadly comparable and suggest that respondent reports on the GOSE questionnaire provide adequate information about global functioning after TBI. Nevertheless, exploratory analyses revealed that there are certain circumstances in which it may be preferable to supplement questionnaire assessments with the GOSE structured interview. In particular, information obtained via the structured interview may be particularly useful in the first 3 months after injury when assessing patients with greater levels of disability or extracranial concomitant injuries/illness. The structured interview may also be useful to distinguish between patients in the upper and lower 'good recovery' categories, as ratings for TBI symptoms were found to be inconsistent between the two GOSE approaches.

At 3 months post-injury, dichotomized GOSE scores revealed that questionnaire responses were systematically less favourable than structured interview ratings for patients with greater levels of disability (i.e., those assigned to the 'vegetative state' and 'severe disability' outcome groups). A possible explanation for this finding is that at 3-month follow-up, patients with poorer outcomes may not have returned to previous daily activities, despite being capable of doing so. They may therefore not have considered whether they would theoretically be capable of activities such as looking after themselves at home, going shopping, or using public transport. In contrast to self-reports on the GOSE questionnaire, when completing the GOSE structured interview, investigators are encouraged to assess whether patients would theoretically be capable of performing activities (Wilson et al., 1998). This may result in more optimistic clinician ratings at the lower end of the scale. Small discrepancies between ratings on the GOSE structured interview and GOSE questionnaire are not particularly important, but

may be problematic in study analyses, particularly if GOSE scores are dichotomized. As the GOSE is often dichotomized in acute clinical trials, conventionally at the division between 'moderate' and 'severe' disability (Horton et al., 2018; McMillan et al., 2016), particular care should be taken when assessing patients who may be unable to participate independently in life roles outside the home.

A significant number of patients in the current study had characteristics that are associated with poorer prognosis (Roozenbeek et al., 2012). For example, they were older than samples in previous TBI studies, reflecting the increasing incidence of TBI in older adults (Brazinova et al., 2016; Peeters, Majdan, Brazinova, Nieboer, & Maas, 2017; Peeters et al., 2015). Most of the patients were admitted to the hospital ward or intensive care unit upon injury and around half of them met criteria for 'major trauma.' Half of the patients had CT abnormalities, and more than one-third also had severe extracranial injuries. Despite the potential for investigator ratings to be influenced by knowledge of prognostic factors, outcomes were found to be similar for the sub-group comparisons. Furthermore, despite the potential for respondent reports to be influenced by lack of insight (Prigatano, 2005a, 2005b), outcomes on the two GOSE approaches were not affected by injury severity. These results suggest that both GOSE approaches can be used with patients with pre-existing functional limitations, epilepsy, and moderate-to-severe TBI. Nevertheless, inconsistencies were found between the two GOSE approaches for patients with functional limitations as a result of extracranial injury/illness in combination with TBI. Agreement was in the moderate range at the 3-month follow-up for patients in this sub-group, but improved at the 6-month follow-up. This finding may be due to differences in the way in which extracranial injuries were rated on the GOSE structured interview and GOSE questionnaire. However, the finding suggests that peripheral injury has a substantial effect on the assessment of global functional outcome, but only in the first few months after TBI. As severe extracranial injuries often occur alongside mild TBI and are associated with poorer long-term functional outcomes (Leong et al., 2013), it is important to pay attention when assessing daily functioning in patients with polytrauma, especially in the first few months after injury.

The GOSE is quick and easy to administer and is associated with better follow-up rates than other types of outcome assessment, such as neuropsychological tests (McMillan et al., 2016). Consistent with guidance from the FDA (U.S. Food & Drug Administration, 2009), the GOSE questionnaire is particularly useful in studies where interviewer bias may be an issue (i.e., surgical trials). The current study indicates that respondent reports on the GOSE questionnaire are broadly equivalent to clinician ratings on the GOSE structured interview and can be used to obtain information about daily functioning after TBI. The clinician-rated interview provided modest added value over the respondent-completed questionnaire in CENTER-TBI. However, the specific choice of outcomes will depend on the purposes of the research. For high stakes situations in which the GOSE is the primary endpoint of the study, it is advisable to use a single approach, and generally that will be the structured interview administered by trained assessors. In circumstances where the GOSE is being collected together with other outcomes and there are logistic constraints, studies may exploit the flexibility of the GOSE, and mixed data collection modes can be utilised to facilitate participant retention at follow-up.

A key benefit of the current study is that the large sample sizes made it possible to explore differences in that way symptoms were rated on the GOSE. Levels of agreement were weakest for the symptoms section of the GOSE and symptoms were less likely to be endorsed by patients if the GOSE questionnaire was completed. This finding is not surprising, as it can be difficult to judge the impact of TBI-related symptoms on daily functioning: symptoms are the most subjective aspect of daily functioning; they can be attributed to other causes; and they may fluctuate over time. Different methods of eliciting information about symptoms have been shown to result in inconsistent responses about TBI-related symptoms. For example, when interviewed using a standardized checklist made-up of common post-mild TBI symptoms, patients were found to report significantly more symptoms than if they are asked to freely identify their symptoms (Villemure, Nolin, & Le Sage, 2011). With this in mind, investigators should be aware of the potential influence different interviewing styles may have on patient disclosures about TBI-related symptoms, and GOSE structured interview guidelines should be followed to ensure that sufficient information is collected about whether symptoms are having

an impact on daily functioning (Wilson et al., 1998). For patients assigned to the 'good recovery' categories, it may be necessary to include a supplementary assessment of TBI-symptoms, such as the Rivermead Post-concussion Questionnaire (RPQ) (King et al., 1995), to gather additional information about the impact of symptoms on daily activities.

### *4.5.1. Limitations*

This study involved analysing CENTER-TBI data. Thus, it was not possible to employ an experimental design. Investigators were not masked to information about prognostic factors or scores on other outcome assessments and patient self-awareness was not measured directly. Furthermore, as the GOSE was not collected in a uniform way across study sites, systematic comparisons between different modes of data collection (i.e., telephone versus face-to-face interviews; patient versus proxy informant) were not possible. Given these limitations, it would be useful to conduct further research in which formal comparisons were made between different data collection modes, using investigators who were masked to all other study measures. However, conducting such a study may not be feasible, as multiple modes of GOSE data collection would increase the burden of assessment and may prove difficult to obtain.

### *4.5.2. Conclusion*

This study indicates that clinician-rated interviews and respondent-completed questionnaires yield broadly comparable information concerning global functional outcome, even when used with patients with pre-existing functional limitations, epilepsy, CT abnormalities, moderate-to-severe TBI, and significant extracranial injuries. The study also suggests that in large-scale studies with pragmatic constraints, information collected via interviews makes little overall difference to GOSE ratings. However, there are certain circumstances in which the GOSE structured interview may provide additional detail that is not captured by the GOSE questionnaire, e.g., when assessing patients with greater functional limitations or significant extracranial injury at 3-month follow-up, and when rating the impact of TBI-related symptoms on daily life.

# CHAPTER 5

## The GOSE as a clinician-reported or patient-reported outcome

The study described in Chapter 4 provides evidence for the comparability of the clinican-rated GOSE structured interview and respondent-reported GOSE questionnaire. However, it did not examine the relationship between the two GOSE approaches and other variables. This chapter will investigate whether there are systematic differences in the constructs being assessed using the GOSE structured interview and GOSE questionnaire by examining how the two GOSE approaches relate to prognotic factors and other outcome measures.

## 5.1. Abstract

The GOSE is conventionally classified as a clinician-reported outcome (ClinRO). However, when administered as a self-completion questionnaire and scored mechanically, it can essentially be considered a patient-reported outcome (PRO). The current study aimed to examine the associations between the GOSE structured interview and GOSE questionnaire with prognostic variables from the IMPACT and CRASH models, as well as with other types of outcome measure, including PROs (measures of HRQoL, psychological status, and TBI symptoms) and PerfOs (measures of cognition and physical functioning). The study used cross-sectional data collected for CENTER-TBI at the 6-month follow-up and examined GOSE assessments which were completed by TBI patients alone or with assistance from a proxy respondent. A total of 537 patients were included in the study. On an 'investigator bias' hypothesis, the GOSE structured interview was predicted to have stronger associations with prognostic variables and measures of cognition and physical functioning than the GOSE questionnaire. On a 'patient perspective' hypothesis, the GOSE questionnaire was predicted to have stronger associations with patient-reported questionnaires than the GOSE structured interview. Most of the examined variables were found to have significant correlations with the two GOSE approaches *(*-0.13 to 0.42 for prognostic factors; 0.29 to 0.65 for PROs; -0.14 to -0.32 for PerfOs), and consistent with previous research, the associations between the GOSE and other outcome measures were modest. The correlations for the two GOSE approaches were comparable, indicating that clinician-ratings and patient-reports of functional outcome were equivalent in terms of how they related to prognostic factors and other outcome measures. The findings therefore suggest that GOSE assignment is not affected by investigator bias or the patient's perspective. The current study also supports recommendations for the GOSE to be used as part of a multi-dimensional approach to the assessment of TBI outcomes.

## 5.2. Introduction

The GOSE provides a global index of function after TBI, in that it addresses what the patient is able to do, and categorises outcome by identifying the area of greatest limitation in daily activities (Jennett et al., 1981). It has most commonly been administered as a clinician-rated interview in RCTs in adult TBI (Horton et al., 2018). However, for pragmatic reasons, and to avoid investigator bias in studies where blinding is not possible, the respondent-completed questionnaire is increasingly being used as a primary mode of GOSE data collection in multicentre clinical trials (Andrews et al., 2015; Gregson et al., 2015; Horton et al., 2018; Hutchinson et al., 2017; Mendelow et al., 2015). The GOSE is conventionally classified as a ClinRO, because when it is administered as a structured interview and rated by the interviewer, outcomes are assigned using the professional judgement of the investigator (McMillan et al., 2016; Powers et al., 2017). Nevertheless, when administered via questionnaire and scored mechanically by algorithm, the GOSE can essentially be considered a PRO, as it offers an insight into the perspective of the respondent without their ratings being interpreted by the investigator (Walton et al., 2015; Wilson et al., 2002).

Evidence concerning the construct validity of the GOSE comes from the wide variety of studies that have used it and from relationships described with clinical characteristics and other outcome measures (McMillan et al., 2016). Recent analyses of the TRACK-TBI pilot study sample indicate that the GOSE has small-to-medium correlations with acute measures of injury severity (-0.18 to 0.39), psychological status (-0.40 to -0.52), TBI symptoms (-0.44 to -0.64), satisfaction with life and HRQoL (0.38-0.42), and cognition (0.17 to 0.30) (Kreitzer et al., 2018; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). Additionally, a recent meta-analysis of the neuropsychological predictors of functional outcome demonstrates that the GOSE has significant correlations with assessments of immediate and delayed verbal memory (0.43), visuo-spatial construction (0.29), set-shifting (response speed) ( -0.31), and generativity (0.44) (Allanson, Pestell, Gignac, Yeo, & Weinborn, 2017). Poorer outcomes on the GOSE are associated with greater injury severity and longer PTA duration, whereas better functional recovery is associated with lower levels of emotional distress, milder

TBI symptoms, better satisfaction with life, and better performance on cognitive tests (Allanson et al., 2017; Kreitzer et al., 2018; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). The effect that GOSE modality of asssessment has on its associations with clinical characteristics and other outcome measures has not specifically been examined. It is therefore unclear whether clinician ratings and patient reports of functional ability are comparable in terms of how they relate to prognostic variables and other outcome domains.

In CENTER-TBI, unmasked outcome assessors may have been aware of acute prognostic factors known to influence outcomes. The associations between the two GOSE approaches and prognostic variables warrant exploration because 'unmasked' interviewers may be unintentionally biased by their knowledge of the patient's clinical status (Sherer et al., 2010). Various prognostic models have been reported in TBI research (Lingsma, Roozenbeek, Steyerberg, Murray, & Maas, 2010). However, the IMPACT (Steyerberg et al., 2008) and CRASH (Collaborators et al., 2008) models are recommended over other prognostic models because they were developed using large datasets and have also been externally validated (Maas, Lingsma, & Roozenbeek, 2015; Roozenbeek et al., 2012). The IMPACT model was developed using data from patients with moderate and severe TBI, whereas the CRASH model also included patients with mild TBI. Both models include three core predictor variables: age, Glasgow Coma Scale (GCS) full score or motor score, and pupillary reactivity to light. The basic CRASH model also includes major extracranial injury as a predictor. The IMPACT and CRASH predictions were derived using different methods of assessing functional outcome: the IMPACT model was developed using guided interviews on the 5-point GOS (Steyerberg et al., 2008); while the CRASH model was developed from a short questionnaire version of the 5-point GOS which was completed primarily via mail (Roberts et al., 2004). It is therefore unclear whether the way in which information was collected about functional outcome affected the final prognostic models.

The associations between the two GOSE approaches and other outcome measures warrant investigation because unmasked outcome assessors' ratings on the GOSE structured interview may be influenced by knowledge of the patients' performance on PerfOs (i.e., cognitive assessments and tests of physical functioning), while patient reports on the GOSE questionnaire may be biased by the patient's perspective. The GOSE self-report questionnaire essentially assesses the perspective of the patient, and one might therefore expect it to have a stronger relationship with PROs than the GOSE structured interview. In clinical studies, it is important to include outcome measures that capture both how the patient functions and how they feel (Walton et al., 2015). In the context of TBI, this involves incorporating tools that measure the patient's perspective within a multi-dimensional outcomes framework (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). ClinROs and PerfOs measure the patient's level of functioning. In contrast, PROs measure how the patient feels. Like PROs, the GOSE questionnaire reflects the perspective of the respondent. However, unlike other PROs, it does not tap into the subjective meaning the patient ascribes to their functional limitations (Koskinen et al., 2011; Nichol et al., 2011; Polinder et al., 2015). The GOSE questionnaire therefore differs from other PROs, in that it is a self-reported index of the patient's level of functioning, rather than how they feel. Table 5.1 illustrates the distinctions between these different types of COA.

Table 5.1: Distinctions between different types of COA and whether they measure how the person functions or how the person feels

| | **"how the person functions"** | **"how the person feels"** |
|---|---|---|
| **ClinRO** | GOSE structured interview | |
| **PRO** | GOSE questionnaire | Measures of HRQoL, psychological status, TBI symptoms |
| **PerfO** | Cognitive tests, assessmnents of physical functioning | |

### 5.2.1. *Study aims*

CENTER-TBI provides an opportunity to investigate how clinician-ratings and patient-reports of functional outcome may differ in their associations with other factors. Thus, the current study aimed to investigate the associations between the GOSE structured interview and GOSE questionnaire with other CENTER-TBI measures, including:

- Prognostic variables from the basic CRASH and core IMPACT models (i.e., age, GCS score, pupil reactivity, and extracranial injury)
- Other types of outcome measure, including PROs (i.e., measures of HRQoL, psychological status, and TBI symptoms) and PerfOs (i.e., measures of cognition and physical functioning)

### 5.2.2. *Hypotheses*

*Investigator bias*

As the GOSE structured interview is based on investigator ratings, which can be influenced by the interviewer's knowledge of the patient, it will have stronger associations with acute stage prognostic variables and PerfOs (i.e., measures of cognition and physical functioning) than the patient-reported GOSE questionnaire.

*Effect of the patient's perspective*

As the GOSE questionnaire is based on the patient's self-report and not influenced by the perspective of the investigator, it will have stronger associations with other PROs than the GOSE structured interview.

## 5.3. Methods

### 5.3.1. *Participants*

Potentially eligible participants were selected from the 6-month CENTER-TBI sub-sample described in Chapter 4, which comprised all surviving adult patients who were assessed using the GOSE structured interview and GOSE questionnaire within a 3-week time interval at 6-month follow-up. Patients were selected for the current study only if the GOSE assessments

were completed alone or with assistance, and not if they were completed by a proxy informant alone.

### 5.3.2. *Design*

This study used cross-sectional data collected for the CENTER-TBI 6-month follow-up, which included the GOSE, as well as the other outcome measures listed below.

### 5.3.3. *Measures* (all measures are described in detail in Chapter 3)

The following acute measures were used:

- American Society of Anaesthesiologists' (ASA) classification of Physical Health (Dripps, 1963)
- Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974)
- CT abnormality
- Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) (Baker et al., 1974)
- Injury severity was also categorised according to clinical care pathway (i.e., emergency room (ER), admission to hospital ward (Admission), intensive care unit (ICU)).

The outcome measures used in this study are organised below according to the CDE outcome domains (Wilde et al., 2010):

*Global outcome*

- GOSE structured interview (Wilson et al., 1998)
- GOSE questionnaire (Wilson et al., 2002)
- 36-Item Short Form Survey - Version 2 (SF-36v2) (Ware & Sherbourne, 1992)

*Health-related quality of life*

- Quality of Life after Brain Injury Scale (QOLIBRI) (von Steinbüchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Sarajuuri, et al., 2010)
- QOLIBRI Overall Scale (QOLIBRI-OS) (von Steinbüchel et al., 2012)

*Psychological status*

- Post-Traumatic Stress Disorder Checklist-5 (PCL-5) (Weathers et al., 2013)
- Patient Health Questionnaire-9 (PHQ-9) (Kroenke, Spitzer, Williams, & Lowe, 2010)
- Generalized Anxiety Disorder-7 (GAD-7) (Spitzer et al., 2006)

*TBI symptoms*

- Rivermead Post-concussion Questionnaire (RPQ) (King et al., 1995)

*Neuropsychological impairment*

- Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996)
- Trail Making Test (TMT) Parts A & B (Strauss et al., 2006)
- Cambridge Neuropsychological Test Automated Battery (CANTAB) Reaction Time (RTI), Paired Associate Learning (PAL), Visual Attention Switching Task (AST), Spatial Working Memory (SWM), Rapid Visual Information Processing (RVP), and Stockings of Cambridge (SOC) (Cambridge Cognition Ltd, 2014)

*Physical functioning*

- 10-meter walk and Timed Up and Go (TUG) (Podsiadlo & Richardson, 1991)

*Recovery of consciousness*

- Galveston Orientation and Amnesia Test (GOAT) (Levin et al., 1979)

The GOAT was used to describe the clinical characteristics of the patients and to screen for post-traumatic amnesia and testability for cognitive assessments at 6-month follow up.

### 5.3.4. *Statistical analysis*

*Demographic and clinical characteristics*

The demographic and clinical characteristics of the current study sample were described using frequencies and percentages, and medians and inter-quartile ratios (IQR) were used for continuous data (i.e., age and total ISS score).

*Associations between the GOSE and other variables*

Associations between the GOSE and other variables were assessed using Spearman correlations. Non-parametric correlations were used because the GOSE is an ordinal scale and because scores on several of the other measures were skewed. The two modes of GOSE data collection were correlated separately with prognostic factors (i.e., age, GCS score, pupil reactivity, and extracranial injury), and with other outcome measures (i.e., measures of HRQoL, psychological status, TBI symptoms, cognition, and physical functioning). The significance level was set at $p<0.01$ (two-tailed) for correlations, given the relatively large sample size. No formal adjustments were made for multiple testing because both type 1 errors (i.e., finding spurious relationships/differences) and type 2 errors (i.e., failing to detect relationships/differences) are relevant to the study aims and hypotheses. Steiger's test (Lee & Preacher, 2013; Steiger, 1980) was used to examine whether the correlations for the GOSE structured interview and GOSE questionnaire were significantly different from each other. All Steiger's tests were two-tailed and they were not performed if the correlations were identical, or if both correlations were non-significant at the $p<0.01$ level. All statistical analyses were conducted using IBM SPSS Statistics 23. The data were downloaded from the INCF Neurobot database (Version 1) on 8 November 2018.

## 5.4. Results

### 5.4.1. *Demographic and clinical characteristics*

A total of 537 patients met the inclusion criteria for this study (i.e., they were eligible for the 6-month follow-up, scored in the 'lower severe disability' category or better, and completed both

types of GOSE assessment alone or with help from a proxy informant, within a 3-week time interval). Tables 5.2 and 5.3 describe the current study sample.

Table 5.2: Demographic characteristics of the current study sample

| | ***n* (%)** |
|---|---|
| **Age band** | |
| 16-25 | 104 (19.4%) |
| 26-35 | 72 (13.4%) |
| 36-45 | 63 (11.7%) |
| 46-55 | 94 (17.5%) |
| 56-65 | 88 (16.4%) |
| 66-75 | 70 (13%) |
| 76-86 | 41 (7.6%) |
| >86 | 5 (0.9%) |
| **Gender** | |
| Male | 347 (64.6%) |
| Female | 190 (35.4%) |
| **Race** | |
| Caucasian | 518 (96.5%) |
| Other | 10 (1.8%) |
| Unknown | 9 (1.7%) |
| **Education** | |
| Primary school or less | 50 (9.3%) |
| High school | 162 (30.2%) |
| Post-high school training | 86 (16%) |
| College/University | 137 (25.5%) |
| Unknown | 102 (19%) |
| **Previous employment** | |
| Working | 264 (49.2%) |
| Not working | 51 (9.5%) |
| Retired | 112 (20.9%) |
| Student/homemaker | 57 (10.6%) |
| Unknown | 53 (9.9%) |
| **Marital status** | |
| Partnered | 251 (46.7%) |
| Previously partnered | 62 (11.5%) |
| Single/unspecified | 177 (33%) |
| Unknown | 47 (8.8%) |

Table 5.3: Clinical characteristics of the current study sample

| | ***n* (%)** |
|---|---|
| **ASA Physical Health** | |
| Healthy patient | 318 (59.2%) |
| Mild systemic disease | 163 (30.4%) |
| Severe/life threatening systemic disease | 43 (8%) |
| Unknown | 13 (2.4%) |
| **Cause of injury** | |
| Road traffic accident | 209 (38.9%) |
| Incidental fall | 221 (41.2%) |
| Violence/assault | 41 (7.6%) |
| Other | 49 (9.1%) |
| Unknown | 17 (3.2%) |
| **Clinical Care Pathway** | |
| Emergency Room | 122 (22.7%) |
| Admitted to hospital | 164 (30.5%) |
| Intensive Care Unit | 251 (46.7%) |
| **GCS Score** | |
| 13-15 | 351 (65.4%) |
| 9-12 | 52 (9.7%) |
| 3-8 | 99 (18.4%) |
| Unknown | 35 (6.5%) |
| **CT abnormality** | |
| Present | 258 (48%) |
| Absent | 215 (40%) |
| Unknown | 64 (12%) |
| **Head & neck injury[1]** | |
| No injury/minor injury | 106 (19.8%) |
| Moderate injury | 79 (14.7%) |
| Serious injury | 131 (24.4%) |
| Severe injury | 99 (18.4%) |
| Critical injury | 121 (22.5%) |
| Unsurvivable injury | 1 (0.2%) |
| **Non-head & neck injury[2]** | |
| No injury/mild injury | 346 (64.4%) |
| Severe injury | 182 (33.9%) |
| Unknown | 9 (1.7%) |
| **Post-traumatic amnesia** | |
| GOAT total score <75 | 7 (1.3%) |
| GOAT total score >75 | 383 (71.3%) |
| Unknown | 147 (27.4%) |

[1]Head & neck injury = combined AIS score for head, neck and cervical regions;
[2]Non-head & neck injury (severe injury= Total ISS >7)

The median (IQR) age for the current study sample was 50 years (30-63). Around two-thirds of the patients were male, and the majority were Caucasian. Most patients had high school, post-high school, or college-university education. Around half of the patients were in employment prior to injury, and around half of them were partnered. Most of the patients were healthy or had mild systemic disease (i.e., conditions with no functional limitation) prior to injury. Road traffic accidents and incidental falls were the most common causes of injury, accounting for around 80% of the sample. Most of the patients were either admitted to the hospital ward or intensive care unit. Around two-thirds of the sample had GCS scores of 13-15, while almost half had CT abnormalities. The median (IQR) total ISS for the sample was 16 (8-27), which is above the threshold for major trauma (i.e., ≥15). A total of 50.3% (*n*=270) of the patients met criteria for major trauma, and around one-third had severe non-head and neck injuries. Most of patients who were tested (i.e., 72.6% of the study sample) scored above 75 on the GOAT and were therefore no longer in post-traumatic amnesia.

### 5.4.2. *Associations between the GOSE and other variables*

The correlation between the structured interview and questionnaire was significant at the 0.01 level (2-tailed, rho = 0.72), indicating a strong positive association between GOSE scores. Spearman correlations for the GOSE structured interview and GOSE questionnaire against other variables are displayed in Tables 5.4 - 5.6. Prognostic variables are displayed in Table 5.4, PROs are displayed in Table 5.5, and PerfOs are displayed in Table 5.6.

Table 5.4 shows that most prognostic variables had significant correlations at the $p<0.01$ level, apart from the correlation between age and the GOSE questionnaire, which was non-significant. The correlations were strongest for GCS Score and total ISS (correlations ranged from 0.37 to 0.42), and weakest for pupil reactivity and age (ranging from -0.04 to -0.19). Steiger's test was significant for age only ($Z$ = -2.80, $p<0.01$), indicating that age correlated more strongly with scores on the GOSE structured interview than it did with scores on the GOSE questionnaire. Nevertheless, the strength of the relationship between age and scores on the GOSE was very weak and accounted for only 2% of the variance. Thus, there was little support

for the hypothesis that the GOSE structured interview would systematically correlate more strongly than the GOSE questionnaire with prognostic factors.

Table 5.4: Spearman correlations between the GOSE and prognostic factors

| | **GOSE structured interview** | **GOSE questionnaire** | **Steiger's Test** |
|---|---|---|---|
| **Age** (*n*=537) | -0.13* | -0.04 | *Z*=-2.80, *p*<0.01* |
| **GCS score** (*n*=502) | 0.37* | 0.39* | *Z*=-0.63, *p*=0.51 |
| **Pupil reactivity** (*n*=491) | -0.19* | -0.17* | *Z*=-0.61, *p*=0.54 |
| **Total ISS** (*n*=528) | -0.37* | -0.42* | *Z*=1.69, *p*=0.09 |

*Correlation is significant at the 0.01 level (2-tailed)

Table 5.5 shows that most PROs had significant correlations with the GOSE at the $p < 0.01$ level. Correlations ranged from rho = 0.26-0.65, and the correlations between the GOSE and PROs were generally stronger than those for prognostic factors and PerfOs. The strongest correlation was found between the GOSE and the SF-36v2 'role - physical' sub-scale (GOSE structured interview = 0.63; GOSE questionnaire = 0.65). Correlations were 0.50 or above for the SF-36v2 'physical functioning' (GOSE structured interview only), and 'social functioning' sub-scales, SF-36v2 PCS Score, QOLIBRI 'daily life & autonomy' and 'physical problems' sub-scales, QOLIBRI total score, and QOLIBRI-OS (GOSE structured interview only). Correlations were 0.40 or above for the SF-36v2 'general health' (GOSE structured interview only), 'role - emotional,' and 'energy and fatigue' sub-scales, QOLIBRI 'cognition' and 'self' sub-scales (GOSE interview only), QOLIBRI-OS (GOSE questionnaire only), and PHQ-9. Correlations were 0.30 or above for the SF-36v2 'pain' and 'mental health' sub-scales, SF-36v2 MCS Score, QOLIBRI 'self' 'and 'emotions' (GOSE questionnaire only) sub-scales, PCL-5, and GAD-7. The lowest correlations were found for the QOLIBRI 'social relationships' and 'emotions' sub-scales (rho = 0.29). Steiger's tests were non-significant for all comparisons, indicating that the GOSE structured interview and GOSE questionnaire were equivalent in terms of strength of

relationships with the PROs. The hypothesis that the GOSE questionnaire would correlate more strongly with PROs than the GOSE structured interview was therefore not supported.

Table 5.5: Spearman correlations between the GOSE and PROs

| | **GOSE structured interview** | **GOSE questionnaire** | **Steiger's Test** |
|---|---|---|---|
| **SF-36v2** | | | |
| Physical functioning (*n*=468) | 0.54* | 0.49* | *Z*=1.73, *p*=0.08 |
| Role – physical (*n*=467) | 0.63* | 0.65* | *Z*=-0.89, *p*=0.43 |
| Pain (*n*=467) | 0.37* | 0.33* | *Z*=1.24, *p*=0.21 |
| General health (*n*=468) | 0.41* | 0.36* | Z=1.58, *p*=0.11 |
| Social functioning (*n*=467) | 0.50* | 0.52* | *Z*=-0.69, *p*=0.49 |
| Role – emotional (*n*=467) | 0.44* | 0.44* | n/a |
| Energy and fatigue (*n*=463) | 0.44* | 0.42* | *Z*=0.65, *p*=0.52 |
| Mental health (*n*=463) | 0.35* | 0.32* | *Z*=0.92, *p*=0.36 |
| MCS Score (*n*=463) | 0.36* | 0.36* | n/a |
| PCS Score (*n*=463) | 0.57* | 0.55* | *Z*=0.72, *p*=0.47 |
| **QOLIBRI** (*n*=456) | | | |
| Cognition | 0.44* | 0.40* | *Z*=1.27, *p*=0.20 |
| Self | 0.40* | 0.37* | *Z*=0.96, *p*=0.35 |
| Daily life & autonomy | 0.59* | 0.58* | *Z*=-0.36, *p*=0.72 |
| Social relationships | 0.29* | 0.29 | *n/a* |
| Emotions | 0.29* | 0.30* | *Z*=-0.30, *p*=0.76 |
| Physical problems | 0.52* | 0.54* | *Z*=-0.69, *p*=0.49 |
| Total | 0.54* | 0.51* | *Z*=1.03, *p*=0.30 |
| **QOLIBRI-OS** (*n*=482) | 0.50* | 0.45* | *Z*=1.70, *p*=0.09 |
| **PCL-5** (*n*=464) | -0.39* | -0.37* | *Z*=-0.63, *p*=0.53 |
| **PHQ-9** (*n*=464) | -0.47* | -0.47* | n/a |
| **GAD-7** (*n*=465) | -0.34* | -0.34* | n/a |
| **RPQ (total)** (*n*=470) | -0.51* | -0.49* | *Z*=-0.68, *p*=0.49 |

*Correlation is significant at the 0.01 level (2-tailed)

Table 5.6 shows that most PerfOs had significant correlations with the GOSE at the $p<0.01$ level. Significant correlations ranged from -0.14 to -0.32. Steiger's tests were non-significant

for all comparisons. Thus, the hypothesis that the GOSE structured interview would correlate more strongly with measures of cognition and physical functioning than the GOSE questionnaire was not supported.

Table 5.6: Spearman correlations between the GOSE and PerfOs

| | **GOSE structured interview** | **GOSE questionnaire** | **Steiger's Test** |
|---|---|---|---|
| **RAVLT** | | | |
| Principal list total score (*n*=361) | 0.18* | 0.12 | *Z*=1.54, *p*=0.12 |
| Principal list 20-minute delay (*n*=355) | 0.16* | 0.10 | Z=1.52, *p*=0.13 |
| **Trail Making Test** | | | |
| TMT A (*n*=375) | -0.32* | -0.24* | *Z*=-2.16, *p*=0.02 |
| TMT B (*n*=372) | -0.28* | -0.25* | *Z*=-0.81, *p*=0.42 |
| **CANTAB** | | | |
| RTI (*n*=239) | -0.21* | -0.18* | *Z*=-0.63, *p*=0.53 |
| PAL (*n*=276) | -0.21* | -0.15 | *Z*=-1.35, *p*=0.18 |
| AST (*n*=265) | -0.14* | -0.15 | *Z*=0.22, *p*=0.83 |
| SWM (*n*=263) | -0.20* | -0.23* | *Z*=0.66, *p*=0.51 |
| RVP (*n*=238) | 0.29* | 0.30* | *Z*=0.22, *p*=0.83 |
| SOC (*n*=260) | 0.16 | 0.18* | *Z*=-0.44, *p*=0.66 |
| **Timed up & go** (*n*=238) | -0.24* | -0.25* | *Z*=0.21, *p*=0.83 |
| **10-metre walk** (*n*=206) | -0.30* | -0.30* | n/a |

*Correlation is significant at the 0.01 level (2-tailed)

## 5.5. Discussion

Due to the pragmatic way in which outcomes were collected for CENTER-TBI (Maas, Menon, et al., 2015), the data provide a novel opportunity to examine whether clinician ratings and patient reports of global functional outcome are equivalent in terms of how they relate to other factors. The current study examined how the GOSE structured interview and GOSE questionnaire relate to prognostic variables and other outcome measures. Scores on the GOSE were strongly positively correlated. Furthermore, most of the variables examined showed

significant associations, albeit small-to-medium in magnitude, in the expected directions with the GOSE. On an 'investigator bias' hypothesis, the structured interview was predicted to have stronger associations with prognostic variables and measures of cognition and physical functioning than the questionnaire; whereas on a 'patient perspective' hypothesis, the questionnaire was predicted to have stronger associations with other patient-reported questionnaires than the structured interview. The two GOSE approaches were comparable in terms of the strength of their relationships with the other variables, suggesting that neither investigator's knowledge about patients, nor the patient's perspective, affected GOSE ratings.

Blinding of outcome assessors is a particularly important methodological aspect of design in clinical trials because investigator bias can give rise to misleading results which are aligned with expected treatment benefits or predictor variables (Schulz et al., 2010; Sherer et al., 2010). A similar problem arises with prognostic studies and observational studies in comparative effectiveness research. As the CENTER-TBI outcome assessors were not masked to information concerning the patient's clinical status and GOSE interviewers potentially had knowledge about the patient's performance on tests of cognition and physical functioning, there was the possibility for clinician ratings on the GOSE structured interview to be biased. Despite this, the prognostic variables and PerfOs examined in the current study were found to have equivalent relations with two GOSE approaches. These findings suggest that ratings on the GOSE structured interview were largely unaffected by the investigators' knowledge of the patient. These findings also have implications for prognostic studies in TBI, as the IMPACT (Steyerberg et al., 2008) and CRASH (Collaborators et al., 2008) predictions were derived using different methods of data collection for the GOS (i.e., guided interviews and postal questionnaires). The similarity between clinician ratings and patient reports with predictor variables suggests that the IMPACT and CRASH models were unlikely to have been affected by the way in which information was collected about global outcome.

Regulators have encouraged the use of PROs in TBI studies because they capture the patient's perspective and provide information about how they are feeling (U.S. Food & Drug

Administration, 2009). The GOSE and SF-36v2 are both categorised as measures of global outcome in the NINDS CDEs (Wilde et al., 2010). Thus, in CENTER-TBI, the GOSE self-report questionnaire and the SF-36v2 both provided information about the patient's perspective about their level of global functioning after TBI. In the current study, both GOSE approaches were found to have the strongest associations with domains relating to physical functioning on the SF-36v2 (i.e., correlations for the 'physical functioning,' 'role-physical,' and PCS score ranged from 0.49 to 0.65). The strength of these associations indicates that the SF-36v2 captures the construct of global functional outcome in TBI, and suggests that it could be used as a substitute for the GOSE. It is important to note, however, that unlike the GOSE, the SF-36v2 does not take prior functional limitations or changes in functional status since TBI into consideration. The language used in the SF-36v2 may also be challenging for patients with cognitive impairment. The SF-36v2 might therefore have limitations when used with TBI patients with pre-existing functional limitations, cognitive impairment, or communication difficulties, whereas the GOSE is appropriate for use with these individuals.

Concerns have been raised about the use of PROs in TBI studies, as patients with more severe injuries may be unaware of their own limitations, and may therefore paint an overly optimistic picture of their recovery (Prigatano, 2005a, 2005b). It may not always be advisable to use PROs, including the GOSE questionnaire, in TBI studies. Nevertheless, in the current study, the two GOSE approaches were found to be equivelant in terms of their associations with PROs, suggesting that patient reports of global functioning can be used in situations where clinician-ratings are not possible due to pragmatic constraints. These findings suggest that patients were able to provide an accurate self-report about global functioning and a realistic appraisal of their HRQoL, psychological status, and TBI symptoms. It would, however, be useful to conduct further research in which self-awareness was examined directly. The use of a direct measure of self-awareness, such as the Patient Competency Rating Scale (Prigatano & Fordyce, 1986), along with the use of proxy only reports on the GOSE questionnaire, would enable a more rigorous examination of this issue.

The associations between the GOSE and other factors were in the expected directions in the current study. Greater disability was associated with older age, greater injury severity, and greater severity of patient-reported PTSD symptoms, depression, anxiety, and post-concussion symptoms. In contrast, better functional recovery was associated with better patient-reported HRQoL and better performance on cognitive assessments and tests of physical functioning. These findings are consistent with previous research (Allanson et al., 2017; Kreitzer et al., 2018; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017), and demonstrate that the variables examined in this study tap into the construct of global functional outcome. Nevertheless, as the associations between the GOSE and other outcome measures were modest, it is clear that the GOSE may miss important details about specific aspects of functioning after TBI, especially in the cognitive domain. A multi-dimensional approach has been recommended by TRACK-TBI and CENTER-TBI investigators to adequately characterise outcome after TBI (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). It should be noted, however, that TBI patients can be a hard to reach population and comprehensive follow-up assessments can be challenging to obtain. Consideration should therefore be given to how feasible it is to include multiple outcome measures in TBI studies.

### 5.5.1. *Limitations*

This study builds upon the findings reported in Chapter 4, as it provides further evidence for the comparability of the GOSE structured interview and GOSE questionnaire and suggests that the two approaches have shared underlying constructs. Nevertheless, some key limitations should be mentioned. Firstly, the observational nature of the CENTER-TBI study meant that it was not possible to employ an experimental design and systematic comparisons between GOSE approaches, including proxy informant reports on the GOSE questionnaire, were not possible. Secondly, as no direct measure of self-awareness was used in CENTER-TBI, the study lacks verification about the accuracy of patients' self-reported difficulties on the GOSE and other PROs. Thirdly, the current study did not consider the effect of baseline predictors of outcome, such as age and injury severity, on the strength of the correlations between the two GOSE

approaches and other outcome measures. The causal relationship between prognostic factors and TBI outcomes was not examined in this thesis, but is a potential area for investigation in future CENTER-TBI analyses.

### 5.5.2. *Conclusion*

This study provides further evidence for the comparability of the GOSE structured interview and GOSE questionnaire and demonstrates that the variables examined tap into the underlying construct of global functional outcome. GOSE assignment was largely unaffected by investigator bias or by the patient's perspective. Therefore, where appropriate, future observational TBI studies can exploit the flexibility of the GOSE and employ a pragmatic approach to GOSE administration, to facilitate data collection and maximise study follow-up rates. As the associations between the GOSE and other outcome measures were modest, the findings from this study also indicate that the GOSE is insufficient on its own for describing the sequelae of TBI. TBI studies should therefore incorporate multiple assessments across outcome domains to capture how the patient feels and functions. However, as the use of multiple outcome measures might not always be feasible, further research is needed to explore how a multi-dimensional approach to assessing TBI outcomes can be implemented.

# CHAPTER 6

## CENTER-TBI outcome measures
## in relation to post-TBI functional level

This chapter examines the CENTER-TBI outcome measures with patients at different levels of functional recovery and considers the practicality of tailoring multi-dimensional outcome assessment to TBI sub-groups.

## 6.1. Abstract

There is increasing awareness of the importance of multi-dimensional outcome assessment in TBI studies in acute care settings, but currently no consensus about how it might be implemented. The current study examined the completeness, sensitivity, and internal consistency of the CENTER-TBI outcome measures in relation to GOSE assignment and considered how multi-dimensional outcome assessment could be tailored for patients with different post-TBI functional levels. The study used cross-sectional data collected from 2573 survivors who were followed up 6 months after injury using the GOSE. Patients with better levels of functional recovery were found to have better outcome completion rates than those with poorer functional recovery, indicating that multi-dimensional outcome assessment is particularly challenging to implement with patients with severe disabilities. Furthermore, PRO completion rates were better than those for cognitive assessments and tests of physical functioning; highlighting the logistic challenge posed by PerfOs in large-scale TBI studies. Most of the PROs and some CANTAB sub-tests had ceiling effects, particularly when completed with patients with better functional recovery. Certain measures therefore lacked sensitivity across the spectrum of recovery. Ceiling effects were most common for patients with better levels of recovery and were most notable on measures of emotional adjustment, TBI symptoms and the CANTAB Paired Associates Learning test. Floor effects were minimal, but present for patients in the 'lower severe disability' group on some of the SF-36v2 sub-scales, and on measures of physical functioning. The PROs had high levels of internal consistency across the GOSE categories, indicating that when questionnaires were completed, they were reliable across the spectrum of recovery. The findings from this study demonstrate that the applicability of TBI outcome measures is strongly driven by level of functional outcome. Thus, a tailored approach to multi-dimensional outcome assessment allows investigators to capture the multi-dimensional impact of TBI across different levels of functional recovery: this approach to outcome assessment has not commonly been implemented in research in acute care settings. The findings from this study have implications for selecting outcomes for retrospective analyses of data collected for CENTER-TBI, for future prospective TBI studies, and for future refinement of the CDE outcome measures for adult TBI.

## 6.2. Introduction

Multi-dimensional outcome assessment is important in TBI, because, in contrast to using a measure of global functioning such as the GOSE, it enables investigators to characterise outcomes in a comprehensive and granular way by capturing changes in domains of specific interest. The implementation of multi-dimensional outcome assessment poses a significant challenge to TBI studies, particularly in acute care settings. Thus, current data standardization initiatives are aiming to increase comparability of studies and validate and refine multi-dimensional sets of outcome measures that can be used across the TBI spectrum (Hicks et al., 2013; Tosetti et al., 2013; Wilde et al., 2010). The heterogeneity of TBI makes the implementation of multi-dimensional outcome assessment particularly complex, because patients with different levels of injury severity and functional recovery represent different contexts of use (U.S. Food & Drug Administration, 2014; Walton et al., 2015) for outcome measures. Certain outcome measures may not be suitable for use across the TBI spectrum. However, this has not always been properly acknowledged in TBI research. Consideration should therefore be given to how appropriate particular assessments are for use with different sub-groups of patients.

There are a number of potential ways of approaching multi-dimensional outcome assessment in TBI, but currently no consensus about how it should be implemented. Selection of the NINDS common data elements (CDE) outcome measures for TBI was based on expert opinion and took into consideration a range of factors, including the applicability of assessments across a range of injury severity and functional levels; how easy assessments are to administer; and their brevity (Hicks et al., 2013; Wilde et al., 2010). The CDEs include recommendations for the use of outcome assessments in two populations (adult and paediatric) and four study types (epidemiology, acute hospital, moderate-to-severe TBI rehabilitation, mild TBI/concussion) (National Institute of Neurological Disorders and Stroke, 2018b). Some advice is also provided concerning the applicability of specific tools; for example, administration of the WAIS processing speed index tests requires “a functional level in the severe disability or above on the GOS/GOSE” (National Institute of Neurological Disorders and Stroke, 2018a). There are other

study types in addition to those included in the CDE recommendations, and in practice there will be study-specific reasons for choosing particular outcome measures.

As the CDE recommendations are not derived from systematic empirical work, research is required to assess the applicability of outcome measures in TBI studies. CENTER-TBI and TRACK-TBI aim to validate the applicability of the CDEs in different contexts of use and both projects have among their objectives that of developing a "sliding" or "flexible" approach in which outcome assessments are tailored for different sub-groups of TBI patients (Maas et al., 2015; Yue et al., 2018; Yue et al., 2013). This type of tailored approach could be used when selecting outcome measures in prospective studies and could also guide retrospective analyses of data collected for large observational studies, such as CENTER-TBI and TRACK-TBI. There are several possible ways in which a sliding approach could be implemented. TRACK-TBI investigators have proposed a prospective flexible outcomes assessment framework in which patients are stratified into two tiers based on scores on the GOAT: the abbreviated outcomes battery is suitable for patients who lack orientation (i.e., GOAT scores < 75); whereas the comprehensive outcomes battery is suitable for patients with GOAT scores of 75 or above (Yue et al., 2018). An alternative would be to use the GOSE to stratify patients into functional recovery sub-groups for tailored outcome assessment. The use of functional status to guide the selection of assessments for individual patients is common in clinical practice, but there has been no formal evaluation of this approach in TBI research.

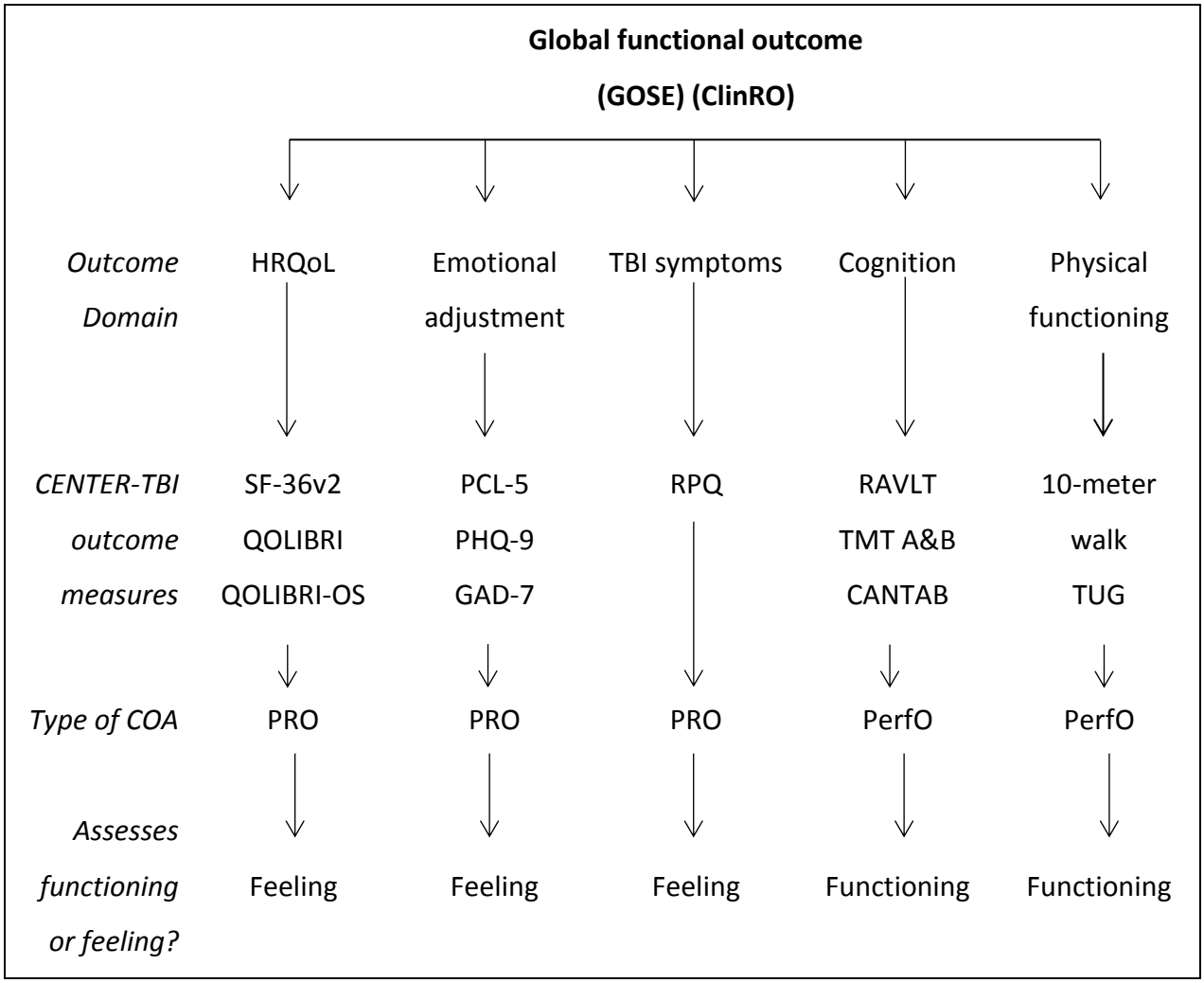
The CDE conception of multi-dimensional outcome assessment places the GOSE alongside other instruments as a specific assessment in the domain of functional outcome (Kean & Malec, 2014; Maas et al., 2017; Wilde et al., 2010). An alternative conception is to consider the GOSE as an overall description of outcome, albeit one that is lacking in detail (Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). The GOSE summarises daily functioning and social reintegration after TBI (Jennett et al., 1981; McMillan et al., 2016), but it does not fully capture specific problems patients may experience, particularly in the domains of emotional wellbeing, cognition, and life satisfaction (Alali et al., 2015; Maas et al.,

2017; McMillan et al., 2016; Menon & Maas, 2015; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017; Nichol et al., 2011; Weir et al., 2012; Wilson et al., 2000). As correlations between the GOSE and other outcome measures are often modest (Allanson et al., 2017; Kreitzer et al., 2018; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017), additional assessment tools are necessary to fully characterise outcome after TBI. The construct of global functional outcome misses important aspects of the patient's feeling and functioning (Walton et al., 2015). Thus, it is important to incorporate other types of COA in TBI studies: PROs capture the patient's perspective and measure changes in how the patient feels, while PerfOs are objective and tap into specific aspects of the patient's functioning (U.S. Food & Drug Administration, 2009; Walton et al., 2015). Figure 6.1 is a schematic diagram, modified from Nelson and colleagues (Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017) depicting the outcome domains, individual outcome measures, and types of COA that were used in the CENTER-TBI study, and whether they assessed the patient's functioning or feeling.

It would be informative to investigate how multi-dimensional outcome assessment could be tailored in relation to post-TBI functional level. Patients assigned to different GOSE categories potentially have different assessment needs and therefore represent different contexts of use for outcome measures (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). Patients with severe disabilities may be unable to complete certain assessments such as questionnaires, cognitive tests, and tests of physical mobility, and may require assistance when completing the GOSE; whereas patients with good functional recovery may meet diagnostic criteria for psychological conditions or have clinically relevant TBI-related symptoms, which the GOSE is unable to fully capture (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). As the measurement properties of outcome assessments can be affected by the setting in which they are used (Walton et al., 2015), it is important to ensure that the instruments selected for specific TBI sub-groups are appropriate for their intended context of use (U.S. Food & Drug Administration, 2014; Walton et al., 2015). Specifically, there is a need for advice on the use of

outcome assessments in studies of groups of patients, such as RCTs or CER, where issues such as completion rates and test sensitivity across the range of patients are of key importance.

Figure 6.1: Multi-dimensional assessment with the CENTER-TBI outcome measures (Modified from Nelson et al., 2017)




In previous longitudinal TBI studies, half or more participants have sometimes been lost to follow-up (Corrigan et al., 2003; Richter et al., 2019). This is problematic because selective attrition of specific sub-groups of patients can result in systematic bias in study outcomes, limiting the generalisability of research findings (Corrigan et al., 2003; Krellman et al., 2014). Predictors of loss to follow-up in TBI studies include factors such as lower socio-economic

status, learning disability, living alone, homelessness, history of substance abuse, and violent injury aetiology (Corrigan et al., 2003; Krellman et al., 2014; Langley, Johnson, Slatyer, Skilbeck, & Thomas, 2010; Yue et al., 2013). Follow-up thresholds of 60-80% have previously been proposed to be acceptable in cohort studies (Altman, 2000; Babbie, 1973; Kristman, Manno, & Cote, 2004). However, outcome completion rates ranged from 46-60% for the TRACK-TBI Pilot study (Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, & McCrea, 2017), indicating that follow-ups may be especially difficult to obtain in large-scale multicentre TBI studies with multi-dimensional sets of outcome measures.

### *6.2.1. Study aims*

CENTER-TBI outcomes were collected, where possible, for patients at all post-TBI functional levels. CENTER-TBI did not use a prospective sliding approach to outcome assessment. However, for patients in a vegetative state, outcomes were measured using the GOSE and JFK Coma Recovery Scale - Revised (Giacino, Kalmar, & Whyte, 2004). The usability of multi-dimensional outcome assessment across the spectrum of functional recovery has not been evaluated. The CENTER-TBI data provide an opportunity to evaluate the quality and validity of different outcome measures in relation to GOSE assignment. The current study therefore aimed to:

- Examine the quality (i.e., completeness of outcomes) and measurement properties (i.e., floor/ceiling effects and internal consistency) of CENTER-TBI outcomes data in relation to post-TBI functional level
- Provide guidance on contexts of use for particular outcome measures that can be used to provide a multi-dimensional description of outcomes for patients at different levels of functional recovery

## 6.3. Methods

### *6.3.1. Participants*

Potentially eligible patients were enrolled in the CENTER-TBI core study (see CENTER-TBI inclusion criteria in Chapter 3).

Additional inclusion criteria for the current study were as follows:

- Adults aged 16 years and over (no upper age limit)
- All injury severities
- GOSE composite score ≥2 (i.e., lower severe disability or better)
- The GOSE must be completed at 6 months post-injury

### *6.3.2. Design*

The study had a cross-sectional design and used CENTER-TBI outcomes data collected 6 months after injury.

### 6.3.3. *Measures* (all measures are described in detail in Chapter 3)

*Acute measures*

- Glasgow Coma Scale (GCS) (Teasdale & Jennett, 1974)
- CT abnormality
- Abbreviated Injury Scale (AIS) and Injury Severity Score (ISS) (Baker et al., 1974)
- American Society of Anesthesiologists' (ASA) classification of Physical Health (Dripps, 1963)
- Clinical care pathway (i.e., ER, Admission, ICU)

*Outcome measures: Assessment of level of disability*

The GOSE was used to assess level of disability in this study. As the GOSE structured interview (Wilson et al., 1998) and GOSE questionnaire (Wilson et al., 2002) were found to be broadly comparable in Chapters 4 and 5, the GOSE composite score (described in Chapter 3), was used to measure level of disability (Wilson & Horton, 2018). Possible GOSE scores ranged from 'lower severe disability' to 'upper good recovery.' Patients assigned to the 'vegetative state'

category were excluded from the analysis because they were not able to complete the outcome measures under consideration.

*Other outcome measures*

Six-month follow-up data was used in this study because all outcome measures, including the GOSE, patient-reported questionnaires, cognitive assessments, and tests of physical functioning, were mandated for collection at this time point. Data collection for CENTER-TBI was complex and challenging and an international collaborative effort was required to obtain follow-ups in the 65 participating study sites. The outcome domains and scoring approaches for each of the CENTER-TBI outcome measures are detailed in Table 6.1 (further detail about the CENTER-TBI outcome measures is included in Chapter 3).

Table 6.1: Outcome domains and scoring approaches for each outcome measure

| **Measure** | **Outcome domain(s)** | **Scoring** |
|---|---|---|
| GOSE | Global functional outcome | The GOSE has 8 hierarchical outcome categories, including: death, vegetative state, severe disability (lower and upper), moderate disability (lower and upper), and good recovery (lower and upper). Composite GOSE scores were calculated centrally as part of the CENTER-TBI data curation process. |
| SF-36v2 | HRQoL (generic) | The SF-36v2 comprises 8 health domains and two summary measures, i.e., physical component summary (PCS) score and mental component summary (MCS) score. The 8 health domains and 2 summary component measures were scored using standardised T-scores (mean=50, SD=10), based on US general population norms in 2009 (normal range=45-55). |
| QOLIBRI & QOLIBRI-OS | HRQoL (TBI-specific) | The QOLIBRI comprises six domains, including four 'satisfaction' scales (cognition, self, daily life and autonomy, social relationships), and two 'bothered' scales (emotions and physical problems), as well as a total score. The QOLIBRI-OS consists of six overall 'satisfaction' questions. Scores range from 0-100. QOLIBRI total scores <60 and QOLIBRI-OS scores <52 = impaired HRQoL (Wilson et al., 2017). |

| | | |
|---|---|---|
| PCL-5 | PTSD symptoms | Total symptom severity scores range from 0-80. PTSD can be provisionally diagnosed if patients score above 33. |
| PHQ-9 | Depression symptoms | Total scores range from 0-27. Cut-offs: no depression=0-4; mild depression=5-9; moderate depression=10-14; moderately severe depression=15-19; severe depression=20-27. |
| GAD-7 | Anxiety symptoms | Total scores range from 0-21. Cut-offs: no anxiety=0-4; mild anxiety=5-9; moderate anxiety=10-14; severe anxiety=15-21. |
| RPQ | Post-concussion symptoms | Post-concussion symptoms were judged to be present if at least 3 symptoms were rated as a moderate or severe problem (Sterr et al., 2006). |
| RAVLT | Cognition | Two summary scores were used, i.e., total score (sum of words recalled across 5 trials) and 20-minute delay (number of words recalled after 20-minute delay). Norms range from 53.9 (6.7) to 37.1 (7.5) for the total score, and from 11.7 (2.2) to 7.0 (2.4) for the 20-minute delayed recall (scores decline with increasing age) (Strauss et al., 2006). |
| TMT A & B | Cognition | Scoring is based on the time taken to complete each part. For CENTER-TBI, Part A was discontinued after 100 seconds and Part B was discontinued after 300 seconds. |
| CANTAB | Cognition | The CANTAB sub-tests (RTI, PAL, AST, SWM, RVP, SOC) were scored using CANTAB Research Suite analysis software. |
| 10-meter walk & TUG | Physical functioning | Scoring was based on the time taken to complete the tests. Scores for the TUG can be interpreted as follows; <10 seconds = normal; <20 seconds = good mobility, can go out alone, mobile without a gait aid; <30 seconds = problems with mobility, cannot go outside alone, requires a gait aid. |

### *6.3.4. Statistical analysis*

*Demographic and clinical characteristics*

The demographic and clinical characteristics for the study sample and for patients without a 6-month GOSE were described using frequencies and percentages for categorical data, and

medians and interquartile ranges (IQR) for continuous data (i.e., age and total ISS score). Differences between the groups were tested using independent samples t-tests for continuous data and Chi-square ($\chi^2$) tests for categorical data.

*Scores on outcome measures*

Means and standard deviations were calculated for scores on the outcome measures. One-way analysis of variance (ANOVA) was used to test for statistically significant differences between the GOSE categories. As 28 ANOVAs were performed, Bonferroni adjusted *p* values were used (i.e., 0.0018) to minimise the risk of type 1 error. The ANOVAs were conducted to provide a context for further analysis of the CENTER-TBI data. No adjustments were made for potentially confounding covariates (e.g., age, education level, pre-injury mental health issues), and the ANOVAs should therefore be interpreted with caution. Detailed analysis of differences between outcome groups is the focus of a separate CENTER-TBI study proposal.

*Data quality and outcome measure validity in relation to post-TBI functional level*

The distribution of GOSE scores was examined to determine the number and percentage of patients assigned to each level of disability. Completeness of outcomes was then examined in relation to GOSE assignment. A recent systematic review showed that at 6-months, follow-up rates tend to be above 90% in interventional studies, whereas follow-up rates typically range from 60% in observational TBI studies (Richter et al., 2019). Completion rates below 60% were therefore considered particularly problematic. The number and percentage of patients who completed each outcome measure was calculated for each GOSE category, and for the total study sample. Some QOLIBRI-OS forms were completed by a proxy alone: these were excluded from the completion rate analyses because the QOLIBRI-OS is a patient-reported outcome and has unknown validity when completed by proxy respondents. Reasons for non-completion of the RAVLT, TMT A & B, CANTAB, and 10-meter walk/TUG were examined and coded using the following categories: (1) Non-neurological or logistic reasons; (2) Cognitive/neurological deficits; (3) Invalid test; and (4) Reason not provided. It was not possible to examine reasons for non-completion of PROs as this information was not collected as part of CENTER-TBI.

Floor and ceiling effects were examined for the completed outcome measures to assess the sensitivity of each measure when used with patients with different levels of disability. Consistent with previous research (Hall et al., 1996), floor and ceiling ranges were generally defined as the top and bottom 10% of the range of possible scores for each outcome measure. Ceiling ranges are not applicable for tests involving latencies and were not calculated for the TMT, RTI, AST, and TUG. The range for the CANTAB sub-tests was defined as the empirical or expected minimum and maximum scores, given the underlying distribution of scores. Outliers are scores which lie outside this range, and present potential problems for analysis. For the Trail Making Test, for example, this problem is dealt with by setting the maximum possible time for the test (i.e the floor). There are no published floor and ceiling ranges for the CANTAB sub-tests. Thus, floor/ceiling ranges were calculated for these tests in the context of adult TBI, and the ranges defined are relative to the total study sample. In CENTER-TBI, some of the CANTAB sub-test score distributions show substantial skew and kurtosis and may be non-normal. Empirical minimum and maximum scores were therefore defined for the CANTAB using Tukey's rule (Tukey, 1977) to exclude outliers in the range. Minimum and maximum scores were calculated as 1.5 times the interquartile range below the $25^{th}$ percentile and above the $75^{th}$ percentile. For example, for the RTI sub-test, reaction times ranged from 218-1813 milliseconds ($25^{th}$ percentile = 324; $75^{th}$ percentile = 424; IQR = 100); thus the floor range was defined as 574-1813. Scores considered at the "ceiling" and "floor" for each relevant outcome measure are defined in Table 6.2. Outcome measures were considered to have good sensitivity if they had minimal floor/ceiling effects (defined in this study as ≤10% of participants).

The internal consistency of the PROs was assessed using Cronbach's alpha (α) (Cronbach, 1951). In line with conventions, α >0.7 was interpreted as acceptable (Nunnally, 1978).

Statistical analyses were conducted using IBM SPSS Statistics 23. The data were downloaded from the INCF Neurobot database (Version 1) on 8 November 2018.

Table 6.2: Definition of floor and ceiling ranges for each outcome measure

| | Measure | Range | Floor | Ceiling |
|---|---|---|---|---|
| SF-26v2 (sub-scales) | Total score (higher = better) | 0-100 | 0-9 | 91-100 |
| QOLIBRI | Total score (higher = better) | 0-100 | 0-9 | 91-100 |
| QOLIBRI-OS | Total score (higher = better) | 0-100 | 0-9 | 91-100 |
| PCL-5 | Total score (higher = worse) | 0-80 | 73-80 | 0-7 |
| PHQ-9 | Total score (higher = worse) | 0-27 | 25-27 | 0-2 |
| GAD-7 | Total score (higher = worse) | 0-21 | 20-21 | 0-1 |
| RPQ | Total moderate/severe symptoms (higher = worse) | 0-16 | 16 | 0 |
| RAVLT | Principal list items recalled (higher = better) | 0-75 | 0-6 | 69-75 |
| TMT Part A | Completion time in seconds (higher = worse) | 10-101 | 91-101 | n/a |
| TMT Part B | Completion time in seconds (higher = worse) | 29-301 | 271-301 | n/a |
| CANTAB RTI | Median five-choice reaction time (higher = worse) | 218-1813 | 574-1813 | n/a |
| CANTAB PAL | Total errors (adjusted) (higher = worse) | 0-194 | 91-194 | 0-8 |
| CANTAB AST | Median reaction latency (higher=worse) | 274-1654 | 1060-1654 | n/a |
| CANTAB SWM | Between errors (higher = worse) | 0-151 | 99-151 | 0-9 |
| CANTAB RVP | A' prime (higher = better) | 0.71-1 | 0.71-0.73 | 0.98-1 |
| CANTAB SOC | Problems solved in minimum moves (higher = better) | 0-12 | 0 | 12 |
| TUG | Completion time in seconds (higher = worse) | 0-30 | 20-30 | n/a |

## 6.4. Results

### 6.4.1. *Demographics and clinical characteristics*

The participant selection process for the current study is displayed in Figure 6.2. Of the 3692 adult patients eligible for follow-up at 6 months post-injury, 2600 were successfully followed-up using the GOSE, and the GOSE was not obtained for 1091 patients. A total of 2573 survivors scored in the 'lower severe disability' category or better. The current study sample therefore comprised 69.7% of all patients eligible for 6-month follow-up.

Figure 6.3 displays the GOSE completion rates for the 'eligible sample' for each of the CENTER-TBI study sites and shows that follow-up rates on the GOSE were variable in this multicentre study.

Figure 6.2: Participant selection process for the current study

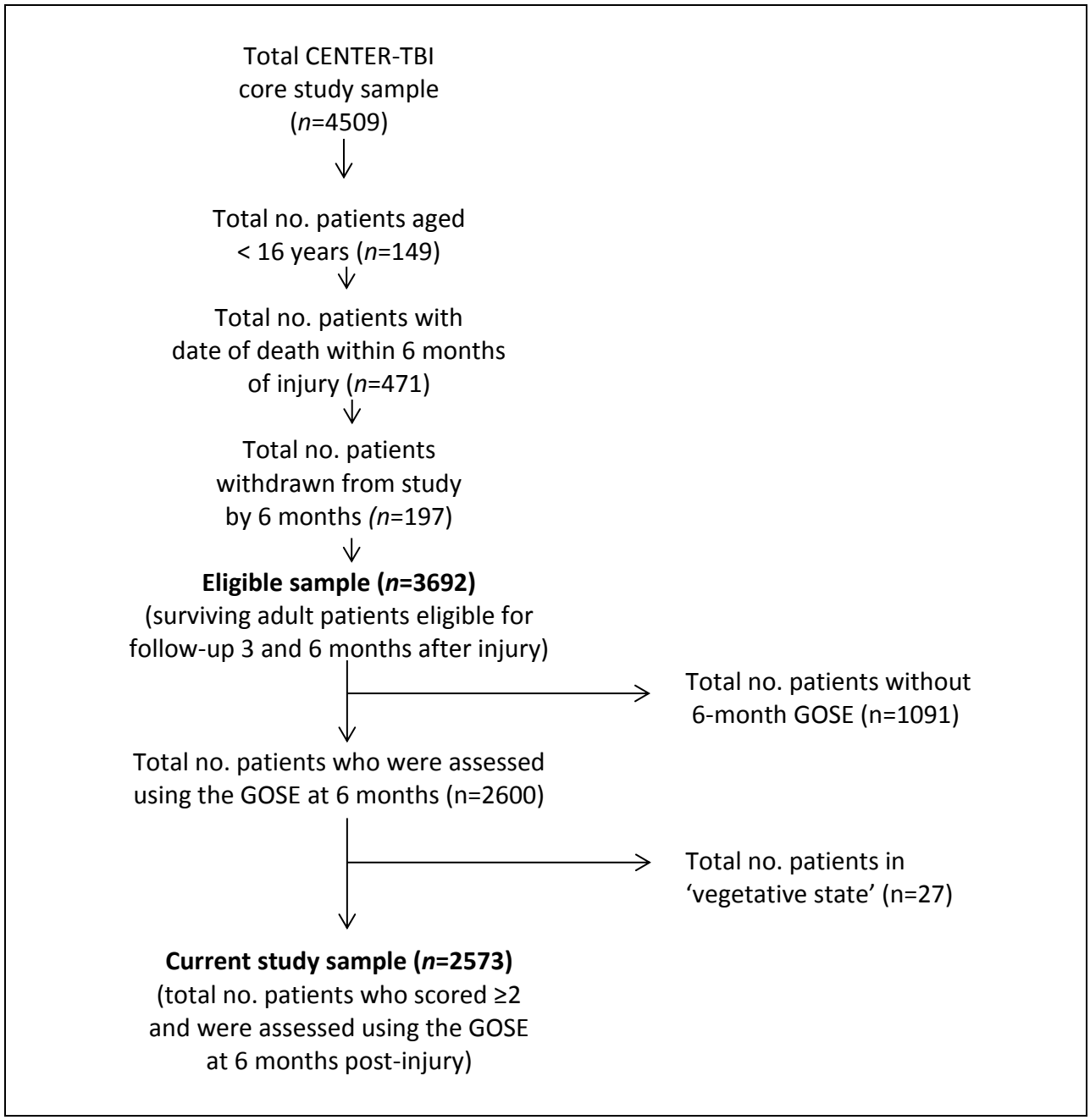
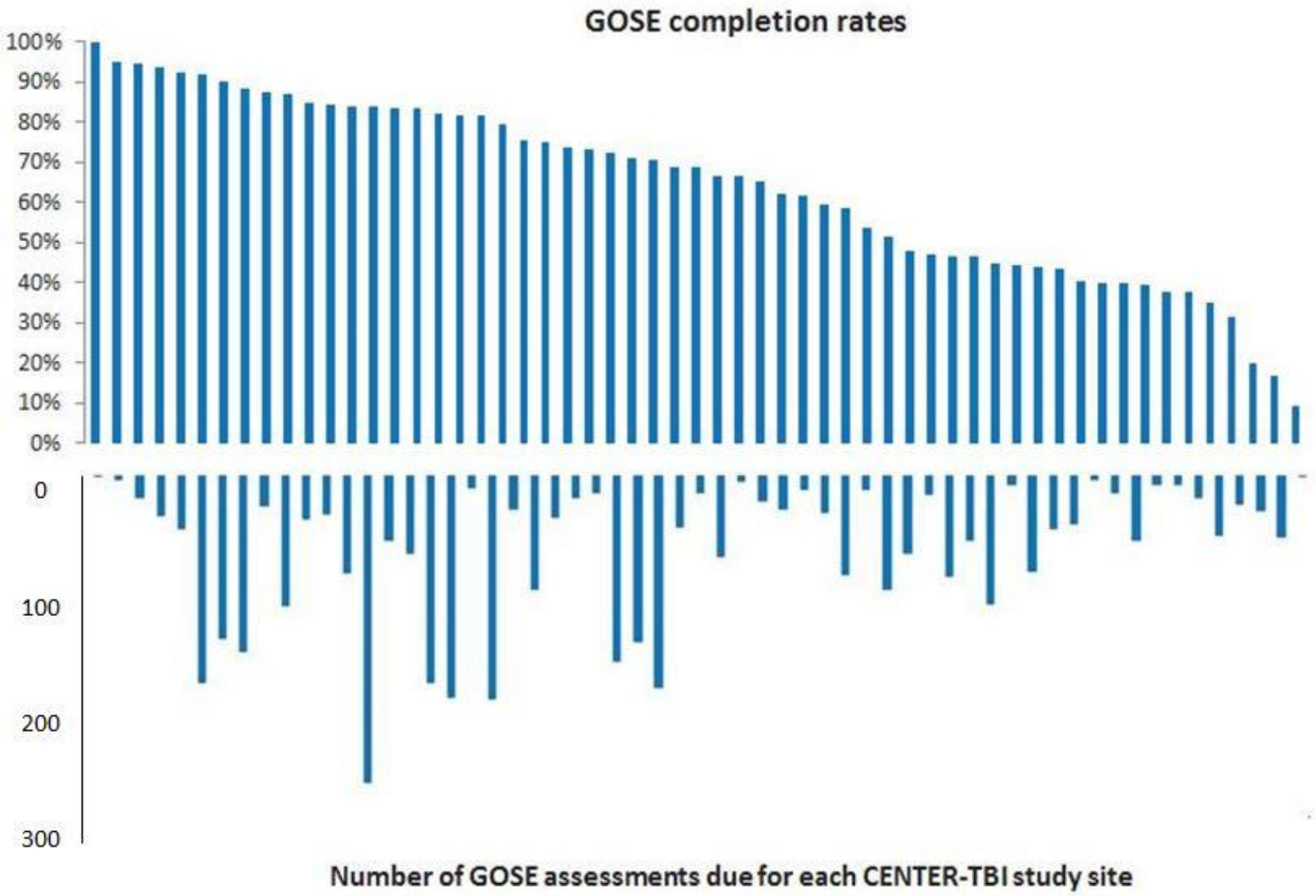


Figure 6.3: GOSE completion rates for the 'eligible sample' and number of GOSE assessments due for each study site



Tables 6.3 and 6.4 summarise the demographic and clinical characteristics of the current study sample (*n*=2573), and for patients without a 6-month GOSE (*n*=1091). Completion rates were 100% for age, gender, clinical care pathway, and AIS score, and above 94% for ASA physical health classification, cause of injury, GCS score, and ISS. Completion rates for education, previous employment, marital status, and CT abnormality ranged from 78-94%.

Table 6.3: Demographic characteristics for the current study sample and GOSE unknown

| | **Current study sample** | **GOSE unknown** | **Chi-square statistics** |
|---|---|---|---|
| **Age band** | | | |
| 16-25 | 433 (16.8%) | 226 (20.7%) | |
| 26-35 | 312 (12.1%) | 158 (14.5%) | |
| 36-45 | 323 (12.6%) | 172 (15.8%) | $\chi^2$=46, df=7, |
| 46-55 | 424 (16.5%) | 180 (16.5%) | *p*<0.001 |
| 56-65 | 467 (18.2%) | 124 (11.4%) | |
| 66-75 | 362 (14.1%) | 116 (10.6%) | |
| 76-86 | 213 (8.3%) | 92 (8.4%) | |
| >86 | 39 (1.5%) | 23 (2.1%) | |
| **Gender** | | | |
| Male | 1710 (66.5%) | 756 (69.3%) | $\chi^2$=2.8, df=1, |
| Female | 863 (33.5%) | 335 (30.7%) | *p*=0.09 |
| **Race** | | | |
| Caucasian | 2416 (93.9%) | 977 (89.6%) | $\chi^2$=1.46, df=1, |
| Other | 91 (3.5%) | 46 (4.2%) | *p*=0.23 |
| **Education** | | | |
| Primary school or less | 330 (12.8%) | 126 (11.5%) | |
| Secondary school/High school | 758 (29.5%) | 341 (31.3%) | $\chi^2$=12.06, df=3, |
| Post-high school training | 478 (18.6%) | 167 (15.3%) | *p*<0.01 |
| College/University | 670 (26%) | 216 (19.8%) | |
| **Previous employment** | | | |
| Working (full-time or part-time) | 1314 (51.1%) | 479 (43.9%) | |
| Not working | 193 (7.5%) | 122 (11.2%) | $\chi^2$=22.28, df=3, |
| Retired | 605 (23.5%) | 220 (20.2%) | *p*<0.001 |
| Student/schoolgoing/homemaker | 277 (10.8%) | 128 (11.7%) | |
| **Marital status** | | | |
| Partnered | 1286 (50%) | 453 (41.5%) | $\chi^2$=11.3, df=2, |
| Previously partnered | 374 (14.5%) | 145 (13.3%) | *p*<0.01 |
| Single/unspecified | 762 (29.6%) | 356 (32.6%) | |

Data are *n* (%)

Table 6.4: Clinical characteristics for the study sample and GOSE unknown

| | Current study sample | GOSE unknown | Chi-square statistics |
|---|---|---|---|
| **ASA Physical Health** | | | |
| Healthy patient | 1472 (57.2%) | 639 (58.6%) | $\chi^2$=3.13, df=2, *p*=0.21 |
| Mild systemic disease | 832 (32.2%) | 318 (29.1%) | |
| Severe/life threatening systemic disease | 233 (9.1%) | 87 (8%) | |
| **Cause of injury** | | | |
| Road traffic accident | 1049 (40.8%) | 349 (32%) | $\chi^2$=35.13, df=3, *p*<0.001 |
| Incidental fall | 1112 (43.2%) | 496 (45.5%) | |
| Violence/assault | 140 (5.4%) | 67 (6.1%) | |
| Other | 214 (8.3%) | 143 (13.1%) | |
| **Clinical Care Pathway** | | | |
| Emergency Room | 525 (20.4%) | 249 (22.8%) | $\chi^2$=3.43, df=2, *p*=0.18 |
| Admitted to hospital ward | 927 (36%) | 396 (36.3%) | |
| Intensive Care Unit | 1121 (43.6%) | 446 (40.9%) | |
| **GCS Score** | | | |
| 13-15 | 1840 (71.5%) | 780 (71.5%) | $\chi^2$=1.24, df=2, *p*=0.54 |
| 9-12 | 195 (7.6%) | 87 (8%) | |
| 3-8 | 460 (17.9%) | 177 (16.2%) | |
| **CT abnormality** | | | |
| Present | 1309 (50.9%) | 415 (38%) | $\chi^2$=22.51, df=1, *p*<0.001 |
| Absent | 957 (37.2%) | 444 (40.7%) | |
| **Head & neck injury**[1] | | | |
| No injury/minor injury | 415 (16.2%) | 240 (21.9%) | $\chi^2$=19.5, df=5, *p*<0.01 |
| Moderate injury | 372 (14.5%) | 149 (13.7%) | |
| Serious injury | 809 (31.4%) | 319 (29.2%) | |
| Severe injury | 461 (17.9%) | 174 (15.9%) | |
| Critical injury | 513 (19.9%) | 209 (19.2%) | |
| Unsurvivable injury | 3 (0.1%) | 0 (0%) | |
| **Non-head & neck injury**[2] | | | |
| No injury/mild injury | 1560 (60.6%) | 682 (62.5%) | $\chi^2$=3.11, df=1, *p*=0.08 |
| Severe injury | 991 (38.5%) | 379 (34.7%) | |

[1]Head & neck injury = combined AIS score for head, neck and cervical regions
[2]Non-head & neck injury (severe injury= Total ISS >7)

Patients in the current study sample were significantly older than those without a 6-month GOSE: the median (IQR) age was 51 years (32-65) for the study sample and 45 years (28-62) for

patients without a 6-month GOSE ($p$<0.001). The two groups were comparable for gender (most patients were male) and race (most patients were Caucasian). However, the current study sample had a higher level of education, significantly more of them were previously employed or retired, and significantly more of them were partnered or previously partnered prior to injury.

Patients in the current study sample were comparable to those without a 6-month GOSE for ASA physical health classification (most patients were healthy or had mild systemic disease prior to injury); clinical care pathway (around 80% of the patients were admitted to the hospital ward or intensive care unit upon recruitment to the study); GCS score (most patients had GCS scores in the 13-15 range); and injuries to other body regions (around one-third of the patients sustained severe non-head and neck injuries). However, the study sample had a higher proportion of patients with injuries caused by road traffic accidents, more patients with CT abnormalities, fewer patients with minor or moderate head and neck injuries, and more patients who met criteria for major trauma (i.e., total ISS >15). Total ISS scores were comparable for the current study sample (median = 16, IQR=9-26) and for patients without a 6-month GOSE (median=14, IQR=8-25) ($p$=0.03).

### 6.4.2. *Scores on outcome measures*

Scores were distributed on the GOSE as follows: patients assigned to the 'severe disability' categories comprised 14.8% of the total study sample (lower SD = 7.8%; upper SD = 7%); patients assigned to the 'moderate disability' categories comprised 23.9% of the sample (lower MD = 10.3%; upper MD = 13.6%); and patients assigned to the 'good recovery' categories comprised 61.4% of the sample (lower GR = 21.7%; upper GR = 39.7%).

Scores for the CENTER-TBI outcome measures are displayed in Tables 6.5 (PROs) and 6.6 (PerfOs). One-way ANOVAs showed that scores were significantly different between GOSE categories on all outcome measures. Scores for the SF-36v2, QOLIBRI, and QOLIBRI-OS were generally better (higher) for patients with better functional recovery and worse (lower) for

patients with poorer outcomes on the GOSE. Scores on the SF-36v2 sub-scales, QOLIBRI and QOLIBRI-OS were generally indicative of good quality of life in patients assigned to the 'moderate disability' and 'good recovery' categories. However, patients with 'severe disability' generally had lower than average quality of life (i.e., below 45 on the SF-36v2 sub-scales and below 60 on the QOLIBRI). Scores on the SF-36v2 MCS and PCS were in the normal range for patients with 'good recovery,' but below average for patients in the 'severe disability' and 'moderate disability' categories. Scores on the PCL-5, PHQ-9, GAD-7, and RPQ were better (lower) for patients with better functional outcomes. The PHQ-9 score for the total study sample was indicative of mild depression. Patients in the 'lower severe disability' group scored in the moderate depression range, patients in the 'upper severe disability,' 'moderate disability', and 'lower good recovery' groups scored in the mild depression range, and the 'upper good recovery' group scored in the 'no depression' range. GAD-7 scores were in the mild anxiety range for the 'severe disability' and 'moderate disability' groups, and in the 'no anxiety' range for patients in the 'good recovery' groups.

Scores on the RAVLT were better (higher) for patients with better functional recovery and worse (lower) for patients with poorer functional outcomes. RAVLT mean scores were within the normal range for the 'moderate disability' and 'good recovery' groups, but below the normal range for the 'severe disability' categories. Scores on the TMT were better (lower) for patients with better functional outcomes, and worse (higher) for patients with poorer outcomes, but in the normal range (i.e., <100 seconds for Part A; <300 seconds for Part B) for all GOSE categories. Scores on the CANTAB RTI, PAL, AST, and SWM were better (lower) for patients with better functional recovery and worse (highest) for patients with poorer functional recovery. Scores on the CANTAB AST and RVP were more uniform across GOSE categories, but generally better (higher) for patients with better functional recovery. Scores on the 10-meter walk and TUG were better for patients with better functional recovery and worse for patient with poorer functional outcomes. TUG mean times were indicative of good physical mobility for all GOSE categories.

### 6.4.3. *Data quality and validity in relation to post-TBI functional level*

*Data completeness*

Table 6.7 displays the outcome measure completion rates. PRO completion rates were above 80% for all outcome measures for the total study sample. The RAVLT and TMT were completed by 68% of the total study sample, while CANTAB completion rates ranged from 52-59% of the total study sample and tests of physical functioning were completed by 51% of the total study sample. Completion rates for all outcome measures were lowest for patients assigned to the 'lower severe disability' category and higher for the other GOSE categories. Completion rates were below 60% for all outcome measures for patients in the 'lower severe disability' group. Furthermore, PerfO completion rates were below 60% for patients in the 'upper severe disability' group. CANTAB RVP and 10-meter walk/TUG completion rates were below 60% for patients in the 'lower moderate disability,' and all CANTAB sub-tests had completion rates below 60% for patients in the 'upper good recovery' group.

Tables 6.8 and 6.9 display the reasons provided for non-completion of the RAVLT, TMT, 10-meter walk/TUG, and CANTAB sub-tests. Around one third of the total study sample did not complete the RAVLT (*n*=820) or TMT (*n*=806): no reason was provided for the RAVLT for 50% of these patients, and no reason was provided for the TMT for 44% of these patients. Where reasons for non-completion were provided, 'non-neurological/logistic reasons' was the most common reason given overall (RAVLT = 42% of the patients; TMT = 48% of the patients). 'Cognitive/neurological deficits' accounted for 7% of uncompleted RAVLT and 8% of uncompleted TMT. A total of 1122 patients (44% of the total study sample) did not complete the 10-meter walk/TUG: no reason was provided for 38% of these patients, and where reasons were provided, 'non-neurological/logistic reasons' accounted for 57% of the patients, and 'cognitive/neurological deficits' accounted for 5% of the patients. 'Invalid test' accounted for a minority of non-completed assessments (RAVLT = 3 patients; TMT = 4 patients; 10-meter walk/TUG = 4 patients). More than one-half of patients in the study sample did not complete the CANTAB sub-tests, and for around two-thirds of these patients, investigators did not provide a reason for non-completion. Where reasons were provided, 'non-neurological/logistic

reasons' was the most common reason given overall (RTI & PAL = 24% of the patients; AST, SWM & SOC = 29% of the patients; RVP = 31% of the patients). 'Cognitive/neurological deficits' accounted for 3-7% of the uncompleted CANTAB sub-tests and 'invalid test' accounted for less than 1% of the uncompleted tests.

*Floor and ceiling effects*

The proportion of patients scoring in the floor and ceiling ranges for each of the completed PROs and PerfOs are displayed in Tables 6.10 and 6.11. The percentages shown are based on the total number of completed outcome measures for each GOSE category and for the total study sample. The PROs with the largest proportion of ceiling effects overall were the RPQ (52%), PCL-5 (49%), SF-36v2 'role-emotional' sub-scale (46%), GAD-7 (44%), SF-36v2 'physical functioning' sub-scale (44%), PHQ-9 (42%), SF-36v2 'social functioning' sub-scale (38%), SF-36v2 'role-physical' sub-scale (32%) and SF-36v2 'bodily pain' sub-scale (29%). Ceiling effects were more common for patients with better levels of functional recovery (e.g., 56-69% of patients in the 'upper good recovery' category scored in the ceiling range on the SF-36v2 'physical functioning,' 'role-physical,' 'social functioning,' and 'role-emotional' sub-scales, and 63-81% in the 'upper good recovery' category scored in the ceiling range on the PCL-5, PHQ-9, GAD-7, and RPQ). Ceiling effects were found mainly for patients in the 'upper moderate disability' and 'good recovery' categories on the SF-36v2 sub-scales, whereas they occurred in all GOSE categories, apart from 'lower severe disability,' on the PCL-5, PHQ-9, GAD-7, and RPQ. Floor effects were found on the SF-36v2 'physical functioning,' 'role-physical' and role-emotional' sub-scales for patients in the 'severe disability' categories.

Floor and ceiling effects were absent on the RAVLT, CANTAB SOC, and CANTAB RVP. Floor effects were minimal on the TMT and TUG, but present for patients with 'severe disabilities.' Floor effects were found for most GOSE categories on the CANTAB PAL and were most notable for patients with poorer levels of functioning. Ceiling effects were found for most GOSE categories on the CANTAB PAL and SWM and were most notable for patients with better levels of recovery.

*Internal consistency*

Cronbach's alpha (α) for the completed PROs are displayed in Table 6.12. For the total study sample, internal consistency was as follows: QOLIBRI-OS, PCL-5, GAD-7, and RPQ ($\alpha \geq 0.90$); QOLIBRI ($\alpha = 0.85$); PHQ-9 ($\alpha = 0.88$); SF-36v2 sub-scales ($\alpha$ ranged from 0.79 to 0.95). For the individual GOSE categories, all PROs had $\alpha \geq 0.80$, apart from the SF-36v2 'general health,' 'social functioning,' and 'energy and fatigue' sub-scales.

Table 6.5: Descriptive statistics for PROs for each GOSE category and for the total study sample

| | GOSE Classification | | | | | | ANOVA statistics | Total study sample |
|---|---|---|---|---|---|---|---|---|
| | Severe Disability | | Moderate Disability | | Good Recovery | | | |
| | Lower | Upper | Lower | Upper | Lower | Upper | | |
| SF-36v2 | | | | | | | | |
| Physical functioning | 31.6 (30.2) | 49.5 (30.7) | 65.5 (27.8) | 74.9 (22.6) | 80 (22.1) | 89.2 (18.4) | F=73.6, *p*<0.001 | 77.3 (27.0) |
| Role – physical | 20.9 (26.7) | 37.2 (29.4) | 38.6 (27.6) | 49.3 (27.6) | 66.7 (26.5) | 83.9 (21.8) | F=259.9, *p*<0.001 | 64.1 (32.0) |
| Bodily pain | 51.6 (27.5) | 53.6 (28.9) | 55.9 (29.0) | 62.6 (27.2) | 65.8 (24.8) | 80.5 (21.9) | F=73.9, *p*<0.001 | 68.7 (27.1) |
| General health | 45.2 (22.5) | 55.4 (21.5) | 56.2 (22.1) | 61.8 (21.0) | 65.7 (21.0) | 75.2 (19.1) | F=73.6, *p*<0.001 | 66.3 (22.3) |
| Social functioning | 40.2 (31.6) | 55.8 (26.5) | 53.8 (27.5) | 65.9 (24.2) | 76.8 (22.2) | 89.6 (16.5) | F=197.8, *p*<0.001 | 74.8 (26.6) |
| Role – emotional | 44.9 (35.4) | 57.5 (31.9) | 57.4 (30.4) | 67.1 (28.0) | 74.1 (25.7) | 87.9 (19.3) | F=111.2, *p*<0.001 | 74.5 (28.4) |
| Energy & fatigue | 39.1 (20.1) | 46.2 (23.1) | 46.3 (21.2) | 50.0 (20.7) | 56.2 (20.3) | 68.1 (18.1) | F=97.2, *p*<0.001 | 57.6 (22.0) |
| Mental health | 56.5 (23.6) | 63.1 (22.9) | 61.4 (22.3) | 65.7 (20.4) | 70.3 (18.3) | 79.8 (15.2) | F=71.6, *p*<0.001 | 71.4 (20.1) |
| MCS Score | 38.2 (14.2) | 42.2 (13.5) | 39.9 (13.3) | 43 (12.2) | 46.2 (11.2) | 52.1 (8.4) | F=82.9, *p*<0.001 | 46.8 (11.9) |
| PCS Score | 32.6 (9.5) | 37.5 (11.3) | 41.3 (10.3) | 44.6 (9.2) | 47.7 (9.1) | 52.5 (7.8) | F=163.1, *p*<0.001 | 47.2 (10.6) |
| QOLIBRI | 46 (18.9) | 59.3 (17.8) | 58.6 (18.2) | 66.6 (17.0) | 71.7 (15.5) | 82.1 (13.7) | F=176.1, *p*<0.001 | 71.9 (18.7) |
| QOLIBRI-OS | 42.1 (24.7) | 52.1 (23.1) | 54.1 (21.5) | 62.8 (19.6) | 67.9 (18.6) | 79.4 (16.8) | F=152.1, *p*<0.001 | 68 (22.1) |
| PCL-5 | 19.2 (15.7) | 16.9 (16.6) | 20.8 (16.4) | 16.9 (14.9) | 13.2 (13.1) | 6.3 (8.7) | F=75.3, *p*<0.001 | 12.2 (13.7) |
| PHQ-9 | 10.3 (6.7) | 7.4 (5.8) | 8.4 (6.3) | 7.0 (5.6) | 5.1 (4.8) | 2.5 (3.3) | F=107.1, *p*<0.001 | 5.1 (5.4) |
| GAD-7 | 6.5 (5.6) | 5.1 (5.1) | 6.0 (5.7) | 5.1 (5.0) | 3.9 (4.3) | 1.8 (2.9) | F=66.9, *p*<0.001 | 3.7 (4.5) |
| RPQ | 20.7 (13.1) | 17.2 (14.6) | 20.1 (13.6) | 16.9 (13.2) | 12.3 (11.0) | 3.9 (7.0) | F=154.8, *p*<0.001 | 11.1 (12.5) |

Data are mean (SD) (rounded to one decimal place)

Table 6.6: Descriptive statistics for PerfOs for each GOSE category and for the total study sample

| | GOSE Classification | | | | | | ANOVA statistics | Total study sample |
|---|---|---|---|---|---|---|---|---|
| | Severe Disability | | Moderate Disability | | Good Recovery | | | |
| | Lower | Upper | Lower | Upper | Lower | Upper | | |
| [A]RAVLT total score | 29.3 (13.7) | 34.8 (13.0) | 40.4 (11.8) | 44.7 (11.6) | 42.3 (12.0) | 44.6 (11.5) | F=29.3, *p*<0.001 | 42.6 (12.3) |
| [A]RAVLT 20-min delay | 4.5 (4.0) | 5.8 (4.2) | 7.4 (3.7) | 8.9 (3.6) | 8.4 (3.7) | 8.9 (3.7) | F=27.1, *p*<0.001 | 8.3 (3.9) |
| [A]TMT Part A time | 80.5 (84.4) | 57.5 (28.8) | 44.5 (22.6) | 37.0 (18.0) | 38.9 (20.4) | 36.8 (22.2) | F=39.4, *p*<0.001 | 40.7 (26.8) |
| [A]TMT Part B Time | 191.2 (127) | 144.3 (81.2) | 108.6 (65.5) | 90.4 (55.6) | 92.5 (59.0) | 88.0 (53.4) | F=39.3, *p*<0.001 | 97.7 (64.5) |
| [B]CANTAB RTI | 534 (189) | 527 (186) | 493 (203) | 435 (147) | 440 (128) | 415 (133) | F=15.9, *p*<0.001 | 442 (152) |
| [B]CANTAB PAL | 55 (51) | 56 (50) | 39 (42) | 28 (35) | 33 (41) | 26 (33) | F=13.3, *p*<0.001 | 32 (39) |
| [B]CANTAB AST | 710 (146) | 731 (194) | 675 (190) | 628 (167) | 642 (176) | 610 (168) | F=10.3, *p*<0.001 | 637 (176) |
| [B]CANTAB SWM | 50 (35) | 42 (22) | 34 (22) | 28 (20) | 30 (23) | 28 (22) | F=8.7, *p*<0.001 | 30 (23) |
| [A]CANTAB RVP | 0.8 (0.1) | 0.8 (0.1) | 0.9 (0.1) | 0.9 (0.1) | 0.9 (0.1) | 0.9 (0.1) | F=11.5, *p*<0.001 | 0.9 (0.1) |
| [A]CANTAB SOC | 7.4 (2.0) | 7.2 (2.2) | 7.8 (1.9) | 8.3 (2.1) | 8.0 (2.1) | 8.3 (2.1) | F=4.8, *p*<0.001 | 8.1 (2.1) |
| [A]10-meter walk | 10.8 (6.3) | 10.2 (5.3) | 8.2 (2.9) | 7.6 (2.3) | 7.7 (2.0) | 7.2 (2.0) | F=22.1, *p*<0.001 | 7.7 (2.8) |
| [A]TUG time | 15.7 (16.1) | 12.2 (5.7) | 9.5 (4.3) | 8.4 (2.9) | 8.5 (2.6) | 8.3 (4.8) | F=24.8, *p*<0.001 | 8.9 (4.8) |

Data are mean (SD) ([A]rounded to one decimal place; [B]rounded to nearest whole number)

Table 6.7: Outcome measure completion rates for each GOSE category and for the total study sample

| | | GOSE Classification | | | | | | Overall completion rates (*n*=2573) |
|---|---|---|---|---|---|---|---|---|
| | | Severe Disability (14.5%) | | Moderate Disability (24.2%) | | Good Recovery (61.2%) | | |
| | | Lower (*n*=200) | Upper (*n*=181) | Lower (*n*=264) | Upper (*n*=349) | Lower (*n*=558) | Upper (*n*=1021) | |
| PROs | SF-36v2 | 91 (46%) | 135 (75%) | 231 (88%) | 312 (89%) | 489 (88%) | 848 (83%) | 2106 (82%) |
| | QOLIBRI | 87 (44%) | 130 (72%) | 228 (86%) | 316 (91%) | 490 (88%) | 846 (83%) | 2097 (82%) |
| | QOLIBRI-OS | 78 (39%) | 129 (71%) | 234 (89%) | 317 (91%) | 501 (90%) | 873 (86%) | 2132 (83%) |
| | PCL-5 | 86 (43%) | 125 (69%) | 226 (86%) | 310 (89%) | 494 (89%) | 847 (83%) | 2088 (81%) |
| | PHQ-9 | 92 (46%) | 127 (70%) | 231 (88%) | 314 (90%) | 490 (88%) | 841 (82%) | 2095 (81%) |
| | GAD-7 | 91 (46%) | 128 (71%) | 231 (88%) | 312 (89%) | 489 (88%) | 843 (83%) | 2094 (81%) |
| | RPQ | 94 (47%) | 135 (75%) | 236 (89%) | 319 (91%) | 499 (89%) | 856 (84%) | 2139 (83%) |
| PerfOs | RAVLT | 48 (24%) | 100 (55%) | 190 (72%) | 275 (79%) | 436 (78%) | 691 (68%) | 1753 (68%) |
| | TMT A&B | 44 (22%) | 98 (54%) | 194 (73%) | 280 (80%) | 436 (78%) | 702 (69%) | 1754 (68%) |
| | CANTAB RTI | 27 (14%) | 76 (42%) | 178 (67%) | 237 (68%) | 382 (68%) | 542 (53%) | 1442 (56%) |
| | CANTAB PAL | 28 (14%) | 80 (44%) | 184 (70%) | 248 (71%) | 395 (71%) | 589 (58%) | 1524 (59%) |
| | CANTAB AST | 25 (13%) | 76 (42%) | 176 (67%) | 236 (68%) | 383 (69%) | 570 (56%) | 1466 (57%) |
| | CANTAB SWM | 25 (13%) | 69 (38%) | 172 (65%) | 240 (69%) | 378 (68%) | 579 (57%) | 1463 (57%) |
| | CANTAB RVP | 23 (12%) | 54 (30%) | 155 (59%) | 227 (65%) | 347 (62%) | 543 (53%) | 1349 (52%) |
| | CANTAB SOC | 19 (10%) | 64 (35%) | 168 (64%) | 236 (68%) | 363 (65%) | 570 (56%) | 1420 (55%) |
| | 10-m walk & TUG | 29 (15%) | 61 (34%) | 140 (53%) | 225 (64%) | 368 (66%) | 500 (49%) | 1323 (51%) |

Data are number (%, rounded to nearest whole number) of completed outcome measures for each GOSE category and overall completion rates for the total study sample  Completion rates <60%  Completion rates >60%

Table 6.8: Reasons for non-completion of RAVLT, TMT, and 10-meter walk/TUG for each GOSE category and for the total sample

| | | GOSE Classification | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|
| | | Severe Disability | | Moderate Disability | | Good Recovery | | |
| | | Lower | Upper | Lower | Upper | Lower | Upper | |
| RAVLT | Non-neurological or logistic reasons | 50 (33%) | 34 (43%) | 34 (47%) | 31 (42%) | 53 (46%) | 140 (43%) | 342 (42%) |
| | Cognitive deficits | 34 (22%) | 4 (5%) | 7 (10%) | 3 (4%) | 7 (6%) | 5 (2%) | 60 (7%) |
| | Invalid test | 1 (1%) | 2 (3%) | 0 (0%) | 0 (0%) | 1 (1%) | 1 (0%) | 5 (0%) |
| | Reason not provided | 67 (44%) | 40 (50%) | 30 (43%) | 39 (53%) | 55 (47%) | 180 (55%) | 413 (50%) |
| | (Totals) | (*n*=152) | (*n*=80) | (*n*=72) | (*n*=73) | (*n*=116) | (*n*=327) | (*n*=820) [A] |
| TMT | Non-neurological or logistic reasons | 59 (39%) | 41 (49%) | 40 (59%) | 29 (44%) | 68 (57%) | 149 (47%) | 383 (48%) |
| | Cognitive deficits | 39 (25%) | 8 (1%) | 5 (1%) | 1 (1%) | 10 (8%) | 5 (2%) | 68 (8%) |
| | Invalid test | 0 (0%) | 1 (0%) | 0 | 1 (1%) | 0 | 1 (0%) | 3 (0%) |
| | Reason not provided | 55 (36%) | 33 (40%) | 25 (37%) | 35 (53%) | 42 (35%) | 162 (51%) | 352 (44%) |
| | (Totals) | (*n*=153) | (n=83) | (*n*=68) | (*n*=66) | (*n*=120) | (*n*=316) | (*n*=806) [B] |
| 10-m walk/TUG | Non-neurological or logistic reasons | 76 (46%) | 60 (57%) | 68 (64%) | 58 (54%) | 106 (64%) | 267 (57%) | 635 (57%) |
| | Cognitive deficits | 36 (22%) | 6 (5%) | 2 (2%) | 3 (3%) | 1 (0%) | 2 (0%) | 50 (5%) |
| | Invalid test | 1 (1%) | 1 (1%) | 1 (1%) | 0 (0%) | 1 (0%) | 0 (0%) | 4 (0%) |
| | Reason not provided | 55 (33%) | 41 (38%) | 35 (33%) | 46 (43%) | 57 (35%) | 199 (43%) | 433 (39%) |
| | (Totals) | (*n*=168) | (*n*=108) | (*n*=106) | (*n*=107) | (*n*=165) | (*n*=468) | (*n*=1122) [C] |

Data are number (%, rounded to nearest whole number) of non-completed outcome measures for each GOSE category and for the total number of non-completed assessments. [A] Non-completed RAVLT comprises 32% of the total study sample. [B] Non-completed TMT comprises 31% of the total study sample. [C] Non-completed 10-meter walk/TUG comprises 44% of the total study sample.

Table 6.9: Reasons for non-completion of CANTAB sub-tests for each GOSE category and for the total sample

| | | GOSE Classification | | | | | | Totals |
|---|---|---|---|---|---|---|---|---|
| | | Severe Disability | | Moderate Disability | | Good Recovery | | |
| | | Lower | Upper | Lower | Upper | Lower | Upper | |
| CANTAB RTI | Non-neurological or logistic reasons | 47 (26%) | 32 (24%) | 36 (28%) | 28 (18%) | 69 (25%) | 142 (24%) | 354 (24%) |
| | Cognitive deficits | 31 (17%) | 8 (6%) | 3 (2%) | 0 (0%) | 4 (1%) | 3 (1%) | 49 (3%) |
| | Invalid test | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) | 1 (0%) | 1 (0%) | 4 (0%) |
| | Reason not provided | 105 (57%) | 96 (71%) | 91 (70%) | 127 (81%) | 204 (73%) | 449 (75%) | 1072 (72%) |
| | (Totals) | (*n*=184) | (*n*=136) | (*n*=130) | (*n*=156) | (*n*=278) | (*n*=595) | (*n*=1479)[A] |
| CANTAB PAL | Non-neurological or logistic reasons | 51 (28%) | 40 (29%) | 45 (33%) | 42 (26%) | 100 (34%) | 179 (30%) | 354 (24%) |
| | Cognitive deficits | 36 (20%) | 15 (11%) | 14 (10%) | 7 (4%) | 17 (6%) | 26 (4%) | 49 (3%) |
| | Invalid test | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (0%) | 4 (0%) |
| | Reason not provided | 96 (52%) | 85 (61%) | 77 (57%) | 115 (70%) | 176 (60%) | 398 (66%) | 1072 (72%) |
| | (Totals) | (*n*=183) | (*n*=140) | (*n*=136) | (*n*=164) | (*n*=293) | (*n*=604) | (*n*=1479)[B] |
| CANTAB AST | Non-neurological or logistic reasons | 53 (29%) | 38 (29%) | 40 (33%) | 36 (24%) | 81 (30%) | 158 (28%) | 406 (29%) |
| | Cognitive deficits | 36 (19%) | 10 (8%) | 5 (4%) | 0 (0%) | 8 (3%) | 6 (1%) | 65 (5%) |
| | Invalid test | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 1 (0%) | 2 (0%) | 4 (0%) |
| | Reason not provided | 96 (52%) | 85 (64%) | 77 (63%) | 133 (75%) | 176 (66%) | 399 (71%) | 946 (67%) |
| | (Totals) | (*n*=185) | (*n*=133) | (*n*=122) | (*n*=150) | (*n*=266) | (*n*=565) | (*n*=1421)[C] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CANTAB SWM | Non-neurological or logistic reasons | 52 (28%) | 34 (25%) | 47 (36%) | 34 (23%) | 79 (30%) | 159 (28%) | 405 (29%) |
| | Cognitive deficits | 36 (20%) | 15 (11%) | 5 (4%) | 0 (0%) | 7 (3%) | 7 (1%) | 70 (5%) |
| | Invalid test | 1 (1%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1(0%) |
| | Reason not provided | 95 (52%) | 85 (63%) | 75 (60%) | 113 (77%) | 175 (67%) | 400 (71%) | 944 (67%) |
| | (Totals) | (*n*=184) | (*n*=134) | (*n*=129) | (*n*=147) | (*n*=261) | (*n*=568) | (*n*=1421)[D] |
| CANTAB RVP | Non-neurological or logistic reasons | 53 (29%) | 44 (30%) | 51 (36%) | 45 (28%) | 94 (32%) | 180 (30%) | 467 (31%) |
| | Cognitive deficits | 35 (19%) | 18 (12%) | 14 (10%) | 6 (4%) | 21 (7%) | 18 (3%) | 112 (7%) |
| | Invalid test | 1 (1%) | 0 (%) | 0 (0%) | 1 (1%) | 2 (1%) | 0 (0%) | 4 (0%) |
| | Reason not provided | 95 (52%) | 85 (58%) | 76 (54%) | 111 (68%) | 176 (60%) | 396 (67%) | 939 (62%) |
| | (Totals) | (*n*=184) | (*n*=147) | (*n*=141) | (*n*=163) | (*n*=293) | (*n*=594) | (*n*=1522)[E] |
| CANTAB SOC | Non-neurological or logistic reasons | 54 (29%) | 38 (28%) | 47 (36%) | 36 (24%) | 86 (32%) | 157 (27%) | 418 (29%) |
| | Cognitive deficits | 36 (19%) | 11 (8%) | 7 (5%) | 2 (1%) | 11 (4%) | 11 (2%) | 78 (5%) |
| | Invalid test | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) | 1 (0%) | 3 (0%) |
| | Reason not provided | 96 (51%) | 86 (64%) | 78 (59%) | 113 (74%) | 176 (64%) | 402 (70%) | 950 (66%) |
| | (Totals) | (*n*=187) | (*n*=135) | (*n*=132) | (*n*=152) | (*n*=273) | (*n*=571) | (*n*=1449)[F] |

Data are number (%, rounded to nearest whole number) of non-completed outcome measures for each GOSE category and for the total number of non-completed assessments. [A] Non-completed CANTAB RTI comprises 57% of the total study sample. [B] Non-completed CANTAB PAL comprises 57% of the total study sample. [C] Non-completed CANTAB AST comprises 55% of the total study sample. [D] Non-completed CANTAB SWM comprises 55% of the total study sample. [E] Non-completed CANTAB RVP comprises 59% of the total study sample. [F] Non-completed CANTAB SOC comprises 56% of the total study sample.

Table 6.10: Floor/ceiling effects on the completed PROs for each GOSE category and for the total study sample

| | | GOSE Classification | | | | | | | | | | | | Total study sample | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Severe Disability | | | | Moderate Disability | | | | Good Recovery | | | | | |
| | | Lower | | Upper | | Lower | | Upper | | Lower | | Upper | | | |
| | | F | C | F | C | F | C | F | C | F | C | F | C | F | C |
| SF-36v2 | Physical function | 20% | 2% | 13% | 12% | 2% | 19% | 1% | 27% | 0% | 40% | 0% | 67% | 2% | 43% |
| | Role – physical | 34% | 2% | 19% | 6% | 16% | 6% | 10% | 9% | 2% | 27% | 1% | 56% | 7% | 31% |
| | Bodily pain | 1% | 13% | 3% | 15% | 2% | 17% | 2% | 21% | 1% | 20% | 0% | 43% | 1% | 29% |
| | General health | 8% | 0% | 1% | 1% | 2% | 6% | 1% | 9% | 1% | 13% | 0% | 26% | 1% | 16% |
| | Social functioning | 14% | 10% | 2% | 11% | 6% | 11% | 0% | 19% | 1% | 32% | 0% | 61% | 1% | 37% |
| | Role - emotional | 14% | 15% | 10% | 22% | 7% | 23% | 3% | 33% | 1% | 41% | 0% | 68% | 3% | 46% |
| | Energy & Fatigue | 3% | 1% | 4% | 1% | 5% | 2% | 2% | 1% | 1% | 4% | 0% | 9% | 2% | 5% |
| | Mental Health | 1% | 8% | 1% | 10% | 0% | 6% | 0% | 7% | 0% | 9% | 0% | 19% | 0% | 13% |
| | MCS Score | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| | PCS Score | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| | QOLIBRI | 3% | 0% | 1% | 3% | 1% | 4% | 0% | 7% | 0% | 12% | 0% | 32% | 0% | 17% |
| | QOLIBRI-OS | 5% | 4% | 4% | 5% | 3% | 3% | 1% | 7% | 1% | 13% | 0% | 32% | 1% | 18% |
| | PCL-5 | 0% | 24% | 0% | 30% | 0% | 23% | 0% | 33% | 0% | 42% | 0% | 72% | 0% | 49% |
| | PHQ-9 | 0% | 8% | 1% | 21% | 1% | 18% | 0% | 24% | 0% | 37% | 0% | 65% | 0% | 42% |
| | GAD-7 | 0% | 22% | 1% | 28% | 2% | 26% | 1% | 31% | 0% | 38% | 0% | 63% | 1% | 44% |
| | RPQ | 0% | 14% | 0% | 25% | 0% | 22% | 0% | 33% | 0% | 43% | 0% | 81% | 0% | 52% |

Data are % patients scoring in the floor/ceiling ranges for each outcome measure (rounded to nearest whole number)
F = Floor effect; C = Ceiling effect; *n* = number of patients who completed each outcome measure in each category

≤10% of patients scored in floor/ceiling range
11-49% of patients scored in floor/ceiling range
≥50% of patients scored in floor/ceiling range

Table 6.11: Floor/ceiling effects on the completed PerfOs for each GOSE category and for the total study sample

| | GOSE Classification | | | | | | | | | | | | Total study sample | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Severe Disability | | | | Moderate Disability | | | | Good Recovery | | | | | |
| | Lower | | Upper | | Lower | | Upper | | Lower | | Upper | | | |
| | F | C | F | C | F | C | F | C | F | C | F | C | F | C |
| RAVLT | 4% | 0% | 1% | 0% | 1% | 1% | 0% | 1% | 0% | 1% | 0% | 1% | 0% | 1% |
| [A]TMT Part A | 27% | | 11% | | 6% | | 1% | | 4% | | 3% | | 4% | |
| [A]TMT Part B | 32% | | 9% | | 5% | | 1% | | 2% | | 2% | | 3% | |
| [A]CANTAB RTI | 0% | | 0% | | 0% | | 0% | | 0% | | 0% | | 0% | |
| CANTAB PAL | 25% | 4% | 29% | 14% | 16% | 22% | 10% | 36% | 13% | 36% | 7% | 38% | 11% | 33% |
| [A]CANTAB AST | 4% | | 7% | | 5% | | 2% | | 3% | | 2% | | 3% | |
| CANTAB SWM | 8% | 16% | 0% | 12% | 1% | 13% | 0% | 23% | 1% | 20% | 1% | 23% | 1% | 20% |
| CANTAB RVP | 4% | 0% | 0% | 2% | 1% | 2% | 0% | 5% | 3% | 5% | 1% | 8% | 1% | 5% |
| CANTAB SOC | 0% | 0% | 0% | 0% | 0% | 2% | 0% | 5% | 0% | 3% | 0% | 6% | 0% | 4% |
| [A]TUG | 21% | | 10% | | 2% | | 1% | | 1% | | 1% | | 2% | |

Data are % patients scoring in the floor/ceiling ranges for each outcome measure (rounded to nearest whole number).
F = Floor effect; C = Ceiling effect. *n* = number of patients who completed each outcome measure in each category
[A]TMT, CANTAB RTI, CANTAB AST, TUG = floor effects only as these tests are time-based

≤10% of patients scored in floor/ceiling range

11-49% of patients scored in floor/ceiling range

Table 6.12: Cronbach's alpha of the completed PROs for each GOSE category and for the total study sample

| | GOSE Classification | | | | | | Overall α for each PRO |
|---|---|---|---|---|---|---|---|
| | Severe Disability | | Moderate Disability | | Good Recovery | | |
| | Lower | Upper | Lower | Upper | Lower | Upper | |
| SF-36v2 Physical functioning | 0.93 | 0.94 | 0.93 | 0.90 | 0.91 | 0.92 | 0.94 |
| SF-36v2 Role - physical | 0.96 | 0.93 | 0.90 | 0.91 | 0.93 | 0.93 | 0.95 |
| SF-36v2 Bodily pain | 0.87 | 0.91 | 0.90 | 0.92 | 0.89 | 0.91 | 0.92 |
| SF-36v2 General health | 0.78 | 0.75 | 0.79 | 0.80 | 0.80 | 0.78 | 0.81 |
| SF-36v2 Social functioning | 0.88 | 0.75 | 0.81 | 0.75 | 0.79 | 0.76 | 0.85 |
| SF-36v2 Role - emotional | 0.94 | 0.93 | 0.90 | 0.92 | 0.93 | 0.90 | 0.94 |
| SF-36v2 Energy & fatigue | 0.67 | 0.81 | 0.76 | 0.78 | 0.75 | 0.72 | 0.79 |
| SF-36v2 Mental health | 0.87 | 0.88 | 0.87 | 0.84 | 0.81 | 0.80 | 0.86 |
| QOLIBRI | 0.86 | 0.81 | 0.81 | 0.83 | 0.83 | 0.88 | 0.85 |
| QOLIBRI-OS | 0.88 | 0.88 | 0.85 | 0.86 | 0.88 | 0.89 | 0.91 |
| PCL-5 | 0.93 | 0.93 | 0.93 | 0.93 | 0.92 | 0.91 | 0.93 |
| PHQ-9 | 0.84 | 0.83 | 0.86 | 0.86 | 0.85 | 0.82 | 0.88 |
| GAD-7 | 0.87 | 0.89 | 0.92 | 0.91 | 0.89 | 0.88 | 0.91 |
| RPQ | 0.86 | 0.91 | 0.90 | 0.91 | 0.88 | 0.90 | 0.92 |

## 6.5. Discussion

This chapter examined the usefulness of implementing multi-dimensional outcome assessment across the spectrum of TBI recovery. Patients were stratified according to GOSE category and the quality and validity of the CENTER-TBI outcome measures were evaluated in relation to level of global functioning. The findings and their implications are discussed below.

### 6.5.1. *Data quality and validity in relation to post-TBI functional level*

*Data completeness*

The completeness of the CENTER-TBI outcome measures provides information about the feasibility of collecting individual assessments in different contexts of use, according to post-TBI functional level at 6 months. In this study, patients with better levels of functional recovery were found to have higher outcome completion rates than those with poorer functional recovery. Completion rates were also found to be better for PROs than for cognitive assessments and tests of physical functioning. PRO completion rates were generally very good across the spectrum of recovery (i.e., >70%), but fell below 50% for patients assigned to the 'lower severe disability' category. PerfOs have greater logistic demands than PROs and were completed less frequently than PROS: certain CANTAB sub-tests and tests of physical functioning fell below 60% across all GOSE categories. The COA completion rates indicate that multi-dimensional outcome assessment was particularly difficult to implement with patients with greater functional limitations. Nevertheless, there was limited information available about the reasons for non-completion of the outcome measures, as CENTER-TBI investigators provided reasons for non-completion of the RAVLT, TMT, and 10-meter walk/TUG assessments, but not for the PROs, and explanations for missing PerfOs were not always provided.

Explanations were missing for up to half of the uncompleted RAVLT, TMT, and 10-meter walk/TUG assessments, and for more than half of the uncompleted CANTAB sub-tests. Thus, the test completion codes were not used particularly well by CENTER-TBI investigators. Where explanations were provided, 'non-neurological or logistic reasons' was the most common reason given. While 'cognitive/neurological deficits' accounted for only a

minority of the uncompleted assessments in the 'upper severe disability,' 'moderate disability' and 'good recovery' categories, this reason accounted for up to one-quarter of uncompleted assessments in the 'lower severe disability' category. Previous research has shown that patients who are more severely affected by TBI are particularly at risk of loss to follow-up due to cognitive impairment, physical disability, or logistic problems such as inability to travel independently to appointments (Sherer et al., 2010). The findings from the current study appear to fit with this. However, it is important to note that there could also be site specific reasons for non-completion of follow-ups, which could not be examined.

More than half of participants may be lost to follow-up in longitudinal TBI studies (Corrigan et al., 2003; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, & McCrea, 2017; Richter et al., 2019). Patients who are lost to follow-up often have systematically different characteristics to those who are retained in longitudinal TBI studies (Corrigan et al., 2003; Krellman et al., 2014; Langley et al., 2010; Yue et al., 2013). Thus, in the current study, the demographic and clinical characteristics of patients who were followed up using the GOSE were compared with survivors that were not followed-up. A total of 30% of the patients eligible for follow up did not have a 6-month GOSE. Some differences were found between the study sample and patients without a 6-month GOSE. For example, patients included in the study were older and better educated than those not followed up. More of them were previously employed or retired and more were partnered or previously partnered prior to injury. In addition, more patients in the study sample were injured in road traffic accidents, and a greater proportion had CT abnormalities and greater injury severity. These demographic and clinical differences suggest that the study findings may have limitations in their generalisability.

*Floor and ceiling effects and internal consistency of PROs*

When tailoring outcome assessments for TBI studies, investigators should consider basic psychometric properties, such as the sensitivity of instruments and the internal consistency of PROs (Andresen, 2000; Frost, Reeeve, Liepa, Stauffer, & Hays, 2007). In this study, PRO ceiling effects were particularly common in the GOSE 'upper good recovery' categories, indicating that patients who had returned to their previous level of functioning typically reported good HRQoL and no clinically significant PTSD, anxiety, depression, or post-

concussion symptoms. PRO ceiling effects were less common for patients with greater levels of disability, but occurred across the recovery spectrum on the PCL-5 and GAD-7, and were also apparent on the RVP for patients in the 'upper severe disability' category and better. Ceiling effects were least common on the QOLIBRI and QOLIBRI-OS, affecting around one-third of patients in the 'upper good recovery' category, and a minority of patients in the other GOSE categories. PRO floor effects were found to be minimal. However, at least 20% of patients in the 'lower severe disability' category scored in the floor ranges on the SF-36v2 'physical functioning,' 'role-physical' and 'role-emotional' sub-scales, suggesting that the SF-36v2 lacks sensitivity when used with patients with greater levels of functional limitation.

The findings indicate that most of the PROs, apart from the QOLIBRI/QOLIBI-OS, lacked precision when completed by patients with better levels of functional recovery. While measures of emotional adjustment focus on negative outcomes (i.e., symptoms of distress), the QOLIBRI scales assess both negative and positive aspects (i.e., life satisfaction). As a result, the QOLIBRI measures are less prone to ceiling effects than measures of emotional distress. The ceiling effects on the RPQ are of particular concern because they indicate that the scale does not pick up symptoms that are relevant to patients with greater functional limitations. The RPQ was originally developed for patients with concussion/mild TBI and focuses on cognitive, emotional and somatic post-concussion symptoms (King et al., 1995; Potter, Leigh, Wade, & Fleminger, 2006; Smith-Seemiller, Fow, Kant, & Franzen, 2003). Thus, it does not capture problems of relevance to patients with severe disabilities, such as reduced mobility and communication difficulties, and should not be used with these patients as the results can be misleading. Despite the ceiling effects, all PROs were found to have excellent internal consistency across the GOSE categories (i.e., $\alpha$ generally >0.80) (Nunnally, 1978), indicating that the internal structure of the questionnaires was not affected by the context in which they were used.

Ceiling effects were found for most GOSE categories on the CANTAB PAL and SWM sub-tests, but were minimal or absent on the other cognitive tests. The ceiling and floor ranges defined for the CANTAB sub-tests may contain information about performance which was not explored in this study. Floor effects were found for patients with 'severe disabilities' on the TMT and TUG and for most GOSE categories on the CANTAB PAL. The floor effect on the

PAL test arises from patients who did not complete the whole test and have adjusted scores. The adjusted scoring procedure for the PAL produces a large number of values that are outliers in comparison to patients who completed the test, and these outliers consequently appear in the floor range. The floor range defined for the PAL in this study may therefore be problematic. Despite this, there may be useful discrimination among low PAL scores. Floor effects were minimal on the RAVLT, CANTAB AST, CANTAB SWM, CANTAB RVP, and CANTAB SOC. Taken together, these findings indicate that most cognitive tests had good sensitivity, apart from the CANTAB PAL and SWM, which showed some lack of sensitivity across GOSE categories, and the TMT and TUG which may not be suitable for patients with the most severe disabilities.

### 6.5.2. *Recommendations*

The current study demonstrates that the completeness and validity of TBI outcome measures in CENTER-TBI was affected by the context in which they were used. A "sliding" or "flexible" approach (CENTER-TBI, 2018; Yue et al., 2018; Yue et al., 2013) may therefore be useful in retrospective analyses of CENTER-TBI data to ensure that outcome assessments are tailored appropriately for different TBI sub-groups. The "flexible battery approach" is popular in clinical practice (Strauss et al., 2006; Sweet, Moberg, & Suchy, 2000a; Sweet, Moberg, & Suchy, 2000b), but has not been used routinely in TBI research, perhaps because the use of different measures for sub-groups of patients reduces comparability between patients and potentially introduces bias. The use of a sliding approach to outcome assessment is not straightforward, and selection of appropriate measures is complex given the heterogeneous nature of TBI. Nevertheless, the current study provides information about which outcome measures may be advisable for patients with different post-TBI levels of functional recovery. This information will be useful when selecting measures for use in future prospective studies and provides guidance for performing retrospective analyses of data collected for CENTER-TBI. It may also provide guidance for other InTBIR studies, such as TRACK-TBI. The findings from the study also have implications for further refinement of the CDEs (Hicks et al., 2013), as they highlight the importance of selecting appropriate measures for use with specific TBI sub-groups. There are study-specific reasons for choosing particular outcome measures; thus a single set of instruments is not appropriate in all study contexts.

Multi-dimensional outcome assessment was found to be particularly challenging to implement for patients with severe functional limitations. Moreover, patients assigned to the 'lower severe disability' category had relatively poorer HRQoL and psychological status than patients with better levels of functional recovery, their performance was relatively poor on cognitive tests, and floor effects were found on assessments of physical functioning, such as the SF-36v2 'physical functioning' and 'role-physical' sub-scales and TUG. An abbreviated set of outcome measures could be useful for patients assigned to the GOSE 'lower severe disability' category. The choice of particular assessments for this group will depend on the purposes of the research, and further work is needed to validate measures that may be suitable. In particular, the Functional Independence Measure (FIM) (Linacre, Heinemann, Wright, Granger, & Hamilton, 1994), could be used with patients who cannot self-report and who are unable to complete cognitive assessments or tests of physical functioning. The FIM can be completed via observational ratings and proxy reports, making it suitable for use with patients who are unable to self-report (Wilde et al., 2010). Furthermore, it measures problems that the RPQ does not capture, such as impaired mobility and communication difficulties, making it suitable for patients with severe functional limitations. As the FIM is best suited for in-patients settings, the potential for ceiling effects (Hall et al., 1996) should be taken into consideration, especially if used with patients who have been discharged from hospital.

Although as a group, most patients in the GOSE 'good recovery' categories reported no psychiatric symptoms or post-concussion symptoms in this study, investigators should be aware that some patients with good levels of functioning may meet diagnostic criteria for psychological disorders, such as clinical depression, anxiety, or PTSD, or have clinically relevant TBI symptoms or impaired performance on cognitive tests (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017). Measures that capture emotional adjustment, TBI symptoms, and cognition are therefore useful to include when assessing outcomes in patients who might otherwise appear to have fully recovered. These assessments may be particularly helpful in distinguishing between patients in the 'lower' and 'upper good recovery' categories, given that the boundary between these categories on the GOSE can be indeterminate.

The findings from this study indicate that multi-dimensional outcome assessment in TBI research could be guided by stratifying patients into groups according to their level of functional recovery on the GOSE. However, it should be borne in mind that the GOSE is not the only measure suitable for this purpose. The GOAT has been used to stratify patients into sub-groups for further tailored outcome assessment in TRACK-TBI (Yue et al., 2018; Yue et al., 2013). In future TBI research, alternative screening measures could be chosen instead of the GOSE or GOAT: one possibility is the Disability Rating Scale (DRS), another CDE measure of global functioning that is applicable across different functional levels (Hicks et al., 2013). Another possibility would be to stratify patients by injury severity. However, as the relationship between injury severity and outcome is indirect, tailoring outcome assessment according to GCS or ISS scores may not be particularly useful.

Detailed outcome assessments can be difficult to obtain in large-scale multicentre studies, such as CENTER-TBI. Thus, a pragmatic approach was used in CENTER-TBI to maximise follow-up rates and outcome assessments could be completed in person, via telephone, via post, or using information from clinical records. Steps were also taken to mitigate failure to return for follow-ups, such as contacting participants early in the follow-up time window, obtaining contact details for relatives/caregivers, and organising and paying for participant transportation (Bodien et al., 2018; Maas, Menon, et al., 2015). Completion of the full set of CENTER-TBI outcome measures was estimated to take around 3 hours per participant, and the final selection of assessments depended on whether the patient was cognitively able, and whether the assessments were logistically feasible (Maas, Menon, et al., 2015).

In this study, PerfO completion rates were relatively low in comparison to PRO completion rates. Investigators should therefore be mindful of practical constraints when obtaining follow-ups. The QOLIBRI and QOLIBRI-OS were found to have good completion rates and sensitivity across all GOSE categories. As meta-analyses have shown that response rates in longitudinal studies are better for questionnaires that are shorter in length (Edwards, Roberts, Sandercock, & Frost, 2004; Rolstad, Adler, & Ryden, 2011), it is advisable to use a short multi-dimensional PRO, such as the QOLIBRI-OS, along with the GOSE, in situations where it is difficult to complete detailed follow-ups. This will help to minimise the burden of assessment, while incorporating multi-dimensional outcome measures that are appropriate

in different contexts of use. In situations where face-to-face visits are feasible, PerfOs should be a priority, since they provide information not available from other outcome measures.

### 6.5.3. *Limitations*

This study demonstrates how multi-dimensional outcome assessment could be tailored according to post-TBI functional level. However, some key limitations should be considered. Firstly, the completion rates obtained in CENTER-TBI may not be generalizable to other studies. Outcome completion rates were better for patients with better levels of functional recovery. However, from the information available, it was not possible to fully examine reasons for missing outcomes. Test completion codes have previously been used in the citicoline brain injury treatment (COBRIT) trial (Bagiella et al., 2010b; Zafonte et al., 2009), and are useful in RCTs and CER as a means of recording reasons for missing outcome measures. GOSE follow-up rates were highly variable between study sites, indicating that there may have been site-specific reasons for non-completion of other outcome measures. Furthermore, reasons were missing for up to half of the non-completed PerfOs, suggesting that test completion codes may be difficult to implement in large-scale multicentre studies such has CENTER-TBI. It is unclear why the completion codes were not adopted by CENTER-TBI investigators for all follow-ups. However, investigator training and monitoring may have helped to ensure that test completion codes were completed more fully. Secondly, outcome completion rates were found to be lowest for patients assigned to the 'lower severe disability' category. Nevertheless, CENTER-TBI did not use a prospective flexible assessment approach and therefore did not include a suitable measure specifically suitable for patients with severe disabilities, i.e., the FIM (Linacre et al., 1994). Further research is therefore needed to assess which instruments are suitable for use with patients with the greater functional limitations, who may be unable to complete measures of feeling (i.e., PROs) and functioning (i.e., PerfOs). Thirdly, most patients in this study were assigned to the GOSE 'good recovery' categories and the sample mainly comprised patients scoring in the GCS 13-15 range, which is conventionally categorised as 'mild' TBI (Teasdale & Jennet, 1974). As patients with more severe injuries and poorer outcomes were a relatively small group, the findings may have limited applicability across the spectrum of TBI severity.

### 6.5.4. *Conclusion*

Outcomes can be difficult to obtain in large-scale multicentre studies, particularly for patients with the greatest levels of disability. In this study, most of the PROs and some CANTAB sub-tests were found to lack sensitivity when completed by patients with better levels of functional recovery. Furthermore, floor effects were found on the TMT, CANTAB PAL, and TUG for patients assigned to the 'lower severe disability' category: measures such as the FIM may therefore be appropriate for use with this sub-group. The findings from this study indicate that a sliding approach could be used in TBI research to tailor outcome assessment for different contexts of use. In particular, the GOSE could be used to guide detailed assessment in specific outcome domains for patients at different post-TBI functional levels. An abbreviated set of outcome measures could be used with patients with the greatest levels of post-TBI functional limitation. Furthermore, in situations where it is difficult to obtain detailed outcome assessment, a short multi-dimensional HRQoL measure, such as the QOLIBRI, may be used in addition to the GOSE. The findings from this study provide information for researchers undertaking further analyses of the CENTER-TBI data, for future prospective TBI studies, and for refinement of the CDEs. The particular measures that are selected in future TBI studies will depend upon the purposes of the research, but investigators should ensure that they are validated for specific contexts of use and capture the multi-dimensional impact of TBI, while taking pragmatic constraints into consideration.

# CHAPTER 7

## Integrated discussion and conclusions

This final chapter draws together the main findings and recommendations from the thesis and provides suggestions for future research.

## 7.1. Integrated discussion

Traumatic brain injury (TBI) affects multiple aspects of health and daily functioning. However, in the acute care setting, researchers have often used single measures of global functional outcome, such as the Glasgow Outcome Scale (GOS), to characterize recovery, and have not routinely incorporated measures that capture the multi-dimensional impact of TBI. Multi-dimensional outcome assessment is an increasingly widely used, but poorly defined, concept in TBI research. Pragmatically, outcome assessments can be considered to be multi-dimensional if they measure two or more aspects of health and daily life. However, consensus is lacking on which particular domains are key. This thesis investigated the measurement of global functional outcome in TBI research and considered the role of the GOSE in multi-dimensional outcome assessment. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) framework for clinical outcome assessments (COAs) was used to examine the usability of clinician-reported outcomes (ClinROs), patient-reported outcomes (PROs), and performance outcomes (PROs) in adult TBI. Chapter 2 examined the patterns of use and reporting quality of COAs, including measures of global functional outcome, in clinical trials in adult TBI. Chapters 4 and 5 evaluated the comparability of clinician ratings and respondent reports of global functional outcome: firstly, by exploring whether the GOSE structured interview provides added value over the GOSE questionnaire, and secondly, by examining how clinician ratings on the GOSE structured interview and patient reports on the GOSE questionnaire relate to prognostic factors and other outcome domains. Chapter 6 considered how multi-dimensional outcome assessment in TBI studies could be tailored for patients with different levels of global functional outcome.

The author of this thesis was responsible for conducting follow-up assessments with patients in NHS Lothian. CENTER-TBI follow-ups could be completed in person, via telephone, via post, or using information from clinical records. The outcomes data collection process involved contacting TBI patients or their relatives/caregivers in advance of the scheduled follow-up date, and, upon contact with the patient (and/or their relative or carer), the most appropriate approach to completing the outcome measures was ascertained in accordance with the needs, preferences, and circumstances of the individual.

CENTER-TBI investigators were encouraged to complete both versions of the GOSE, where possible. Thus, the data provided an opportunity to compare clinician ratings and patient reports of global functional outcome in the studies presented in Chapters 4 and 5.

Consistent with CENTER-TBI guidelines, the author of this thesis took steps to mitigate against participant drop-out, such as contacting patients early in the follow-up time window, obtaining contact details for relatives/caregivers, and organising and paying for participant transportation (Maas, Menon, et al., 2015). Despite this, data collection for some of the NHS Lothian follow-ups was found to be challenging: this experience appeared to be common among CENTER-TBI outcome assessors. The process of contacting patients and organising follow-ups could be laborious at times. Furthermore, clinical judgement was required when determining which assessments were appropriate for completion with specific individuals. Of particular relevance to this thesis, several of the NHS Lothian patients were assigned to the GOSE 'lower severe disability' category upon follow-up (particularly at 3 months after injury). These patients were unable to complete the full set of CENTER-TBI outcome measures, highlighting the difficulties associated with implementing multi-dimensional outcome assessment across spectrum of recovery, and providing the motivation for the study presented in Chapter 6.

### 7.1.1. *Participant characteristics*

The participants described in this thesis were selected from the CENTER-TBI core study (Maas, Menon, et al., 2015). The patients included in the study samples were, on average, older than those enrolled in European studies in previous decades (Murray et al., 1999), and approximately one-quarter were 66 years or older and retired. Around two-thirds of the patients were male, and almost all of them were Caucasian. Incidental falls were the most common cause of injury overall, followed by road traffic accidents. Consistent with previous studies (Leong et al., 2013; van Leeuwen et al., 2012), a considerable proportion of the participants in the study samples had co-morbid extracranial injuries (i.e., 34-40% had severe injuries to non-head and neck body regions). Approximately two-thirds had scores in the GCS 13-15 range (Teasdale et al., 1979). Furthermore, 44-51% of the participants in the study samples were admitted to ICU, around half had CT abnormalities, and total ISS scores (Baker et al., 1974) were above the threshold for major trauma in all study samples.

The demographic and clinical characteristics of the study samples are broadly comparable to the total CENTER-TBI core study sample and reflect the changing epidemiology of TBI in Europe: the average age of TBI is increasing, and falls are now the most common cause of injury in high-income countries, particularly in older adults (Brazinova et al., 2016; Maas et al., 2017; Peeters et al., 2017; Peeters et al., 2015). The increased incidence of TBI in older adults has implications for the use of study outcome measures. For example, as cognitive functioning declines with increasing age (Strauss et al., 2006), it may be necessary to adjust for the effect of age on performance on cognitive assessments in TBI studies. Adjustments for potentially confounding covariates such as age and acute stage prognostic factors (e.g., injury severity) were not performed in this thesis, but the impact of these factors will be examined in further CENTER-TBI analyses.

### 7.1.2. *Approaches to measuring global functional outcome*

The first main theme of this thesis was the comparison between clinician-ratings and patient-reports on the GOSE. This comparison is important for two main reasons. Firstly, despite the drive towards use of PROs in clinical research (U.S. Food & Drug Administration, 2009; Walton et al., 2015), patients with TBI may be unable to provide an accurate self-report on the GOSE questionnaire (Prigatano, 2005a, 2005b; Wilson et al., 2002). Secondly, as investigators are often not masked in observational studies, such as CENTER-TBI, clinician ratings on the GOSE structured interview may be influenced by knowledge about prognostic factors, e.g., injury severity (Sherer et al., 2010), as well as knowledge about performance on other outcome measures, e.g., cognitive tests. CENTER-TBI provided an opportunity to examine these issues as a pragmatic approach was taken to data collection, and the GOSE could be completed as a clinician-rated structured interview (Wilson et al., 1998) or as a self-completion questionnaire (Wilson et al., 2002).

The systematic review in Chapter 2 (Horton et al., 2018) demonstrated that the GOS/E is the most commonly used COA in previous clinical trials in adult TBI. However, the review also showed that the GOS/GOSE was not used uniformly across the studies and insufficient information was provided about how it was used. The scale was mainly used in RCTs in acute study settings, often as a primary endpoint, and most of the studies in the review

collected information via guided or structured interviews rather than using the GOSE questionnaire. In terms of reporting quality, none of the articles provided information about whether extracranial injuries were included in GOS/GOSE ratings. Most articles did not state whether patients with pre-existing severe disability were excluded, or who the respondent was. Furthermore, around half of the articles did not state the primary method of contact for GOS/GOSE assessments. As discussed previously, heterogeneity in implementing the GOS/E is potentially problematic because different modes of data collection may not be equivalent (Eremenco et al., 2014; Powers et al., 2017; Walton et al., 2015). Thus, the way in which the GOS/GOSE is used may influence study findings. As noted in Chapter 2, this is an important issue when pooling data for secondary analyses.

The findings from Chapter 2 provided the motivation for the studies presented in Chapters 4 and 5. Chapter 4 demonstrated that GOSE structured interview and GOSE questionnaire scores were similar in different contexts of use, including with patients with pre-existing functional limitations, epilepsy, CT abnormalities, and moderate-to-severe TBI. In addition, Chapter 5 showed that GOSE assignment was not affected by investigator bias or by the patient's perspective. Together, these findings indicate that clinician ratings and patient reports of global functional outcome are broadly comparable. Nevertheless, the findings also revealed that there are certain circumstances in which it is advisable to supplement information obtained via the GOSE questionnaire with information from the GOSE structured interview. Firstly, due to the subjective nature of TBI-related symptoms, the boundary between the 'lower' and 'upper good recovery' categories can be difficult to determine. In Chapter 4, the impact of TBI symptoms on daily functioning was found to be under-reported on the GOSE questionnaire. This issue can at least partly be overcome by collecting additional information about symptoms using the GOSE structured interview, or by re-scoring the symptoms section of the GOSE questionnaire. Secondly, Chapter 4 showed that inconsistencies can occur between clinician ratings and respondent reports when the GOSE is completed with patients with greater levels of disability and those with extracranial injuries, but only in the first few months after injury. The GOSE structured interview is therefore useful at 3-month follow-up when assessing patients with greater levels of disability, and for gathering additional information about the reasons for functional limitations in patients with significant injuries to other body regions.

Previous TBI studies have provided limited information about the comparability of clinician ratings and patient reports of global functional outcome. Thus, the studies presented in Chapters 4 and 5 are novel because they directly compared clinician ratings and patient reports of global functional outcome in large samples of TBI patients. The large number of participants in CENTER-TBI made it possible to conduct a detailed investigation of agreement on individual GOSE sections; enabled exploration of the effect of factors such as extracranial injury on GOSE assignment; and allowed the effect of investigator bias and the patient's perspective on GOSE scores to be examined, none of which have formally been investigated. Nevertheless, as CENTER-TBI was an observational project, the studies presented in Chapters 4 and 5 did not have an experimental design. The GOSE was not collected in a uniform way across the CENTER-TBI study sites. Thus, systematic comparisons between different modes of data collection (i.e., face-to-face versus telephone interviews, and patient versus proxy reports on the GOSE questionnaire) were not possible. Additionally, as patient self-awareness was not measured directly as part of the CENTER-TBI follow-ups, the study presented in Chapter 5 lacked verification about the accuracy of patient's self-reports.

In light of the limitations presented above, it would be useful to make systematic comparisons between different modes of GOSE data collection in a future prospective study in which investigators were masked. Information could be obtained from independent investigators via face-to-face and telephone interviews, and then compared, to determine whether face-to-face contact with the investigator adds any added value when assessing functional recovery. A direct comparison between patient reports and reports from other informants was not possible in this thesis due to the way that the CENTER-TBI outcomes were collected. However, as lack of self-awareness may be problematic when measuring global functional outcome, particularly when assessing patients with greater injury severity (Prigatano, 2005a, 2005b), it would also be useful compare patient and proxy reports on the GOSE questionnaire and use the Patient Competency Rating Scale (Prigatano & Fordyce, 1986) to verify the accuracy of patients' self-reports. These suggestions notwithstanding, it is important to note that systematic comparisons between GOSE approaches are difficult to implement, as repeated administration of the scale is time consuming and potentially

difficult to achieve, especially if other outcome assessments are incorporated. Conducting such a study may therefore be difficult and only practical in certain settings.

Taken together, the findings from Chapters 4 and 5 indicate that information collected via structured interviews makes little overall difference to GOSE assignment and suggest that mixed modes of GOSE collection can be used to facilitate participant retention in studies with pragmatic constraints. CENTER-TBI investigators were encouraged to complete both versions of the GOSE, if possible, and the scale was not used uniformly across study sites (Maas, Menon, et al., 2015). A composite GOSE score (Wilson & Horton, 2018), comprising clinician ratings and patient reports, was therefore created as part of the CENTER-TBI data curation process, to maximise outcome completion rates. When creating the GOSE composite, information collected via the GOSE structured interview was prioritised, if available. As the information obtained via the GOSE structured interview and GOSE questionnaire was found to be comparable in Chapters 4 and 5, the GOSE composite was used in Chapter 6 of this thesis.

### *7.1.3 Tailoring outcome assessment in relation to level of global outcome*

The second main theme in this thesis was consideration of the usefulness of tailoring multi-dimensional outcome assessment for patients with different levels of functional recovery. CENTER-TBI and TRACK-TBI both have the goal of validating individual outcome measures in different contexts of use. Furthermore, both projects are investigating approaches to tailoring outcome assessments for TBI sub-groups, for example, using the Galveston Orientation and Amnesia Test (GOAT) (Yue et al., 2018; Yue et al., 2013) or injury severity (CENTER-TBI, 2018) to stratify patients. In clinical practice, neuropsychological assessments are tailored to the particular needs of the individual, and the choice of instruments often depends on the information available about the patient, as well as the specific reasons for referral (Strauss et al., 2006). The "flexible battery approach," which incorporates variable but routine sub-sets of tests for different patient types, has been favoured by clinical neuropsychologists for decades (Sweet et al., 2000a; Sweet et al., 2000b). However, the concept of a "flexible" or "sliding" approach to outcome assessment is relatively novel in TBI research, and there is currently no consensus about how tailored outcome assessments could be implemented in TBI studies.

Patients assigned to different GOSE categories represent different contexts of use for outcome measures (Maas et al., 2017; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017; Walton et al., 2015). Therefore, the study presented in Chapter 6 considered the quality and validity of the CENTER-TBI outcome measures when used with patients assigned to different GOSE categories. The applicability of individual outcome measures has not been formally investigated in relation to the patient's level of functional recovery. However, it is presumably already taken into consideration by researchers when planning and designing TBI studies. Chapter 6 showed that multi-dimensional outcome assessment was more challenging to implement with patients with greater functional limitations. Furthermore, ceiling effects were found to be present on several outcome measures, mainly for patients with better functional levels, whereas floor effects were minimal and only occurred in the 'lower severe disability' group. These findings demonstrate that the applicability of outcome assessment in TBI research is strongly driven by level of global functional outcome. Due to the heterogeneity of TBI, few outcome measures can be applied with all patients. A one-size-fits-all approach to characterising outcomes in TBI studies is therefore insufficient, and consistent with CENTER-TBI and TRACK-TBI objectives, a tailored approach is necessary to characterise recovery in different TBI sub-groups. It should be noted, however, that use of a tailored approach may not be applicable in all TBI study types, as it reduces the comparability between patient sub-groups and potentially introduces bias.

Detailed outcome assessments can be difficult to obtain in large-scale multicentre studies. This is potentially problematic because selective attrition of participants in longitudinal TBI studies can result in systematic bias is study findings (Corrigan et al., 2003; Krellman et al., 2014; Langley et al., 2010). Completion of the full set of CENTER-TBI outcome measures was estimated to take around 3 hours per patient and assessments were conducted if they were logistically feasible and patients were cognitively able (Maas, Menon, et al., 2015). Cognitive assessments and tests of physical functioning were found to have the lowest completion rates: these measures must be completed face-to-face, making them more difficult to obtain than outcomes that can be collected via telephone or post. Furthermore, they can only be completed with patients who are able, making them potentially unsuitable

for patients with severe disabilities. Due to the limited information available, it was not possible to make conclusions about the reasons for non-completion of these outcome measures in Chapter 6. Failure to complete CENTER-TBI follow-ups was partly due to logistic constraints and patient-specific limitations, but it could also be due to site-specific issues that could not be addressed in this thesis. There was variability in the follow-up completion rates between study-sites. Thus, the outcome completion rates presented in this thesis may not be generalizable beyond CENTER-TBI.

The findings from Chapter 6 are relevant to other researchers as they provide guidance for selecting outcome measures in different contexts of use (Walton et al., 2015), i.e., according to post-TBI functional level. The findings are of relevance to further CENTER-TBI analyses. Firstly, they will inform other CENTER-TBI outcomes analyses, which will examine the outcome measures in more detail with the overarching objective of developing a multi-dimensional tool for classifying outcomes after TBI (CENTER-TBI, 2018). The responsiveness, sensitivity, and parsimony of the outcome measures will be examined by other CENTER-TBI researchers, and structural equation modelling will be done to identify predictors, moderators and confounders in TBI outcome assessment. The findings from Chapter 6 will also inform other strands of the CENTER-TBI project and may be useful for investigators with a background in acute TBI, who have limited knowledge about outcomes research. The information obtained about outcome completion rates for different GOSE categories could be used to help guide the selection of outcome measures for comparative effectiveness research (CER). CER aims to improve clinical decision-making by investigating differences in care and outcome in observational studies (Maas, Menon, et al., 2015). It exploits the natural variability in clinical practice and allows investigators to identify which treatments work best in ordinary clinical settings (Maas et al., 2012). Selection of sensitive outcome measures with good completion rates is important in CER because it reduces the likelihood of bias due to selective attrition of patients (i.e., patients with severe disabilities may have poor completion rates due to cognitive or physical impairment).

Chapter 6 also provides guidance for designing future prospective studies as it indicates that researchers should be aware of practical constraints when designing studies and conducting outcome assessments in TBI. In situations where outcomes are particularly

challenging to obtain, a short TBI-specific PRO, such as the QOLIBRI or QOLIBRI-OS (von Steinbüchel, Wilson, Gibbons, Hawthorne, Hofer, Schmidt, Bullinger, Maas, Neugebauer, Powell, von Wild, Zitnay, Bakx, Christensen, Koskinen, Sarajuuri, et al., 2010; von Steinbüchel et al., 2012), could be used in addition to the GOSE to gather information about the multi-dimensional impact of TBI. Where more detailed follow-ups are practical, the use of cognitive tests with good sensitivity across the spectrum of recovery is advisable. Measures of emotional adjustment should also be included, where practical, to capture problems such as depression and anxiety in patients who may otherwise appear to have fully recovered on the GOSE (Maas, Menon, et al., 2015; Nelson, Ranson, Ferguson, Giacino, Okonkwo, Valadka, Manley, McCrea, et al., 2017).

Multi-dimensional outcome assessment has not been implemented routinely in previous TBI clinical trials, particularly in acute study settings (Horton et al., 2018). Thus, researchers designing future studies, particularly those comparing the effectiveness of acute treatments and interventions, should aim to select outcome measures that capture the multi-dimensional impact of TBI, while also taking practical issues into consideration. The findings from this thesis indicate that while completion rates for the GOSE are relatively good compared to other outcomes, it does not provide sufficient detail about specific aspects of the patient's functioning and feeling which are relevant in TBI. TBI researchers may therefore need to compromise between using a brief, but blunt measure, such as the GOSE, which is appropriate for use across the TBI spectrum; versus a more detailed set of outcome assessments, which capture the multi-dimensional impact of TBI, but which are time consuming and potentially difficult to obtain.

Chapter 6 provides information about the sensitivity and internal consistency of the CENTER-TBI outcome measures with patients with different levels of post-TBI functioning. However, further validation of TBI outcome measures is now required. CENTER-TBI and TRACK-TBI researchers are currently working on this task. The data from these studies will be used to validate outcome measures in different contexts of use (i.e., paediatric TBI, adult TBI, epidemiology, acute hospital, moderate-to-severe TBI rehabilitation, mild TBI/concussion), and this will inform further refinement of the NINDS CDEs (National Institute of Neurological Disorders and Stroke, 2018b). The NINDS CDEs (Hicks et al., 2013;

Wilde et al., 2010) were introduced to reduce heterogeneity in the use of outcome measures in TBI studies. Future refinement of the CDEs will allow researchers to pool data for secondary analyses. Nevertheless, variability in the use of outcome measures is likely to remain an issue in TBI research, due to the complexity of TBI, heterogeneity in TBI studies, and wide range of outcome measures available.

## 7.1. Conclusions

This thesis makes an original contribution to the field of TBI research: firstly, because it highlights the issues of heterogeneity, limited use of multi-dimensional outcomes, and incomplete reporting of outcome measures in clinical trials in TBI; secondly, because it directly compares clinician ratings and patient reports of global functional outcome in TBI using large numbers of patients; and thirdly, because it considers the applicability of multi-dimensional outcome assessment in TBI studies in relation to level of global functional outcome. Chapters 4 and 5 demonstrate that clinician ratings and patient reports provide broadly comparable information about global functional outcome after TBI. Furthermore, Chapter 6 suggests that TBI outcome measures could be tailored to capture the multi-dimensional impact of TBI across the spectrum of functional recovery. These findings indicate that mixed modes of GOSE data collection can be used to maximise follow-ups in studies with pragmatic constraints. The findings also demonstrate that the applicability of individual outcome measures is strongly driven by level of global functional outcome. This PhD project was part of the CENTER-TBI outcomes research strand (Maas, Menon, et al., 2015). The findings therefore have immediate implications for further CENTER-TBI analyses. The findings also have implications for selecting outcome measures in future prospective studies, for refining the CDE outcome measures in TBI (Hicks et al., 2013; Wilde et al., 2010), for conducting comparative effectiveness research (CER) (Maas et al., 2012), and for pooling data for secondary analyses conducted as part of InTBIR (Tosetti et al., 2013).

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## Appendix 2: 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 (Chen et al., 2002) | 120 | 33.6 (18-60) | severe | acute single centre | Glasgow Outcome Scale (GOS) (6 months) | n/a | not stated | U | U |
| CRASH Corticosteroid Study (Edwards et al., 2005; Roberts et al., 2004) | 10,008 | not stated (adults) | all | acute multicentre | GOS (6 months) | n/a | 97% | U | L |
| CRASH-2 Tranexamic Acid (Perel et al., 2011) | 270 | 36.5 (adults) | all | acute multicentre | modified Oxford Handicap Scale (mOHS) (6 months) | n/a | 100% | L | L |
| Intensive Insulin Therapy (Cinotti et al., 2014) | 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 (Cruz, Minoja, & Okuchi, 2001) | 178 | 29 (adults) | severe | acute single centre | GOS (6 months) | n/a | 100% | L | U |

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| Mannitol (Cruz, Minoja, & Okuchi, 2002) | 141 | 30 (adults) | severe | acute single centre | GOS (6 months) | n/a | 100% | L | U |
| Valproate (Dikmen, Machamer, Winn, Anderson, & Temkin, 2000) | 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%<br>6m = 53%<br>12 m = 38% | L | L |

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| Erythropoietin (Li et al., 2016) | 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 (Maas et al., 2006) | 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 (Nichol et al., 2015) | 606 | 30.5* (16-83) | moderate/ severe | acute multicentre | GOSE (6 months) | n/a | 98% | L | L |
| Erythropoietin (Robertson et al., 2014) | 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 (Shakur et al., 2009) | 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 (Skolnick et al., 2014) | 1195 | 34.5*(16-70) | severe | acute multicentre | GOS (6 months) | GOSE, SF-36 | 99% | L | L |
| Magnesium (Temkin et al., 2007) | 499 | 34.4 (14 and over) | moderate/ severe | acute single centre | Composite comprising 39 individual measures, including mortality, seizures, functional | n/a | 93% neuropsych. tests = 72% | L | L |

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| | | | | | 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, 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 (Wright et al., 2014) | 882 | 35* (adults) | moderate/ severe | acute multicentre | GOSE (6 months) | DRS | 94% | L | L |
| Intensive insulin therapy (Yang et al., 2009) | 240 | 45.5 (adults) | severe | acute single centre | Mortality (6 months) | GOS | 97% | U | L |
| Traxoprodil (Yurkewicz, | 404 | 31.3 (16-70) | severe | acute multicentre | GOS (6 months) | DRS, Cognitive Abilities Screening Instrument (CASI), | 93% | L | U |

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| Weaver, Bullock, & Marshall, 2005) | | | | | | GOSE | | | |
| Tranexamic acid (Yutthakasemsunt et al., 2013) | 238 | 34.5 (16 and over) | moderate/ severe | acute single centre | Intracranial haemorrhage (at hospital discharge) | GOS | 100% | L | L |
| Citicoline, COBRIT trial (Zafonte et al., 2012) | 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 (Andrews et al., 2015) | 387 | 37 (legal age of consent and over) | moderate/ severe | acute multicentre | GOSE (6 months) | modified Oxford Handicap Scale (mOHS) | 97% | L | L |
| Hypothermia (Clifton et al., 2001) | 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, | 96% | U | U |

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| | | | | | | TMT Part B, COWAT, Grooved Pegboard Test | | | |
| Hypothermia (Clifton et al., 2011) | 232 | 28.5 (16 - 45) | severe | acute multicentre | GOS (6 months) | DRS | 92% | L | L |
| Hypothermia (Jiang et al., 2006) | 215 | 32.9 (18-45) | severe | acute multicentre | GOS (6 months) | n/a | 100% | U | U |
| Hypothermia, B-HYPO study (Maekawa, Yamashita, Nagao, Hayashi, & Ohashi, 2015) | 148 | 39 (15-69) | severe | acute multicentre | GOS (6 months) | n/a | 99% | **L** | L |
| Physiology of hypothermia (Yan, Tang, Deng, Zhong, & Yang, 2010) | 148 | 27.3 (18-64) | severe | acute single centre | Physiology & GOS (1-7 years) | GOS | unclear | U | U |
| Hypothermia (Zhi, Zhang, & Lin, 2003) | 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) (Cooper et | 155 | 24.2* (15-59) | severe | acute multicentre | GOSE (6 months) | n/a | 100% | L | L |

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| al., 2011) | | | | | | | | | |
| STICH Surgical trial (Gregson et al., 2015; Mendelow et al., 2015) | 170 | 48 (16-83) | all | acute multicentre | Postal GOSE (6 months) | Rankin Scale, EuroQol (EQ-5D) | 99% | L | H |
| Decompressive Craniectomy (Hutchinson et al., 2017) | 408 | 33.6 (10-65) | severe | acute multicentre | GOSE (6 months) | GOSE, SF-36 | 98% | L | L |
| Standard vs limited Craniectomy (Jiang et al., 2005) | 486 | 44.5 (14-70) | severe | acute multicentre | GOS (6 months) | n/a | 100% | L | L |
| Surgical trial of Decompression (Li et al., 2012) | 182 | 36.8 (14-72) | severe | acute single centre | GOS (5-60 months) | n/a | 91% | U | U |
| Surgical trial of Craniectomy (Lü et al., 2003) | 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 (Bernard et al., 2010) | 312 | 40.7 (15 and over) | severe | acute multicentre | GOSE (6 months) | GOSE dichotomised | 96% | L | L |

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| Acute osmotic therapy. Early hypertonic fluids (Bulger et al., 2010) | 1331 | 38.9 (15 and over) | severe | acute multicentre | GOSE (6 months) | DRS | 85% | L | L |
| Acute osmotic therapy. Pre-hospital hypertonic saline (Cooper et al., 2004) | 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 (Chesnut et al., 2012) | 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, COWAT, Category Fluency - Animals and Actions, PASAT (6 months) | n/a | 92% | L | L |
| Technology/monitoring - CPP display | 157 | 37 (16 and over) | moderate/ severe | acute single centre | GOSE and FSE (6 months) | n/a | 100% | L | L |

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| (Kirkness, Burr, Cain, Newell, & Mitchell, 2006) | | | | | | | | | |
| Bed rest for mTBI (de Kruijk, Leffers, Meerhoff, Rutten, & Twijnstra, 2002) | 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 (Giacino et al., 2012) | 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 (Hammond et al., 2015) | 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 (Menn, Yang, & Lankford, 2014) | 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 | Epworth Sleepiness Scale (ESS), MSLT, Clinical Global Impression of Severity of Illness (CGI-S), Clinical Global | 73% to 98% | U | U |

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| | | | | | recruited 1-10 years post-injury) | Impression of change (CGI-C) | | | |
| Rivastigmine (Silver et al., 2006) | 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 (Tenovuo, Alin, & Helenius, 2009) | 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 wash-out, after 2nd period. Patients recruited at least 1 year after injury) | n/a | 68% | L | L |

| 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 (Bedard et al., 2014) | 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 (Bell et al., 2005) | 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, Modified Perceived Quality of Life (PQOL) (1 year) | Individual measures and composites of measures in a common outcome domain | 92% | L | L |
| Telephone counselling (Bell et al., 2008) | 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% | | |

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| Telephone counselling (Bell et al., 2011) | 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%<br>2 year: 81% | L | L |
| Self-advocacy intervention (Brown et al., 2015) | 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 (Elgmark Andersson, Emanuelson, Bjorklund, & Stalhammar, 2007) | 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 (Fann et al., 2015) | 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 | 100% | L | L |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | with Depression Care, Working Alliance Inventory - Short Form, SF-36, Head Injury Symptom Checklist | | | |
| Multidisciplinary rehab for mTBI (Ghaffar, McCullagh, Ouchterlony, & Feinstein, 2006) | 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, WAIS III Letter-Number Sequencing, WAIS III Matrix-Reasoning (6 months) | n/a | 89% | U | U |
| Early rehab for mTBI (Matuseviciene, Borg, Stålnacke, Ulfarsson, & de Boussard, 2013) | 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 (Powell, Heslin, & Greenwood, 2002) | 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 (Salazar et al., 2000) | 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 (Sander et al., 2012) | 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 (Vanderploeg et al., 2008) | 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 | 92% | L | L |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Scale | | | |
| Multidisciplinary outpatient treatment for mTBI (Vikane et al., 2017) | 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 (Vuletic et al., 2016) | 365 | 29.3 (20-54) | mild | post-acute multicentre | Pittsburgh Sleep Quality Index (PSQI)<br>(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%<br>12 months = 72% | L | U |

## Appendix 2 References


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## Appendix 3: 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 |

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|---|---|---|---|---|---|
| 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 |

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|---|---|---|---|---|---|
| 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