Challenges encountered in surgical traumatic brain injury research: A need for methodological improvement of future studies

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Challenges Encountered in Surgical Traumatic Brain Injury Research: A Need for Methodological Improvement of Future Studies

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■ BACKGROUND: **Investigating neurosurgical interventions for traumatic brain injury (TBI) involves complex methodological and practical challenges. In the present report, we have provided an overview of the current state of neurosurgical TBI research and discussed the key challenges and possible solutions.**

■ METHODS: **The content of our report was based on an extensive literature review and personal knowledge and expert opinions of senior neurosurgeon researchers and epidemiologists.**

■ RESULTS: **Current best practice research strategies include randomized controlled trials (RCTs) and comparative effectiveness research. The performance of RCTs has been complicated by the heterogeneity of TBI patient populations with the associated sample size requirements, the traditional eminence-based neurosurgical culture, inadequate research budgets, and the often acutely life-threatening setting of severe TBI. Statistical corrections can mitigate the effects of heterogeneity, and increasing awareness of clinical equipoise and informed consent alternatives can improve trial efficiency. The substantial confounding by indication, which limits the interpretability of observational research, can be circumvented by using an instrumental variable analysis. Traditional TBI outcome measures remain relevant but do not adequately capture the subtleties of well-being, suggesting a need for multidimensional approaches to outcome assessments.**

■ CONCLUSIONS: **In settings in which traditional RCTs are difficult to conduct and substantial confounding by indication can be present, observational studies using an instrumental variable analysis and "pragmatic" RCTs are promising alternatives. Embedding TBI research into standard clinical practice should be more frequently considered but will require fundamental modifications to the current health care system. Finally, multimodality outcome assessment will be key to improving future surgical and nonsurgical TBI research.**

INTRODUCTION

Traumatic brain injury (TBI), defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force,"[1] is probably as old as humankind. Its neurosurgical treatment with burr holes or trepanation is believed to be the oldest surgical procedure, with

Key words
- Methodology
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- Traumatic brain injury

Abbreviations and Acronyms
ADAPT: Approaches and Decisions in Acute Pediatric Traumatic Brain Injury Trial
CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury
CER: Comparative effectiveness research
CREACTIVE: Collaborative research on acute traumatic brain injury in intensive care medicine in Europe
CRASH: Corticosteroid randomisation after significant head injury
GOS: Glasgow outcome scale
GOS-E: Glasgow outcome scale — extended
IMPACT: International mission on prognosis and analysis of clinical trials in traumatic brain injury
Net-Qure: Neurotraumatology quality registry
RCT: Randomized controlled trial
RESET-ASDH: Randomized evaluation of surgery in elderly with a traumatic acute subdural hematoma
STITCH-trauma: Surgical trial in traumatic intracerebral haemorrhage
TBI: Traumatic brain injury
TRACK-TBI: Transforming research and clinical knowledge in traumatic brain injury

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archaeological evidence dating back to the Neolithic period.[2] Over the centuries, several important technical advancements—from the tumi knife in ancient Peru to high-speed cranial drills—and our increasing knowledge of neuroanatomy and neurophysiology have aided in the modernization of these ancient techniques.[2] Together with the evolution of trauma care systems, advancements in neurocritical care, and the widespread introduction of computed tomography scanners and intracranial pressure monitors, the mortality rates for patients with severe TBI have decreased dramatically from >80% in the 1940s to 20%–35% in modern well-resourced hospitals.[3,4] However, even today, TBI remains the greatest cause of death and severe disability for young adults, and its incidence has been rapidly increasing among the elderly and in developing countries.[5]

In the pursuit of improving care for TBI patients, randomized controlled trials (RCTs) have been considered the reference standard for evidence generation. However, many RCTs of TBI have failed to convincingly demonstrate efficacy despite strong experimental evidence of efficacy.[6,7] In particular, nearly all trials investigating the efficacy of neuroprotective agents showed no benefit for the agent under investigation. In addition, many surgical interventions for TBI for which uncertainty exists cannot be readily assessed in RCTs. An alternative approach to generate evidence is provided by comparative effectiveness research (CER) using observational data to evaluate differences in care and outcomes, thus turning natural variability into an asset. The large regional differences in TBI management and outcomes have made CER a welcome complementary approach to clinical trials.

Investigating surgical interventions involves additional challenges compared with nonsurgical medical research because of the complexity of perioperative procedures, surgical learning curves, patient and surgeon equipoise, blinding issues, and cultural or psychological barriers toward the use of randomization.[8,9] Initiatives for improving surgical research such as the IDEAL (idea, development, exploration, assessment, long-term study) framework have addressed some of these issues.[10] However, research on neurosurgical interventions for TBI poses specific challenges related to the heterogeneity of the population, acuteness of the situation, limited patient information in the absence of proxies, and the complex pathophysiological mechanisms of brain injury.[11] In the present report, we have provided an overview of research on neurosurgical interventions for TBI and discussed the critical methodological and design challenges and possible solutions.

METHODS

The content of our report was determined by an extensive nonsystematic review of the literature and the personal knowledge and expert opinions of senior neurosurgeon researchers and epidemiologists.

RESULTS

Evolution of Observational Studies

The advent of the Glasgow coma scale in 1974 and the Glasgow outcome scale (GOS) in 1976, later succeeded by its extended version (GOS-E), laid the foundation for modern TBI research by allowing for the quantification of TBI severity and standardizing the outcome assessments, respectively.[4,12-14] Shortly after these key publications, British and Dutch neurosurgeons pioneered prospective data collections.[15] Their efforts resulted in the recognition of patient age, the Glasgow coma scale score, and pupillary reactivity as the main predictors of outcome in patients with TBI. Later, the Traumatic Coma Data Bank in the United States added hypoxia and hypotension as determinants of the outcome.[16] These, and other developments, inspired the drafting of evidence-based guidelines in 1996, led by the Brain Trauma Foundation, regarding the management of severe TBI.[17] Subsequent work by the European brain injury consortium demonstrated the predictive value of the evolution of computed tomography lesions and traumatic subarachnoid hemorrhage.[18,19] To date, the largest prospective data collection for TBI has been the CENTER-TBI (collaborative European neurotrauma effectiveness research in traumatic brain injury) project, which was conducted in 65 hospitals across Europe and Israel.[20] The main results of the CENTER-TBI core study cohort have recently been reported, and many more reports have already followed.[21] Comparable largescale observational TBI research initiatives include the North American TRACK-TBI (transforming research and clinical knowledge in traumatic brain injury) and ADAPT (approaches and decisions in acute pediatric traumatic brain injury trial), the European CREACTIVE (collaborative research on acute traumatic brain injury in intensive care medicine in Europe), and the Dutch Net-Qure (neurotraumatology quality registry) projects.[22-25] The critical issue enabling meaningful analysis of any observational study is that the study must be large enough. Only too often has clinical practice been influenced by data from case reports, case series, and small observational studies. A recent example is the increasing use of cisternostomy for the treatment of an elevated intracranial pressure resulting from positive case report findings and some small cohorts.[26,27] As such, the strength of the CENTER-TBI and analogous state-of-the-art observational studies lies to a great extent in their size and generalizability to real world practice.

Landmark Neurosurgical RCTs

Although most studies used to be observational evaluations using historical controls, multicenter RCTs of TBI began in the mid-1980s.[6] Compared with other medical fields, the prevalence of neurosurgical RCTs has been rather low, with <1% of studies reported in leading neurosurgical journals being RCTs,[28] probably related to the unique challenges inherent to the field. Nonetheless, in the quest for evidence-based neurosurgery,[29] 6 landmark RCTs have been pivotal and have been summarized in **Table 1**.[30-35] The common thread of these RCTs has been their focus on whether the interventions actually work in clinical reality, that is, do they work (effectiveness) instead of can they work (efficacy). Although the latter is often obvious for neurosurgical interventions for TBI, the success of these RCTs lies in their focus on clinical relevance.

Remaining Uncertainties—The Need for Improved Research

Although much progress has been made since the 1970s, the TBI research apparatus has been unable to alleviate—or even substantially reduce—the uncertainties in neurosurgical decision-making for TBI. Thus, the question remains whether a particular TBI patient will benefit from neurosurgical intervention in terms

Table 1. Key Neurosurgical Trials of TBI

Landmark RCT	Patients	Intervention	Controls	Outcome	Main Findings	Important Critiques
Large vs. limited DC[30]	Patients with severe TBI and refractory intracranial hypertension caused by unilateral massive contusion and/or swelling	STC with unilateral frontotemporoparietal bone flap (12 × 15 cm)	LC with smaller temporoparietal bone flap (6 × 8 cm)	GOS at 6 months	Higher rate of favorable outcomes in STC group than in LC group	Less relevant to regions where STC was already standard of care
DECRA[31]	Patients with severe diffuse TBI and refractory intracranial hypertension (>20 mm Hg for >15 minutes)	Bilateral frontotemporoparietal DC	Standard ICU care	GOS-E at 6 months	Higher rate of unfavorable outcome (death, VS, or SD) in DC group; no significant difference after post hoc adjustment for baseline pupillary reactivity	Imbalances in baseline characteristics and revision of primary outcome measure during trial
RESCUE-ICP[32]	Patients with TBI and refractory elevated ICP (>25 mm Hg for 1—12 hours)	DC (either large unilateral or bilateral frontotemporoparietal)	Ongoing standard medical ICU care	GOS-E at 6 months (proportional odds analysis)	Lower mortality and higher rates of VS, LSD, and USD in DC group (descriptively reported because proportional odds assumption violated)	Relatively large proportion in medical group received DC (37.2%); 10 patients excluded from analysis because of withdrawal or lack of valid consent
STITCH-Trauma[33]	Patients within 48 hours of TBI and 1 or 2 TICH >10 mL on CT for whom treating neurosurgeon was in equipoise	Early surgery	Initial conservative treatment	GOS-E at 6 months (dichotomized analysis)	Halted prematurely by funding agencies owing to concerns regarding insufficient patient recruitment in the UK; more favorable outcomes (although not significant) in early surgery group	Lack of power owing to low numbers
RESCUE-ASDH[34]	TBI patients requiring surgery to evacuate an ASDH	DC (leaving out bone flap)	Replacing bone flap	GOS-E at 12 months	Results awaited	Results awaited
BEST-TRIP[35]	Patients with severe TBI treated in ICU in Bolivia or Ecuador	ICP monitoring with guideline-based management focused on maintaining ICP at ≤20 mm Hg	Treatment determined imaging and clinical examination findings	Composite of survival time, impaired consciousness, functional status at 3 and 6 months, and neuropsychological status at 6 months	ICP-guided therapy was not superior to treatment determined by imaging and clinical examination findings	Trial setting in developing countries in Latin America with suboptimal perihospital facilities, relatively long duration of increased ICP in ICP monitored group

TBI, traumatic brain injury; RCTs, randomized controlled trials; DC, decompressive craniectomy; STC, standard trauma craniectomy; LC, limited craniectomy; GOS, Glasgow outcome scale; DECRA, decompressive craniectomy in patients with severe traumatic brain injury; ICU, intensive care unit; GOS-E, Glasgow outcome scale — extended; VS, vegetative state; SD, severe disability; RESCUE-ICP, randomised evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure; LSD, lower severe disability; USD, upper severe disability; STITCH-trauma, surgical trial in traumatic intracerebral haemorrhage; TICH, traumatic intracerebral hemorrhage; CT, computed tomography; RESCUE-ASDH, randomised evaluation of surgery with craniectomy for patients undergoing evacuation of acute subdural haematoma; ASDH, acute subdural hematoma; BEST-TRIP, benchmark evidence from South American trials: treatment of intracranial pressure; ICP, intracranial pressure.

of survival, neurological outcomes, and quality of life. An additional question is what type of surgical intervention (e.g., intraparenchymal/intraventricular pressure monitor, hematoma evacuation, decompressive craniectomy) should be preferred.

The current Brain Trauma Foundation guidelines are still predominantly based on low-quality evidence, and the scarcely available level I evidence lacks generalizability.[36,37] Moreover, prognostic models such as the IMPACT (international mission on prognosis and analysis of clinical trials in traumatic brain injury)[38] and the Medical Research Council CRASH (corticosteroid randomisation after significant head injury)[39] models allow for predictions on the population level, but do not provide adequate guidance for surgical decisions for individual patients. Thus, guideline adherence has been low, and large treatment variations between centers and even between neurosurgeons within centers continue to exist.[40,41] Hence, room for improvement is present in the methodology, design, and analysis of neurosurgical TBI studies.

Managing Heterogeneity

One of the main challenges is the heterogeneity of TBI populations with respect to the severity and baseline prognosis, which is often believed to preclude the translation of promising treatments into clinical practice.[42] Estimating an overall treatment effect in a heterogeneous population requires a very large sample size to compensate for the heterogeneity.[43] Such sample sizes are often not feasible, as demonstrated by the relatively frequent (26.6%) premature discontinuation of neurosurgical RCTs, which has mainly resulted from insufficient patient recruitment.[44] It is now generally believed that the vast majority of trials of TBI has been grossly underpowered.[45] However, even when large sample sizes can be obtained, the results can be difficult to interpret because they are likely determined from averaged heterogeneous treatment effects in undefined subgroups. Opposite effects between subgroups can even cancel each other out, leading to an absent net effect.[46] A potential solution in line with the current trend toward precision medicine would be to target highly specific patients, albeit at the cost of reduced external validity. Another solution advocated by the IMPACT recommendations for the design and analysis of TBI trials is to use broad inclusion criteria with subsequent covariate adjustment for prespecified baseline variables to mitigate the effects of heterogeneity.[47] This practice, if followed by subsequent subgroup analyses, which should be predefined to prevent chance findings, could reduce sample size requirements and also facilitate rapid trial recruitment and enhance the generalizability of the results.[47]

Recent developments in the field of big data have sparked the hope of overcoming the challenges related to heterogeneity.[4] Although it is true that a certain quantity of data is required for meaningful statistical analysis, extremely large datasets tend to result in less detailed and lower quality data. The statement that "big data is not better, it's just bigger"[48] contains a significant kernel of truth and should temper expectations regarding the revolutionary potential of big data for TBI research.

Neurosurgical Exceptionalism and Clinical Equipoise

Neurosurgical TBI research can also be complicated by the idea that commonly used research methods from other medical disciplines are unsuitable owing to the unique nature of neurosurgery and surgery, an idea referred to as "surgical exceptionalism."[49] Neurosurgical training embodies the traditional concept of eminence-based medicine,[9] placing great value on lessons taught by mentors and does not catalyze a transition to an evidence-seeking culture. Thus, randomizing TBI patients could seem unnatural to some neurosurgeons because they do not have doubts about the best treatment for a specific patient, despite the lack of evidence. This has been especially evident in trials with clinical equipoise as an explicit inclusion criterion, such as the prematurely halted STITCH-trauma trial (surgical trial in traumatic intracerebral haemorrhage).[33] Although the definition of clinical equipoise was introduced in 1987 as "a state of genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment,"[50] it is still often misinterpreted as doubt or uncertainty, which are terms neurosurgeons tend to avoid in their decisions for TBI patients. Increasing understanding about the concept of clinical equipoise and improving methodological expertise of neurosurgeons might avoid unnecessary trial failures.

Research Budgets and Pragmatic RCTs

The COVID-19 (coronavirus disease 2019) vaccine race has demonstrated how fast research can proceed when funding agencies join forces and scientists are provided with almost inexhaustible resources. However, the daily reality for most research fields—including TBI—is that the lack of resources (e.g., research staff, equipment, infrastructure) impedes the conduct of clinical studies, especially in low and middle income countries.[51] A potential solution could be to integrate research more into standard clinical practice using routinely collected data and, thereby, minimize expenses. Thus, the use of pragmatic RCTs aims to determine the effectiveness of treatments in the real world and are designed to balance the internal validity of RCTs with external generalizability and clinical relevance.[52,53] The multicenter pragmatic RESET-ASDH (randomized evaluation of surgery in elderly with a traumatic acute subdural hematoma) trial to compare early surgery with initial conservative management for elderly patients with an acute subdural hematoma has recently started patient inclusion.[54] The widespread clinical implementation of such embedded research projects will, however, require fundamental modifications to the current healthcare system.

Confounding by Indication

Nonexperimental CER is considered an elegant method to circumvent the difficulties of performing RCTs, because it exploits existing treatment variability for comparisons in real-world conditions. Thus, neurosurgical strategies can be linked to outcome variations while controlling for case-mix.[55,56] Political interest in CER has stemmed from its potential to improve the efficiency of healthcare by providing cost-effective alternatives to RCTs.[57] A major limitation of observational CER, however, remains the inability to establish definite causality from nonrandomized data. An important reason for this is confounding by indication, which occurs when patients receiving an intervention are not selected randomly, but treatment decisions are based on other (uncontrolled) factors. Thus, when severe TBI patients who have

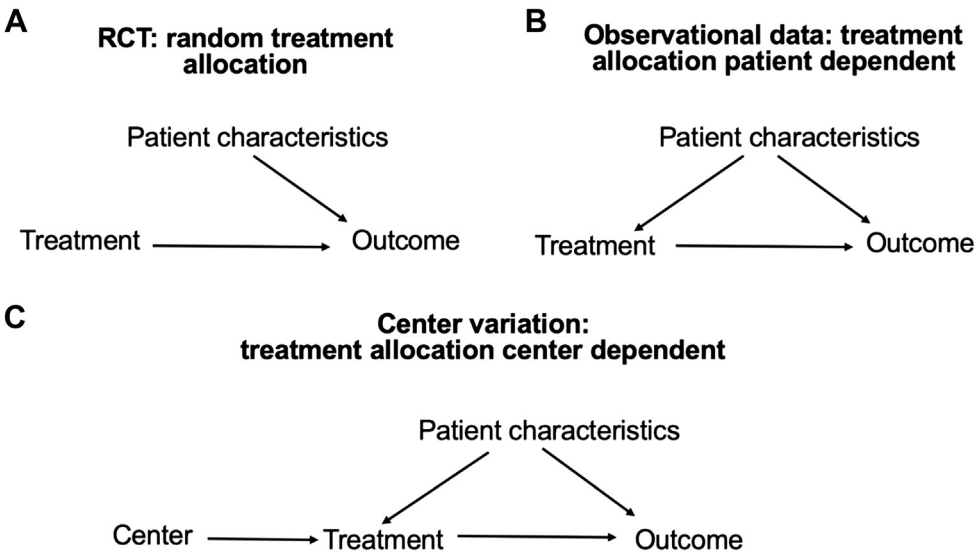

Figure 1. Instrumental variable analysis to reduce confounding by indication compared with randomization in randomized controlled trials and traditional analysis in observational studies. Randomization separates treatments from patient characteristics and thereby ensures no confounding when estimating the effects of treatment on outcome (**A**). Effect estimation in observational data relies on statistical correction (e.g., regression modeling or propensity scores) but unmeasured confounding could remain a problem (**B**). In instrumental variable analysis (**C**), the instrumental variable center "allocates" patients to be exposed to different likelihoods of receiving treatment. In analyzing treatment as a center characteristic instead of a patient characteristic, the intervention is again independent of the patient characteristics (no *arrow* from patient characteristics to center, just as with randomization).

been perceived as salvageable tend to be selected for surgery and surgical treatment is more frequently withheld for patients with a poorer presumed prognosis, the comparisons will be skewed in favor of surgical intervention.[58] The traditional methods to control for confounding in observational studies can be used but will fall short when certain confounders remain unmeasured.[59] In such cases, an instrumental variable analysis can be applied, which has also been called "pseudorandomization," because it uses an instrumental variable—a factor influencing the chance of receiving a treatment that is unrelated to patient characteristics or prognosis—to mimic randomization in observational data (Figure 1). This method can control for both measured and unmeasured confounding; however, the interpretation of the results is complex and their validity depends on strict assumptions.[60,61]

Outcome Measures

The GOS and GOS-E are the most commonly used outcome measures in TBI studies and enable outcome comparisons across studies.[62] However, the GOS remains a relatively crude metric of functional outcome that does not include essential subtleties of well-being. Hence, recognition has been increasing for the need for multidimensional approaches to outcome assessments after TBI. Whether this should be in the form of targeted assessments or by creating a composite score is currently being explored. Using a standardized set of outcome measures, as proposed by the common data elements for TBI,[6] will increase comparability and facilitate pooling of future data. Thus, in-hospital and long-term TBI-related costs should be included because they represent a substantial health care and economic burden but are often inadequately reported.[63-65]

A common method of reporting results is to dichotomize an ordinal or continuous outcome scale into a binary favorable versus unfavorable outcome. This practice is questionable for 2 reasons. First, it can be argued that an outcome considered unfavorable will not necessarily be unacceptable to patients and their proxies and vice versa.[11] Establishing a consensus regarding acceptable and unacceptable outcomes, however, has remained very challenging owing to the multidimensional nature of outcomes and the nonfixed preferences of patients and proxies, as described in the disability paradox.[66] Second, reducing a continuous or ordinal measure to a binary scale will discard valuable information from a clinical and statistical perspective.[67] Although power calculations typically assume that every patient's a priori risk of an unfavorable outcome is ~50%, many patients will not have a realistic opportunity to cross the dichotomization threshold because they will be either too severely or too mildly injured and will, thus, not contribute data to the analysis, resulting in lower statistical power. One solution for this is prognostic targeting (i.e., only including patients with a certain intermediate risk estimate)[68]; however, this is likely to slow recruitment rates.[69] Another solution is to replace dichotomized analyses with ordinal statistical methods. In the

sliding dichotomy model, patients are compared with their own predicted outcome based on a robust prediction model with the intent to detect better than expected outcomes.[47] A second approach is the proportional odds model, also referred to as "shift analysis,"[70] which appreciates changes across the full range of the outcome measure by considering every method in which an ordinal scale can be dichotomized.[71,72] The choice between sliding dichotomy, which is more intuitively interpretable, and the proportional odds model, which is statistically more efficient, remains a value judgment.[47] The IMPACT recommendations have underscored that using an ordinal statistical approach, together with broad inclusion criteria and subsequent covariate adjustment, can yield a 40% increase in statistical efficiency.[47]

Informed Consent

Clinicians and researchers are generally expected to obtain written informed consent from patients or proxies before initiating study-related procedures and should respect patients (and proxies) fundamental right to refuse study participation.[73,74] In acute neurosurgical TBI studies, obtaining patient or proxy consent can be challenging owing to the short therapeutic windows, impaired decision-making capacity of many patients and proxies, and/or the absence of proxies in the acute moment.[75] Excluding patients from whom obtaining informed consent is not feasible will slow recruitment rates and cause a selection bias.[76] To address this problem, informed consent alternatives such as "deferred consent," which allows study procedures to start without prior patient or proxy consent, have been increasingly used in neurosurgical, neurological, and endovascular stroke trials.[34,77,78] To continue study-related activities after deferred consent, obtaining patient or proxy consent as soon as possible is still required. When it has been deemed impossible to obtain patient or proxy consent at any point, the alternative of a "waiver of consent" can be used. Although both alternatives are ethically permissible, socially acceptable, and generally compliant with regulations, they have remained underused in TBI research.[79] Increasing awareness about these valid consent options could improve the efficiency and quality of future studies.

DISCUSSION

Several methodological and practical challenges complicate the conduct of neurosurgical TBI research. These include the heterogeneity of the populations, inefficient analysis of relatively crude outcome measures, the traditionally eminence-based neurosurgical culture, inadequate research budgets, and difficulties related to obtaining patient informed consent in an emergency situation. In this setting, in which traditional RCTs are difficult to conduct and substantial confounding by indication could be present, observational studies using an instrumental variable analysis and "pragmatic RCTs" are promising alternatives. Improving methodological expertise and increasing awareness about the concept of clinical equipoise in the neurosurgical community could benefit future trials. Also, TBI trialists should be aware of the available informed consent alternatives to optimize patient recruitment. Embedding TBI research into standard clinical practice could reduce expenses and lower the threshold for study participation, although it will require fundamental modifications to the current healthcare system. Conventional outcome measures can be analyzed more efficiently using ordinal statistical analysis methods such as sliding dichotomy or proportional odds models. Also, our research group is currently involved in international collaborations toward multimodality outcome assessments after TBI, ranging from neurological outcomes and quality of life to societal participation. Because TBI affects all aspects of life, we believe this is a key development toward improving future surgical and nonsurgical TBI research. Finally, we encourage neurosurgical TBI researchers—being early pioneers—to proceed in their endeavor toward evidence-based neurosurgery.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ranjit D. Singh: Conceptualization, Methodology, Writing — original draft. **Jeroen T.J.M. van Dijck:** Conceptualization, Methodology, Writing — original draft. **Andrew I.R. Maas:** Conceptualization, Methodology, Writing — review & editing, Supervision. **Wilco C. Peul:** Conceptualization, Methodology, Writing — review & editing, Supervision. **Thomas A. van Essen:** Conceptualization, Methodology, Writing — review & editing.

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