



Universiteit
Leiden
The Netherlands

Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice

Dijck, J.T.J.M. van

Citation

Dijck, J. T. J. M. van. (2021, September 16). *Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice*. Retrieved from <https://hdl.handle.net/1887/3210899>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3210899>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <https://hdl.handle.net/1887/3210899> holds various files of this Leiden University dissertation.

Author: Dijck, J.T.J.M. van

Title: Decision-making in severe traumatic brain injury: patient outcome, hospital costs, and research practice

Issue Date: 2021-09-16

CHAPTER 1

GENERAL INTRODUCTION

Worldwide, an estimated fifty to sixty-nine million people a year sustain a traumatic brain injury (TBI).^{1,2} The all-cause, all-severity global yearly incidence of TBI is estimated at 939 cases per 100,000 people, of which an estimated 5.48 million people (73/100,000) suffer severe TBI (s-TBI).² In Europe, there are an estimated 2.5 million new cases of TBI each year.¹ Numbers from The Netherlands show almost 35,000 annual emergency department visits.³ The most common causes of TBI are road traffic accidents and falls.¹ In recent years, the number of falls is increasing, especially in the elderly.^{1,3,7} The medical consequences of TBI are substantial and range from symptoms like headache and fatigue to severe disabilities and even death.⁷⁻¹¹ The high occurrence and acute and chronic consequences of TBI contribute to the substantial healthcare- and socioeconomic burden and cause harm to patients, proxies and societies.¹

Diagnosis and classification

TBI is defined as 'an alteration in brain function, or other evidence of brain pathology, caused by an external force'.¹² It can be diagnosed and classified by using trauma mechanism, clinical severity, presence of structural damage on neuroimaging, and prognostic risk.¹³ Clinical severity is the most frequently used classification method and usually indicated by the level of consciousness as represented by the Glasgow Coma Scale.^{1,14,15} The combined sum score (3 to 15) of the eye (1-4), verbal (1-5) and motor (1-6) components is used to categorize patients in three severity groups: severe TBI (GCS 3-8), moderate TBI (GCS 9-12), and mild TBI (GCS 13-15). These severity groups account for an estimated 8%, 11% and 81% of all TBI patients respectively.²

Although these TBI severity groups are frequently used in clinical practice and research, the clinical presentation of patients within these categories remains highly variable.¹⁶ Variability in TBI is very common and complicates diagnosis, classification and clinical practice. It is the result of differences in patient characteristics, or particulars of trauma, such as type, intensity, direction, and duration of the external forces, but also by uncertainties related to the complexity of the brain.^{1,13} Many aspects of the pathophysiological mechanisms of TBI are still unknown. The mechanism of TBI can be best understood by distinguishing primary and secondary brain injury.^{1,13,17}

Primary and secondary brain injury

Primary brain injury occurs at the time of the initial injury and causes diffuse or localized brain tissue destruction and areas of intracerebral or extracerebral haemorrhage. Primary injury is irreversible by definition and therefore unsuitable

for treatment. It could only be anticipated by preventative measures.¹⁸ More extensive primary injury is usually seen in more severely injured TBI patients, and is likely to be related to the development of secondary brain injury.

Secondary brain injury occurs from insults to the brain in the hours, days or months after the initial injury.^{13,17} It is mainly triggered by hypoxia and hypovolaemia caused by systemic insults or increased intracranial pressure (ICP) as a result of intracranial hematomas, brain swelling, cerebral oedema or ischemia.¹³ Other causes are impaired haemostasis, the consequences of neurotransmitter release, or a damaged blood-brain barrier with leakage of immune cells and a subsequent increased neuroinflammatory response with brain swelling.^{13,17} Secondary injury is considered to be reversible and is suitable for treatment.^{13,17}

Treatment strategies

Immediate treatment in the pre-hospital or hospital setting could prevent or reverse secondary injury and associated brain dysfunction and might therefore be beneficial for patient outcome.^{1,13} Trauma patients are usually treated by using the ATLS (Advanced Trauma Life Support) principle: 'treat first what kills first'.¹⁹ When necessary, this includes the prevention and/or normalisation of hypoxia and hypovolaemia by using intubation, oxygen supplementation, fluid resuscitation, or acute treatment of extracranial injuries, before focussing on the neurological status of the patient.¹⁹ After neurological assessment, a CT scan is made to identify potential treatable or operable traumatic intracranial abnormalities, including diffuse axonal injury, diffuse swelling, subarachnoid haemorrhage, contusions, and epidural or subdural hematomas (Figure 1). Traumatic intracranial hematomas are rare in patients with mild TBI, but occur in 25-35% of patients with s-TBI and in 5-10% of patients with moderate TBI and could require immediate or delayed surgical intervention to prevent secondary injury.^{13,20}

Surgical intervention options include the placement of an ICP monitor or extraventricular drain, a craniotomy with evacuation of a haemorrhagic focus, or a decompressive craniectomy.²⁰ Surgical management is often combined with perioperative ICU treatment that also focusses on the prevention of secondary injury and the optimisation of conditions for brain recovery.^{13,21} The necessary individualised and targeted approaches are nearly only possible at specialised ICUs.²¹ When ICU admission is not required, patients will be admitted to a medium care or general ward. Provided care obviously depends on a patients' clinical condition,

their medical needs and the local possibilities to provide care. Deciding to initiate or withhold surgical and/or non-surgical treatment during the acute treatment decisions-making process is often very difficult for treating physicians.

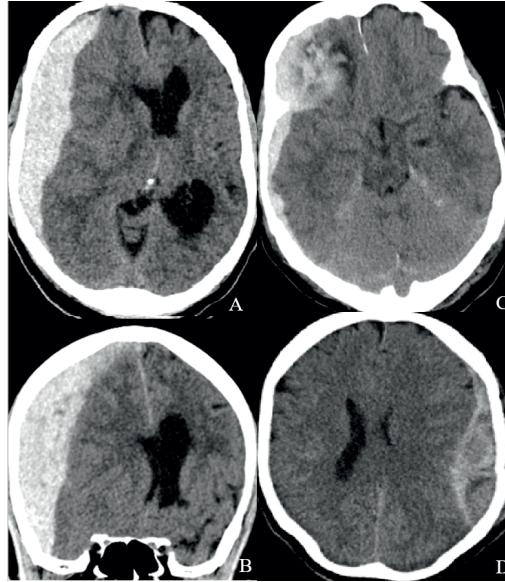


Figure 1. Computed tomography (CT) scans of patients with traumatic intracranial abnormalities. A and B: Subdural hematoma. C: Contusion and parenchymal hematoma. D: Epidural hematoma.

The acute treatment decision-making process

Several evidence-based guidelines, treatment protocols, and consensus-based recommendations are made to support physicians in this decision-making process.^{20,22-26} Despite their existence, adherence to TBI guidelines is generally poor. This is caused by the low evidence level on which recommendations are based^{27,28}, delay between literature search and publication, the fact that recommendations are not restated in subsequent guideline versions, and downgrading of a recommendations' evidence level.²⁹ In addition, there are several areas of uncertainty that are not included in available guidelines because essential evidence is not available.^{23,24}

The extent of the problem of evidence availability is also reported in two recent reviews. The first review of 191 completed randomized controlled trials for acute TBI management found very little translatable evidence because of multiple methodological shortcomings.³⁰ The second investigated systematic reviews on the acute management of moderate to s-TBI patients and concluded a lack of currency, completeness and quality.³¹

The many problems with the availability of high-quality evidence results in a lack of consensus, decision-making difficulties, and an inability to practice evidence-based medicine. This enables treatment variation, which is reported in nearly all fields of TBI management, including the use and implementation of guidelines in European neurotrauma centers³², structures and processes of TBI care³³, monitoring and treatment policies in patients with TBI and intracranial hypertension³⁴, general supportive and preventive measures at ICUs³⁵, and neurosurgical strategies or management.^{36,37}

Future research is needed to improve the quality and completeness of evidence on the treatment of TBI patients. Reliable information on patient outcome and treatment effectiveness is likely to substantially improve the treatment decision-making process for physicians.

Patient outcome

The effectiveness of treatments can be assessed by measuring achieved patient outcome, because the main goal of providing healthcare is to achieve best possible patient outcome. Despite available treatment interventions, TBI patients still show high rates of mortality and unfavourable outcome, especially in patients with s-TBI. In a recent meta-analysis, the in-hospital mortality for moderate TBI and s-TBI patients was 57.2% and the 'all time point' mortality was 65.3% for s-TBI, 34.3% for moderate TBI and 12.3% for mild TBI patients.³⁸ Other studies reported lower mortality rates of 0.45% to 8% for mild TBI³⁹, 0.9% to 8% for moderate TBI⁴⁰ and 39% - 40.4% for s-TBI.

^{41,42}

In addition to mortality rates many investigators report functional patient outcome by using the Glasgow Outcome Score - Extended.⁴³ (Table 1) A so called 'favourable outcome' (GOSE 5-8), indicating independency in daily life, was achieved by 29% - 40% of s-TBI patients, 55.3% - 87% of moderate TBI patients, and 85.4% of mild TBI patients.^{40,41,44} Unfortunately, outcome rates are difficult to generalize because they depend on multiple factors such as age, injury severity, initial neurologic condition and TBI severity (i.e defined by GCS).^{38,45}

Besides short term outcome, many studies report long-term sustained healthcare problems, which are not limited to s-TBI patients, but also reported after mild TBI.^{10,11,46-51} Several authors therefore consider TBI to be a chronic health condition and suggest that it should be addressed as such by healthcare providers, researchers and policymakers.^{52,53}

Table 1 Explanation of Glasgow Outcome Scale (- Extended).⁴³

Glasgow Outcome Scale (GOS)	Glasgow Outcome Scale – Extended (GOSE)	Brief description	U/F
1. Death	1. Death	Death	Unfavourable outcome
2. Vegetative state	2. Vegetative state	Absence of awareness of self and environment	
3. Severe disability	3. Lower severe disability	Needs full assistance in daily life	
	4. Upper severe disability	Needs partial assistance in daily life	
4. Moderate disability	5. Lower moderate disability	Independent, but cannot resume work/school or all previous social activities	Favourable outcome
	6. Upper moderate disability	Some disability exists, but can partly resume work or previous activities	
5. Good recovery	7. Lower good recovery	Minor physical or mental deficit that affects daily life	
	8. Upper good recovery	Full recovery or minor symptoms that do not affect daily life	

Patient outcome after TBI and thereby the effectiveness of available, generally unproven, treatment strategies is still considered to be unsatisfactory.^{1,9,21,24,29} A critical appraisal of treatment effectiveness and patient outcome will hopefully decrease the number of patients that achieve an outcome that they would have never wanted and might even prevent associated but ineffective healthcare expenses.^{9,54-56}

In-hospital costs

The annual global economic burden of TBI is estimated to be US\$ 400 billion.¹ Direct costs (i.e. healthcare costs) represent a substantial part of the total economic burden^{3,57-60}, but the indirect costs (i.e. loss of productivity and intangible costs) are considered to be the largest contributor.^{1,61,62} TBI related healthcare costs are increasing annually, which is problematic when healthcare budgets remain restricted.⁶³⁻⁶⁵ These high and rising healthcare costs could endanger the affordability of national healthcare systems and thereby public health.^{66,67} The importance of investigating the cost of care for TBI patients is therefore widely recognized by healthcare professionals and societies.¹ Healthcare professionals and policy makers are nowadays even expected to study the cost-effectiveness of treatments.^{68,69}

When focussing on the hospital setting, patients with s-TBI show the longest hospital or ICU length of stay and have the most (neuro)surgical and medical interventions compared to other TBI severities.^{42,70,71} These patients also show the highest individual costs of all TBI patients.⁷⁰ In The Netherlands, the mean direct and indirect costs for TBI patients were €18,030 per patient³, and when including rehabilitation and nursing home costs, patients with s-TBI costed €40,680 to €44,952.⁷²

Understanding and generalizing the in-hospital costs of individual TBI patients from available literature however remains difficult because methodological heterogeneity of TBI cost studies is high and study quality often inadequate.^{73,74} Input from high quality cost research is essential to achieve a rational and righteous distribution of limited resources, to guarantee the highest quality of care for the lowest costs.⁷³⁻⁷⁵ To achieve this, several difficulties in conducting TBI research have to be improved.

Difficulties in conducting TBI research

Conducting research in patients with TBI is complicated by several factors; largely unknown pathophysiological mechanisms of brain injury, the acute and stressful situation, unavailable necessary information (i.e. trauma mechanism, medical history, use of anticoagulants), and a patients' inability to provide informed consent. As stated, to meet the need for more high-quality research, the efficiency of future research initiatives needs to be improved. This can be achieved by optimizing several aspects of TBI research. This thesis will focus on the use of informed consent procedures and the process of institutional review board approval.

Informed consent

Physicians and researchers are obligated to inform patients and obtain informed consent before executing diagnostic tests or treatment interventions as part of a clinical study.^{76,77} The right to refuse informed consent and thus study participation is internationally recognised and formalised in many declarations, regulations, directives and laws.⁷⁶⁻⁷⁸ Obtaining informed consent respects the principle of autonomous people and their autonomous choices and actions. It establishes a shared responsibility between professionals and patients.

Obtaining patient informed consent is however not possible in patients with an inability to provide informed consent due to acute TBI. As a result of limited formal guidance in this context, most Institutional Review Boards (IRB) have pragmatically accepted that proxies may provide prior consent on behalf of the patient. Because proxies are frequently unavailable or unable to provide informed consent within the limited time window, potentially eligible patients may not always be recruited, and study progress suffers delays.⁷⁹⁻⁸¹

To allow essential emergency research initiatives, several alternatives are introduced to overcome this problem. It is accepted to start the study without prior patient or proxy informed consent with (deferred consent) and without (exception from consent, waiver of consent) the requirement to obtain informed consent for study continuation later.⁸²⁻⁸⁴ As in TBI management, there is substantial practice variation in used informed consent procedures, within and between EU Member States, and also globally.^{85,86} Variation in informed consent procedures complicates multicentre international studies because it may lead to inclusion problems, bias, and delay in institutional review board approval.^{87,88}

Institutional review boards

An institutional review board is usually appointed to review research protocols to ensure their compliance with ethical standards and national laws. IRBs have an essential role in (clinical) research to protect the dignity, fundamental rights, safety, and well-being of research participants and their formal approval is compulsory before a clinical study can start.⁸⁹ Although several international models exist to improve the harmonization of ethical principles, the functioning of IRBs is subject to national legislation and regulation, which refine their structure and function to better serve local needs and cultural preferences.^{90,91} Approval of research protocols submitted to IRBs is subject to these differences, which may complicate the conduct of international research.

Lack of procedural harmonization 'leads to a complex and uncertain framework for ethical review and for participant informed consent, resulting in numerous inefficiencies in observational studies'.⁹² Greater procedural harmonization is generally considered desirable, because it could improve quality and efficiency by decreasing costs, increasing statistical validity,⁹³⁻⁹⁵ optimizing data management⁹³, allowing choice of relevant and generalizable outcome variables,⁹⁵ promoting uniform product safety regulations⁹⁴, and minimizing waste of resources due to inefficiencies.⁹⁴

The efficiency of future research initiatives could be improved by assessing the procedural details, and quantifying the differences, problems and challenges regarding informed consent and IRB procedures. This could improve efficiency and quality of future research initiatives and thereby contribute to the evidence base on patient outcome and treatment cost-effectiveness. This might benefit future treatment decision-making and ultimately patient outcome.

AIM AND OUTLINE OF THIS THESIS

This thesis aims to describe and improve the acute treatment decision-making process and research practice in patients with s-TBI.

The following research questions will be answered to address this aim:

1. What is the outcome of patients with s-TBI?
2. What is the in-hospital healthcare consumption and how high are the in-hospital costs of patients with s-TBI?
3. What challenges are encountered in the acute treatment decision-making process in patients with s-TBI?
4. What difficulties are encountered in current TBI research practice?

Accordingly, this thesis consists of two parts.

Part I is about the challenges of the treatment decision-making process in patients with (s-)TBI and focusses on three factors considered to be important in this process: patient outcome, in-hospital healthcare consumption, and in-hospital costs. *Chapter 2* is a literature review of acute neurosurgical management in patient with very severe TBI (Glasgow Coma Scale 3-5), where several factors related to surgical intervention and patient outcome are investigated. *Chapter 3* is a systematic review and quality assessment of available literature on the in-hospital healthcare consumption and in-hospital costs of patients after sustaining s-TBI. *Chapter 4* presents functional and patient-reported outcome and in-hospital healthcare consumption and in-hospital costs of a retrospectively investigated regional cohort of patients with a traumatic acute subdural hematoma. *Chapter 5* investigates patient outcome, in-hospital healthcare consumption and in-hospital costs of TBI patients that were regionally included in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Chapter 6* summarizes the result of multiple focus group sessions and explores the difficulties of acute decision-making in s-TBI patients.

Part II analyses procedural difficulties in TBI research practice. It focusses on the process of institutional review board approval and the use of informed consent procedures in patients with TBI with an inability to provide informed consent. *Chapter 7* describes how the CENTER-TBI study protocol is reviewed and approved by 66 European institutional review boards. *Chapter 8* analyses the policy and practice regarding informed consent procedures in patients with an acute inability to provide

informed consent in the CENTER-TBI study. *Chapter 9* contains an extensive overview on informed consent procedures for emergency interventional research in patients with acute TBI and ischaemic stroke.

A summary and general discussion are included to complete this thesis.

REFERENCES:

1. Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16**(12): 987-1048.
2. Dewan MC, Rattani A, Gupta S, et al. Estimating the global incidence of traumatic brain injury. *J Neurosurg* 2018: 1-18.
3. Scholten AC, Haagsma JA, Panneman MJ, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. *PLoS One* 2014; **9**(10): e110905.
4. Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of Traumatic Brain Injury in Europe: A Living Systematic Review. *J Neurotrauma* 2018.
5. Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *The Lancet Public Health* 2016; **1**(2): e76-e83.
6. Peeters W, van den Brande R, Polinder S, et al. Epidemiology of traumatic brain injury in Europe. *Acta Neurochir (Wien)* 2015; **157**(10): 1683-96.
7. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 2019; **18**(10): 923-34.
8. Beck B, Gantner D, Cameron P, et al. Temporal trends in functional outcomes following severe traumatic brain injury: 2006-2015. *J Neurotrauma* 2017.
9. Fountain DM, Koliass AG, Lecky FE, et al. Survival Trends After Surgery for Acute Subdural Hematoma in Adults Over a 20-year Period. *Ann Surg* 2017; **265**(3): 590-6.
10. De Koning ME, Scheenen ME, Van Der Horn HJ, Spikman JM, Van Der Naalt J. From 'miserable minority' to the 'fortunate few': the other end of the mild traumatic brain injury spectrum. *Brain Inj* 2018; **32**(5): 540-3.
11. van der Naalt J, Timmerman ME, de Koning ME, et al. Early predictors of outcome after mild traumatic brain injury (UPFRONT): an observational cohort study. *Lancet Neurol* 2017; **16**(7): 532-40.
12. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil* 2010; **91**(11): 1637-40.
13. Maas AIR, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol* 2008; **7**(8): 728-41.
14. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. *The Lancet* 1974; **304**(7872): 81-4.
15. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: standing the test of time. *Lancet Neurol*; **13**(8): 844-54.
16. Saatman KE, Duhaime AC, Bullock R, Maas AI, Valadka A, Manley GT. Classification of traumatic brain injury for targeted therapies. *J Neurotrauma* 2008; **25**(7): 719-38.
17. Pearn ML, Niesman IR, Egawa J, et al. Pathophysiology Associated with Traumatic Brain Injury: Current Treatments and Potential Novel Therapeutics. *Cell Mol Neurobiol* 2017; **37**(4): 571-85.
18. Iaccarino C, Carretta A, Nicolosi F, Morselli C. Epidemiology of severe traumatic brain injury. *J Neurosurg Sci* 2018; **62**(5): 535-41.
19. The ATLS Subcommittee ACoSCoT, group tIAw. Advanced trauma life support (ATLS®): The ninth edition. *J Trauma Acute Care Surg* 2013; **74**(5): 1363-6.
20. Bullock MR, Chesnut R, Ghajar J, et al. Guidelines for the Surgical Management of Traumatic Brain Injury Author Group. *Neurosurgery* 2006; **58**(3): S2-vi-S-vi.
21. Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017; **16**(6): 452-64.
22. Picetti E, Rossi S, Abu-Zidan FM, et al. WSES consensus conference guidelines: monitoring and management of severe adult traumatic brain injury patients with polytrauma in the first 24 hours. *World J Emerg Surg* 2019; **14**: 53.
23. Hutchinson PJ, Koliass AG, Tajsic T, et al. Consensus statement from the International Consensus Meeting on the Role of Decompressive Craniectomy in the Management of Traumatic Brain Injury : Consensus statement. *Acta Neurochir (Wien)* 2019; **161**(7): 1261-74.
24. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* 2017; **80**(1): 6-15.
25. Kochanek PM, Tasker RC, Carney N, et al. Guidelines for the Management of Pediatric Severe Traumatic Brain Injury, Third Edition: Update of the Brain Trauma Foundation Guidelines, Executive Summary. *Neurosurgery* 2019; **84**(6): 1169-78.

26. Hodgkinson S, Pollit V, Sharpin C, Lecky F. Early management of head injury: summary of updated NICE guidance. *BMJ* 2014; **348**: g104.
27. Khormi YH, Gosadi I, Campbell S, Senthilselvan A, O'Kelly C, Zygum D. Adherence to Brain Trauma Foundation Guidelines for Management of Traumatic Brain Injury Patients and Its Effect on Outcomes: Systematic Review. *J Neurotrauma* 2018; **35**(13): 1407-18.
28. Cnossen MC, Scholten AC, Lingsma HF, et al. Adherence to Guidelines in Adult Patients with Traumatic Brain Injury: A Living Systematic Review. *J Neurotrauma* 2016.
29. Volovici V, Steyerberg EW, Cnossen MC, et al. Evolution of Evidence and Guideline Recommendations for the Medical Management of Severe Traumatic Brain Injury. *J Neurotrauma* 2019; **36**(22): 3183-9.
30. Bragge P, Synnot A, Maas AI, et al. A State-of-the-Science Overview of Randomized Controlled Trials Evaluating Acute Management of Moderate-to-Severe Traumatic Brain Injury. *J Neurotrauma* 2016; **33**(16): 1461-78.
31. Synnot A, Bragge P, Lunny C, et al. The currency, completeness and quality of systematic reviews of acute management of moderate to severe traumatic brain injury: A comprehensive evidence map. *PLoS One* 2018; **13**(6): e0198676.
32. Volovici V, Ercole A, Citerio G, et al. Variation in Guideline Implementation and Adherence Regarding Severe Traumatic Brain Injury Treatment: A CENTER-TBI Survey Study in Europe. *World Neurosurg* 2019; **125**: e515-e20.
33. Cnossen MC, Polinder S, Lingsma HF, et al. Variation in Structure and Process of Care in Traumatic Brain Injury: Provider Profiles of European Neurotrauma Centers Participating in the CENTER-TBI Study. *PLOS ONE* 2016; **11**(8): e0161367.
34. Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Crit Care* 2017; **21**(1): 233.
35. Huijben JA, Volovici V, Cnossen MC, et al. Variation in general supportive and preventive intensive care management of traumatic brain injury: a survey in 66 neurotrauma centers participating in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study. *Crit Care* 2018; **22**(1): 90.
36. van Essen TA, den Boogert HF, Cnossen MC, et al. Variation in neurosurgical management of traumatic brain injury: a survey in 68 centers participating in the CENTER-TBI study. *Acta Neurochir (Wien)* 2019; **161**(3): 435-49.
37. van Essen TA, de Ruiter GC, Kho KH, Peul WC. Neurosurgical Treatment Variation of Traumatic Brain Injury: Evaluation of Acute Subdural Hematoma Management in Belgium and The Netherlands. *J Neurotrauma* 2017; **34**(4): 881-9.
38. McIntyre A, Mehta S, Aubut J, Dijkers M, Teasell RW. Mortality among older adults after a traumatic brain injury: a meta-analysis. *Brain Inj* 2013; **27**(1): 31-40.
39. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic Review of the Prognosis After Mild Traumatic Brain Injury in Adults: Cognitive, Psychiatric, and Mortality Outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014; **95**(3, Supplement): S152-S73.
40. Einarsen CE, van der Naalt J, Jacobs B, et al. Moderate Traumatic Brain Injury: Clinical Characteristics and a Prognostic Model of 12-Month Outcome. *World Neurosurg* 2018; **114**: e1199-e210.
41. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *The Lancet* 2012; **380**(9847): 1088-98.
42. Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010; **27**(7): 1343-53.
43. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. *J Neurotrauma* 1998; **15**(8): 573-85.
44. McIntyre A, Mehta S, Janzen S, Aubut J, Teasell RW. A meta-analysis of functional outcome among older adults with traumatic brain injury. *NeuroRehabilitation* 2013; **32**(2): 409-14.
45. Krishnamoorthy V, Vavilala MS, Mills B, Rowhani-Rahbar A. Demographic and clinical risk factors associated with hospital mortality after isolated severe traumatic brain injury: a cohort study. *J Intensive Care* 2015; **3**(1): 46.
46. Andelic N, Howe EI, Hellstrom T, et al. Disability and quality of life 20 years after traumatic brain injury. *Brain Behav* 2018; **8**(7): e01018.
47. Forslund MV, Perrin PB, Roe C, et al. Global Outcome Trajectories up to 10 Years After Moderate to Severe Traumatic Brain Injury. *Front Neurol* 2019; **10**: 219.
48. Grauwmeijer E, Heijenbrok-Kal MH, Peppel LD, et al. Cognition, Health-Related Quality of Life, and Depression Ten Years after Moderate to Severe Traumatic Brain Injury: A Prospective Cohort Study. *J Neurotrauma* 2018; **35**(13): 1543-51.

49. Ruet A, Bayen E, Jourdan C, et al. A Detailed Overview of Long-Term Outcomes in Severe Traumatic Brain Injury Eight Years Post-injury. *Front Neurol* 2019; **10**: 120.
50. Moskowitz E, Melendez CI, Dunn J, et al. Long-Term Effects of Decompressive Craniectomy on Functional Outcomes after Traumatic Brain Injury: A Multicenter Study. *Am Surg* 2018; **84**(8): 1314-8.
51. Ventura T, Harrison-Felix C, Carlson N, et al. Mortality after discharge from acute care hospitalization with traumatic brain injury: a population-based study. *Arch Phys Med Rehabil* 2010; **91**(1): 20-9.
52. Wilson L, Stewart W, Dams-O'Connor K, et al. The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol* 2017; **16**(10): 813-25.
53. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Crit Care* 2016; **20**(1): 148.
54. Beck B, Gantner D, Cameron PA, et al. Temporal trends in functional outcomes after severe traumatic brain injury: 2006-2015. *J Neurotrauma* 2018; **35**(8): 1021-9.
55. Honeybul S, Janzen C, Kruger K, Ho KM. Decompressive craniectomy for severe traumatic brain injury: is life worth living? *J Neurosurg* 2013; **119**(6): 1566-75.
56. Chierigato A, Venditto A, Russo E, Martino C, Bini G. Aggressive medical management of acute traumatic subdural hematomas before emergency craniotomy in patients presenting with bilateral unreactive pupils. A cohort study. *Acta Neurochir (Wien)* 2017; **159**(8): 1553-9.
57. Faul M, Xu L, Wald M, Coronado V. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths, 2002-2006. *Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control* 2010: 1-74.
58. Garcia-Altes A, Perez K, Novoa A, et al. Spinal cord injury and traumatic brain injury: a cost-of-illness study. *Neuroepidemiology* 2012; **39**(2): 103-8.
59. Tuominen R, Joelsson P, Tenovu O. Treatment costs and productivity losses caused by traumatic brain injuries. *Brain Inj* 2012; **26**(13-14): 1697-701.
60. Humphreys I, Wood RL, Phillips CJ, Macey S. The costs of traumatic brain injury: a literature review. *Clinicoecon Outcomes Res* 2013; **5**: 281-7.
61. Gustavsson A, Svensson M, Jacobi F, et al. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**(10): 718-79.
62. Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jonsson B. The economic cost of brain disorders in Europe. *Eur J Neurol* 2012; **19**(1): 155-62.
63. Raj R, Bendel S, Reinikainen M, et al. Costs, outcome and cost-effectiveness of neurocritical care: a multi-center observational study. *Crit Care* 2018; **22**(1): 225.
64. Marin JR, Weaver MD, Mannix RC. Burden of USA hospital charges for traumatic brain injury. *Brain injury* 2017; **31**(1): 24-31.
65. Frontera JA, Egorova N, Moskowitz AJ. National trend in prevalence, cost, and discharge disposition after subdural hematoma from 1998-2007. *Crit Care* 2011; **39**(7): 1619-25.
66. Xu K, Soucat A, Kutzin J, et al. New perspectives on global health spending for universal health coverage Geneva: World Health Organization 2018; (WHO/HIS/HCF/HFWorkingPaper/18.2) Licence: CC BY-NC-SA 3.0 IGO: 1-44.
67. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. *JAMA* 2018; **319**(10): 1024-39.
68. De Minister van Volksgezondheid. Kamerbrief over beëindiging 'sluis' nivolumab per 1 maart 2016. 2016. <https://www.rijksoverheid.nl/documenten/kamerstukken/2016/01/28/kamerbrief-over-beeindiging-sluis-nivolumab-per-1-maart-2016>. Accessed on June 22, 2018.
69. Porter M, Lee T. The strategy that will fix health care. *Harv Bus Rev* 2013; **91**(10).
70. Te Ao B, Brown P, Tobias M, et al. Cost of traumatic brain injury in New Zealand: evidence from a population-based study. *Neurology* 2014; **83**(18): 1645-52.
71. Carroll LJ, Cassidy JD, Cancelliere C, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014; **95**(3 Suppl): S152-73.
72. Saltzherr TP, Goslings JC, Bakker FC, et al. Cost-effectiveness of trauma CT in the trauma room versus the radiology department: The REACT trial. *Eur Radiol* 2013; **23**(1): 148-55.
73. Alali AS, Burton K, Fowler RA, et al. Economic Evaluations in the Diagnosis and Management of Traumatic Brain Injury: A Systematic Review and Analysis of Quality. *Value Health* 2015; **18**(5): 721-34.
74. Lu J, Roe C, Aas E, et al. Traumatic brain injury: methodological approaches to estimate health and economic outcomes. *J Neurotrauma* 2013; **30**(23): 1925-33.

75. Porter ME. A strategy for health care reform-toward a value-based system. *N Engl J Med* 2009; **361**(2): 109-12.
76. Grady C, Cummings SR, Rowbotham MC, McConnell MV, Ashley EA, Kang G. Informed Consent. *N Engl J Med* 2017; **376**(9): 856-67.
77. World Medical Association. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects 2018. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>. Accessed July 7, 2020.
78. Wolf SM, Clayton EW, Lawrenz F. The Past, Present, and Future of Informed Consent in Research and Translational Medicine. *The Journal of Law, Medicine & Ethics* 2018; **46**(1): 7-11.
79. Shalowitz DI, Garrett-Mayer E, Wendler D. The accuracy of surrogate decision makers: a systematic review. *Arch Intern Med* 2006; **166**(5): 493-7.
80. Wrigley A. Proxy consent: moral authority misconceived. *J Med Ethics* 2007; **33**(9): 527-31.
81. Cirolidi M, Cariou A, Adrie C, et al. Ability of family members to predict patient's consent to critical care research. *Intensive Care Med* 2007; **33**(5): 807-13.
82. Jansen TC, Kompanje EJ, Bakker J. Deferred proxy consent in emergency critical care research: ethically valid and practically feasible. *Critical Care Med* 2009; **37**(1 Suppl): S65-8.
83. European Commission Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC OJ L158:1–76: 2014.
84. Food and Drug Administration. Department of Health and Human Services. Protection of Human Subjects; Informed Consent and Waiver of Informed Consent Requirements in Certain Emergency Research; Final Rules. Fed Regist 1996; Volume 61, Number 192: 51498–531.
85. Kompanje EJ, Maas AI, Menon DK, Kesecioglu J. Medical research in emergency research in the European Union member states: tensions between theory and practice. *Intensive Care Med* 2014; **40**(4): 496-503.
86. van Belle G, Mentzelopoulos SD, Aufderheide T, May S, Nichol G. International variation in policies and practices related to informed consent in acute cardiovascular research: Results from a 44 country survey. *Resuscitation* 2015; **91**: 76-83.
87. Burns KE, Zubrinich C, Tan W, et al. Research recruitment practices and critically ill patients. A multicenter, cross-sectional study (the Consent Study). *Am J Respir Crit Care Med* 2013; **187**(11): 1212-8.
88. Ecarnot F, Quenot JP, Besch G, Piton G. Ethical challenges involved in obtaining consent for research from patients hospitalized in the intensive care unit. *Ann Transl Med* 2017; **5**(Suppl 4): S41.
89. Steering Committee on Bioethics. Guide for Research Ethics Committee Members. 2012. https://www.coe.int/t/dg3/healthbioethic/activities/o2_biomedical_research_en/Guide/Guide_EN.pdf. Accessed on July 7, 2020
90. World Health Organization. Standards and operational guidance for ethics review of health-related research with human participants. 2011.
91. Emanuel E CR, Lie R, et al. The Oxford Textbook of Clinical Research Ethics. Oxford. *Oxford University Press*; Reprint edition 2011.
92. Urushihara H, Parmenter L, Tashiro S, Matsui K, Dreyer N. Bridge the gap: The need for harmonized regulatory and ethical standards for postmarketing observational studies. *Pharmacoepidemiol Drug Saf* 2017; **26**(11): 1299-306.
93. Bowles KH, Potashnik S, Ratcliffe SJ, et al. Conducting research using the electronic health record across multi-hospital systems: semantic harmonization implications for administrators. *J Nurs Adm* 2013; **43**(6): 355-60.
94. Aledort LM. Harmonization of clinical trial guidelines for assessing the risk of inhibitor development in hemophilia A treatment. *J Thromb Haemost* 2011; **9**(3): 423-7.
95. Oliver Daly J. Harmonisation of research outcomes for meaningful translation to practice: The role of Core Outcome Sets and the CROWN Initiative. *Aust N Z J Obstet Gynaecol* 2018; **58**(1): 15-6.