Traumatic brain injury

integrated approaches to improve prevention, clinical care, and research

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Executive summary

A concerted effort to tackle the global health problem posed by traumatic brain injury (TBI) is long overdue. TBI is a public health challenge of vast, but insufficiently recognised, proportions. Globally, TBI is the leading cause of mortality in young adults and a major cause of death and disability across all ages, with the substantial burden of disability and death occurring in low-income and middle-income countries (LMICs). This Commission for *The Lancet Neurology* aims to provide information and expert recommendations on TBI care and research to a broad audience of policy makers, funders, and patient representatives, as well as health-care professionals and researchers. The Commission addresses current and past deficiencies in TBI prevention, clinical care, and research, outlines key requirements to advance knowledge and care in TBI, and suggests new paths for progress in the field.

Worldwide, about 50 million people have a TBI each year, and it is estimated that about half the world's population will have one or more TBIs over their lifetime. In the European Union (28 Member States), approximately 1·5 million people are admitted to hospital and 57 000 die each year because of TBI. In LMICs, TBI is an even greater problem. In India, for example, nearly one death from TBI is estimated to occur every 3 minutes. The epidemiology of TBI is changing: in high-income countries (HICs), the number of elderly people with TBI is increasing, mainly due to falls, while in LMICs, the burden of TBI from road traffic incidents is increasing. TBI costs the global economy approximately $US400 billion annually.

Reported incidence and mortality rates for TBI, as well as information regarding the economic impact of TBI, are often incomplete and vary between countries and continents. Variations in data collection and reporting might contribute to these reported differences. Accurate epidemiological monitoring and robust health-economic data collection are important for informing health-care policy and prevention programmes, and require improvement. Highly developed and coordinated systems of care are crucial for management of patients with TBI. However, in practice, implementation of such frameworks varies greatly and disconnects exist in the chain of care. Optimisation of systems of care should be high on the policy agenda and could yield substantial gains both in terms of outcome to patients and costs to society.

TBI is a complex condition, and strong evidence to support treatment guidelines and recommendations is scarce. Most multicentre clinical trials of medical and surgical interventions

have failed to show efficacy, despite promising preclinical results. At the bedside, treatment strategies are generally based on guidelines that promote a one-size-fits-all approach and are insufficiently targeted to the needs of individual patients. Attempts to individualise treatment are hampered by the diversity of TBI, and by the use of simplistic methods for characterising its initial type and severity. Advances in genomics, blood biomarkers, advanced magnetic resonance imaging (MRI), and pathophysiological monitoring, combined with informatics to integrate data from multiple sources, offer new research avenues to improve disease characterisation and monitoring of disease evolution. These tools can also aid understanding of disease mechanisms and facilitate targeted treatment strategies for individual patients.

Evaluating the effectiveness of treatment and care processes depends on accurate quantification of outcomes. In practice, however, the use of simplistic methods hinders efforts to quantify outcomes after TBI of all severities. Development and validation of multidimensional approaches are essential to improve measurement of clinical outcomes of TBI, both for research and patient care. In particular, we need need to find better ways to characterise the currently underdiagnosed risk of long-term disabling sequelae in patients with relatively mild injuries.

Prognostic models are important to help clinicians provide reliable information to patients and relatives, and to facilitate comparative audit of care between centres and countries. There is an urgent need for further development, validation, and implementation of prognostic models in TBI, particularly for less severe TBI.

This multitude of challenges in TBI—encompassing systems of care, clinical management, and research strategy—demands novel approaches to the generation of new evidence and its implementation in clinical practice. Comparative effectiveness research (CER) offers opportunities to capitalise on the diversity of TBI and systems of care and enables assessment of therapies in real-world conditions; high-quality CER studies can provide strong evidence to support guideline recommendations. The global challenges posed by TBI necessitate global collaborations and a change in research culture to endorse broad data sharing.

This Commission covers a range of topics that need to be addressed to confront the global burden of TBI and reduce its effects on individuals and society: epidemiology (section 1); health economics (section 2); prevention (section 3); systems of care (section 4); clinical management (section 5); initial characterisation of TBI (section 6); outcome assessment (section 7); prognosis (section 8); and new directions for acquiring and implementing evidence (section 9). Table 1 summarises key messages from the Commission and provides recommendations to advance clinical care and research in TBI.

We must increase awareness of the scale of the challenge posed by TBI. If we are to tackle the individual and societal burden of TBI, these efforts need to go beyond a clinical and research audience and address the public, politicians, and other stakeholders. We need to develop and implement policies for better prevention and systems of care in order to improve outcomes for individuals with TBI. We also need a commitment to substantial long-term investment in TBI research across a range of disciplines so that we can determine best practice and facilitate individualised management strategies. To achieve these aims, we need a combination of innovative research methods and global collaboration, and ways to effectively translate progress in basic and clinical research into clinical practice and public health policy.

Table 1: Key messages and recommendations

Key messages	Recommendations	Read more
Worldwide, traumatic brain injury (TBI) is a leading cause of injury-related death and disability, and a huge burden to patients and their families.	Concerted efforts to address this vast global health problem should focus on policies aimed at reducing the burden and impact of TBI, through better prevention, improved access to care, and promotion of clinical research to improve treatment standards.	Sections 1, 3, 4, 9
In low-income and middle-income countries, the incidence of TBI due to traffic incidents is increasing, while in high-income countries, TBI increasingly affects elderly people, mostly due to falls. Methodological variations, however, confound comparisons of epidemiological patterns of TBI between regions, countries, and continents.	An international consensus is needed on definitions and standardised epidemiological monitoring of TBI, to allow accurate measurement of incidence, prevalence, and mortality, and comparison of rates of access to community, hospital, and institutional care.	Sections 1, 4
TBI might represent an important modifiable risk factor for epilepsy, stroke, and late-life neurodegenerative disease.	Studies are needed, in children and adults, to better understand links between TBI of all severities and an increased risk of these diseases.	Section 1
TBI results in substantial health-care and societal costs.	More effective strategies for TBI prevention are vital, and could	Section 2

	deliver cost savings that help to fund research and improved access to health care for TBI.	
Repetitive concussions that occur before recovery from an initial concussion can be associated with more severe symptoms and more prolonged recovery than a single injury of similar severity; therefore, any risk of an early second injury after even a mild TBI should be avoided.	Professional sporting organisations should set an example for children and amateur athletes by immediately removing from play anyone with a suspected concussion.	Section 3
Access to health care is often inconsistent between centres, regions, and countries, especially for acute and postacute care.	Health-care policies should aim to improve access to acute and postacute care to reduce the effects of TBI on patients, families, and society.	Section 4
Evidence underpinning guidelines for medical and surgical interventions and rehabilitation for TBI is weak.	Increased funding is needed to develop robust evidence to inform medical, surgical, and rehabilitation interventions, and hence improve outcomes for patients with TBI.	Section 5
Methods of diagnosis and classification of patients with TBI are inadequate to permit targeting of current and new therapies to the needs of individual patients.	Funding bodies should implement targeted funding calls for research that improves the precision of diagnosis, classification, and characterisation of TBI using multidomain approaches.	Section 6
Trauma disturbs the brain in complex ways, affecting multiple outcome domains. Refined outcome assessments could guide improved clinical management and support high-quality research.	Targeted funding calls are needed to facilitate the development and validation of multidimensional outcome constructs that quantify the overall burden of disability from TBI.	Section 7
A validated set of quality indicators is essential for the benchmarking of quality of care, but none exists for TBI.	Funding bodies should stimulate the development of a set of quality indicators for TBI that includes structure, process, and outcome metrics.	Section 8

Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for comparative effectiveness research to improve the strength of evidence.	Comparative effectiveness research should be funded to identify best practices and to improve the level of evidence for systems of care and diagnostic and therapeutic interventions.	Section 9
Coordinated research efforts on a global basis are needed to address the growing public health problem of TBI.	A commitment of governmental and non-governmental funding bodies, as well as industrial partners, is needed to facilitate global collaborations and legacy research.	Section 9

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force.[1] It varies in severity from mild TBI (which includes concussion) to moderate and severe TBI. Severe TBI has a high mortality rate, estimated at 30–40% in observational studies on unselected populations.[2] Survivors experience a substantial burden of physical, psychiatric, emotional, and cognitive disabilities, which disrupt the lives of individuals and their families, and pose huge costs to society. Such disabilities are not restricted to severe cases, but also occur frequently after moderate or mild TBI.

TBI is a growing public health problem of substantial proportions. More than 50 million TBIs occur internationally each year.[3] The incidence of TBI in high-income countries (HICs) has increased in the elderly to a greater extent than might be expected from demographic ageing,[94–96] whereas increased use of motorised vehicles in low- and middle-income countries (LMICs) has led to a rise in TBI from road traffic incidents.[160] Across all ages, TBI represents 30–40% of all injury-related deaths, and neurological injury is projected to remain the most important cause of disability from neurological disease until 2030 (2–3 times higher than the contribution from Alzheimer's disease or cerebrovascular disorders).[4] TBI costs the international economy approximately US$400 billion annually, which, given an estimated standardised gross world product of $73·7 trillion,[5] represents approximately 0·5% of the entire annual global output.

Wide variations in the clinical manifestations of TBI are attributable to the complexity of the brain, and to the pattern and extent of damage, which depends on type, intensity, direction, and duration of the external forces that cause TBI. In traffic-related injuries, acceleration–deceleration forces can result in immediate shearing of connecting nerve fibres or trigger progressive loss of connectivity over time. Forces generated by a fall or blow to the head more often cause bruises (contusions). Individuals can react very differently to similar injury forces. Conceptually, it is important to distinguish between the primary damage, inflicted at the time of injury, and secondary damage, which evolves over hours, days, weeks, months, or even over a lifetime in some cases. Secondary damage is driven substantially by host responses to the primary injury. As a bruised ankle might swell following injury, so can the brain. The difference is that the brain is contained within the rigid skull and any swelling results in increased pressure within the skull (intracranial pressure). This increased pressure, in turn, can lead to life-threatening shifts of brain structures or impair blood flow through the brain, resulting in ischaemia and deprivation of oxygen to the brain. TBI is best viewed as a collection of different disease processes (figure 1), with different clinical patterns and outcomes, each requiring different approaches to diagnosis and management.

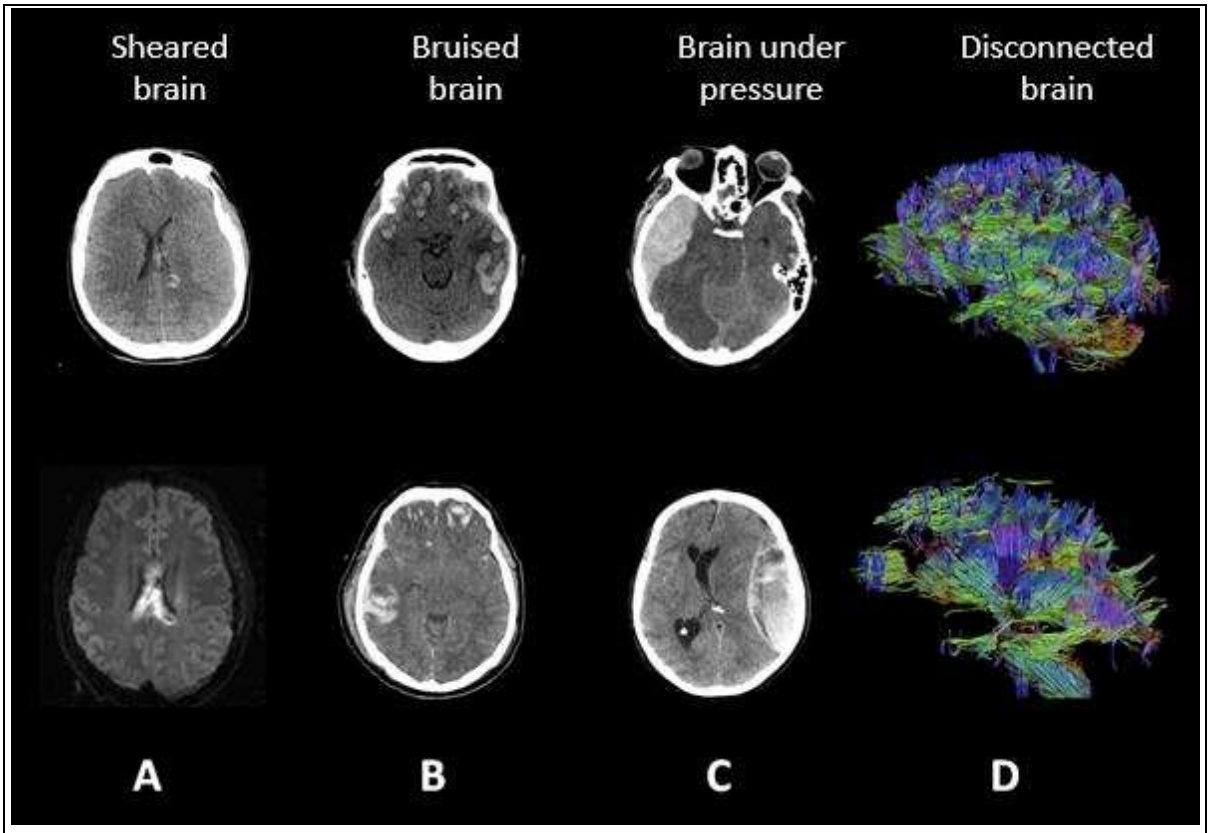


Figure 1: **The multiple faces of traumatic brain injury**

(A) Sheared brain: the typical picture of diffuse axonal injury on CT (top panel) and MRI using susceptibility-weighted imaging (lower panel) in an adult patient with TBI. Note the greater sensitivity of MRI for dection of microbleeds, which are commonly associated with diffuse axonal injury. (B) Bruised brain: contusional brain injury on CT in two elderly patients with TBI, typically located in the frontal and temporal regions. (C) Brain under pressure: a typical epidural haematoma (bleeding between the skull and outer coverings of the brain) on CT in two adult patients with TBI. The haematoma in the top panel is an example of injury that compresses the brainstem; the haematoma in the lower panel causes midline shift and indirect compression of the brainstem due to raised intracranial pressure. Both are life-threatening, and constitute a neurosurgical emergency. Patients can recover completely if operated on quickly. (D) Disconnected brain: white matter tracts visualised on MR tractography in an adult patient with TBI 12 days after the injury (top panel) and at 6-month follow-up (lower panel). Note the extensive progressive late white matter loss over time. CT=computed tomography. MRI=magnetic resonance imaging. TBI=traumatic brain injury.

TBI might also confer a long-term risk for neurodegenerative disorders,[6,7] stroke,[8,9] parkinsonism,[10–12] and epilepsy,[13] and is associated with an increased long-term mortality rate[14,15] compared with of the general population. These risks also occur in milder forms of TBI, especially after repetitive

injuries. This accumulating knowledge makes it clear that TBI is not a single event, but can be a chronic and often progressive disease with long-term consequences. Even after an ostensibly good recovery, patients might have to live with a continuing process of coping and adaptation (panel 1).

Panel 1: **Living with traumatic brain injury—a patient testimony**

In 2011, James Piercy sustained a traumatic brain injury (TBI) in a car accident in the UK. Like many people with TBI, he lives with the long-term effects of brain injury. He is now an ambassador for the UK Acquired Brain Injury Forum. In the following patient testimony (abridged), Piercy describes the aftermath of his injury and highlights what can be achieved with high-quality management and support. However, for many patients with TBI, systems of care are still suboptimal, poor, or even absent in some regions. For the full testimony, see appendix.

The injury

Like many others, I acquired my TBI in a car accident. I was unconscious at the scene (Glasgow Coma Scale score of 3 to 5). By good fortune, I was attended very soon after the accident by a police officer with good first-aid training. He kept my airway open until a doctor and paramedic from the air ambulance could take over my care. I was sedated and intubated at the scene before transfer to the local trauma centre. A scan revealed a bleed in my frontal lobe and smaller haemorrhages through the brain. Prognostic indicators gave a poor chance of good outcome after 6 months, but I have done better than expected. Better prognostic models for individual patients and families would be very valuable. I was monitored closely, emerging from post-traumatic amnesia after 25 days and transferring to a hospital closer to home. I was discharged after 7 weeks and began slow rehabilitation.

The aftermath

After 5 years, I am doing well. I have made a very good recovery and am back to work part-time. I need to plan my time carefully and avoid stressful and unpredictable situations, which leave me very fatigued. This fatigue can be very debilitating, leaving me with speech problems and making decision-making and concentration very difficult. Learning to live with the chronic conditions which follow TBI remains a huge challenge for the individuals and the services which aim to support them. I consider myself very lucky to have done so well and put the recovery down to good, prompt intervention, strong support from family and friends, and my own determination to improve.

Clinical progress has not kept pace with the rising global burden of TBI and recognition of the prolonged effects of injury. The most recent major breakthrough in clinical management was the introduction of computed tomography (CT) scanning into routine care—now more than 40 years ago. Since then, there have been no major improvements in outcome after TBI in HICs with developed trauma systems. This lack of progress can be attributed to many factors, both in thepolicy and clinical domains. Public and political awareness of the magnitude of the problems caused by TBI—including the clinical impact on patients, families, and society, and public health burden and costs to society—

is low. Additionally, there has been insufficient clinical recognition of the complex heterogeneity of TBI, in terms of disease type, outcome, and prognosis. Treatment approaches provide insufficient recognition of specific needs of individual patients, and disconnects exist along the chain of trauma care, especially between acute and postacute care. Clinical research has, until recently, focused mainly on more severe TBI, but the vast majority (70–90%) of patients suffer from mild TBI. Although the individual impact of mild TBI is less, the category as a whole makes the largest contribution to the global burden of disability, and timely intervention and structured follow-up in this group could deliver substantial gains in public health and societal costs.[16]

We believe that strategic global collaboration is required at several levels. First, policy makers and funders need to support an integrated effort by the entire neurotrauma community to identify improved approaches to TBI prevention and best practices for systems of care and management. Second, research strategies are needed to enable better characterisation of TBI through the disease course, and emerging research paradigms and tools need to be incorporated into clinical studies. In addition to the undeniable need for increased research funding, organisational improvements across the chain of trauma care are essential to maximise the benefits of developing global research collaborations and to achieve the best possible returns on research funding. Finally, we need an intensive knowledge transfer exercise to implement the outputs of these efforts in clinical practice. Such implementation requires that we inform and involve health policy makers, health-care professionals, and the general public, about the magnitude of the problem, the extent of (and gaps in) our current knowledge, and emerging advances.

The overall aims of this Commission are to set out directions for improvements in clinical care and to establish research priorities. We aim to provide a foundation for implementation of policy measures that minimise the risk of TBI and maximise chances of recovery when it does happen. This manuscript represents the efforts of a consortium of leading health-care professionals with expertise in epidemiology, health economics, diagnosis, treatment, outcome assessment, biology, and ethics, all of whom are involved in the International Initiative for Traumatic Brain Injury Research (InTBIR) studies, with input provided by other collaborating specialists and, crucially, by patients. In conjunction with this Commission, four Series papers on clinical advances in TBI, aimed at health-care professionals, have been published in recent issues of *The Lancet Neurology*.

Section 1. Epidemiology of TBI

Globally, traumatic brain injury (TBI) is a leading cause of injury-related death and disability,[4,33,39] imposing a huge burden on patients, their families, and society. In low-income and middle-income countries (LMICs), the rising burden of TBI from increases in road traffic incidents predominantly affects young individuals.[160] The changing epidemiology of TBI in high-income countries (HICs) is attributable to a high and increasing incidence of TBI in paediatric and elderly subpopulations.[29,41,94–96,103] Increases in TBI are also reported in the contexts of sports[131–133] and armed conflict.[137]

Reported incidence and mortality rates for TBI vary greatly between countries and regions. This partly reflects variations in acquisition and reporting of epidemiological data, and makes interpretation of official statistics difficult. There is considerable variability in definitions of TBI (panel 2), resulting in difficulties in diagnosis and case ascertainment. Relatively few epidemiological studies of TBI report age-adjusted data, which are required for valid comparisons between countries with differing population demographics. Moreover, for many countries or regions, epidemiological studies have not been done or available data capture only a proportion of all TBIs, so the scale of the problem is likely to be considerably greater than current figures suggest.

Panel 2: **Definitions of traumatic brain injury**

World Health Organization definition[17]

"An acute injury to the brain from mechanical energy to the head from external forces, excluding injuries relating to drugs, alcohol or substance abuse, medication or cause by other injuries or treatment."

This broad definition of traumatic brain injury (TBI) is widely used, but some ambiguity exists as to what constitutes "an acute injury to the brain".

American Congress of Rehabilitation Medicine definition[18]

"A patient with mild traumatic brain injury is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: (1) any period of loss of consciousness; (2) any loss of memory for events immediately before or after the accident; (3) any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused); and (4) focal neurological deficit(s) that may or may not be transient; but where the severity of the injury does not exceed the following: loss of consciousness of approximately 30 minutes or less; after 30 minutes, an initial Glasgow Coma Scale score of 13–15; and posttraumatic amnesia (PTA) not greater than 24 hours."

This definition is specific to mild TBI and excludes patients with more severe TBI, which conflicts with the concept that the severity of TBI lies along a continuum. Note that the term "concussion" is often used synonymously with "mild TBI".[19] See figure 2 for classification of clinical severity with the Glasgow Coma Scale.

National Institute of Neurological Disorders and Stroke definition[1]

"TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force."

This statement acknowledges potential confounders to TBI diagnosis, and suggests that symptomatology, imaging, details of the incident, and wider context should all be taken into account to inform diagnosis.[1]

Figure 2: **Classification of clinical severity of traumatic brain injury with the Glasgow Coma Scale**

Responses are assessed in three domains (eye, motor, and verbal), and individual scores are added to give a Glasgow Coma Scale (GCS) sum score for mild, moderate, or severe traumatic brain injury (TBI).[294]

Addressing the vast global health problem posed by TBI requires substantial efforts to correct current deficiencies in epidemiological monitoring. Robust epidemiological data are essential to quantify the public health burden of TBI, to inform policies for prevention, to understand the health-care needs of patients, and to allow appropriate allocation of health-care resources.

In this section, we provide an overview of the epidemiology of TBI, highlight the increasing burden of TBI in LMICs, and review the evidence for changing patterns of epidemiology in HICs. We propose ways to enhance epidemiological data collection and to improve the usefulness of such data in informing health-care policy and prevention programmes.

[H3] Incidence of TBI

Reported incidence rates of TBI across the world vary considerably, with substantial gaps in robust data for many parts of the world, particularly in LMICs, where TBI rates are likely to be high (figure 3).[3,20–34] Substantially higher incidence rates for TBI are seen in population-based studies with broad definitions of TBI (811–979 per 100 000 people per year)[3,29,32] than in studies based on hospital discharge rates (47·5–643·5 per 100 000 people per year).[32,33] Projections from such studies suggest that 50–60 million new TBI cases occur annually worldwide, over 90% of which are mild TBIs.[3] For the European Union (EU; 28 member states), we estimate that at least 2·5 million new cases of TBI occur each year (table 2), and in the USA, the total number of patients with a new TBI has been reported to approach 3·5 million per year.[35] Results from a recent study using standardised Eurostat data from 24 European countries suggested that 1·5 million TBI-related hospital discharges and 57 000 TBI-related deaths occurred in 2012 in the 28 Member States of the EU.[33] The pooled age-adjusted incidence rate of TBI (hospital discharges) was 287·2 per 100]000 people per year, with

enormous differences between countries (figure 4) that are likely to reflect differences in study methodology rather than true variation.[33]

Figure 3: **Worldwide incidence of traumatic brain injury**

Age-adjusted hospital discharge rates after traumatic brain injury were available for the USA (69·7–106·3 per 100 000 people per year),[20–29,457] Canada (47·5–83·1),[30–32] Europe (287·2),[33] and South Africa (316·4).[34] Population-based incidence rates were available for the USA (823·7 per 100 000 per year),[29] Canada (979·1),[32] and New Zealand (811·0).[3] The map highlights the absence of robust data for most regions and the variation in available data between countries. Reported estimates of hospital discharge rates also vary between individual countries, as highlighted for Europe (81·0–643·5 per 100 000 per year; expanded view).

	European Union	**USA**
Population (millions)	510	321
Total number of new cases annually (indexed per 100 million population)	2·5 million (0·49 million)	3·5 million (1·09 million)
Total number of hospital admissions annually (indexed per 100 million population)	1·5 million (0·30 million)	282 000 (0·09 million)
Total number of deaths from TBI annually (indexed per 100 million population)	57 000 (11 220)	56 000 (17 445)
Percentage of all injury-related mortality caused by or associated with TBI	39%	30·5%

Table 2: **Estimated annual traumatic brain injury volume in the European Union and the USA**
Estimates for the EU are based on four studies.[33,40–42] Estimates for the USA are based on five studies.[29,35,39,43,457] Figures have been rounded for easier comparison where appropriate.
TBI=traumatic brain injury.

Figure 4: **Hospital discharge rates after traumatic brain injury in Europe**

Age-adjusted hospital discharge rates after traumatic brain injury in a single year (2012) are shown for 24 European countries, with a pooled age-adjusted estimate of overall hospital discharge rate across these 24 countries. The figure highlights the wide variation in reported rates between countries. Data from Majdan and colleagues.[33]

The US Centers for Disease Control and Prevention (CDC) surveillance studies of TBI have used standardised case definitions and methods of data collection for nearly three decades,[36,37,457] and

focus on emergency department visits, admissions to hospital, and deaths. Recent data indicate that each year over 2 million Americans with TBI are treated and released from an emergency department, over 282 000 are admitted to hospital and discharged alive, and 56 000 die as a consequence of TBI.[29,457]

Figures for the EU and the USA are discordant (table 2). Relative to population size (EU 510 million, US 321 million), the number of deaths due to TBI is lower in the EU than in the USA. Much of this difference might be explained by the high death rate from firearms-related wounds in the USA—estimated at 10·5 per 100 000 people per year—since head wounds are often involved in fatalities.[44] This rate of firearms-related deaths is exceeded only by some Latin American nations and is far higher than the average rate in the EU of 1·1 per 100 000 people per year.[45]

Relative to population size, the reported number of hospital admissions for TBI is more than three times higher in the EU than in the USA.[29,33,38,457] By contrast, the reported number of new cases per year in the USA, adjusted for population size, is double that of the best estimate of new cases in the EU (table 2). These differences are probably mainly due to methodological diversity in epidemiological studies, including differences in case ascertainment, although variation in hospital admission policies might also be a factor. Discrepancies and differences in epidemiological findings and health-economic data (section 2) within the EU and between the EU and the USA motivate further study and highlight the need to standardise the global conduct and reporting of incidence studies. Furthermore, studies in LMICs are urgently needed (panel 3).

Panel 3: **Traumatic brain injury—a big problem in big countries**

China

China has a population of 1·3 billion. No reliable nationwide data are available on the incidence of traumatic brain injury (TBI). Several large-scale population-based studies, conducted in the 1980s,[79–81] report an incidence of head trauma of 55·4–64·1 per 100 000 people per year. This incidence is much lower than the estimates reported for other countries, and probably reflects incomplete case ascertainment. The current burden of care for TBI is very high in many Chinese hospitals, with many neurosurgical departments nearly exclusively treating TBI.

Traffic incidents are the most common cause of TBI (54%), followed by falls (32–33%) and violence (9–11%).[82,83] The high rate of traffic-related TBI is unsurprising, as car ownership has increased at a

compound rate of about 12% per annum between 1980 and 2009, resulting in a 35-times increase in car ownership (from 0·018 to 0·628 per capita).[84]

In response to a high rate of traffic-related deaths and injuries associated with alcohol use, the Chinese ministry of public safety issued the national alcohol penalty law on May 1, 2011, which stated that all drunk drivers should be sent to jail.[509] Since then, alcohol-related accidents have declined rapidly—eg, a recent study, using data from China's Disease Surveillance Points system, reported a decrease in TBI mortality from 17·06 per 100 000 people in 2008 to 12·99 per 100 000 people in 2013.[510] Implementation of the law on drinking and driving is likely to have contributed to this decrease in mortality.

Falls as a cause of TBI seem to be increasing from a rate of 12% in 2004[85] to 29% in 2008–2009.[82] Interpersonal violence is among the top three leading causes of TBI in China,[86] but gunshot wounds as a cause of TBI are rare (<1%). According to Chinese law, a Chinese citizen or foreigner in China is sentenced to jail if he or she owns, sells or buys, or transports firearms.

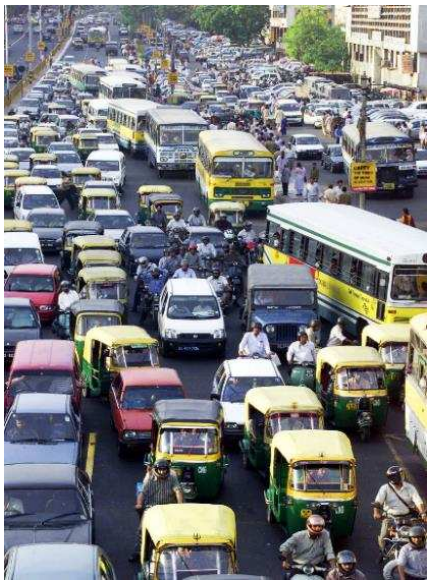
India

India has a population of 1·3 billion. Accurate data on TBI epidemiology in India are lacking, and there is no national trauma registry. The National Crime Records Bureau in India reported a total of 413 457 accidental deaths in India in the year 2015,[90] and this is likely an under-estimation of the actual number.[556] This represents an increase in accident-related deaths of 49% over the period 2004–2015, while population growth was 16·4%. Approximately 50% of trauma deaths are likely related to TBI (Roy, personal communication), which would imply that about one TBI-related death occurs every 3 minutes. Nearly a million people are disabled owing to TBI in India each year,[87] and between 60% and 70% of TBIs result from road traffic incidents.[88,89]

Poor recognition and inadequate early management of brain injuries, delays between injury and reaching specialist care (only 24% arrive within 1 hour, 30% arrive within 2–3 hours, and 24% take more than 24 hours), lack of adequate pre-hospital care services, and limited trauma care services might account for poor outcomes in individuals who sustain a TBI in India.[556,557] High-level care can be provided in the few specialised neurotrauma centres, but access to such resources is scarce.[91] Many districts lack computed tomography (CT) scanners and crucial equipment such as mechanical ventilators, and a great need exists for rehabilitation services.[90–93]

Towards improved epidemiological monitoring

Reliable epidemiological data and improved awareness of TBI in India and China are sorely needed to understand fully the scale of the problem, to drive forward prevention programmes (section 3), and to guide provision of health-care resources for the management and ongoing care of patients (section 4). Accomplishing this will be no simple task. Experience in Europe has shown that despite uniform approaches to collection and analysis of administrative data, wide variations in reported incidence and mortality rates exist between countries,[33] restricting interpretation of such data. Close interaction between governmental authorities and health-care professionals is required to derive the best model for capturing the extent of the burden of TBI in these large countries.



[H3] Prevalence of TBI

Accurate data on TBI prevalence are even more limited than for incidence, particularly for LMICs. A meta-analysis of 15 prevalence studies[46] revealed that of a total sample of 25 134 adults, 12% had experienced a serious TBI with loss of consciousness, with men being at more than double the risk of women. Prevalence is higher in young adults—eg, one birth-cohort study showed that more than 30% of participants had experienced at least one TBI requiring medical attention before the age of 25 years.[47] In view of the increasing incidence of TBI in elderly populations, it is reasonable to conclude that about half the world's population have had a TBI. This inference is supported by the results of a population-based survey with random sampling in Colorado, USA, in which 42% of respondents reported at least one TBI in their lifetime (36% mild and 6% moderate-to-severe injury).[48] TBI has a substantial ongoing health impact: in the USA, an estimated total of 3·17 million people live with permanent sequelae of a past TBI.[49] TBI is among the top three specific neurological

conditions accounting for neurodisability globally, both at present and in projections up to 2030.[4] Concerted efforts are required to reduce this high burden of disability.

[H3] Mortality and years of life lost from TBI

Death rates after TBI are variably reported as mortality rates or case-fatality rates. Mortality rates relate the number of deaths over a specific timeframe to the population size—eg, the number of deaths per 100 000 people per year. Case-fatality rates refer to the proportionof reported cases in a specified disease or condition, which are fatal within a specified timeframe (usually the acute treatment phase)—eg, the death rate for patients admitted to hospital with TBI. Case-fatality rates are therefore greatly influenced by case-mix, and will be higher for patients with severe TBI than for those with mild TBI. These parameters capture the number of deaths relative to different populations at risk. However, the public health consequences of TBI deaths are better captured by the concept of years of life lost (YLL), which gives an estimate of the number of years a person would have lived if he or she had not died prematurely—eg, from a TBI.

Reported mortality rates vary widely between countries, with figures ranging from 0·33 (Spain)[50] to 39 (Brazil)[51] per 100 000 person-years. According to the US CDC, population-based mortality due to TBI was 17·1 per 100 000 people in 2010.[29] Using Eurostat data from 25 European countries, Majdan and colleagues calculated an age-adjusted mortality rate of 11·7 per 100 000 people (95% CI 9·9–13·6) in 2012,[33] but noted that methods (eg, diagnostic criteria and case ascertainment) varied substantially between countries, and studies did not always differentiate deaths directly due to brain injury from those due to other complications. Most studies have focused on severe TBI, usually defined according to the Glasgow Coma Scale (GCS; figure 2),[294] and little is known about the contribution of non-severe TBIs to mortality. Patterns of TBI mortality depend on age and injury mechanisms and can change over time. HICs show declining rates of traffic-related TBI deaths and increasing death rates from fall-related TBI.[52] The highest mortality is in adults over 60 years of age.[52] A recent meta-analysis of 24 studies in patients with moderate and severe TBI, with a pooled sample size of 93 115 older adults (≥60 years), revealed an in-hospital case-fatality rate of 57% (95% CI 43–71) and a 6-month case-fatality rate of 75% (62–84).[119]

Studies with estimates of YLL attributable to TBI are scarce: the YLL related to TBI has been estimated at 118 207 years for the Netherlands (2010–2012)[53] and at 14 386 years for New Zealand (2010).[54] A recent analysis of data from 16 European countries revealed a total of almost 400 000 YLL related to TBI, which translates to a pooled age-adjusted rate of 271·4 (95% CI 214·7–328·2) YLL per 100 000

person-years and to an average of 25·4 (23·0–27·9) YLL with each TBI death. Nearly 74% of all YLL due to TBI affect individuals in age groups with potential to work (15–64 years).[511]

The high acute mortality in severe TBI is well recognised: TBI is a contributing factor in 39% of all injury-related deaths in the EU[33] and about a third (30·5%) of all injury-related deaths in the USA (with an average reported number of 169 000 injury-related deaths per year in the USA between 2002 and 2006).[39] Long-term mortality in TBI is a substantial, but less well recognised, problem: TBI survivors continue to experience mortality rates that exceed those in age-matched and sex-matched population controls and in similar cohorts with non-TBI trauma for many years.[55] In a Scottish study of patients aged 15–54 years, the death rate 13 years after TBI was more than six times higher than in community controls.[14] The Global Burden of Disease studies showed a pooled standardised mortality ratio of 2·18 (95% CI 1·88–2·52) for TBI survivors.[56] This excess mortality is in part attributable to expected consequences and associations with TBI, such as epilepsy, but also due to an increased risk of illnesses not directly related to injury, such as pneumonia, septicaemia, and respiratory and digestive disorders.[57] TBI has been shown to shorten life expectancy by 6 years.[58]

[H3] TBI as a risk factor for later neurological disease

TBI might be a major risk factor for late neurodegenerative disorders such as dementia and Parkinson's disease, reinforcing the view that TBI can evolve into a progressive lifelong illness. A meta-analysis of 15 case-control studies showed a pooled odds ratio of 1·58 (95% CI 1·21–2·06) for development of later-life dementia after a single TBI with loss of consciousness.[6] Autopsy studies have shown accelerated development of tau and amyloid pathology in a third of TBI survivors who died of non-TBI-related causes decades after the initial injury.[455] TBI sustained after 55 years of age is associated with a 44% increased risk of developing Parkinson's disease within the subsequent 5–7 years.[11] A population-based clinical and neuropathology survey confirms this association for the incidence and progression of parkinsonism, and for Lewy body disease, but not for dementia or dementia-related pathology more generally.[12] By contrast, a recent Finnish study showed that in working-aged people, a history of moderate-to-severe TBI is associated with an increased risk for future dementia, but not for Parkinson's disease or amyotrophic lateral sclerosis.[512]

TBI-associated dementia might be clinically and pathologically distinct from Alzheimer's disease, with more patients experiencing behavioural symptoms such as depression, agitation, and irritability.[59] Preliminary estimates of population-attributable risk, based on TBI prevalence and relative risk of dementia in TBI survivors, indicate that as much as 5–15% of the population burden of dementia could be due to brain trauma.[60]

Repetitive mild TBI can result in a distinct pathology known as chronic traumatic encephalopathy (CTE).[61] In his landmark clinical account of punch-drunk syndrome in boxers, Martland provided the first clinical description of the progressive neuropsychiatric sequelae associated with repetitive mild TBI,[62] and its neuropathological substrate was detailed by Corsellis and colleagues.[63] Recent autopsy studies have found similar associations with clinical features in non-boxer athletes from sports with high risk of concussion or mild TBI, such as American football, ice hockey, soccer, and rugby, as well as in ex-military personnel. In these descriptions, the distinguishing clinical features comprise a triad of behavioural, mood, and cognitive deficits,[64,513] which have been variably associated with pyramidal and extra-pyramidal dysfunction and cerebellar impairment in retired professional football players,[65] and might represent the clinical correlate of CTE pathology.[66,513] The risks of developing CTE in individuals who play these sports remains unclear. Although a recent autopsy series reported a rate of CTE of ~99% in professional American football players, this was a highly selected group of individuals, and extrapolation to more generalised estimates of risk is not appropriate**.**

A related, but distinct, issue is the fact that some TBI survivors experience ongoing cognitive decline in the medium term (months to years), rather than showing clinical improvement or remaining stable. Long-term disability could change with time, and age-related decline in cognitive reserve might unmask the consequences of an earlier TBI.[7,514] A 13-year longitudinal study in Glasgow, Scotland,[14] reported such late deterioration in up to 50% of patients, which can be visualised by progressive changes on advanced neuroimaging.[67] Furthermore, a decline in outcomes from 1 year to 5 years after injury was recently reported in 36 of 50 (72%) US military service members with concussive blast TBI.[515]

Other evidence suggests that TBI is an independent risk factor for stroke.[8] A retrospective case-control study from Taiwan showed that a past history of TBI doubled the risk of stroke (hazard ratio 1·98; 95% CI 1·86–2·11) and increased post-stroke mortality (odds ratio 1·57; 95% CI 1·13–2·19).[9]

Post-traumatic epilepsy is a well recognised complication of TBI,[13] occurring in up to 20% of patients with severe brain trauma and 3–5% of those with moderate TBI.[68,69] Even mild TBI leads to a 1·3-times increased risk of epilepsy in those affected compared with the general population.[69] TBI accounts for approximately 4% of cases of epilepsy in the general population and is the leading cause of epilepsy with onset in young adulthood.[68]

The association between TBI and an increased risk of late neurological disease[62,70] remains poorly understood, largely owing to the retrospective nature and limited scope of many past studies and

small cohort sizes in recent, more comprehensive reports. There is a pressing need for research into the incidence, clinical presentations, and risk factors in TBI-associated neurological diseases and their overlap with existing, better characterised disorders, such as Alzheimer's disease and Parkinson's disease.

[H3] Changing epidemiological patterns of TBI

The epidemiology of TBI in HICs is changing. TBI due to traffic-related incidents has decreased, and falls are now the leading cause of TBI, particularly in elderly patients.[41,94] The average age of patients with TBI in HICs has nearly doubled since the 1980s (appendix). Evidence for these changes has often come from comparisons between studies, which are confounded by differences in enrolment criteria, but a few longitudinal studies are available. The Nordic countries were among the first to describe an increase in TBI in elderly patients.[95,96] In Europe, a decrease in overall TBI incidence rates since the late 1990s, mainly due to a decrease in traffic-related injuries, has been reported in Scotland, UK,[97] Spain,[98] and Portugal.[99] Most of these studies reported an increase in incidence of TBI in elderly patients. The observed decrease in hospital admissions for TBI in Europe has not been reported for other high-income countries such as Canada[100] and the USA.[35] Since the 1970s, a decrease in mortality due to TBI has been reported in many studies,[52,101] mainly attributable to fewer traffic-related deaths.

The results of a systematic review of TBI mortality over the past 150 years suggested that improvements in the clinical management of severe TBI (according to the GCS, or coma at presentation in the pre-GCS era) have reduced case-fatality rates by more than 50%.[102] However, case-fatality rates appeared to have stagnated over the past 25 years,[102] an impression confirmed by a comparative overview of observational studies, which showed similar rates of unfavourable outcome over the past decades (appendix).[2] Further improvements in care are needed to reduce mortality and to improve outcomes for survivors of TBI.

[H3] TBI in specific populations

[H4] TBI in children and adolescents

Despite the growth and dissemination of injury-prevention programmes and education (section 3), TBI remains the leading cause of death in children and adolescents in HICs.[29] In fact, the full scope of the public health crisis of TBI is only now emerging. According to US CDC data,[457] in 2013 there were more than 640 000 TBI-related emergency department visits for children aged 14 years or younger.

However, this staggering number is likely to be an underestimate: data from large health networks suggest that about 80% of children and adolescents with mild TBI present to primary care physicians and not to hospitals,[104] indicating a real incidence that is 4–5 times higher. CDC data[457] show that US emergency department visits for TBI increased between 2007 and 2013 for the 0–4 year and 5–14 year age groups, rising by 37·8% in the youngest age group (1591·5 cases per 100 000 people), which has the second highest incidence for any age group after adults over 75 years of age.

TBI affects more boys than girls, with a 1·4-times higher incidence in boys less than 10 years old and a 2·2-times higher incidence in boys more than 10 years old compared with girls.[105] Additional disparities in incidence and outcomes exist in relation to race and ethnicity. For instance, African-American children were at a 40% increased risk of TBI compared with non-Hispanic white children.[106] African-American, Hispanic, and native American children were more likely to experience TBI from violence and have more severe TBI and higher mortality rates than were non-Hispanic white children in the USA.[107–109]

Injury causes also vary with age. Falls predominate in the 0–4 year age group, falls and being struck by (or having the head strike) an object are equally common in the 5–14 year age group, and motor vehicle incidents predominate in the 15–24 year cohort.[457] The rates of TBI and its complications in children and adolescents seem to be similar in Europe and the USA, but are higher in other regions, such as China, India, and South America.[110]

A unique aspect of TBI in children is that it includes injuries inflicted by child abuse. In abusive head trauma, children are generally too young—or sometimes too injured—to be reliable historians, and investigations are required to eliminate further risks for the injured child and any other children in the environment and discover the circumstances surrounding the injury. A comprehensive analysis of data from the past 15 years appeared to show declining rates for fatal abusive head trauma.[111] Nevertheless, recent evidence suggests that abusive trauma is the most common cause of severe TBI in children under 2 years of age.[112] Although some studies have shown poorer outcome in children with abusive head trauma compared with those injured by other mechanisms,[516,517] this was not confirmed in a recent study.[518]

At a societal level, the effect of childhood TBI is enormous, with burdens on the health-care system, scarce resources for rehabilitation and school systems, and a substantial socioeconomic impact on families (sections 2, 4).

[H4] TBI in the elderly

The definition of elderly in the context of TBI is variable: cutoffs in published papers range from 55 to 75 years of age. However, regardless of the cutoff used, older patients are clearly at a higher risk of TBI and experience more severe consequences than do younger patients, even from seemingly mild TBIs.[3,29,39,113] Demographic projections suggest that future rates of TBI among older individuals in LMICs are likely to approach current levels in HICs,[459] and hence the future health economic and public health burden of TBI is likely to increase dramatically.

People over 65 years of age represent 10% of TBI cases, but account for 50% of TBI-related 10-year mortality risk[114] and have high and increasing rates of TBI-related hospital admissions.[28] The rise in TBI incidence in older patients is not solely attributable to an ageing population. Many elderly patients remain mobile and semi-independent owing to decreasing morbidity from cardiovascular disease and cancer. They are then at risk of falls, which are the main cause of TBI in this group.[37,41,94,115] Loneliness and depression might also lead to alcohol abuse, which is increasingly being recognised in older individuals and can potentially increase the risk of falls and compromise chances of recovery owing to decreased cognitive reserve.[116] Moreover, increased use of computed tomography (CT) imaging might have improved case ascertainment for TBI in older people.

Age is among the strongest outcome predictors in TBI, with mortality and unfavourable outcome increasing continuously with age (appendix).[117,118] The perception of a universally poor outcome has sometimes led to therapeutic nihilism and less aggressive treatment for older patients with TBI, who experience delayed CT imaging, a lower likelihood of transfer to specialist neurosurgical facilities, and care by more junior medical staff.[120] Treatment-limiting decisions might be taken sooner in older patients. The poor outcome resulting from such suboptimal treatment might fuel self-fulfilling prophecies of poor prognosis and reinforce current prejudices. Such nihilism is unjustified: overall, when older patients are treated aggressively and promptly following ICU admission, favourable outcomes are seen in 39% of patients aged 60–69 years.[121] Epidemiological studies will be crucial in helping to understand the burden of TBI and response to treatment in the elderly population. Moreover, improved epidemiological monitoring in the elderly could help to raise awareness of the risks of head trauma in this group and inform prevention programmes (section 3).

[H4] Sports-related TBI

Sports-related concussion is a frequent cause of TBI, and is currently the focus of public debate and controversy, owing to uncommon (but dramatic) clinical presentations such as second-impact syndrome[122,123] and the association of concussion with later cognitive decline[65,124] and CTE. In the USA, the CDC estimates that between 1·6 and 3·8 million concussions occur annually.[125] However,

this might be a considerable underestimate, as many concussions do not reach medical attention. In the USA, cycling is responsible for the majority of sports-related concussion, according to the American Association of Neurological Surgeons,[126] whereas in New Zealand, rugby (both league and union combined), cycling, and equestrian sports have been linked to the highest rates of sports-related concussion.[127] A recent systematic review of 13 studies of concussion in 12 sports reported an overall pooled incidence of 0·23 (95% CI 0.19–0.28) per 1000 athlete exposures to sport, with the highest incidences in rugby, ice hockey, and American football.[128] Variations in participation between sports and in definitions of concussion between countries result in inconsistent statistics. Concussion rates vary by age group, sport, and gender, and are generally reported to be higher in competition than in practice.[129] In terms of head injuries per hours of sport, equestrian sports appear to have the highest rate of concussions.[130] There is a lack of research on the epidemiology of sports-related injury, across all sports, in Europe.

Notwithstanding inconsistencies, the reported incidence of sports-related concussion is steadily rising. The CDC reported a 62% increase in sports-related TBI treated in emergency departments between 2001 and 2009,[131] and annual increases of 7–15% have been suggested for concussion rates in collegiate and high-school sports in North America[132,133] over the past two decades. These concerns are not confined to the USA. For example, the English Rugby Football Union[134] has reported year-on-year increases in concussions in professional rugby since 2003.[135] These trends are generally attributed to increased awareness and reporting of concussion, partly promoted by media attention. Concerns have also been expressed about players becoming progressively heavier and stronger, and more emphasis being placed on the physical element of sport. Nevertheless, the underlying true rate of concussion remains unclear, as the majority of these injuries are not reported, either deliberately or due to lack of awareness.[136] Further efforts to understand and increase awareness of the consequences of sports-related TBI are needed, with improved detection of and response to concussion, to prevent or reduce the effects of such injuries (section 3).

[H4] TBI in military conflict situations

Current global conflicts, and the increasing burden of terrorism across the world, have resulted in a steady increase in the number of patients with military and military-type injuries.[137] US data show that TBI is the signature injury of the Iraq and Afghanistan conflicts, accounting for approximately 20–25% of the combat casualties reported in the Joint Theater Trauma Registry.[140] Between January 2010 and August 2016, 352 619 TBIs were reported in US service members.[141] Of these, 82% were classified as mild, 9% as moderate, and the remaining 9% as severe or penetrating, or not classifiable (including instances of death in action and inadequate or incomplete documentation). As with civilian

populations, mild TBI constitutes the largest proportion of TBI in military personnel, and although most individuals with mild TBI return to full duty with no lasting complications, approximately 10% have symptoms that do not resolve.

Overall, combat-related TBI is a substantial cause of morbidity and mortality, and unlike civilian TBI, often includes blast-related TBI and extracranial polytrauma such as amputation, internal haemorrhage, and burns. Blast as an injury mechanism was until recently largely confined to conflict settings, but has become more relevant in civilian populations owing to an increase in terrorist incidents. Injury mechanisms can be more complex than in non-blast TBI, and experience in the military setting suggests that the clinical course can also be different.[142] Several active research programmes are focused on the differences between blast-related TBI and TBI of other causes. The most comprehensive of these, from the US Department of Defense, includes efforts to understand the epidemiology, identification, management, and treatment of mild TBI, including protocols for mandatory screening and detailed clinical recommendations.[143,144]

US data from recent conflicts in Iraq and Afghanistan document the lowest killed-to-wounded ratio in the history of warfare,[519] with many casualties surviving what would previously have been fatal injuries. Although advances in body armour might help to explain increased survivial, developments in military medical care have likely made a substantial contribution.[146] However, a key consideration is development of an integrated and effective chain of trauma care in conflict settings (section 4). Although the impact of these improvements on TBI outcomes may be less impressive than for other trauma (see section 4), understanding the epidemiological and clinical issues facilitates improvements in TBI outcome. The lessons learned—eg, about the effects of improvements in care pathways on the burden of TBI—apply beyond conflict settings and have relevance to the civilian population.[139,147]

[H4] TBI in offenders

There is evidence for an association between TBI and crime: TBI appears to be a risk factor for criminal behaviour, and a criminal lifestyle might inrease risk of TBI.[520] Importantly, there are shared risk factors for TBI and criminal behaviour, including socioeconomic adversity and conditions such as attention deficit hyperactivity disorder (ADHD), mental health disorders, and alcohol or drug misuse. In support of these links, a Finnish birth-cohort study showed that a TBI during childhood or adolescence was associated with a four-times increased risk of having a mental health disorder with coexisting criminality in men.[71] A 35-year, retrospective, total-population study in Sweden showed a substantially increased risk of violent crime in people with TBI: 8·8% of those with TBI had committed

violent crime, compared with 3% of the population controls (adjusted odds ratio 3·3, 95% CI 3·1–3·5); risk was attenuated when those with TBI were compared with unaffected siblings (adjusted odds ratio 2·0, 1·8–2·3).[72] Prevalence of TBI is much greater—3–8 times as high—in offender populations than in non-offender groups.[73] In a UK prison study, Williams and colleagues found that 16% of inmates had experienced a moderate-to-severe TBI and 48% had had a mild TBI.[74] About half of young offenders have had loss of consciousness, with repeated injury being common.[73] TBI in offenders is associated with earlier offending, higher levels of re-offending,[74] violence,[75] and suicidality.[76] A neuroimaging study of prisoners in Germany showed that offenders had a significantly higher rate of structural brain abnormalities,[77]and that violent offenders had significantly higher rates compared with non-violent offenders and controls.

There are intricate links between TBI and ADHD: ADHD can be a consequence of TBI, but it is also a risk factor for TBI, and can be complicated by the injury.[466] Since ADHD is common in offender groups, studies of TBI in these populations should consider the contribution of this condition. In a non-TBI study, intervention with medication for ADHD in offenders led to a 30% reduction in criminality, possibly owing to improved impulse control.[78,456] Screening for and management of TBI in offenders is possible,[76] and specialist services tailored to offenders with TBI, and comorbid mental health and neurodevelopmental disorders, might support changes in behaviour that potentially lead to a reduction in crime.

There is a pressing need for more research to characterise the association between TBI and criminal behaviour in offender populations. In particular, longitudinal studies are needed to understand the increased risks of crime in those with TBI, the causal relations between TBI and criminal behaviour, and the factors that contribute to these risks. Furthermore, studies are needed to characterise imaging abnormalities and neuropsychological impairments associated with TBI in offender populations to understand how brain injury affects behaviour, including risk of reoffending.[520]

[H3] Improving epidemiological studies of TBI

TBI is a huge but poorly quantified public health problem. The considerable differences in reported incidence and mortality rates between countries highlight a need for better standardisation of epidemiological data gathering on TBI, for both administrative purposes and research. Recommendations for improving epidemiological studies are summarised in the appendix, and emphasise the need for standard definitions, standard methods, and standard data presentation. Future studies also need to use more standardised methods of data collection, especially for mild TBI, to facilitate pooling of data and comparisons between countries and over time.

We need population-based studies on the prevalence, incidence, and mortality of TBI across the lifespan, particularly in LMICs, to improve the accuracy of estimates of the global impact of TBI. Capture–recapture methods[148,149] could usefully supplement population-based studies, particularly when resources are limited. More advanced metrics, including YLLs, years of life with disability (YLD), or disability-adjusted life years (DALYs)—a measure of overall disease burden, expressed as the number of years lost due to ill health, disability, or early death—should be used to better quantify the burden of TBI. A simple and cost-efficient approach might be to include a question on TBI in routinely conducted health interviews, such as the European Health Interview Survey, which has a section on self-reported injury in the past 12 months, and could yield insight on incidence and prevalence of TBI in the general population.

Improvements in completeness and quality of epidemiological data are required for development and implementation of policy measures through detection of high-risk populations (such as the very young and very old) and identification of key targets for improved prevention and management of TBI (sections 3, 4).

[H3] Key messages and recommendations

(1) Worldwide, TBI is a leading cause of injury-related death and disability, and a huge burden to patients and their families. Concerted efforts to address this vast global health problem should focus on policies aimed at reducing the burden and impact of TBI, through better prevention, improved access to care, and promotion of clinical research to improve treatment standards.

(2) Current epidemiological monitoring is incomplete, especially for mild TBI. Rigorous epidemiological studies are needed to capture the changing patterns of epidemiology and identify high-risk groups and key targets for improved prevention and management of TBI.

(3) In LMICs, the incidence of TBI due to traffic incidents is increasing, while in HICs, TBI increasingly affects elderly people, mostly due to falls. Methodological variations, however, confound comparisons of epidemiological patterns of TBI between regions, countries, and continents. An international consensus is needed on definitions and standardised epidemiological monitoring of TBI to allow accurate measurement of incidence, prevalence, and mortality, and comparison of rates of access to community, hospital, and institutional care.

(4) TBI might represent an important modifiable risk factor for epilepsy, stroke, and late-life neurodegenerative disease. Studies are needed, in children and adults, to better understand links between TBI of all severities and an increased risk of these diseases.

Section 2. Health economics of TBI

Traumatic brain injury (TBI) has a huge economic impact on affected individuals and families, and on society as a whole. Understanding the health economics of TBI is an important step in efforts to improve efficiency of care and prevention worldwide. However, accurate estimates of TBI costs are scarce for many regions, and there is wide variation in reported costs between available studies. This partly reflects differences in methods used to calculate costs and variations in definitions of direct, indirect, and lifetime costs used in research studies (panel 4).

Panel 4: **Definitions of types of costs used in health-economic studies of traumatic brain injury**

Direct costs

All resources consumed (quantified in costs) within the health-care sector as a result of the traumatic brain injury (TBI). Direct costs could also include out-of-pocket expenses and resources outside the health-care sector.

Indirect costs

All resources foregone as a result of TB. Costs included in this category vary by study but most include productivity loss, which arises when people who would otherwise be employed are not able to work or work fewer hours because of their TBI. Indirect costs could also include intangible costs due to TBI, such as those associated with reduced quality of life or time and effort spent by family members on care.

Lifetime costs

Costs incurred over a lifetime to provide services to people with TBI that would not be required in the absence of the injury, such as ongoing medical care and community services.

Understanding of costs associated with TBI can provide insight into the magnitude and scope of the problem and generate the knowledge necessary to anticipate and budget for health-care services needed to prevent, detect, and treat TBI. Accurate cost estimates allow assessment of potential savings that could be made with interventions aimed at reducing the incidence or improving the treatment of TBI. Costs can also be considered to reflect resources used per individual and provide a proxy measure of health-care use. Identification of disparities and inequities in access to and delivery of health care, crucial for the provision of good treatment, allows researchers and decision makers to recognise areas where public health interventions could be beneficial.

In this section, we review available health-economic data on the costs related to TBI and discuss the implications for health-care policy. Furthermore, we suggest directions for future health-economic

studies to improve understanding of costs and patterns of health-service use after TBI, which could facilitate decisions on prevention strategies and health-service planning.

[H3] Direct and indirect costs

The economic consequences of TBI for individuals and for society are enormous. TBI-related costs in Europe for 2010 have been estimated at €33 billion (equivalent to about US$48·7 billion in 2016), of which direct costs accounted for 41% and indirect costs accounted for 59%.[150,151] In the USA, reported aggregated direct and indirect cost estimates ranged from US$60·4 billion (about US$84·2 billion in 2016) in 2000[152] to US$221 billion (about US$248·9 billion in 2016) in 2009.[153] In the earlier USA study,[152] 15% of the costs were accounted for by lifetime medical costs and 85% by lifetime productivity losses. The data from 2009[153] showed that 31% of the costs were due to loss in productivity and 62% resulted from intangible costs (lost quality of life). The higher total cost estimates in the later study might be explained by the inclusion of intangible costs. Costs attributable to TBI in Australia in 2008 were estimated to be AUS$8·6 billion (about US$7·7 billion in 2016), of which absence from work or productivity loss due to TBI accounted for 55%.[154]

Lifetime costs of TBI are high owing to loss of productivity in a substantial number of younger patients, but these long-term costs are not considered in all studies. For example, in Europe the reported health-service-related and indirect costs for stroke have been estimated to be twice as high as those for TBI,[150,151] but these comparisons limit reported cost estimates for TBI to the direct and indirect costs for the first year after injury. Such calculations grossly underestimate the actual societal costs of TBI.

The average lifetime cost of TBI in the USA was estimated to be US$396 000 per person (equivalent to about US$544 000 in 2016).[155] In Australia, per-person long-term health-care costs for the first 6 years after injury ranged from AUS$139 427 for moderate TBI (about US$122 138 in 2016) to AUS$226 361 for severe TBI (about US$198 292 in 2016).[154] Many studies, especially from the USA, use the charges payable by individuals or insurers as a proxy for unit prices (ie, the actual costs of provision of care);[53] such cost calculations could underestimate total costs, as many patients with mild TBI do not seek immediate medical care or are misdiagnosed.

The omission of mild TBI from many cost studies might result in an overestimate of the average cost per individual, but an underestimate of the total cost to society. This is partly because accurate population-level data about resource use and the health impact of TBI are scarce. The recently completed Brain Injury Outcomes New Zealand in the Community (BIONIC) study was the first to

assess the incidence of TBI for all severities across all age groups, in both rural and urban populations.[3] The BIONIC collaborators found that the cost of treating TBI varies greatly, with first-year and lifetime costs per person for mild TBI (calculated at US$3395 and US$4636, respectively) being significantly lower than those for moderate-to-severe TBI (US$21 379 and US$36 648, respectively).[16] Other estimates, based on patients admitted to a rehabilitation facility (about $350 000 for severe TBI,[156] for example), underline the high costs of efforts to promote recovery in survivors, as rehabilitation interventions are often intensive and prolonged. Costs of care in individual patients can be ten times higher, and vary with both injury severity and demographic features.[156,521] Despite the lower treatment costs of mild TBI for individual cases, the high incidence of mild TBI results in a total treatment cost of nearly three times that for moderate-to-severe TBI.[16] Accurate estimates of total global costs of TBI are lacking, but extrapolation from estimates of new mild (52–56 million) and moderate-to-severe (2·2–3·6 million) TBIs per year worldwide from the BIONIC study[16] suggests that the global economic burden of TBI could range from US$355 billion (€268 billion) to US$436 billion (€329 billion) in 2016, which equates to 0·5% of the annual global output, estimated at US$73·7 trillion.[5] The actual costs could be even higher as intangible costs, such as those related to loss of quality of life or the time and effort spent by family members on care, are not taken into account in these estimates.

Although all studies attest to the high societal costs of TBI, in terms of both medical costs and lost productivity, the variation in estimates is striking. Some differences are probably real; however, rigorous comparison of these figures is impossible, since the source data are of relatively poor quality, calculations involve several assumptions and variable methods, inflation-related changes in exchange rates are usually ignored, and the precise cost items included in estimates (and the duration of post-injury period to which they refer) vary substantially, or are simply not specified (appendix).

Other indirect consequences, which have rarely (if ever) been taken into account in calculating TBI-related costs, include caregiver time and expense, caregivers' working ability and health, increased psychiatric morbidity and injury risk among TBI survivors, increased likelihood of alienation, and societal costs, as well as costs related to long-term complications of TBI, including those of dementia care.[157] Taken together, these limitations underline the need to interpret with caution current estimates of health-service use and costs of services. As with other epidemiological data, there is a pressing need to ensure uniformity of reporting of health-economic data (section 1).

[H3] Implications for health-care policy

The huge economic burden of TBI worldwide necessitates improved prevention and treatment strategies from a health-economic perspective. However, accurate data on costs as a proxy measure of health-care use are lacking. Current estimates of the range of total costs are incomplete for both mild and severe TBI. For patients with severe TBI, we need better insight into the long-term costs of specialised hospital and rehabilitation care. There is a crucial need to couple improved epidemiological and economic data collection to rigorous analysis of health-care and lifetime costs of TBI, so that we can identify patient groups with high costs of care and deficiencies in access to services, and make rational decisions about allocation of health-care resources. Models for predicting lifetime costs for individual patients are now emerging, and might also be useful in assigning costs to the care needs of survivors of TBI.[521]

Data on total costs of TBI, and on indirect costs in particular, are limited. We need improved understanding of the negative effects of TBI on work performance, and resulting production losses, which dominate the economic burden of TBI. Future research should incorporate the productivity costs in cost assessments, as this provides important input for policy decisions and enables priority setting on the basis of the total direct and indirect expenses due to injuries. These data are also vital to calculate the cost-effectiveness of programmes or treatments to improve the chances of returning to work in working-age survivors of TBI.

Substantial cost savings could be achieved by preventing TBI. At the level of individuals, cost savings might be more relevant at the severe end of the spectrum, but the large number of patients with mild TBI suggests that effective prevention strategies to reduce incidence of mild injuries could be more beneficial at a societal level. Realisation of such cost savings will require investment in prevention (section 3). As well as increased governmental investment, additional funds could be made available by following the example set by Italy, where a portion of the fees for traffic law violations must be spent on traffic incident prevention.[522]

[H3] Key messages and recommendations

(1) TBI results in substantial health-care and societal costs. More effective strategies for TBI prevention are vital, and could deliver cost savings that help to fund research and improved access to health care for TBI.

(2) High-quality data on the health-economic effects of TBI are not available for many regions and countries, especially for lifetime costs. Increased funding is needed for rigorous and long-term health-economic studies on direct and indirect costs, which are necessary to inform rational decisions about allocation of resources for clinical care and research in TBI.

(3) Methodological variations confound comparisons of the health-economic impact of TBI across regions, countries, and continents. International standardisation of methods in health-economic research are needed to enable consistent measurement and comparison of costs of TBI care.

Section 3. Prevention of TBI

Traumatic brain injury (TBI) is, to a great extent, preventable, and the benefits for society of decreasing its occurence are far-reaching: TBI prevention saves lives, reduces prevalence of disabilities, and saves costs inside and outside the health-care system. Although TBI prevention strategies (such as those aimed at road traffic safety) in some regions have been remarkably successful, these achievements are not universal. Increased use of motor vehicles in low-income and middle-income countries (LMICs), coupled with an inadequate infrastructure and insufficient adoption of safety measures, have resulted in substantial increases in the burden of TBI.[160] Successes achieved in prevention of TBI from road traffic incidents in high-income countries (HICs) need to be replicated in LMICs. Furthermore, steps need to be taken to address increases in TBI in other demographic contexts, including specific measures to reduce the incidence of TBI caused by falls in the elderly, and to prevent brain damage in children and in amateur and professional athletes.

Prevention measures that target injury occurrence, whether primary or secondary measures, should be informed by knowledge of epidemiology, TBI cause, and identification of risk groups. Primary prevention is directed at prevention of injury occurrence, whereas secondary prevention aims to reduce the occurrence of TBI or limit its severity if an injury happens.

Primary and secondary approaches can be effective in isolation, but use of both prevention strategies is needed to maximise benefits. Prevention initiatives can be applied at a population level (eg, with legislation, improvements in infrastructure, vehicle safety design, trauma care, and workplace safety measures). Alternatively, prevention measures can focus on high-risk subgroups. Examples include the targeting of drivers and cyclists to prevent alcohol-impaired driving, speeding, and distracted driving; promotion of seat belt, child restraint, and helmet use; a focus on elderly people living alone and at risk of falls; and strategies aimed at children at risk of abuse. Finally, it might also be possible to specifically target individuals to address their behaviour and risk-taking patterns.[159] Irrespective of the target population, information campaigns should employ a range of measures to raise awareness of key issues in prevention and care of TBI.

In this section, we discuss approaches to reduce the occurrence and impact of TBI, focusing on prevention of TBI from road traffic incidents, TBI in children and adolescents and the elderly, and sports-related TBI.

[H3] Prevention of TBI from road traffic incidents

Globally, TBI remains predominately a disease of the young, with road traffic incidents being the major cause in LMICs, where vulnerable road users (pedestrians and cyclists) are particularly at risk.[160] Even though LMICs have only half of the world's vehicles, 90% of the world's road fatalities occur in these regions,[460] a substantial proportion of which are preventable.

Reduction of traffic-related injuries is the focus of the UN Decade of Action for Road Safety (2011–2020), which aims to halve the 1·3 million traffic-related deaths each year by 2020 through improved road-safety management, enhanced road and vehicle safety, better-informed road users, and an improved post-crash response.[161] These improvements are relevant to TBI, since it is a major cause of all injury-related deaths (section 1).[33,35,162] A recent World Health Organization (WHO) report on road safety[158] provides specific recommendations for improving road safety, based on interventions with proven efficacy. Reductions in speed limits have played a crucial part in decreasing crash incidence and injury severity.[163–165] A systematic review of studies from HICs confirmed that enforcement of traffic rules decreases road-user deaths.[166,167] Non-legislative approaches are equally relevant, and include developing safer roadway infrastructure (separating pedestrians and cyclists from motorised vehicles), introducing traffic-calming measures, and implementing vehicle and safety-equipment standards.[168] Other effective population-wide strategies for preventing road crashes, injuries, and fatalities include the installation of red-light cameras[169] and street lighting.[170]

Secondary prevention strategies include use of protective head gear and car safety measures. Mandatory helmet use has decreased the number and severity of head injuries in both motorcycle[171] and bicycle users.[172–174] In Taiwan, introduction of the motorcycle helmet law in 1997 reduced motorcycle-related head injuries by 33%, and injuries that did occur were less severe and associated with shorter hospital stays.[175] Despite strong evidence on the efficacy of helmets to reduce the severity of injuries from motorcycle crashes and increase the likelihood of survival, helmet laws are not universally implemented, even within the USA.[523]

In HICs, recent attention has focused on the risks incurred by distracted drivers.[177] The likelihood of a safety-critical event occurring while driving has been reported to be six times higher for drivers dialling a cell phone and 23 times higher for those texting. Although campaigns aimed at influencing

drivers' behaviour remain relevant, technological solutions should also be considered. In particular, there have been suggestions to develop smart solutions to recognise and block non-hands-free cell phone use while driving.[177]

[H3] Prevention of TBI in children and adolescents

The topic of TBI in children and adolescents has substantial emotional, legal, and financial ramifications. Children and adolescents are at particularly high risk of accidental TBI, and such injuries in this group can have substantial effects on families and communities worldwide. Most prevention strategies outlined for road traffic incidents and for sports injuries—particularly those related to concussion detection and prevention from sports injuries, and helmet laws for bicycles, motorcycles, and other motorised vehicles—apply to both children and adults. However, two aspects of injury prevention are unique to children: the use of car seats and the concept of multi-agency safeguarding for children at risk of abuse, with infants being the most vulnerable.[112]

Community-based interventions to promote the use of child car-seat restraints can reduce the risk of motor vehicle occupant injuries by 33–55%.[176] In the USA and other areas of the world, local laws state that children should be restrained in car seats while the motor vehicle is in motion. For example, in Pennsylvania, USA, all children under 8 years of age travelling by car are required to be in a child-restraint system, with children under the age of 2 years in rear-facing seats. Furthermore, the law mandates the use of seat belts for children aged 8–18 years. These state laws[178] are broadly replicated in the national best practice recommendations of the US Preventive Services Task Force.[461] Similar laws or guidance exist in many other countries (eg, the European Union [EU], UK, Australia);[462–464] however, such regulations are not universal, and even when in place, are inconsistently applied.[465]

Child abuse or non-accidental trauma has become more widely recognised as an important cause of TBI in infants and children. Since awareness of child abuse has increased and family risk factors have been elucidated, local programs have been developed in the USA and other countries to educate parents about the dangers and long-term effects of brain injury, and to provide caregiver relief and advice on coping skills for stress. In the USA, the concept of safe havens for children at risk of abuse has been advanced,[179] whereby parents who fear they might harm their baby or child can leave the child without risk of prosecution. These safe havens are often paediatric hospitals or family refuge shelters that provide emergency medical care for the child and assume protective custody until the appropriate state authorities can find a more definitive or optimum placement. Whether these legal remedies have reduced the incidence of TBI in these children is not clear, and the possibilities of

furthering the cycle of abuse in alternative placements has not been studied.[466] More research is therefore needed to understand the effectiveness of this and other potential interventions, along with efforts to educate caregivers and others involved in the lives of children and adolescents to prevent TBI in this vulnerable group.

[H3] Prevention of TBI in the elderly

Prevention strategies need to take account of changing epidemiological patterns, which show increases in fall-related TBI in older individuals (section 1).[41,94,180–183] Frail elderly people are more likely to fall, more likely to suffer a TBI when a fall occurs, and more likely to suffer long-term adverse effects even from a seemingly mild TBI.[524] There is a clear need, therefore, to address causal risk factors and to explore preventive strategies that address the association between frailty and vulnerability to TBI through falls.

Assessment of frailty now involves the use of validated tools, and can be implemented as part of health policy.[184] Such assessment is clearly important as a primary TBI prevention strategy. Detection of frailty can trigger assessment and modification of the home environment (including the provision of safety rails for stairs and steps), and prompt critical evaluation of the risk–benefit ratio of drugs that increase the likelihood of an adverse impact of falls (eg, sedative drugs and medications associated with postural hypotension, and anticoagulant and antiplatelet drugs). Frailty assessments (and subsequent interventions) were originally the domain of geriatricians rather than primary care physicians, and initial trials focused on reducing falls and fall-related injuries in acute hospital settings.[185] However, emerging data suggest that these interventions can be more usefully applied in primary care.[186] An example is the Stopping Elderly Accidents, Deaths, and Injuries initiative of the US Centers for Disease Control and Prevention (CDC).[187] Risk assessment for falls, followed by implementation of an individualised management plan, has been shown to reduce falls by 24%,[188,189] highlighting the crucial importance of fall prevention in the elderly as a highly effective TBI-preventive approach.

[H3] Prevention of sports-related TBI

Ongoing research aims to determine the long-term consequences of single concussive injuries. However, increasing evidence indicates that multiple concussive and subconcussive impacts can have cumulative effects, including more severe symptoms and more prolonged recovery than after a single injury of similar severity, as well as increased vulnerability to brain injury and heightened risk of any subsequent injury.[190,191] In children and adolescents, there are additional concerns about

cumulative cognitive and behavioural sequelae of multiple concussions on brain development and learning.[192] Children and young adults are also at increased risk of second-impact syndrome.[122,123]

These emerging concerns underscore the importance of immediately removing anyone from play when there is any suspicion of a possible TBI. This recommendation is highlighted in training programmes for coaches and parents but, unfortunately, is not always applied in professional sports. During the FIFA (Fédération Internationale de Football Association) World Cup in 2014, there were several incidents of apparent concussion in players who were allowed to continue play, which led to a change in the FIFA Medical Committee's protocol, whereby a team doctor now has the responsibility and sole authority to make an assessment about suspected concussion and decisions about return to play.[193] We argue that professional sports organisations should be obliged to remove any player with a suspected TBI from play immediately, thus setting an example for amateur athletes and, in particular, young players. Such decisions should not be taken by interested parties (eg, coaches), but rather by a neutral party such as an independent medic or—if not available—the referee. Various international efforts have been initiated to develop, refine, and implement rational guidance for players, parents, and coaches about the time that needs to be spent away from training and contact sport following a concussion.[525,526] However, further refinement in diagnosis is needed, as is guidance on action required when concussion is reliably diagnosed.[194,195]

[H3] Key messages and recommendations

(1) TBI is, to a great extent, preventable, and societies can achieve considerable gains by decreasing its occurrence. Policies aimed at reducing the burden of TBI should focus on awareness campaigns and prevention of TBI in general, and on strategies to specifically target high-risk groups.

(2) In LMICs, the incidence of TBIs due to traffic incidents is increasing. The recommendations of WHO on road safety[158] need to be implemented in all countries.

(3) Children and adolescents are at particularly high risk of accidental TBI. Prevention programmes should target contexts in which such injuries typically occur—eg, promotion of better car safety worldwide, promotion of helmet use by bicycle and motorcycle users and in sports such as ice hockey, and education for coaches and parents of children who participate in sporting activities are needed.

(4) Non-accidental injury is an increasingly recognised cause of TBI in infants and children, and although some policies to reduce this risk are currently in place, their effect is uncertain. Further

research is needed to evaluate current initiatives and to explore new options for reducing TBI due to child abuse.

(5) In HICs, epidemiological patterns of TBI are changing, with an increase in elderly patients with TBI-related falls. Prevention programmes and health-care delivery need to be tailored to these changing epidemiological patterns, and specifically to prevention of falls in the elderly.

(6) Repetitive concussions that occur before recovery from an initial concussion can be associated with more severe symptoms and more prolonged recovery than a single injury of similar severity; therefore, any risk of an early second injury after even a mild TBI should be avoided. Professional sporting organisations should set an example for children and amateur athletes by immediately removing from play anyone with a suspected concussion.

Section 4. Systems of care for TBI

In an ideal world, all patients would have access to optimum care for traumatic brain injury (TBI), meeting standards of best practice, with continuity of care guaranteed from prehospital to postacute care. In reality, systems of care for patients with TBI show substantial variation between and within countries,[196–199] with disconnects in the trauma chain, particularly between acute and postacute care. Understanding such variation is crucial: practice variations influence TBI outcome and health-care costs (section 2), and broad implementation of best practices and guidelines to improve care pathways has great potential for improving cost-effectiveness and overall outcome after TBI.

The spectrum of clinical care for TBI extends from immediate on-site emergency care (lasting minutes to hours) to long-term postacute care (extending for years or even a lifetime). This care pathway includes several decision points with competing options for care (figure 5). Appropriate choices can enable delivery of high-quality, cost-effective care, whereas poor choices incur the risk of disrupting continuity and reducing quality of care. Variations in systems of care are largely driven by differences in resource availability, local practice, financial frameworks,[200] and physician preferences, in addition to a general lack of strong evidence to support guideline recommendations.

Figure 5: **The chain of trauma care for traumatic brain injury**

The pathway of trauma care—from on-site emergency care to postacute care—includes several decision points. Continuity of care through the trauma chain enables delivery of high-quality, cost-effective care. Any delays or inappropriate interventions at these decision points, or miscommunication between links in the trauma chain, can reduce quality of care and lead to increased risk of complications, poorer recovery, or death.

In this section, we discuss the current structure and practice of health care for patients with TBI, focusing on variations in systems of care in the prehospital, acute, and postacute phases, and we consider the cost-effectiveness of interventions. We also address specific challenges in low-income and middle-income countries (LMICs) to understand the barriers and opportunities for implementation of improved systems of care and best practice.

[H3] Prehospital care

Prehospital care marks the start of the chain of trauma care and comprises various components: first responders, dispatch systems, basic response, mobile medical team, helicopter emergency medical services, and hospital choice.[201] Together, they form the essential bridge to definitive care. The concept of the initial post-injury golden hour is especially pertinent to TBI. Suboptimal care in the prehospital phase could result in a progressive cascade of events with detrimental effects throughout the subsequent disease course.

Lack of adequate prehospital care is a particular problem in LMICs (panels 3, 5, 6, 7). The BEST-TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial,[202] conducted in Bolivia and Ecuador, showed that a third of patients with severe TBI were brought to hospital in vehicles other than ambulances, and long transit times were reported. In high-income countries (HICs), large variations exist in the structure and processes of prehospital care.[203–207] Several specific questions remain to be answered—eg, whether it is beneficial to spend time stabilising patients at the scene of injury before transfer rather than transferring them to hospital as rapidly as possible (so-called stay and play *vs* scoop and run). Whether transfer teams should include physicians, and when the use of helicopters becomes clinically beneficial and cost-effective also remain unclear. A survey conducted in 71 neurotrauma centres in Europe revealed striking differences in dispatch systems (23% dynamic *vs* 73% selective), in basic response (58% advanced life support *vs* 41% basic life support), and with regard to policy at the scene (35% scoop and run *vs* 51% stay and play. Uncertainty exists about best practice and whether this should depend on local settings (eg, rural or urban) and distances between the injury location and the hospital (general or specialist) offering care.

Panel 5: **Challenges for traumatic brain injury care in Latin America**

Although intensive care unit (ICU) management in Latin America often meets high standards of care despite resource and funding limitations, such facilities are not universally available,[554] and prehospital and postacute care are underdeveloped. Over a third of patients with traumatic brain injury (TBI) arrive at hospital in vehicles other than ambulances,[202] and ambulances generally provide only transportation without major resuscitation interventions. In the post-ICU phase, nurse-to-patient ratios are very low, much routine care is left to families, and rehabilitation services are largely unavailable. In a recent clinical trial, none of the 324 study participants received rehabilitation care.[202] Although the risk-adjusted ICU death rate is similar to that for high-income countries (HICs) at 14 days, mortality after ICU discharge is three times higher.[202] Since post-ICU support does not match the high level of ICU care, the benefits on long-term outcome are compromised. These deficiencies could be addressed not only through increased resource allocation, but also by implementing change at the systems and policy levels to improve TBI outcomes in LMICs. Prospective trials of specific interventions (eg, physiotherapy, inpatient rehabilitation) are impossible in HICs, where their availability is standard, but are feasible and ethical in LMICs. When appropriate decisions are taken at each step in the care pathway and the links in the trauma chain remain connected, high-quality care with positive outcomes can be achieved (panel 6). Access and continuity of care should, however, be structurally assured, and not dependent on chance or socioeconomic privilege.

Panel 6: **When all the pieces fall into place—a patient testimony**

In 1988, at the age of 12 years, Laura E Gonzalez-Lara fell down an orchestra pit and suffered a traumatic brain injury (TBI) as she took part in a concert in a small town in Mexico. In the following patient testimony (abridged), Gonzalez-Lara describes what is possible when high-quality, joined-up acute and postacute care are made available, even after a delay in the identification of TBI. At present, such care is inconsistently available to patients in low-income and middle-income countries. Gonzalez-Lara benefited from the support of her parents, both physicians, and extended family. For the full testimony, see appendix.

Hospital presentation and admission

During the fall, I fractured my skull, causing a tear in one of the blood vessels overlying the brain. At the time, I only complained of a headache. We went through with the concert, though I was feeling short of breath by then and felt the stage lights were too bright: I could not actually play and only pretended by moving my fingers. Later, as we were getting on the bus, I felt nauseous and vomited. It was on the bus where I finally lost consciousness. Back in my hometown of Puebla, my mother immediately took me to the local university hospital where she was an attending physician. By the time I arrived, my Glasgow Coma Scale score was estimated to be around 7. I benefited from the combined experience of two neurosurgeons to evacuate the haemorrhage roughly 5 hours after the fall. Next morning, I was transferred to the best intensive care unit in the city by ambulance.

Postacute care and rehabilitation

Before the week was over, a physiatrist prescribed exercises for my parents to do with me. By the end of the week, I was able to walk and move my right arm. I was released from the hospital a week and a day after the fall to the care of my parents at home. My physiatrist followed up regularly during the first month and adjusted exercises as needed. I had absence seizures and was on anticonvulsant medications until I was around 21 years old. I had regular blood work, electroencephalograms (EEGs), and follow-ups with neurologists and neurosurgeons to make sure everything was under control. The other sequela that lingered was a short-term memory impairment. I continued to work on fine motor

control for some time; after several months, I was playing the recorder and the flute again and even rejoined the orchestra.

Panel 7: **Evolution of traumatic brain injury care in China**

Care for patients with traumatic brain injury (TBI) in China is coordinated primarily by neurosurgeons. Progress of Chinese neurosurgery, first founded with Russian cooperation in the 1950s, was completely halted during the Cultural Revolution from 1966 to 1975. Since then, the implementation of modern imaging and monitoring equipment has advanced TBI care. This process has been enhanced by periods of training for Chinese neurosurgical trainees in Europe and North America. Improved systems for prehospital management and transfer to nearby (level I or level II) trauma hospitals have gradually been implemented. The 120 free-call emergency telephone system has been set up in most areas of the country to facilitate rapid response and quick transportation.

In the past decade, the rapid economic growth in China has been accompanied by substantial advances in the care of patients with TBI. Specific gains have been achieved through legislation on alcohol and driving, improved prehospital management, increased access to CT scanners, wider availability of neurosurgical services out of hours and at weekends, and increased access to neurointensive care. Teaching programmes and other implementation strategies have increased awareness of the importance of guideline-based management of TBI. Chinese TBI guidelines have been issued for management, drug treatment, intracranial pressure (ICP) monitoring, and decompressive craniectomy.[251–254] Catheters for ICP monitoring, however, still need to be paid for by patients' families, resulting in a low rate (24·5%) of ICP monitoring for severe TBI in China.[82] International collaborations are increasingly being established, facilitating integration of Chinese research into the international community. Comparative analyses that emerge from such collaborations provide cause for optimism: mortality and unfavourable outcome after severe TBI (Glasgow Coma Scale scores 3–8) in specialised centres are 22% and 50%, respectively,[82] which compare favourably with reported rates in HICs.[102]

Nevertheless, despite these advances, long transport times from the scene of accident to hospital are common because of large distances or major traffic jams in most Chinese cities (very few patients with severe TBI are transported to hospital by helicopter or medical airplanes). Further challenges include incomplete cost coverage, as well as shortages of trained neurosurgeons and limited access to specialist care, especially in the western regions of China and outside large cities. Moreover, the implementation of evidence-based management across China still has a long way to go. Despite efforts towards standardisation, use of treatments without proven therapeutic effects, such as neuroprotective agents, is common, and many neurosurgeons in China still treat patients with TBI according to their personal experience. Increased awareness of these challenges is needed to guide health policy and direct investment to close the gaps in TBI care in China.

These uncertainties about the delivery of prehospital care for TBI, and the involvement of multiple emergency providers (paramedic, fire, and police services), highlight the need for clear and widely accepted practice recommendations for prehospital trauma care. Evidence and experience from settings in which risk of TBI is high, such as military settings, might support the development of recommendations more broadly.

As with civilian TBI, a key consideration in military settings is the need for an integrated and effective chain of care throughout the casualty care continuum, including battlefield first-responder care, tactical field and evacuation care, and subsequent care across the global military care system.[145] While developments in military medical care in the past decade have clearly made a substantial contribution to improved overall survival rates for military personnel injured in conflict areas,[146,519] advances in the treatment of TBI, especially on the battlefield and in the postacute phase, have been less impressive.[146,527] In more severely injured patients, potential challenges in this context include triaging intracranial bleeds and the stabilisation or treatment of concomitant polytrauma accompanying TBI at the point of injury and during transportation to specialist trauma centres, which can provide the advanced multidisciplinary expertise needed for optimal management of TBI.[146] TBI-related disabilities pose formidable challenges for treatment and rehabilitation, and strategies to address these issues include ambitious plans to bring advanced care closer to the injury location to ensure rapid intervention within the golden hour.[147] These advances are important not only for military TBI (and trauma in general), but also for civilian TBI, since the technologies and systems developed and refined through these initiatives can inform civilian TBI care.[147]

[H3] Hospital care

Controversy exists about whether patients with more severe TBI should be transported to the nearest hospital or taken directly to a specialist trauma centre with specialist care facilities that should encompass neurosurgery, neurocritical care, neuroradiology, and neurorehabilitation. This controversy is partly due to challenges in reliably diagnosing and categorising the severity of TBI at the scene of injury. Retrospective analyses[210–212] of administrative and registry databases suggest that transfer from non-specialist hospital settings to specialist trauma centres, and possibly to high-volume centres, can reduce mortality and improve functional outcome and cost-effectiveness. Additionally, many studies suggest that care in centres that practice intensive protocol-driven therapy (typically including intracranial pressure [ICP] monitoring) is associated with lower mortality and better outcomes in patients with severe TBI.[213–218] Although the benefits of concentration of care are generally accepted for patients requiring neurosurgical intervention, identification of such patients at the scene of injury is seldom possible—in one study, only 7% of patients triaged with TBI required neurosurgery.[209] Consequently, policies regarding primary transfer to trauma centres vary widely.

Transfer to specialist centres might also benefit patients who do not require operative neurosurgical intervention at presentation. Supporting evidence comes from registries,[210] and from the large

prospective RAIN (Risk Adjustment In Neurocritical care) study of patients with TBI who required intensive care, which corrected for key known covariates.[219] This study showed substantial improvements in the risk-adjusted odds ratio for mortality (0·52, 95% CI 0·34–0·80) in patients treated in a specialist trauma centre compared with those who were managed in non-specialist centres.[219] An equally important consideration is identification of patients who do not benefit from acute transfer to a specialist centre, since avoidance of such transfers could have substantial health-economic and social benefits. Additionally, there are clear risks of transfer, such as deteriorating oxygenation or low blood pressure, which could be detrimental even at levels above the commonly quoted systolic threshold of 90 mm Hg.[220] These risks need to be balanced against the advantages of care in a specialist centre, which include specialist expertise and other supportive services, the benefits that accrue from increased caseload, and more rapid access to neurosurgical intervention if the need for surgery emerges. Furthermore, for the most severely injured patients, experience and multidisciplinary approaches are essential to deal professionally with questions concerning diagnosis of brain death and possible organ donation. Despite some uncertainty and inconsistent implementation, authoritative national and regional guidelines recommend the transfer of patients with more severe injuries to specialist centres,[221] and although not completely implemented, this practice seems to show outcome benefits for adults with severe TBI in some settings.[218]

Overall, the evidence for centralisation of care in specialist centres is stronger for paediatric TBI, particularly for more severely injured children and adolescents.[222,223] At the milder end of the TBI spectrum, dissemination of knowledge about best care of patients with TBI to community professionals, who manage the vast majority of children and adolescents with minor or mild TBI, might be more advantageous. In adults and children, the effects of so-called mild TBI should not be underestimated: postconcussion symptoms have been reported in up to 64% of patients with mild TBI.[224,225] Written discharge instructions and standard follow-up care, either in the hospital outpatient setting or by general practitioners, are advocated but inconsistently implemented. A survey of 71 European neurotrauma centres[528] found that the majority of centres (n=54, 79%) had printed discharge information available for patients with mild TBI who had been seen in the emergency department, but that only 10% of centres routinely scheduled follow-up visits for these patients.[226]

[H3] Postacute care

For the postacute phase, there are great disparities in systems of care and patient management between countries, within countries, between institutions, and even from patient to patient within

centres of care. A common disconnect between acute and rehabilitation services further compounds these problems. Inadequate access to rehabilitation services can slow or complicate recovery, increasing the burden of care and compromising functional outcomes. Patients who experience discontinuities in care have poorer outcomes than those in whom the chain of rehabilitation is continuous.[227]

A substantial proportion of people with severe TBI regain functional independence between 1 and 5 years after injury,[228,229] but this depends on provision of specialised neurorehabilitation.[230] In practice, many patients (up to 55%) are discharged home or referred to a non-specialist facility after acute care—often without any referral to rehabilitation therapy.[231,232] This raises questions about equity of access to health care, which should be high on the policy agenda.

[H3] Cost-effectiveness of systems-level management strategies

Although the clinical benefit of care for patients with severe TBI in specialist trauma centres has reasonably wide acceptance, formal assessments of the cost-effectiveness of such strategies are scarce. The RAIN study suggested that transfer to specialist trauma centres was cost-effective, even when neurosurgical intervention was not indicated.[219] An analysis from the UK National Institute for Health and Care Excellence (NICE) found that adoption of algorithms for the selection of patients with TBI for CT imaging of the head and spine, incorporated into NICE guidelines for TBI management, was cost-effective.[221] However, a recent systematic review showed that evidence of economic benefit was not available for most other interventions for TBI (panel 8), and much of the existing evidence was of poor quality.[233]

Panel 8: **Cost-effectiveness of interventions for traumatic brain injury**

- Selective secondary transfer to specialist trauma centres for patients who present with a Glasgow Coma Scale score of less than 9 at the injury scene: could save £20 000 per quality-adjusted life-year* (QALY) gained.[209]
- Management of patients with TBI in dedicated specialist trauma centres: could save £14 000 per QALY gained.[239]
- Early transfer of patients with TBI to specialist trauma centres in the absence of need for definitive neurosurgery: could save £11 000 per QALY gained.[239]
- Liberal use of computed tomography (CT) scanning in children and adults with suspected mild TBI on the basis of a high-sensitivity decision rule: could save costs and gain QALYs. [236, 237]

- Selective CT scanning of adults with mild TBI on the basis of the Scandinavian Neurotrauma Committee Guidelines , with addition of the biomarker S100B: could save up to €71 per patient if guidelines are strictly followed.[238]
- Management of patients with severe TBI according to the Brain Trauma Foundation Guidelines: implemention across the USA could yield societal savings of more than US$3 billion.[155]
- Early initiation of continuous chain of rehabilitation care: could save more than US$4000 per patient.[227]

Cost-effectiveness analyses are not available for many TBI interventions, and for those that are available, the evidence is mainly of poor quality. *One quality-adjusted life-year corresponds to a year spent in perfect health.

Evidence on the cost-effectiveness of rehabilitation interventions for TBI is also inadequate. A US National Institutes of Health (NIH) consensus statement in 1998[234] noted a scarcity of quality publications on this topic and made recommendations to address evidence gaps. There has been little progress since then. Some organisational approaches, such as the appointment of a case manager to facilitate rehabilitation access, have face validity and are highly valued in anecdotal accounts from patients and families, but there has been little formal evaluation of cost-effectiveness.[235] By contrast, a recent decision-tree analysis of rehabilitation for TBI concluded that, compared with a broken chain of care, adopting a more integrated approach yielded a clinically relevant decrease in disability, while saving more than US$4000 per patient.[227]

Good data on cost-effectiveness of systems of care for TBI are crucial for planning resource allocation and for identifying the most cost-effective interventions. Such data need to be viewed in relation to local case mix, resource availability, and cultural contexts. Thus, patients with mild and severe TBI will have different rehabilitation needs, and survivors who have the support of extended family might have different rehabilitation needs compared with those who do not. Different treatment recommendations might apply to different subgroups, and cost-effectiveness models should be developed separately for each subgroup. Sensitivity analyses are essential when cost-effectiveness assessments are undertaken in potentially heterogeneous groups.

[H3] Specific challenges in low-income and middle-income countries

About 90% of trauma-related deaths occur in LMICs.[460] Disability-adjusted life years (DALYs) due to injury progressively rise with decreasing national income levels.[240] Moreover, the relative proportion of TBI in injury cases is greater[241] and the odds of dying as a result of TBI are more than doubled in

low-income settings.[242] These poorer outcomes are caused largely by insufficient prehospital services, lack of postacute care, and inconsistent access to care (panels 5, 7). In particular, the lack of postacute care could offset any potential benefit obtained in the acute phase. However, notwithstanding the substantial burden of disease, disability, and death in LMICs, the development of centres of excellence in TBI treatment has meant that many of these countries are strong contributors to international TBI research—eg, in influential international randomised controlled trials (RCTs), such as the CRASH (Corticosteroid Randomisation After Significant Head injury)[243] and CRASH-2[244] studies—and occasionally they provide the sole context for key studies, such as the BEST-TRIP trial[202] of ICP monitoring in TBI. This involvement in knowledge generation has not yet been translated to international clinical guideline development—a disparity that reflects the narrative of the 10/90 gap [245] within the context of a single disease.

There is a pressing need to involve LMICs in the guideline development process, beginning with centres of excellence and taking advantage of local developments that might provide opportunities for change. For example, the recent Indian Transportation Research and Injury Prevention Programme report[246] provided a comprehensive assessment of road safety in India, and triggered policy initiatives[247] that promise to improve emergency trauma care along key national highways. These operational guidelines, published by the Indian Ministry of Health and Family Welfare,[248] aim to reduce case-fatality rates from road traffic incidents to 10% by developing a pan-Indian trauma care network, where designated basic (level III) trauma centres, which have facilities and personnel for resuscitation and onward transfer, are available roughly every 100 km. Emergency neurosurgical interventions would take place in more specialised (level II) trauma centres, available roughly every 250 km on key national highways, and could in some cases be done by general surgeons with some neurosurgical training, thus increasing access to emergency neurosurgery within the limitations of existing resources. Other countries also need to develop their own health-care strategies in the context of local priorities and resources (section 3).

[H3] Current challenges and future goals

Management of patients with TBI is complex and requires appropriate expertise, coordination, and organisation. Timely interventions delivered by well coordinated multidisciplinary teams of experts will increase the opportunities for optimising outcome. However, there are wide variations in systems of care throughout the trauma chain, and evidence for best practice to inform guidelines is lacking, especially for prehospital and postacute care. Therefore, there is a pressing need for new evidence to support clinical recommendations, but in the absence of robust evidence, expert

consensus-based recommendations are preferarable to no recommendations (section 9). The wide variations in systems of care lend themselves to novel approaches such as comparative effectiveness research (CER; section 9) to determine best practice. High-quality cost-effectiveness studies of TBI interventions are also warranted to establish the optimum systems of care and to improve access to acute and postacute care in particular.

With regard to hospital care, the cumulative evidence strongly suggests that patients with more severe TBI benefit from transfer to specialist trauma facilities, irrespective of whether or not they need definitive neurosurgical intervention.[210–212,219] Implementation of such a policy is not simple, and requires adequate infrastructure and clear communication. Crucially, such initiatives need to be supported by high-quality practice recommendations that reach and influence key clinical stakeholders. The creation of a network of major trauma services in the UK, for example, along with the clear national guidelines for TBI triage, has increased compliance with current best practice[249] and improved outcomes.[250] However, the available infrastructure (eg, number of beds in trauma centres) could make full compliance with guidelines difficult. Success of any strategies will therefore depend not only on effective knowledge transfer to clinical practitioners (section 9), but also on allocation of adequate resources to make changes in practice possible. Achieving improvement is an incremental process, and the gains that are targeted (and achieved) will need to take account of local health-care systems and resources.

The rigorous assessment of needs and the articulation of effective policies are particularly relevant to LMICs. Some LMICs are moving towards models of care delivery, which, although ambitious by recent standards, adopt pragmatic approaches to specialist care, such as the policy initiatives[246–248] to reduce road traffic incidents and improve emergency trauma care in India. The challenge in these settings is to allocate new resources in ways that best serve local needs, rather than using frameworks developed for the health economies of HICs.

[H3] Key messages and recommendations

(1) Access to health care is often inconsistent between centres, regions, and countries, especially for acute and postacute care. Health-care policies should aim to improve access to acute and postacute care to reduce the effects of TBI on patients, families, and society.

(2) Substantial variation exists in systems and quality of care for TBI between centres, regions, and countries. For systems or interventions for which best practice is reasonably well defined, such approaches should be used as a treatment standard to improve quality of care. In cases for which best practice is not defined, increased funding to identify best practice is needed.

Implementation of best practice could improve patient outcomes and cost-effectiveness of TBI care.

(3) For optimum care, patients should be moved along a chain of trauma care, from prehospital though to postacute care, with excellent communication between caregivers. Improving systems of care for patients with TBI and ensuring continuity of care—through urgent and acute care, rehabilitation, and community reintegration—should be high on the policy agenda.

(4) Centres with higher caseloads and specialised facilities have better outcomes for patients with severe TBI than do smaller centres. Incentives need to be implemented to stimulate transfer of adult and paediatric patients with severe TBI to specialist centres.

(5) The epidemiology of TBI and challenges of TBI care in LMICs are different from those seen in HICs. Solutions for improving TBI care and outcomes in LMICs should be tailored to local needs and resource availability, rather than replicating strategies in HICs.

Section 5. Clinical management of TBI

Management of traumatic brain injury (TBI) is currently based on a combination of medical and surgical strategies, and, ideally, rehabilitation to promote recovery and social reintegration and address the longer-term complications of TBI. However, many randomised controlled trials (RCTs) of interventions for TBI have not shown beneficial effects, or have produced results that cannot be generalised to the wider population of patients with TBI. Therefore, when guidelines are available, they are often based on weak evidence, supplemented by expert consensus or local protocols (section 9).

Clinical management in the intensive care unit (ICU) has evolved over the past two decades towards standardised approaches. The international guidelines that underpin these approaches are based on evidence from selected patient groups or on targets derived from population averages, which might not apply to all patients. Although efforts to develop evidence-based guidelines for routine use in the ICU are a step in the right direction, this one-size-fits-all approach ignores the complex clinical and mechanistic heterogeneity of TBI.

International guidelines for the surgical treatment of TBI are not supported by strong evidence, and are implemented inconsistently across geographical regions. Furthermore, there is considerable uncertainty and debate about which subgroups of patients might benefit most from some types of surgery and the optimum timing of surgery. The decision to operate might be influenced by local policy or the surgeon's experience, and also depends on other factors, such as alternative medical options, expected outcome, and patient and family preferences.

Evidence-based guidelines are not available for most rehabilitation interventions. Even when there is recognised best practice, implementation is inconsistent between centres, and often does not account for the diversity of disability after TBI, which warrants individualised application of robust recommendations.

In this section, we consider the challenges in medical, surgical, and rehabilitation management of TBI, and emphasise the need for more robust evidence to underpin guidelines. Such guidelines should allow a flexible approach to enable better targeting of treatment based on improved understanding of individual pathophysiology and clinical needs.

[H3] Intensive care management of severe TBI

Before transfer to the ICU, the priorities for initial hospital care are stabilisation of the patient, and rapid detection and emergency surgical treatment of intracranial bleeding (see below). In the ICU,

current guidelines for the medical management of TBI emphasise prevention of second insults, such as hypoxia and hypotension, and, for patients with severe TBI, optimisation of cardiorespiratory physiology, control of intracranial pressure (ICP), and maintenance of cerebral perfusion pressure (CPP).[255] Initial ICU management comprises a range of medical approaches to attain these targets, including sedation, hyperosmotic infusions (to reduce brain oedema), limited hyperventilation (to reduce intracranial volume through hypocapnic cerebral vasoconstriction without causing ischaemia), drainage of cerebrospinal fluid, and varying degrees of temperature control (ranging from meticulous control of normothermia to induced hypothermia). Aggressive cooling (to core temperatures of 32–34°C), deep sedation (to achieve deep metabolic suppression as evidenced by a near-isoelectric encephalogram [EEG]), more intensive hyperventilation, and decompressive craniectomy (removal of a portion of the skull to accommodate brain swelling) are often classified as third-tier therapies and reserved for patients with refractory ICP elevation.[256] Such stratification, with prioritisation of more conservative medical approaches, is rational since none of these treatments is risk-free and they can be associated with a worse outcome.[257,258] However, some clinical trials of these interventions have not replicated common clinical settings or timing of interventions in clinical practice.[259,260]

Current treatment approaches aim to maintain single target values (or target ranges) for ICP and CPP, derived from analyses in populations of patients with TBI.[255] Evidence in support of this single goal-directed approach is inconsistent: one meta-analysis suggests benefit from treatment in a centre with ICP-driven management,[261] but two meta-analyses suggest no overall benefit from aggressive, ICP-guided management.[262,263] The only available RCT on this approach to management, from Latin America, suggests that clinical care based on imaging and serial clinical examination is not inferior to care based on ICP-guided management—at least in that setting.[202] The generalisability of these results, from low-income and middle-income countries (LMICs), to practice in high-income countries (HICs) is debated, since substantial differences in the chain of trauma care exist between the two settings (panel 6).

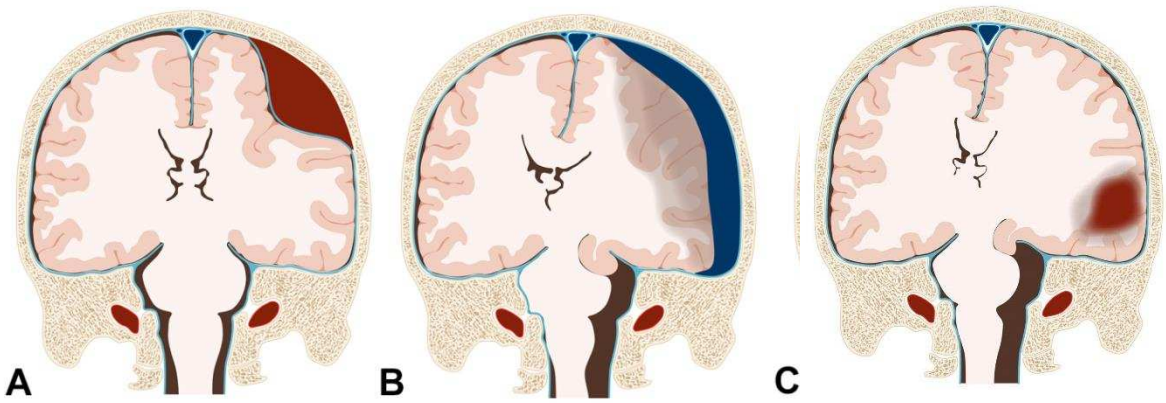
A number of neuromonitoring modalities (ICP measurement being the best known) can be used to detect incipient secondary injury. However, all these techniques, taken in isolation, are at best indirect, and at worst crude measures of a complex disease in a very complex organ. Therefore, proving efficacy of treatments on the basis of such unidimensional targets is challenging. Furthermore, there is a lack of certainty about the thresholds that justify therapies for raised ICP, all of which have intrinsic hazards; these hazards should be balanced against the harm caused by intracranial hypertension. Therefore, characterisation of a clinically relevant dose (level and

duration) of intracranial hypertension remains an important goal[264] and is only just beginning to be quantified in a systematic way.[265] The recently updated international guidelines for management of severe TBI recommend an ICP threshold of 22 mmHg for initiating intensive treatment.[255] However, there have been challenges that the implicit precision of this threshold is unfounded.[467,468] Moreover, although population-based targets of ICP and CPP management provide a useful initial basis for care, required target values or ranges might depend on the specific pathology[529,530] and should preferably be directed to the needs of individual patients. TBI is pathophysiologically heterogeneous, and the dominant pathological processes can vary between patients, within individual patients over time, and even between different parts of the brain at any given time. Furthermore, preinjury factors, coagulation status, and systemic responses vary between patients. Using a one-size-fits-all management strategy is therefore unlikely to be optimum, and more rational decisions about therapy choice and intensity must account for individual and temporal variations in pathophysiology.

[H3] Surgical management of TBI

Different types of traumatic intracranial haematoma exist (figure 6), all of which can compress the brain and could be life-threatening. Timely surgery can be life-saving, but this depends on rapid patient transfer to a centre with surgical facilities (section 4). Initial surgical treatment of TBI can be either causally directed (eg, to remove space-occupying intracranial haematomas)[266] or symptomatic (eg, to decrease pressure on the brain to prevent or minimise damage to important structures and prevent life-threatening herniation events). Symptomatic approaches include insertion of an external ventricular drain for drainage of cerebrospinal fluid[267,531] and decompressive craniectomy, which can be performed in the same setting as the evacuation of a haematoma, or later to treat diffuse brain swelling that is refractory to conservative medical management.

Figure 6: **Different types of post-traumatic intracranial haematoma**



(A) Epidural haematoma. Epidural haematomas are located between the skull and the outer membrane covering the brain (dura mater). They are mostly arterial in origin and can thus rapidly expand, causing clinical deterioration and—if untreated—death. (B) Subdural haematoma. Acute subdural haematomas are located underneath the dura mater, and are generally associated with bruising of the underlying brain tissue (contusions). (C) Haemorrhagic contusion or Intracerebral haematoma. These lesions reflect similar underlying pathologies that range from local bruising (contusions) to bleeding into the brain tissue (haematoma). Figure courtesy of Maartje Kunen, Medical Visuals, Arnhem, Netherlands.

There is substantial variation in surgical practice owing to an inadequate evidence base for international guidelines on surgical indications.[268–270] Additionally, at an individual patient level, there is debate among clinicians regarding which patients might benefit from some procedures (such as surgical treatment for traumatic intracranial lesions and for raised ICP) and uncertainty regarding the optimum timing of surgery. Surgery might be life-saving and preserve neurological function in some patients,[271] but others might survive with an unfavourable functional outcome, ranging from severe neurological and cognitive deficits to a persistent vegetative state.[272–274] Conversely, surgery might not always be necessary. Indeed, a substantial proportion of patients who are managed conservatively have favourable outcomes.[275–279] Therefore, when deciding whether to operate, medical therapies that might be effective in achieving the same physiological goals as surgery should also be considered. Surgical indications that are too liberal could lead to an increased number of survivors with complications of unecessary surgery in less severe injury, or severe disabilities in devastating TBI. Conversely, inappropriate conservative management might result in unnecessary death and disability. The decision to operate is based not only on medical but also on ethical considerations. Patients' and relatives' views of a meaningful quality of life might be different from our medical perception of a favourable outcome. These differences could depend on several factors, including cultural and religious considerations. If discussion of the expected outcome with relatives is possible, past views expressed by patients on an acceptable quality of life should be taken into account.[532]

Accumulating evidence provides useful support for such decision-making. An illustrative example is the use of decompressive craniectomy for intracranial hypertension. Although the procedure can be life-saving by lowering ICP, it is associated with surgical complications, and structural distortions associated with removal of a portion of the skull might cause additional brain injury in some patients.[280] Initially used over a century ago, the intervention came back into use over the last two decades, but given the need to balance risks and benefits, a clear definition of its role was difficult.[281–283] Two important RCTs have provided useful guidance in this context. The DECRA trial[257] showed

that very early use of decompressive craniectomy for modest rises in ICP in patients with diffuse injuries was associated with worse outcomes. More recently, the RESCUEicp trial[284] showed that, when used for refractory severe intracranial hypertension, decompressive craniectomy can save lives, but resulted in a 9% increase in survival with severe dependance at 6 months. However, by 12 months there were 13% more survivors who were at least independent at home. As the intervention is not uniformly beneficial, individual wishes should be taken into consideration.

Other studies have addressed similar surgical dilemmas. A recent study suggested that in patients with a traumatic acute subdural haematoma, early evacuation was associated with better outcome than a more conservative approach.[285] Similar trends were noted in the STITCH trial, [286] which reported better outcome with early surgical management in patients with traumatic intracerebral haematoma. However, the results of the STITCH trial were not statistically significant owing to an inadequate sample size caused by premature discontinuation of the trial by the funding agency.[286] Although surgical trials are challenging, funding bodies should recognise that these and ongoing studies (eg, the RESCUE-ASDH trial, ISRCTN registry identifier ISRCTN87370545) are crucial for creating a rational evidence base for surgical practice. Clinical decision-making could be greatly improved by identification of patient subgroups most likely to benefit from the intervention, and, importantly, patients who are not likely to benefit.

[H3] Rehabilitation after TBI

The sequelae of TBI include long-term physical, cognitive, behavioural, and emotional impairments (panels 2, 7), and difficulties with activities of daily life, community integration, work, social life, family functioning, and partner relationships (section 7). [484] Rehabilitation for patients with TBI is a complex process, and varies with time after injury, the nature of TBI, premorbid functioning, and levels of social support.[230]

Succesful rehabilitation after TBI is determined by patient potential, and depends on both the timely delivery of therapy and the availability of good metrics to characterise the intensity and effects of such therapy. Recent summaries of the available data report that strong evidence in support of many rehabilitation therapies is limited, However, these summaries largely concentrate on evidence from RCTs, which are difficult to design and conduct in this area. As in other areas of TBI (see Section 9), this makes the case for alternative approaches for clinical evidence generation to underpin practice.[558,559] Medical or health-care insurance payors often justify bypassing specialised rehabilitation programmes by highlighting the absence of RCT evidence for rehabilitation strategies in TBI, and disparities exist in the level of postacute care provided depending on insurance status and

race.[287,533] Acquisition of stronger evidence in support of rehabilitation therapies is challenging. First, treatment would need to be withheld from the most severely injured patients who are most in need of care, which is uncommon in other specialty areas. Second, rehabilitation schemes should be targeted to the specific needs of individuals, which would complicate the design and implementation of clinical trials.

Different rehabilitation interventions are appropriate at different phases after injury (panel 9). In the subacute phase, the focus is typically on retraining activities of daily life and adjusting environmental factors that enable discharge home. In the longer term, rehabilitation goals focus on community reintegration, such as social participation, return to work, and other meaningful activities that restore quality of life. However, the optimum timing for rehabilitation is debated: some centres advocate early in-hospital initiation,[227] but most rehabilitation centres accept patients only when they are trainable—ie, after return of consciousness and once they are out of post-traumatic amnesia. Therefore, in practice, these goals are often addressed—if at all—by different health-care providers, and such services tend to develop in isolation. Rigorous studies are needed on best practice in the acute setting and optimum timing of specific rehabilitation approaches.

Panel 9: **Categories of rehabilitation interventions for traumatic brain injury**

Restitutional rehabilitation

Strategies that focus on strengthening or re-establishing previously learned patterns of behaviour through repetition and rehearsal.

Example: repeated exercises and drills aimed at restoring specific cognitive domains, such as attention.[469]

Compensatory rehabilitation

Strategies that exploit intact strengths to substitute for impaired functions.

Example: use of assistive technology (eg, calendars, paging systems, electronic memory devices, and alarms) for mild-to-moderate memory impairment[470] and errorless learning strategies for severe impairment.[471]

Adaptive rehabilitation

Strategies that accommodate residual impairment or disability through reappraisal of self-perception (eg, cognitive restructuring); this relates to psychosocial adjustment after injury.

Example: problem-focused coping and management of self-efficacy beliefs (eg, reduced use of avoidance, wishful thinking, and emotional restrictions) to promote positive psychosocial adjustment.[472]

The diversity and complexity of the consequences of TBI are best addressed with a comprehensive, holistic approach to rehabilitation delivered by a specialised multidisciplinary team, in close liaison

with the patient and family or caregivers (the patient-centred care approach).[473] Evidence from two RCTs supports the effectiveness of holistic neuropsychological rehabilitation in both civilian and military populations.[474,475] This is consistent with the International Classification of Functioning, Disability and Health (ICF), which provides a framework for understading disability that is endorsed by the World Health Organization (WHO).[288] An important feature of the ICF is that it goes beyond traditional biomedical approaches to assessment of disability, providing a biopsychosocial, integrative, and comprehensive approach that incorporates factors such as health condition, body structure and function, activities and participation, and various contextual factors (personal factors and environmental factors) relevant to the patient. This is crucial because the level of functioning for a patient is determined not only by what is happening at the level of the body, but also by how the environment can affect overall disability level. This approach facilitates identification of rehabilitation needs and targets for intervention (panel 10). Further research on rehabilitation needs, type, quality, and effects of services is needed to guide clinicians in the use of appropriate interventions and policy makers in the development of rehabilitation services for individuals with TBI.

Panel 10: **Domains of rehabilitation and intervention targets after traumatic brain injury**

Physical
Speech, movement, sensation, perception

Behavioural
Initiation, persistence, flexibility, impulse control

Cognitive
Concentration, memory, executive function, communication

Emotional
Management of anger, irritability, anxiety, frustration

Personal
Family-related functioning, socialisation, schooling, employment

Environmental
Access to health-care services and technologies, transportation and mobility, community attitudes and social support resources

[H3] Future goals for intervention studies and guideline development

Clinical care for patients with TBI is often broadly based on international or local clinical guidelines. However, weaknesses in available evidence confound strong guideline recommendations, and most guidelines fail to capture the complexity and heterogeneity of TBI and its sequelae. The shortcomings in guidelines reflect the limitations of clinical trials in this field. Many clinical trials of medical and surgical interventions for TBI have involved strict protocols and recruitment criteria, typically restricted by age, Glasgow Coma Scale (GCS) score, and comorbidities. Despite these restrictions, such trials have largely failed to show benefit, perhaps in part because they have not accounted for patient heterogeneity and hence treatments have not been matched to individual patients or groups of patients.[260,289–291] In studies that have recorded a clinical effect of an intervention,[390] selected patient groups and small sample sizes have limited the generalisability of the results to the wider population of patients with TBI.

In view of the substantial knowledge gaps about optimum management and the challenges of conducting clinical trials of interventions for TBI, alternative approaches to evidence generation are needed for the development of robust guidelines for best practice. For example, conventional evidence-generation methods such as RCTs could be supplemented with comparative effectiveness research (CER; section 9), in combination with high-quality observational studies, to determine the optimum medical, surgical, and rehabilitation interventions and care models.

Future approaches to management and guidelines for best practice need to account for the clinical and mechanistic heterogeneity of TBI and enable therapies to be more carefully matched to patients. Clinical studies should be designed to identify (sub)groups of patients of sufficient size in whom the target mechanism is dominant. Patient stratification for clinical and research interventions will depend on improved characterisation of initial severity and mechanisms (section 6). Advances in outcome assessment are needed for rigorous evaluation of therapeutic effects (section 7), while improvements in prognostic schemes could inform research design, facilitate comparisons between studies, and provide opportunities for comparative audits to improve quality of health-care delivery (section 8).

Besides these general considerations, progress in specific aspects of care could lead to improved management. For example, technical advances in invasive and non-invasive monitoring of blood flow, brain metabolism, and electrical activity combined with neuroinformatic methods provide novel approaches to targeted therapy development and implementation in the ICU setting (section 6). Studies of surgical interventions for TBI should focus on identification of subgroups of patients most likely to benefit from surgery, rather than investigate its use across all possible patients. Future

guidelines should allow a flexible approach to take into consideration non-medical aspects such as patient and family preferences and beliefs about the value of life and acceptable levels of disability. There is a clear need for studies to inform guidelines on rehabilitation approaches and optimum timing of rehabilitation in TBI. Such guidelines would need to take into account the growing evidence that the diversity of disability after TBI is best addressed through a holistic approach to rehabilitation delivered by a multidisciplinary team.

A change in focus in the clinical management of TBI is required, with interventions based on an understanding of the pathophysiology and clinical needs of individual patients. Implementation of such an individualised approach to management should occur in the context of robust evidence-based guidelines. Thus, new studies need to be rapidly integrated into the evidence base and translated into guidelines that reflect the latest findings—aspirations that are being addressed through development of living systematic reviews and living guidelines (section 9). Implementation of such guidelines will necessitate effective transfer of the latest knowledge into clinical practice.

[H3] Key messages and recommendations

(1) Evidence underpinning guidelines for medical and surgical interventions and rehabilitation for TBI is weak. Increased funding is needed to develop robust evidence to inform medical, surgical, and rehabilitation management to improve outcomes for patients with TBI. Consensus-based guidelines might be needed for aspects of management for which evidence is not clinically definitive.

(2) Existing guidelines for clinical management, based on population targets, promote a one-size-fits-all approach and do not take into account clinical and mechanistic variability, either between patients or within patients at different stages of injury evolution. Research funding is needed for clinical studies that account for these differences. New evidence-based guidelines should emphasise implementation of best practice in the context of an understanding of individual pathophysiology and clinical needs, and permit flexibility to achieve an individualised approach to management.

(3) Existing guidelines are not implemented consistently between centres and across geographical regions. Information campaigns to improve awareness among clinicians about guidelines and recommendations for best practice are needed.

Section 6. Characterisation of TBI for precision medicine

Detailed characterisation of injury severity, type and expected outcome is needed to stratify patients with traumatic brain injury (TBI) for optimum clinical management. Such characterisation can also be used in research to classify goups of patients with similar disease mechanisms to develop and test novel therapies in RCTs or identify best practices in comparative effectiveness research (see section 9). Conventionally, the initial severity of TBI has been classified as mild, moderate, or severe, on the basis of assessment of the level of consciousness, measured with the Glasgow Coma Scale (GCS; figure 2).[294] However, this unidimensional classification ignores the mechanistic heterogeneity of TBI. Pathoanatomical insights into the nature of TBI have come from neuropathology studies,[300] which have highlighted the importance of ischaemic[476] and inflammatory[304] responses after TBI, and have led to the recognition of diffuse axonal injury[302,477] and chronic traumatic encephalopathy (CTE)[61,66,478] as specific entities in the acute and chronic phases of TBI, respectively.

In TBI, as in other diseases, specific interventions and management strategies need to be tailored to the characteristics and needs of individual patients, moving away from the conventional one-size-fits-all approach (section 5).[293] Improved characterisation and better understanding of pathophysiology in individual patients will be necessary to permit appropriate targeting of therapy and evaluation of outcome. This approach reflects the concept of precision medicine, as advocated by the US National Academy of Science,[291] which is defined as “an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle”.[292]

Opportunities for improvements in this area come from progress in the fields of genomics, blood biomarkers, and advanced magnetic resonance imaging (MRI), as well as new approaches to pathophysiological monitoring, coupled with informatics to integrate data from multiple sources (figure 7). These technologies are at varying stages of maturity in terms of integration into TBI clinical care: some, such as genomic stratification for therapy and outcome prognostication, are at a very early stage of development, while others, such as use of the blood biomarker S100 astroglial calcium-binding protein B (S100B) to stratify patients for CT imaging during the acute phase, have already been integrated into some clinical guidelines,[324] although not widely accepted.

In this section, we consider current approaches to characterisation of TBI, discuss the continuing relevance of neuropathological studies, and explore how incorporation of emerging technologies could improve disease characterisation and monitoring to advance the aims of precision medicine in TBI. We also consider the challenges and opportunities in integrating multiple sources of data to

facilitate translation of these aims. In subsequent sections, we discuss the need for multidimensional approaches to outcome assessment in patients with TBI (section 7), and consider how linking initial severity and pathoanatomical characteristics of TBI to multiple outcome domains could lead to improved prognostic models (section 8), with substantial benefits for patients and their families.

Figure 7: **Application of precision-medicine approaches to traumatic brain injury**

Findings from observational studies based on clinical medicine and from biomedical research can contribute to the body of evidence on TBI (the information commons) and knowledge can be combined and shared (the knowledge network) to improve characterisation of traumatic brain injury. Improved characterisation and understanding of the disease process will lead to more accurate diagnosis, targeted treatment, and improved clinical outcomes. ICU=intensive care unit.

[H3] Current approaches to classification and characterisation

There are wide variations in TBI type and severity. Additionally, the full, integrated picture of TBI comprises a range of pathological changes (eg, diffuse axonal injury, contusions, brain swelling, and brain(stem) compression by extracerebral haematomas), which contribute in varying degrees to the different clinical pictures in individual patients. It is common to separate penetrating TBI from closed TBI because the injury biomechanics are very different and the infection risk in penetrating TBI is higher. The management principles therefore differ substantially between penetrating and closed TBI. However, there has been little attempt to use the full range of pathoanatomical lesions—within both closed and penetrating TBI—in a systematic way as a basis for rational planning of management. Classification of TBI severity is also challenging: presentation can range from a hit to the head with symptoms of disorientation or some alteration of consciousness that quickly resolves, to high-energy insults leading to loss of consciousness and coma. There are currently no refined criteria for classification of TBI severity. The GCS[294] is the most commonly used approach to quantify the clinical severity of TBI[295] (figure 2), but this is relatively crude and does not reflect different pathoanatomical subsets of TBI. Moreover, the increasing use of prehospital sedation and tracheal intubation often confounds assessment with the GCS and has reduced its usefulness as a metric of injury severity.[296]

Existing International Classification of Diseases codes[479] also do not adequately capture severity of TBI.[534] Alternative TBI coding taxonomies—including the Abbreviated Injury Scale (AIS), which categorises severity of intracranial and extracranial injury,[297] and the Marshall classification system, which is based on head computed tomography (CT) findings[298]—are anatomically oriented and summarise the type, location, and severity of injuries. The AIS, which is used globally by trauma registries, classifies each patient's regional anatomical injuries, from which an aggregated Injury

Severity Score can be derived.[299] However, scoring with this scale is generally retrospective, and severity ratings can be influenced by factors such as admission to hospital or intensive care unit (ICU) or by decisions regarding surgical intervention. The Marshall classification system is unidimensional, being restricted to CT findings, and is essentially based on only two discriminating features: the need for surgery and radiological signs of raised intracranial pressure (ICP).

There is increasing recognition that appropriate characterisation of the initial type and severity of TBI should not be restricted to one dimension (eg, GCS or CT classification), but should include multiple domains such as clinical and pathophysiological features, neuroimaging findings, and other factors that might influence clinical outcome.

[H3] Brain banks and lessons from neuropathology

Efforts to improve clinical characterisation of TBI can be informed by neuropathological research, which has provided a foundation for our current understanding of key pathological processes in TBI, including diffuse axonal injury,[302,477] ischaemia,[476] neuroinflammation,[304] and amyloid deposition in association with neurodegeneration.[61,66,303] However, despite the insights afforded by detailed neuropathological examination of human brain tissue,[300] there are remarkably few research archives containing biospecimens suited to studies in TBI. Indeed, only one comprehensive archive of human brain tissue exists—the Glasgow TBI Archive[301]—which is dedicated to studies across the spectrum of TBI. This unique archive contains material from the brains of patients with a range of injury severities, survival times, and ages. The value of this resource can be traced through the literature, with over 150 peer-reviewed publications supported by material from the archive, including many of the landmark studies of diffuse axonal injury and neurodegenerative pathology associated with TBI.[302–304] More recent high-profile reports of CTE[66,305,535–538] have facilitated accrual of brain tissue from retired athletes, which has enabled development of a dedicated brain bank at the Boston University CTE Center. Nevertheless, this growing, albeit focused, archive and the Glasgow TBI Archive cannot reasonably sustain the international field of TBI research.

There remains a pressing need to archive brain tissue linked to robust and prospectively accrued clinical information from patients with TBI. The richness of knowledge provided by these resources could be substantially amplified by post-mortem imaging studies, which would allow correlation between the gold standard of neuropathology and the findings of so-called virtual autopsies[306] based on advanced and tailored MRI techniques.[307,308] Finally, these precious archive resources must be networked and made widely accessible to be suitable for international collaborative research.

[H3] Genetic analysis

Outcome after TBI is highly variable (sections 7, 8), and some of the differences in disease course are likely to be accounted for, at least in part, by genetic variability between patients (figure 8). In oncology, precision-medicine approaches are based mainly on knowledge of the molecular genetics of the tumour, whereas in TBI, a key focus for precision-medicine strategies is the genomics of the host response, which can modulate injury course as well as repair. Compared with oncology, genomic characterisation of TBI is in its infancy. If further developed, identification of relevant genetic risk or protective factors early after TBI could potentially be used to inform individualised management approaches and thus improve outcomes.

Figure 8: **Potential effects of genetic variation on clinical course and outcome of traumatic brain injury**

Genetic factors might influence an individual's risk of and response to traumatic brain injury (TBI), contributing to functional outcomes in the short and longer term. Although still speculative, possible applications of such knowledge could include use of genetic factors that might modulate TBI outcome (eg, *APOE*)[310] in a comprehensive prognostic scheme, or stratification of patients for clinical trials of treatments on the basis of genotypes that modulate the host response (eg, proinflammatory response)[542] or influence regenerative capacity (eg, brain-derived neurotrophic factor concentrations).[481]

The most extensively studied gene in the field of TBI is apolipoprotein E (*APOE*), which encodes a protein that has a central role in lipid transport in the central nervous system (CNS), including movement of cholesterol into cells to aid repair of damaged neurons.[480] Three *APOE* variants (alleles) have been characterised—ε2, ε3, and ε4—and ε4 has been reported to have pro-inflammatory effects in mice[309] and to increase the risk of late-onset Alzheimer's disease in humans.[60,313] In TBI, although the risk of late neurodegenerative disease scales with injury severity, possession of an ε4 allele might modulate this risk.[60] Possession of an ε4 allele has been found to double the risk of dementia in the general population, but this risk might be increased by up to ten times in people with TBI.[313] Moreover, in a group of patients who had sustained a single mild TBI, only those with an ε4 allele had an increased risk of dementia in the long term compared with the general population.[314]

APOE genotype has also been variably shown to modulate TBI outcome.[310] One large study[311] of patients with TBI undergoing rehabilitation showed that ε4 carriers had worse outcomes 2 years after injury compared with ε2 or ε3 carriers. However, initial findings that the ε4 allele had a deleterious effect on TBI outcome[315] could not be replicated in a larger cohort by Teasdale and colleagues,[312] and a recent systematic review[310] concluded that this effect might be limited to

patients with severe TBI. These contrasting findings might reflect an interaction between age and genotype on outcome, as suggested by Teasdale and colleagues.[312] They found that, although there was no effect of *APOE* genotype for all age groups combined, children (≤15 years) and young adults (≤30 years) who were ε4 carriers experienced significantly worse outcomes than ε2 or ε3 carriers, suggesting that younger age does not protect against the adverse effects of ε4 carriage on outcome after TBI. Despite extensive research, the precise relationship between *APOE* genotype and TBI outcome remains uncertain. Other genetic targets of interest include the mitochondrial DNA haplotype, mediators of inflammatory responses, and genetic factors involved in regenerative and neurotrophic responses such as brain-derived neurotrophic factor (BDNF).[481]

The applications of emerging genomic information to TBI care and research are evolving (figure 8). Potential roles include better characterisation of injury, identification of patients at increased risk of progressive damage, and therapeutic stratification to facilitate an individualised approach to management, as well as more accurate prognostication (section 8), and identification of molecular targets for future drug development. Current evidence is limited by insufficiently powered studies. Exploration of the role of genetic characterisation for precision medicine in TBI requires large, prospective studies that can be used to simultaneously analyse the effects of multiple genes in well defined populations. *APOE* is an obvious candidate, but genes with a greater predictive value for early catastrophic clinical outcomes, such as death or haemorrhagic events, might be of greater clinical use.

[H3] Blood biomarkers

There is an unmet medical need for rapid blood-based biomarker tests, as an adjunct to imaging studies, to optimise diagnosis, track disease progression, and improve outcome prediction (section 8) in TBI to facilitate individualised management. Substantial scientific advances in the past decade have resulted in identification of a large number of blood-based protein biomarkers that are relevant to different phases of TBI (figure 9; appendix).[316–318,541] Ongoing research efforts[319–321,539,540] are yielding new classes of biomarkers, including metabolomic and lipid markers, microRNAs, and exosomes. All of these hold potential for diagnosis, prognosis, and therapeutic stratification, but are not yet in advanced clinical development.

Acute-phase biomarkers—eg, glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1)—have substantial potential for use in the prehospital setting and emergency departments where large numbers of patients present with head trauma, the vast majority of whom will have normal brain CT findings.[322,323] Compared with other stages of TBI management, protein

biomarkers for the acute phase are probably closest to clinical implementation, and one of these—S100B—is already included in an algorithm to triage patients with mild TBI for CT imaging after head trauma in Scandinavian guidelines.[317,324] In the subacute phase, neurofilament protein and autoantibody biomarkers could be used to track disease progression.[325–327] In the chronic stages, markers of neurodegeneration (eg, tau and phosphorylated tau) are being explored for in-vivo detection of long-term sequelae, including neurodegenerative disorders linked to TBI such as CTE and Alzheimer's disease.[328–330,541]

Figure 9: **Schematic representation of the time course of blood-based protein biomarkers linked to pathophysiology in traumatic brain injury**

Individual plots depict current (and still evolving) understanding of the temporal signatures of peripheral blood biomarkers that are indicative of pathophysiological changes at different stages after traumatic brain injury. AutoAb-[GFAP]=autoantibodies to GFAP. BBB=blood–brain barrier. CTE=chronic traumatic encephalopathy. GFAP=glial fibrillary acidic protein. MBP=myelin basic protein. P-tau=phosphorylated tau. S100B=S100 astroglial calcium-binding protein B. SBDP120=αII-spectrin breakdown product 120 kDa. UCH-L1=ubiquitin C-terminal hydrolase-L1.[326] For a more complete biomarker list, see appendix. Modified from Zhang et al,[482] by permission of Springer.

Despite the multitude of candidate molecules proposed, translation and widespread adoption into clinical diagnostics remain elusive. Progress has been hampered by studies with small numbers of patients, variability in sample processing and storage, differences in the assay techniques used, lack of reference standards, and incomplete understanding of underlying biomarker biology. Transport of biomarkers from damaged tissue to the blood is much more complex in the brain than in the heart owing to additional clearance pathways, such as the cerebrospinal fluid and glymphatic systems. It is therefore less straightforward to relate brain-specific biomarker concentrations to the presence and extent of brain damage in TBI than it is to relate cardiac troponin concentrations, for example, to the extent of heart damage following myocardial infarction.[483,543] Moreover, small lesions in vital brain areas can lead to deep coma, even though numbers of cells lost, and thus changes in biomarker concentrations, might be relatively small, whereas more extensive damage in relatively silent areas might be associated with high biomarker concentrations in the absence of major clinical symptoms.[331] Further, the rapid dynamic changes in biomarker levels following TBI make it essential that we account for time after injury when using these as diagnostic or prognostic markers.[560,561] We anticipate a shift from a single-marker approach, which is starting to be implemented in clinical practice,[324] towards compilation of biomarker panels that can be used to overcome diagnostic confounders (eg, extracerebral sources and haemolysis and avoid the overinterpretation or misinterpretation of information based on a single-marker analysis.[544] Development of a panel of multiple biomarkers that reflect many pathogenic mechanisms holds promise for personalised TBI care.

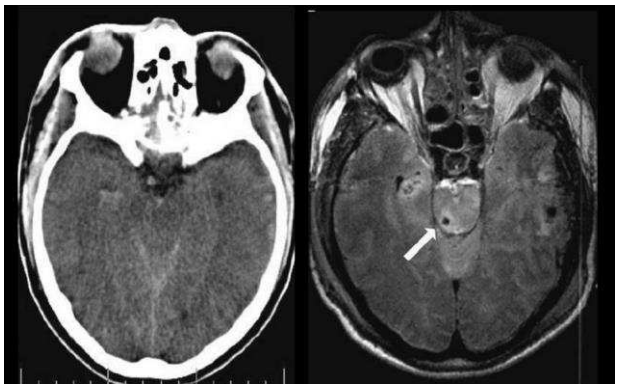
High-quality, large-scale studies are needed to provide robust evidence of analytical validity and clinical utility to lay the foundations for integration of TBI biomarkers into clinical practice.[332] Crucially, regulatory authorities need to oversee standardisation and comparability of assay results across different platforms, and ensure a clear distinction between approval for research purposes and use as diagnostic standard in clinical practice.[333,545]

[H3] Neuroimaging

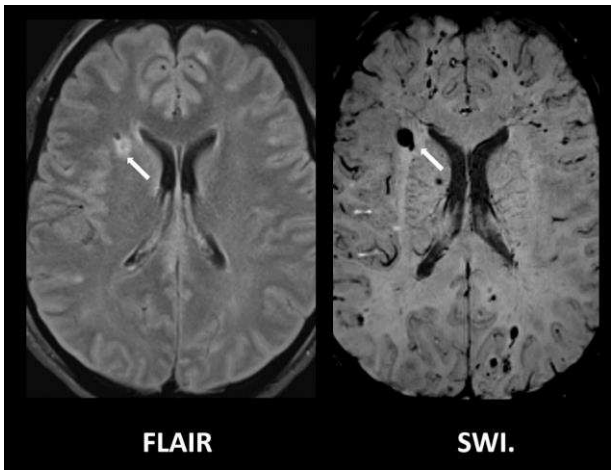
CT is the primary imaging modality for TBI, driving key decisions about the need for surgical intervention for space-occupying lesions. Scanning times are fast and image processing instantaneous. However, CT is relatively insensitive, and in patients suspected of having a mild TBI, less than 5% will have CT abnormalities.[249,322,323] Standard clinical MRI provides greater sensitivity than CT for parenchymal lesions, especially in the posterior fossa, brainstem, and superficial cortical areas (figure 10). Advanced MRI can be used to characterise pathophysiology from ictus to outcome and across the spectrum of outcome – from predicting recovery from postconcussional state in mild TBI to predicting emergence from coma in the most severely injured subjects.[334,562] Diffusion tensor imaging and susceptibility-weighted imaging are particularly sensitive for mapping diffuse axonal injury and the microhaemorrhages that accompany it (figure 10), and functional MRI can be used to map functional disconnections that underlie clinical deficits. Although MRI protocols are speeding up,[335] when compared with CT, MRI scanning generally takes longer (30–45 min), limiting its use in emergency settings.

Figure 10: **Detection of structural brain damage after traumatic brain injury with magnetic resonance imaging and computed tomography**

A



B



(A) Computed tomography (CT) scan on admission to hospital (left panel) and magnetic resonance imaging (MRI) scan (fluid-attenuated inversion-recovery sequence [FLAIR]) within 48 hours of admission from a patient with traumatic brain injury. MRI shows a dorsolateral brainstem haemorrhage and surrounding oedema that was not detected with CT, highlighting the greater sensitivity of MRI to structural damage compared with CT. (B) MRI scans with a FLAIR sequence (left) and susceptibility-weighted imaging (SWI; right) from the same patient. Microhaemorrhages associated with diffuse axonal injury are visible only on the SWI sequence, showing that advanced MRI is superior to CT for detection of diffuse axonal injury.

Although the potential importance of advanced MRI methods for refining characterisation of TBI is undeniable, generalisability to everyday clinical practice remains an enormous challenge. Readily available and inexpensive MRI-compatible clinical monitoring equipment is needed to allow use in the most injured patients. More open (often low-field) MRI systems might ease some logistical difficulties in this context. However, use of low-field systems would be contrary to prevailing trends: 3 Tesla systems are increasingly the standard field strength for clinical use, and 7 Tesla systems are on the cusp of approval for clinical imaging.

Regardless of the field strength of MRI, regulatory authorities and vendors must address cross-centre (and inter-device) comparability of images, particularly with regard to quantitative assessments. Complete standardisation might not be possible. CT images can be calibrated in Hounsfield units, but such a calibration unit does not exist for MRI. Experience of international collaborations in TBI research, however, does suggest that harmonisation of protocols can and should be achieved.[336,337] Such harmonisation is essential for large, multicentre clinical studies. Translation of research protocols to routine clinical imaging will be a challenging task that requires extensive interaction between vendors, MRI experts, and regulatory authorities.

[H3] Physiological monitoring

Current technology now offers opportunities to dissect pathophysiological mechanisms to define individualised treatment targets and personalise ICU management of TBI. Such technology includes the use of advanced signal processing of ICP waveforms to derive measures of autoregulation, and the addition of more novel sensors to monitor oxygenation, metabolism, and the inflammatory response, as well as cortical electrical activity and spreading depolarisations.[338–342,546,547]

The combination of these different sources of information provides a more complete understanding of brain physiology than is possible with measurement of a single variable, and preliminary evidence from a recent RCT shows that such improved understanding—and appropriate targeting of treatment—can improve treatment results.[548] However, these approaches have the inherent disadvantage of requiring the insertion of multiple intracranial sensors, each with its own operative risk. Although these risks can be partly mitigated by use of a single access device (figure 11), a better solution would be the development of multiparametric sensors, which incorporate all the monitoring modalities in a single device.[343] An alternative approach, which completely removes these risks, is to develop and validate noninvasive monitors.[343] Unfortunately, the medical field is lagging behind technological developments, and such advances will require substantial input from industry, academia, and funding bodies.

Figure 11: **Multimodal monitoring of brain physiology after traumatic brain injury**

Several physiological variables in the brain can be measured simultaneously with the use of a single intracranial access device with three lumens for separate sensors. Typically, an intracranial pressure (ICP) sensor and a probe for measuring the partial pressure of brain tissue oxygen ($Pbt0_2$) and brain temperature are inserted through two of the lumens. The third probe can be used for a microdialysis catheter, cerebral blood flow sensor, or depth electrode for electroencephalography (EEG) monitoring or other monitoring probe. In this example, a contusion is shown in the temporobasal region. Whether the sensor should best be postioned in the proximity of a lesion or in a relatively undamaged part of the brain, and thus be more representative of the global situation, is debated. Figure courtesy of Maartje Kunen, Medical Visuals, Arnhem, Netherlands.

[H3] Data integration: challenges and opportunities

The integration of data from multiple pathophysiological monitoring modalities—whether from invasive or noninvasive sensors or from multiple sensors or single multiparametric sensors—into an understandable format to ensure that it is clinically useful is a major challenge. Merging of diverse information streams requires substantial information technology input. In the ICU setting, multimodal monitoring is emerging as a clinical tool, and guidelines for monitoring of the partial pressure of brain tissue oxygen ($PbtO_2$)[338] and for microdialysis[340] have been developed. However,

the accompanying developments in neuroinformatics that are needed to ensure optimum synthesis and interpretation of these data are in their infancy.[344] The idea of identifying clinically important and treatable parameters, not immediately obvious from raw bedside data, using computational and informatics techniques, is compelling and potentially rewarding, but challenging. In recent years, the field of machine learning has developed new and sophisticated statistical and computational techniques to process high-dimensional data, which have diverse applications in science and engineering. Such approaches (so-called big data solutions) might also prove valuable for the analysis of time-dependent neuromonitoring data, both for real-time prediction of events and for characterisation of physiological states that respond to specific therapies, thus facilitating clinical decisions about critically ill patients.

Improved characterisation and classification of TBI will, ultimately, require integration of information not only from multimodal monitoring methods, but also from a range of sources including clinical, neuroimaging, genetic, and biomarker techniques. Such integration of information will be a considerable endeavour, but has the potential to enable classification of patients into groups with more homogeneous pathophysiological mechanisms for targeted trials of novel neuroprotective interventions.[549] This approach depends on access to large data sources and substantial input from the field of neuroinformatics and computational sciences, both of which require interdisciplinary and intercentre collaboration (section 9).

[H3] Key messages and recommendations

(1) Methods of diagnosis and classification of patients with TBI are inadequate to permit targeting of current and new therapies to the needs of individual patients. Funding bodies should implement targeted funding calls for research that improves the precision of diagnosis, classification, and characterisation of TBI using multidomain approaches.

(2) Few tissue archives containing specimens suited to TBI research exist, and their future sustainability is insufficiently guaranteed. Funding agencies need to secure existing research archives and develop new archives of well characterised human tissue to support collaborative research in TBI.

(3) Advances in genetics, biomarker research, advanced neuroimaging, and pathophysiological monitoring promise improved characterisation of clinical and mechanistic types of TBI as well as outcome and prognosis, but progress is limited owing to small study sizes. Increased funding is needed for studies using emerging technologies to allow improved targeting of treatment strategies to individual patients on the basis of clinical and pathophysiological characteristics.

(4) Progress in biomarker and neuroimaging studies is hampered by lack of standardisation. Regulatory agencies should mandate standardisation (or at least harmonisation) of biomarker technology and advanced neuroimaging to facilitate data sharing in large studies and accelerate improved management and outcomes of patients with TBI.

(5) Developments in digital analysis of large datasets have the power to improve clinical decision making, especially for critically ill patients with TBI, in which the volume of physiological monitoring data is challenging. Targeted funding of so-called big data solutions is needed to develop decision-support systems, especially for critically ill patients with TBI.

Section 7. Assessment of TBI outcome: towards multidimensional approaches

While improved characterisation of initial injury severity is a prerequisite for the development of precision-medicine approaches to traumatic brain injury (TBI; section 6), more refined assessment of clinical outcome is equally essential to guide individualised management in the postacute phase. Accurate characterisation of outcome is also necessary to evaluate patterns of recovery and deterioration in the long term, to predict long-term care needs for patients and their families, to understand the impact of clinical care, to compare outcomes between centres, and to assess the efficacy of conventional and novel therapeutic interventions.

Functional outcome is equally, or perhaps more, relevant than is mortality in TBI owing to the high rate of disability in survivors, and is generally assessed with the Glasgow Outcome Scale (GOS)[345] or its extended version (GOSE).[346] Despite their clinical appeal, the GOS and GOSE are based on broad categories and therefore insufficiently account for the multidimensional nature of outcomes after TBI, which can include long-term changes in functional, physical, emotional, cognitive, and social domains.

In this section, we discuss the limitations of current approaches to outcome assessment and classification in TBI, and emphasise the need for multidimensional outcome scales for clinical practice and research, underlining challenges in the development of such approaches.

[H3] Current approaches to outcome assessment

At present, characterisation of outcome in patients admitted to hospital with TBI is based mainly on the GOS[345] or the GOSE.[346,347] These are valuable but relatively simplistic scales for assessment of global outcome. The GOS was introduced by Jennett and Bond in 1975[345] as a five-category scale to capture functional outcome: alterations in major roles such as work and independent living, as assessed by the investigator, are used to summarise the effects of diverse changes caused by injury. Although attractively simple, the limited sensitivity of the GOS led to the development of the GOSE, in which the categories of severe disability, moderate disability, and good recovery are subdivided into lower and upper subcategories (figure 12). A structured assessment was proposed to facilitate standardised administration.[346] However, despite more refined outcome characterisation, the eight-category GOSE scale still lacks sensitivity to changes within specific domains of function (eg, cognition, emotional well-being, and life satisfaction). Even patients with mild TBI—who would be considered to have (lower) good recovery on the GOSE—often have long-term health problems across a number of outcome domains, including pain, sleep disorders, and mental health.[70,484,550,551]

Figure 12: **Classification of outcome of traumatic brain injury with the Extended Glasgow Outcome Scale**

Decisions involved in assigning an outcome using the Extended Glasgow Outcome Scale (GOSE). The eight-point GOSE was formed by subdividing three of the categories on the five-point GOS into upper and lower bands.[345–347]

The GOS and GOSE are not commonly used for formal categorisation of outcome in everyday clinical practice, as summary outcome measures do not allow clinicians to target management of specific problems in individual patients. Furthermore, they are unlikely to facilitate future precision-medicine approaches by enabling identification of subgroups of patients in whom mechanistically specific therapies can be used. Furthermore, the GOS and GOSE do not provide sufficient discrimination to reliably detect small, but clinically relevant recovery or deterioration of function and effects of treatment over time.[485] These considerations suggest the need for detailed assessments that are sensitive to smaller transitions in outcome and that take account of a range of aspects of outcome.[354–356,486] Nevertheless, summary or integrated measures of outcome could still provide a useful basis for allocating patients to broad care pathways, and such applications are worth developing.

Insensitivity of outcome metrics also decreases the chances of detecting treatment effects in clinical trials, and this problem is exacerbated by the common practice in TBI of dichotomising the GOS or GOSE (jointly referred to subsequently as GOS(E)) into two categories: unfavourable (dead, vegetative, severe disability) versus favourable (moderate disability, good recovery). This approach is statistically inefficient and should be discouraged.[349,350] Currently recommended approaches for analysing GOS(E) data in clinical trials involve the use of a proportional odds analysis (evaluation of a shift across the categories of outcome) or a sliding dichotomy approach (in which the GOS(E) is still dichotomised, but the point of dichotomy varies according to individual baseline prognostic risk).[351] However, even this more refined application of the GOS(E) would be unsatisfactory for assessment of patients with mild TBI, who might achieve the best possible outcome (GOSE score 8) but still have clinically important cognitive or psychological problems such as post-traumatic stress disorder or other depressive or anxiety disorders.[352,353]

In addition to the GOS and GOSE, a multitude of instruments for assessing outcome is available: recent overviews have identified nearly 1000 (mostly non-overlapping) outcome assessment

instruments for TBI (appendix).[357–360] Diversity in outcome assessment is an asset in clinical practice, and has been embraced for many years, particularly in the management of TBI after the acute stage. However, this diversity is a major obstacle to research progress in TBI owing to difficulties in selecting single endpoints for use in clinical trials and in pooling of data and conduct of meta-analyses. Moreover, although different assessments might be needed for different purposes, their relevance is debated and there is no consensus on a key set of assessments.

[H3] Multidimensional assessment of outcome

Heterogeneity in the consequences of TBI and the wide variety of short-term and long-term recovery patterns place high demands on outcome assessment. It is increasingly evident that a single outcome parameter is insufficient to demonstrate treatment effects in the clinical setting or to be an endpoint in clinical trials, and that multidimensional outcome scales that cover a broad range of domains (figure 13)[361] are essential to describe the consequences of TBI. Crucially, these scales should include outcome domains such as cognitive deficits, psychological health, and quality of life (including the effects of common symptoms such as sleep disturbance and pain).[354–356] Development of refined, multidimensional outcome assessments is a challenging aspiration and various approaches need to be considered: (1) identification and standardisation of a core set of outcome instruments; (2) recognition that patients who have different grades of outcome will need different assessment tools, both generally and to address specific problems that are more relevant to a specific outcome category or severity of impairment; and (3) development of more refined global assessementsor composite endpoints.

Importantly, acceptance of the need for multidimensional outcome measures by regulatory authorities is essential. Although it is commonly perceived that regulators require the use of the GOS or GOSE as an efficacy parameter for clinical trials, experience suggests that they are open to considering other early or late outcome measures,[362] if there is evidence to support their use and clinical validity. In the USA, the Food and Drug Administration (FDA) has recently implemented a formal qualification process for clinical outcome assessments that should facilitate adoption of a range of instruments in TBI clinical trials. Collaboration between the FDA and clinical investigators has been established in the context of the TBI Endpoints Development project.[363]

Figure 13: **Multidimensional outcome assessment of traumatic brain injury**

Domains of outcome assessment included in both adult and paediatric Common Data Elements for traumatic brain injury (TBI; specific instruments are included in brackets). Outcome is defined by selecting multiple subdomains and choosing measures that reflect each subdomain. CRS-R=Coma Recovery Scale–Revised.

GOS=Glasgow Outcome Scale. GOSE=Extended GOS. QOLIBRI=Quality of Life after Brain Injury Scale. QOLIBRI-OS=QOLIBRI Overall Scale. RPQ=Rivermead Post-concussion Symptom Questionnaire. SF-36=Short-Form 36. Adapted from Kean and Malec,[364] by permission of Elsevier.

Identification of a subset of assessments that cover key dimensions of outcome beyond those assessed with the GOSE, and that could be used across studies and over time, would be a major step forward. Assessment methods have different strengths and weaknesses, and few can be applied across the complete TBI severity spectrum. Approaches considered include health-related quality-of-life measures, neuropsychological assessments, and composite endpoints. Health-related quality-of-life assessment can effectively combine different domains, but a quality-of-life measure in isolation would still only rarely be considered adequate as an endpoint in TBI clinical trials, and people with severe injuries might be too cognitively impaired to complete these assessments. The reliability of exclusively self-reported measures can be hampered by limited self-awareness of deficits, necessitating access to caregivers' views, which might be different and possibly more accurate than those of patients.[365] Neuropsychological tests cover a range of domains, and provide a sensitive index of impairments, but can be challenging to complete for TBI survivors: in a trial of hypothermia only just over half of patients with severe TBI completed cognitive assessment at 6 months.[366] Moreover, interactions might exist between cognitive performance and the presence of post-traumatic stress disorder or depressive symptoms.[552]

The use of different approaches and combinations of instruments would depend on the level of disability—eg, patients who have persistent postconcussional symptoms after mild TBI would have different assessment needs to those with disorders of consciousness after severe TBI. This need to accommodate different outcomes or levels of severity of impairment is concordant with the concept of the sliding dichotomy for outcome analysis of the GOS(E), in which the point of dichotomy of the GOS(E) is differentiated by initial baseline risk.[351] Different outcome instruments might map to different levels of disability (figure 13), and accurate characterisation of specific problems (eg, paroxysmal sympathetic hyperactivity, which is common after more severe injuries) can provide a robust base for targeted treatment of these problems.

Composite endpoints have been pioneered in a few clinical trials,[361,367,368] including the recent BEST-TRIP (Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure) trial.[202] However, use of composite scores comprising two or more outcome measures can be problematic with regard to traditional methodological and statistical approaches, whereby a single measure is typically used to calculate the required sample size to reliably detect a treatment effect. In the context of composite scores in clinical trials, selection of a parameter that is likely to change over

time might lead to sample sizes with insufficient power to detect effects of other outcomes, whereas use of the measure that is least likely to change could necessitate impractical sample sizes.[361] Other issues with the use of global tests or composite measures include the need to weight individual test components and how best to achieve this, as well as interpretation of the overall results.

There have been major initiatives to develop a core set of standardised multidimensional assessment methods with global measures or composite endpoints that can be used across different diseases. The Cambridge Neuropsychological Test Automated Battery (CANTAB)[369] and the National Institutes of Health (NIH) Toolbox[370] are sets of computerised measures designed to assess cognition, emotion, and motor and sensory functions. The Patient Reported Outcomes Measurement Information System (PROMIS) project[371,553] has developed a set of instruments that can be used across a wide range of chronic conditions. These tools could be useful in both research and clinical settings. Practical problems might, however, hamper implementation of any comprehensive scheme in an international setting (panel 11), and completion of all assessments could be challenging for TBI survivors. Further work is therefore needed to establish multidimensional and composite outcomes as endpoints for clinical studies of TBI.

Panel 11: **Barriers to widespread adoption of recommended outcome assessments in an international setting**

Language
Lack of availability of good-quality versions in languages other than English

Cultural applicability

Lack of cross-cultural validation of assessments

Cost
Initial costs of some instruments and stipulation of payment per use

Copyright
Copyright issues and related difficulties in reproducing materials

Access
Restriction of some assessments to particular professional groups

Scoring
Charges and restrictions imposed by proprietary scoring systems

Limited availability of many instruments in languages other than English is a major barrier to their use in international settings. Additionally, ensuring cultural applicability of assessment methods is an important challenge when collecting and analysing data across countries. The CANTAB and the

NIH Toolbox have the advantage of being language-independent, and the PROMIS instruments are available in many languages; in the context of the CENTER-TBI project (section 9), translations of common outcome assessments have been linguistically validated and will be made available without restrictions to the neurotrauma community. However, such validation is not simple, since it is very time-consuming and resource-intensive, and high priority should be given to the funding of cross-cultural validation of assessments.[372] Charges and restrictions on proprietary measures are a substantial hurdle in the internationalisation of many instruments. We strongly believe that outcome assessments advocated by the Common Data Elements for TBI should be freely available to the clinical and research communities without charge, and that public funding should support ready access to high-quality instruments. Developing multidimensional outcome tools and novel ways to integrate the various outcome domains will require collaborative efforts in large-scale studies with novel approaches to data sharing (section 9).

[H3] Key messages and recommendations

(1) Trauma disturbs the brain in complex ways, affecting multiple outcome domains. Refined outcome assessments could guide improved clinical management and support high-quality research. Targeted funding calls are needed to facilitate the development and validation of multidimensional outcome constructs that quantify the overall burden of disability from TBI.

(2) A substantial number of patients with even mild TBI experience long-term pain, sleep disorders, and mental health illnesses, including post-traumatic stress disorder and major depression. Understanding the long-term effects of TBI and implementing best practice for ongoing care—in particular, for appropriately targeted health management in the chronic phase of TBI with continuing support in the long term—should be prioritised by politicians and health-care professionals.

(3) Patients with TBI can have late deterioration or recovery of function even 1 year or more after injury. Improved multidimensional outcome measures could facilitate long-term characterisation of changes in outcome after TBI. Increased funding is needed for long-term longitudinal studies to better capture occurrence of late deterioration and the recovery process after TBI.

Section 8. Prognosis in TBI: linking patient and injury characteristics to outcome

Outcome in traumatic brain injury (TBI) depends not only on the quality of care provided, but also on patient and injury characteristics such as premorbid state (eg, age or comorbidities), mechanism of trauma, injury severity, presence and severity of extracranial injuries, patient response, and social environment. Linking patient and injury characteristics at presentation to outcome is the science of prognosis and prognostic modelling.[487] Prognostic models combine a range of characteristics in a mathematical formula and have diverse applications (panel 12) in clinical practice and research in TBI. These applications include provision of personalised information on expectations to patients and their relatives, adjustment for differences in case-mix between clinical research studies, and calculation of standardised outcome rates for benchmarking of quality of care.

Robust prognostic models have been developed for moderate and severe TBI. However, they are not used in mainstream clinical practice, and their precision could be improved, primarily with better characterisation of injury severity and patient factors at presentation (section 6), and by including outcome measures beyond the Glasgow Outcome Scale (GOS) and the Extended GOS (GOSE). Prognostic schemes for mild TBI are far less established than are those for moderate-to-severe TBI and will require more refined description of outcome (section 7).

In this section, we explore how prognostic models can be used to link patient and injury characteristics to outcomes. We consider the applications of prognostic models in clinical practice and research, and also discuss the developments and refinements needed to improve prognostic models and enhance their use.

Panel 12: **Applications for prognostic modelling in traumatic brain injury**

- To provide realistic information to patients and relatives
- To inform triage decisions
- To provide insight into possible causes of poor outcomes
- To enable identification of potentially modifiable causes of poor outcomes
- To enable risk adjustment for comparisons of patient series
- To improve design of clinical trials and analyses of trial data
- To enable benchmarking of quality of care

[H3] Applications for prognostic modelling in TBI

Outcome predictions form an integral part of clinical medicine and serve various purposes—eg, to provide information about expected outcomes to patients and their relatives and to assist with treatment and triage decisions (panel 1). Clinicians' expectations of patients' outcomes have an inherent degree of uncertainty, and prognostic models could help to refine these expectations by providing a probability of a specific outcome.

Prognostic models can further be used to inform our understanding of cause and effect, and provide insight into potentially modifiable causes of poor outcomes. However, since an association might not be causal, clinical benefit of correction of a modifiable factor would need to be proven with thorough evaluation of an intervention, preferably in a randomised controlled trial (RCT). Use of prognostic models could also facilitate more efficient design of clinical trials and analysis of trial data,[350,487] and enable adjustment for differences in case-mix when comparing patient series. As outcome depends not only on treatment, but also to a large extent on patient characteristics and injury severity, making comparisons between different patient populations is inappropriate, unless these comparisons are risk-adjusted for differences in case-mix. Prognostic models could be used to provide estimates of expected outcomes for case series adjusted for patient and injury characteristics; any differences between observed and expected outcomes might are then with more certainty attributable to differences in treatment. Adjustment for injury and patient characteristics is particularly relevant to TBI owing to its complex heterogeneity, including differences in injury type and severity between patients.

Similarly, prognostic models could be used for risk adjustment when comparing outcomes between hospitals. Such benchmarking is a specific approach to enable implementation of the best available evidence into practice and to optimise quality of care. It allows continuous comparisons between hospitals and identification of areas for improvement. Ideally, a set of quality indicators for benchmarking would include outcome indicators (eg, mortality rate), process indicators (eg, guideline adherence), and structure indicators (presence of facilities to provide good care). However, the development of quality indicators for TBI is challenging since mortality is a poor outcome metric for benchmarking in TBI: survival with extremely severe disability is generally considered to be an undesirable outcome and, for many, survival in a vegetative state might be an outcome worse than death. There are currently no broad quality indicators for TBI, and the development of an internationally accepted set of indicators should be considered a high priority to ensure implementation of evidence-based care and to optimise quality of care for patients with TBI.

[H3] Prognostic models for outcome prediction in moderate and severe TBI

Many prognostic models have been developed since the 1970s, with varying methodological quality.[373,374] One aim in developing some of these models was to refine efficacy analyses in clinical trials. These models have specifically focused on baseline risk assessment using characteristics available at hospital admission, and on mortality and GOS scores at 6 months after injury as outcomes of interest. For moderate and severe TBI, two sets of prognostic models have been developed on large datasets using state-of-the-art methods: the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) models, based on eight large datasets,[375] and the CRASH (Corticosteroid Randomisation After Significant Head injury) models, based on the database of a large clinical trial.[376] However, the development populations for both models were weighted towards severe TBI, and patients with moderate TBI were underrepresented;[377] thus, an additional focus on moderate TBI is required.

The IMPACT and CRASH models share some key predictors of outcome: age, Glasgow Coma Scale (GCS) scores—the full score in CRASH, the motor component in IMPACT—pupillary reactivity, presence of second insults (hypoxia and hypotension), computed tomography (CT) characteristics, and laboratory parameters. Most predictive information is contained in the core predictors—age, GCS motor score, and pupillary reactivity—which together explain approximately 35% of the variance in outcome[487] (appendix). Both the CRASH and IMPACT models have been extensively validated in cohorts outside the populations of the original studies, an essential step to test the generalisability of a prognostic model beyond the development setting.[378] In the absence of external validation, prognostic effects are likely to be overestimated. External validation should therefore be a key requirement for all new models and when new predictors are added to existing models. Repeated validation over time with updating of models should be done to account for the changing epidemiology of TBI (section 1) and changes in care processes and treatments.

[H3] Prognostic models for outcome prediction in mild TBI

The sequelae of mild TBI can include physical symptoms, behavioural disturbances, and cognitive dysfunction, any of which could interfere with return to work or resumption of social activities.[484,487] Prognostic analyses can enable identification of patients at increased risk of such symptoms, who could then be followed more closely and receive early interventions to alleviate the psychological burden of injury. Mortality is not an appropriate endpoint for prognostic analyses in these patients,

and the usefulness of the GOS is doubtful, because although a substantial number of patients with so-called mild TBI might have disabling complaints, most will have outcome scores in the upper segment of the GOS categories.[379] Ceiling effects of the GOS might partly explain why methods for predicting outcome in patients with milder forms of TBI are scarce. More sensitive outcome measures (section 7) as endpoints for prognostic analyses are required, although these have so far been insufficiently or inconsistently investigated. Although prognostic models are now beginning to emerge for mild TBI, they have not been fully validated, their generalisability has not been determined, and they are less well established than those for moderate-to-severe TBI.[380–382,403,484,489] Therefore, there is an urgent need for robust validation and further improvement of models in this patient group.

[H3] Advancing the science of prognosis in TBI

The availability of robust and well validated prognostic models for moderate-to-severe TBI is a major step forward. They allow us to deal appropriately with the inherent heterogeneity of TBI populations. However, as these models each explain at most only 35% of the variance in outcome,[486,490] other key patient and injury characteristics are likely to contribute to outcome. Identifying these characteristics could improve prognostication and, if modifiable, could provide therapeutic targets. Genetic variance, advanced neuroimaging, and other precision-medicine features (section 6) might explain part of the residual variance. Inclusion of these features could provide some refinement of prognostic models, but treatment differences and centre effects are also likely to contribute to the variance in TBI outcome.

Panel 13: **Directions for advancing prognostic modelling in traumatic brain injury**

- Refinement of models for moderate and severe traumatic brain injury (TBI) to adapt to changing epidemiology and outcome
- Exploration of new markers, tests, and imaging (eg, magnetic resonance imaging [MRI] and genotype)
- Development of dynamic predictions beyond baseline assessment (eg, serial clinical or imaging assessment)
- Development and validation of models for mild TBI using sensitive endpoints
- Development and validation of models to predict quality of life and other outcomes

Various directions for prognostic research in TBI have been identified (panel 13). Prognostic models could be improved by including new predictors, by better characterising existing predictors, by

adding new information as it becomes available with disease evolution (dynamic predictors), and by predicting other relevant outcomes. Various studies have explored the prognostic value of new predictive methods, including biomarkers and advanced magnetic resonance imaging (MRI; section 6), often reporting promising results. However, most have been limited to relatively low numbers of patients studied and have compared predictions based on admission characteristics (eg, with the IMPACT and CRASH models) with performance of the new predictive method at a later stage (eg, advanced MRI at 1–3 weeks).[383,384] A more rigorous approach would be to compare performance of the new predictive method (eg, MRI) with the predictive value of clinical information obtained at the same time. Prognostic models could also incorporate information that becomes available over time, such as repeated CT or additional MRI scans. Such dynamic predictions are complex and require specific statistical techniques to capture repeated measures from the same patient.[385] Recently developed machine-learning techniques might hold promise for use with complex data structures, but they have performed inconsistently in predicting outcome after TBI.[491,492]

We need to focus on the incremental value of new or extended predictive markers—ie, their prognostic value beyond readily available characteristics. Such evaluation should be phased, starting with technical validation of marker measurements, followed by evaluation in small patient series, and, ultimately, with rigorous validation in independent cohorts, since development of new models without external validation is likely to lead to false-positive identification of features of prognostic importance and result in limited generalisability. Several statistical measures have recently been proposed to quantify the effect of a marker on classification.[386] Decision analyses[387] and cost-effectiveness analyses should also be done to assess the clinical usefulness of any new marker.[388]

A related challenge is to make predictions optimally targeted to the specific clinical setting. The CRASH model was developed with variants for high-income countries (HICs) and low-income and middle-income countries (LMICs).[376] Further site-specific customisation could be attempted using advanced statistical approaches such as random-effect models, which take into account the clustering of patients within sites and incorporate this clustering into the prognostic estimates. Such model adaptations aim to improve the calibration of predictions for individual patients in specific settings,[389] recognising that trauma organisation and treatment policies might differ between sites or change over time.[378]

International collaborative studies that collect high-quality data on large numbers of patients across the full injury severity spectrum, including mild TBI, are required to advance the science of prognosis in TBI (section 9). Outcome measures beyond the currently established GOS and GOSE assessments

are required. Prognostic models are needed that extend over a long timeframe and include multidimensional outcomes, such as cognitive, psychosocial, health-related quality-of-life, and other patient-reported outcome measures (section 7). The absence of good prognostic models for mild TBI highlights an important gap in our knowledge that requires attention.

[H3] Key messages and recommendations

(1) Prognostic models can help clinicians to provide realistic information to patients and families and can facilitate treatment and triage decisions. There is an urgent need for further development, validation, and implementation of prognostic models in TBI, especially for mild TBI.

(2) TBI affects multiple outcome domains (section 7), and prognostic models are needed to predict this range of outcomes, including quality of life. Funding agencies should support the development of new prognostic models that focus on predicting outcome beyond mortality and GOS scores.

(3) A validated set of quality indicators is essential for the benchmarking of quality of care, but none exists for TBI. Funding bodies should stimulate the development of a set of quality indicators for TBI that includes structure, process, and outcome indicators.

Section 9. New directions for acquiring and implementing evidence

The heterogeneity of the population at risk of traumatic brain injury (TBI), variations in injury patterns, and wide disparities in systems of care pose particular challenges for the generation and implementation of clinical evidence in the field of TBI. Evidence underpinning guidelines for trauma care pathways and clinical interventions is often weak, and recommendations are inconsistently implemented (sections 4, 5). Conventional approaches to reduce heterogeneity in randomised controlled trials (RCTs) of medical or surgical interventions have mostly involved use of strict enrolment criteria and tight protocols, typically focusing on age, Glasgow Coma Scale (GCS) scores, and preinjury morbidity, while neglecting differences in injury mechanisms (section 5). This approach has reduced the generalisability of results, while increasing duration and therefore costs of studies. Moreover, most multicentre RCTs in TBI have failed to demonstrate efficacy of interventions in the populations studied.[289,390] A recent systematic overview of RCTs in acute moderate-to-severe TBI identified 191 completed RCTs, of which 26 were considered to be robust (high quality, with sufficient numbers). Of these, only six showed a statistically significant effect—three positive and three negative. The authors concluded that considerable investment of resources had resulted in very little translatable evidence.[390]

There is an increasing appreciation that current views that overemphasize the pre-eminence of RCTs for clinical evidence generation may be mistaken.[555] We must rethink approaches to the generation, analysis, and implementation of evidence.[291,555] An alternative approach could be to exploit the heterogeneity of TBI in terms of disease type, management, and outcome using comparative effectiveness research (CER), rather than attempting to reduce the heterogeneity as is common in RCTs. Such research would enable assessment of therapies in real-world conditions. CER requires large studies, international collaboration, and advanced statistical expertise. It also demands a change in research culture to recognise CER outputs as high-quality evidence, and to embrace broad data sharing. Large-scale collaborative studies and data sharing are also needed to generate high-quality research on characterisation of TBI, outcome assessment, and prognosis (sections 6, 7, 8). Such research would help to advance precision-medicine approaches to target treatment strategies to individual patients on the basis of clinical and pathophysiological characteristics. Such paradigm changes are endorsed by the International Initiative for TBI Research (InTBIR), a collaboration of funding agencies. Global collaborations modelled on the InTBIR need to be promoted.

In this section, we evaluate the application of CER approaches, and explore the advantages and challenges of collaborative efforts and data sharing in TBI research. We also discuss a novel approach to continually update systematic reviews to optimise existing evidence, and we review the potential for knowledge transfer to facilitate implementation of evidence into practice.

[H3] Comparative effectiveness research

CER is the generation and synthesis of evidence to compare the benefits and harms of different approaches to delivery of care, or of methods to prevent, diagnose, monitor, or treat a clinical condition. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.[391] The applicability of research results to daily clinical practice is central to CER. Approaches to CER can include both experimental and non-experimental designs. Experimental designs include pragmatic RCTs, which, in contrast to traditional RCTs, use broad inclusion criteria to increase generalisability of results while maintaining the benefits of randomisation.[392] Non-experimental designs are generally based on observational studies, which exploit existing variability in care and outcome to compare systems of care or interventions. Non-experimental designs are methodologically challenging and there is a high risk of so-called confounding by indication—ie, finding an association between an intervention and an outcome in the absence of a causal connection because the selection of patients who receive the intervention is not random, but influenced by patient characteristics, physician preferences, or other uncontrolled factors. Expert methodological input is required to deal with the potential problems of confounding by indication. Large-scale studies based on collaborative efforts that capture sufficient detail are essential for robust CER study design and analysis plans.

Application of CER to TBI

CER has particular potential in the field of TBI for several reasons.[290] First, there are large between-centre and between-country differences in both outcome and management. Second, robust risk-adjustment models are available for TBI, allowing adjustment for patient characteristics that might affect outcome. Third, advanced statistical models, including random-effects models, are available to analyse differences between centres. Existing variability could relate to structural parameters (eg, level 1 *vs* level 2 trauma centres, or high *vs* low patient volume centres) or process parameters (eg, choice of surgical procedures, use of intracranial pressure [ICP] monitoring, acute management protocols, and choice of rehabilitation interventions).

In the IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI) studies, data were analysed from 9578 patients with moderate or severe TBI from 265 centres, and a 3·3-times difference in the odds of unfavourable outcome was found at 6 months between centres at the two extremes of the outcome range (2·5th *vs* 97·5th percentiles). This difference persisted after adjustment for chance effects and differences in case-mix.[393] Similarly, an analysis of 9987 patients across the TBI severity spectrum from 237 centres in 48 countries from the CRASH (Corticosteroid Randomisation After Significant Head injury) trial showed a 6·6-times difference in 14-day mortality between centres with the lowest (2·5th percentile) and highest (97·5th percentile) mortality rates after adjustment for chance and case-mix (appendix).[394] Both studies, however, had insufficiently detailed data to relate these outcome differences to differences in structure or process of care.

Many interventions that are part of current clinical practice are not readily assessed using RCTs. In many instances, this is because the uncertainties about the interventions involve complex protocols of management (such as the order in which aggressive therapies should be used for intracranial hypertension) rather than efficacy of individual treatments. In other instances, RCTs might be challenging owing to lack of clinical equipoise within individual centres where a given approach is strongly established, despite substantial heterogeneity in practice between these centres (as is the case with surgery for contusions). CER approaches could provide a more cost-effective means of evaluating these interventions (and, potentially, novel therapies) in real-world settings. Early evidence in support of non-experimental designs as a promising approach for severe TBI comes from studies that relate outcomes to structural parameters[210,211,219] (section 4) or that compare surgical or medical interventions (ie, process parameters)[268] (section 5) using CER.

In guideline development, however, evidence from non-randomised clinical studies is regarded as inferior to that generated by RCTs. The recent update of the guidelines on management of severe TBI[255]—which resulted in level 1 recommendations for just one topic—illustrates the methodological rigour with which evidence is currently being evaluated. We suggest that evidence from high-quality non-randomised and observational studies could be as valuable as that from RCTs, since the increased generalisability of such studies provides specific practical benefits.

[H3] Collaborative approaches to accelerate TBI research

Since the 1970s, there has been a rich tradition of academic collaboration for advancement of TBI management. In the 1980s, the National Traumatic Coma Data Bank in the USA[395] provided important data on acute physiology and outcome, which underpins much of current clinical practice. This tradition continues in the USA, perhaps best exemplified by the TBI Model Systems program,

which provides valuable data based on everyday practice, particularly for post-acute services, in collaborating US centres. More recently, US and Indian neurosurgeons formed a new coalition, "The Indian Traumatic Brain Injury Consortium" and have implemented a pilot project in the southern Indian State of Andhra Pradesh to improve outcome after TBI by optimizing systems of care and care pathways.[556] Important outputs have resulted from international consortia (such as the CHIRAG study group[563] and the European Brain Injury Consortium,[396,397] clinical trials consortia (such as the Australia and New Zealand Intensive Care Society Clinical Trials Group,[257,398,399] or national audit programmes (the UK Intensive Care National Audit and Research Centre.[219] More recent initiatives address TBI Endpoints Development[363] and chronic effects of neurotrauma.[400] However, the past few years have seen a more strategic approach to encouraging such collaboration, which represents synergistic efforts not only of researchers, but also of national and international funding agencies.

[H4] International Initiative for TBI Research

A need for a reappraisal of research design and implementation of broad-based, sustainable multidisciplinary and international approaches was recognised in 2010 by major funding agencies. This led to the establishment of the InTBIR, which represents a concerted effort to tackle the vast global health problem posed by TBI. The InTBIR initially arose as a collaboration between the European Commission, the US National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke, and the Canadian Institute of Health Research,[401] and was more recently joined by One Mind (a non-governmental organisation) and by the US Department of Defense. Table 3 summarises the studies supported within the InTBIR collaboration, which cover the entire spectrum of TBI. Each has a different focus but a common goal: to better understand TBI, and to improve its prevention, treatment, and outcomes.

Project title (trial identifier)	Project acronym or short title	Target enrolment	Current enrolment*	Study design or approach	Focus of study	Study duration	Funding agency	Funding
Europe								
Collaborative European NeuroTrauma Effectiveness Research in TBI (NCT02210221)[402]	CENTER-TBI	5400 adult and paediatric patients with TBI of all severities	Core data: 4582 patients; registry: 20 885 patients	CER	Improved characterisation and identification of best practices (biomarkers, classification, prognosis; systems of care, management, and interventions)	2013–2020	European Commission	€29 998 310
Collaborative REsearch on Acute Traumatic brain Injury in intensiVe care medicine in Europe (NCT02004080)	CREACTIVE	7000 paediatic and adult patients with TBI in intensive care	4574 patients	CER	Improved characterisation and identification of best practices (biomarkers, imaging, prognosis; systems of care, management, and interventions)	2013–2018	European Commission	€5 443 350
USA								
Transforming Research and Clinical	TRACK-TBI	2700 adult patients with TBI	2266 patients	CER	Improved characterisation and precision	2013–2018	NIH–NINDS	US$18 800 000

Knowledge in Traumatic Brain Injury (NCT02119182)		of all severities; 300 controls			medicine (biomarkers, classification, prognosis; systems of care, management, and interventions)			
Approaches and Decisions in Acute Pediatric TBI Trial	ADAPT	1000 paediatric patients with TBI in intensive care	Completed: 1000 patients	CER	Identification of best practices for treatment of severe TBI in the pediatric population (actute interventions)	2013–2018	NIH–NINDS	US$16 147 544
Managing Severe TBI Without ICP Monitoring—Guidelines Development and Testing (NCT02059941)		780 adult patients with TBI in intensive care	256/256 patients for phase 1; 250/354 patients for phase 2	CER	Creation and assessment of guidelines for treatment of severe TBI in the absence of ICP monitoring	2012–2017	NIH–NINDS	US$2 586 216
Canada								
Predicting and Preventing Postconcussive Problems in Pediatrics	5P	Paediatric and adolescent patients with mild TBI: derivation cohort 2000 patients;	Completed: 3063 patients	Prospective cohort study	Development of prognostic tools (clinical prediction rule	2013–2018	CIHR	CAN$1 273 705

Study[403,493,494] (NCT01873287)		validation cohort 800 patients			derivation and validation)			
Improving the Diagnosis and Treatment of mTBI in Children and Youth using common data elements	PedCDE	500 patients with mild TBI aged 6–17 years; 50 controls 300 patients with mild TBI aged 0–5 years; 50 controls	Completed: 434 patients aged 6–17 years; 50 controls 55 patients aged 0–5 years	Prospective cohort study	Tool standardisation (CDEs), prognosis	2013–2018	CIHR	CAN$1 400 000
Safe to Play: A 5-year longitudinal cohort study of mTBI in youth ice hockey players	Safe to Play	1000 paediatric and adolescent ice hockey players without TBI at baseline	2800 pediatric and adolescent ice hockey players (with yearly replacements for any loss to follow-up)	Longitudinal cohort study	Prevention (epidemiology, risk factors), diagnosis, prognosis, management	2013–2018	CIHR	CAN$1 500 000 ($300 000 per year for 5 years)
Post-Concussion Syndrome Affecting Youth: GABAergic Effects of Melatonin (NCT01874847)[502]	PLAYGAME	99 children and adolescents with postconcussion syndrome; 38 patients who have recovered from mild TBI as biomarker; 30 healthy controls	Recruitment complete: target numbers met	RCT (three parallel group design)	Treatment (3 mg melatonin *vs* 10 mg melatonin *vs* placebo); biomarker development	2013–2018	CIHR	CAN$855 000

NeuroCare: A Clinical Decision-Making Tool in Youth mTBI	NeuroCare	1400 paediatric and adolescent athletes; 140 paediatric and adolescent patients with mild TBI; 140 controls	941 athletes; 62 patients with mild TBI; 48 controls	Longitudinal case-control study	Tool development (neurophysiological detection of readiness for return to activity after mild TBI)	2013–2019	CIHR	CAN$1 065 728
TBI-Prognosis Multicentre Prospective Study (NCT02452541)	TBI-Prognosis	315 critically ill adults with severe TBI	Completed: 320 patients	Multicentre prospective cohort study	Development of prognostic models (biomarkers, imaging, electrophysiology, classification)	2013–2018	CIHR	CAN$1 053 131

Table 3: **Current studies supported by the International Initiative for Traumatic Brain Injury Research**

Cofunding partners of the CIHR for the InTBIR team grants are the Fonds de recherche du Québec Santé, the Hotchkiss Brain Institute, the Ontario Brain Institute, and the Ontario Neurotrauma Foundation. Cofunding of CENTER-TBI is provided by One Mind and the Hannelore Kohl Stiftung (Germany). CDEs=common data elements. CER=comparative effectiveness research. CIHR=Canadian Institutes of Health Research. ICP=intracranial pressure. InTBIR=International Initiative for Traumatic Brain Injury Research. mTBI=mild TBI. NIH=National Institutes of Health. NINDS=National Institute of Neurological Disorders and Stroke. RCT=randomised controlled trial. TBI=traumatic brain injury.

The InTBIR studies will include over 40 000 patients with TBI of all severities, many of whom will provide novel genomics, biomarker, and advanced imaging data. The outputs are expected to provide a rational basis for optimising health-care delivery for populations and clinical management for individual patients (figure 14). Additionally, these studies will establish well curated biorepositories and databases, which will provide a legacy for future research on blood samples from well characterised populations of patients with TBI as new methods are developed or longer follow-up becomes possible. All projects comply with standards based on the Common Data Elements, which allow clinical investigators systematically to collect, analyse, and share data across the research community.[404] European and Canadian studies will address the internationalisation of these Common Data Elements, allowing a US-based process to be applied globally, and promote global data standards for TBI research. This harmonised data collection will permit meta-analyses of data from large numbers of patients—essential for CER and improvement of TBI characterisation—and deliver outputs that would be impossible with any individual study.

This collaboration of international funding agencies is unique. The total overall funding for the InTBIR studies listed in table 3 will be approximately US$90 million between 2012 and 2020, which represents an enormous increase from past levels of funding for TBI research, but this is still disproportionally low when compared with that for other neurological diseases. An estimate based on figures from the International Alzheimer's Disease Research Portfolio[405] suggests that global funding for research into dementia, a disease with a comparable impact to TBI, was US$3·4 billion between 2008 and 2014.[406] Furthermore, between 1998 and 2008, an estimated US$432 million was spent globally on research into frontotemporal dementia,[407] a condition with a global incidence of 2·7–4·1 per 100 000 people per year.[408] Given the large number of patients with TBI and the huge cost burden worldwide, substantial increases are warranted in the funding to support neurotrauma research.

Figure 14: **The aims of the International Initiative for Traumatic Brain Injury Research**
The International Initiative for Traumatic Brain Injury Research studies will involve collection of clinical and outcome data in observational studies, pragmatic trials, and established biorepositories, creating a highly detailed information commons (the body of evidence on TBI). The aims of these studies are to improve understanding of the causes and mechanisms of traumatic brain injury to inform prevention strategies (prevention) and of disease characterisation to facilitate diagnosis and targeted treatment (precision medicine). Data from CER will be analysed with the aims of identifying the most effective and targeted therapies (best practice) and translating them into practice recommendations. The increased data on patient and injury characteristics should improve prognostic accuracy, which in turn could enable improved benchmarking of care (quality of care). CER=comparative effectiveness research.

[H4] Towards global collaborations

The concept of large-scale observational studies combined with CER, as implemented in the InTBIR initiative, has attracted global interest and resulted in a number of linked collaborative projects. In China, a large-scale observational study was initiated in August 2015 and recruitment was completed in June 2017. In total, 13 583 patients with TBI were included from 61 sites (Gao G, unpublished). In India, an observational study named CINTER-TBI (Comparative Indian Neurotrauma Effectiveness Research) was initiated in June 2016 and recruitment was recently expanded to six centres (Gupta D, unpublished). The inclusion of China and India, with their large populations and dramatically increasing TBI burden, provides a platform for high-quality research in these countries. Both studies are autonomous and conducted nationally, and were investigator-driven with minimal or absent local funding. Data collection in both studies is harmonised with CENTER-TBI to enable meta-analyses across studies. Therefore, for the first time, data collection in the field of TBI is globally harmonised and coordinated.

In view of the trend for clinical trials initiated by pharmaceutical companies to be moved from Europe and the USA to east Asia, the international collaborations described above could deliver key insights into the generalisability of results. These initiatives reflect increasing recognition of the potential benefits of broad collaborations[503] and represent a new approach to research, to which funding agencies must adapt to enable truly global collaborations. Major challenges include a lack of funding mechanisms for global research and restrictions to crossborder data transfer owing to privacy legislation. Despite the collaborative ethos of the InTBIR initiative, the studies conducted under its aegis are funded independently by respective funding agencies, and funding is not currently planned for meta-analyses across InTBIR studies, or with linked projects such as the initiatives in China and India. The greatest synergies will emerge from integrated analyses of the combined data in all relevant studies. The initiative established by the InTBIR needs to be expanded globally, and consolidated by facilitating meta-analysis across studies, thus ensuring future research continuity.

[H3] Data sharing

CER and precision-medicine research in TBI require large sample sizes and data sharing. Funding bodies, journal editors, and research regulators promote such data sharing.[409–416,504] Although the principle of data sharing receives almost universal support, implementation is not easy. Any solution must comply with privacy and ethical regulations, ensure high-quality data standards, promote sensible data use, maintain incentives for researchers who collect data, and appropriately account for the true costs of data sharing. Balancing these competing demands is challenging.[417]

[H4] Consent issues

In TBI, particular challenges arise from loss of capacity to consent and from the need to initiate data collection as early as possible after injury. In the USA, the Health Insurance Portability and Accountability Act regulations[418] recognise proxy consent in principle, and permit the use of a waiver of consent, particularly if underpinned by community consultation. The regulatory situation in European Union (EU) jurisdictions is in a state of flux: the General Data Protection Regulation (regulation 2016/679) will apply from May 2018,[419] and although it makes provisions for research, it remains ambiguous with regard to incapacitated patients in emergency situations. There is a strong case for explicitly defining the acceptable use of data for legitimate clinical research in this context, and doing so in a way that meets the research needs of TBI and other acute diseases that could be characterised by lack of capacity to consent.

[H4] Intellectual capital and costs of data sharing

The emergence of open data sharing has created clear tensions with the way in which research success is currently measured. Given that the conventional currency of such success is based on publications and grant awards, the data that underpin these are viewed as academic capital by many researchers. The perceived loss of such capital in the context of unrestricted data sharing is therefore seen as an obstacle to its implementation by individual researchers and institutions. Although this challenge is recognised, it remains unresolved.[504,505] These tensions are a particular issue for TBI, since the demands of data collection at the acute stage can be substantial in patients who are critically ill and often have multiple injuries. Most of these patients will not have the capacity to provide consent, and obtaining proxy consent from distraught family members requires sensitive and experienced research staff who need to be available around the clock. Provision of staff and support for patient recruitment is demanding on resources and is rarely fully recompensed in publicly funded studies. Additional costs accrue from the process of data sharing itself. A recent commentary[420] identified four major categories of costs for data sharing, including infrastructure and administration, data standardisation, human resources, and opportunity costs. It is essential that funders recognise these additional data-related costs, estimated to represent up to 15% of study costs.[420]

[H4] Approaches to data sharing

The desire to obtain a justifiable return on intellectual capital and local resource subsidies has led many researchers to make data available primarily in the context of a collaboration, with an

anticipated reward of at least one joint publication, which benefits all collaborating parties. This recapitulates arrangements in the open-source community, where source code licences (such as the GNU General Public License)[421] encourage the return of any improvements or new developments in the software product to the owner, thus ensuring a collaborative approach to product development. Many of the major InTBIR studies have elected to formalise such collaborative ventures through data-use agreements, which provide a clear understanding of data use between the collaborating parties.[422,423]

The NIH have mandated that all data from US publicly funded TBI studies must be deposited in the Federal Interagency Traumatic Brain Injury Research[424] informatics system, but transfer of data from European InTBIR studies to this repository might contravene the new EU data privacy legislation. However, data collected in a standard manner do not necessarily have to be stored together to be integrated for combined analyses. The pros and cons of central versus individual repositories for specific studies were explored in a recent Wellcome Trust Report[417] and an abstracted summary is listed in the appendix.

Irrespective of how data are stored, enabling open access while ensuring personal privacy remains a work in progress. An additional privacy concern is that new data-mining tools could allow identification of individuals in supposedly anonymised datasets.[425] One possible solution could be provided by so-called gatekeeper software, which allows access while balancing the seemingly irreconcilable demands of openness versus privacy through differential privacy algorithms.[426,427] However, technology can provide solutions only in the context of rational regulation, and any digital solutions will need to be underpinned by new paradigms of consent[428] and social contracts between researchers and patients.[429] Emerging trends provide cause for optimism in this context.[430,431]

[H3] Optimising existing evidence: living systematic reviews

Health-care decisions should be informed by knowledge about what works and what does not. Such understanding is best achieved with systematic reviews that assess and critically appraise integrated results from multiple studies using transparent and reproducible methods.[432] However, conventional systematic review processes are labour-intensive and time-consuming, often undertaken by small teams working in isolation, and seldom updated as new research is published. In an analysis of 792 studies incorporated into 73 systematic reviews across 28 neurotrauma topics, the median time from primary study publication to its inclusion in a published systematic review ranged from 2·5 to 6·5 years.[433,434] Therefore, systematic reviews are often outdated by the time they are published.[435]

An innovative knowledge-management approach known as living systematic reviews (LSRs)[434,436] is currently being pioneered within the CENTER-TBI project. LSRs are timely and high-quality online summaries of health research that are updated as new studies become available.[434] LSRs transform the production of systematic reviews from a process of undertaking sporadic large projects every few years to an activity characterised by ongoing surveillance and more frequent smaller packages of work as new research findings emerge. Whereas the main questions driving conventional reviews relate to the totality of evidence and what it tells us about the effectiveness of an intervention or the accuracy of a diagnostic test, the real-time nature of LSRs shifts the emphasis to the question of how the new evidence changes what we already know.

By pairing clinical TBI experts with experts in systematic review methods, the teams leading the InTBIR studies are laying the foundations for an ongoing dynamic TBI knowledge base and community. To date, two LSRs have been published,[94,207] and topics planned for future LSRs cover diagnosis, prognosis, and interventions. Completed reviews are published in an open-access format. Searches are being automatically run every 3 months, and machine-learning technology is being piloted to reduce the workload.[437–439] LSRs are a new challenge for academic publishers, but the *Journal of Neurotrauma* has agreed to include updates in the online versions of reviews at approximately 3–6 month intervals. The LSR author groups will also seek to publish updates as new manuscripts—subject to peer review—when new evidence leads to a change in conclusions.

Interest in LSRs is growing rapidly, with multinational research collaborations being formed to maintain and curate the evidence base in a range of clinical areas.[440,441] Notably, Cochrane, the global producer of systematic reviews, is also piloting LSRs. In the field of TBI, these pioneering efforts of CENTER-TBI are now being integrated within the InTBIR initiative. However, funding is limited to the duration of current InTBIR studies. We need mechanisms to ensure future continuity, in terms of both knowledge management and funding.

One of the most attractive aspects of a living evidence synthesis model is the potential to produce living clinical practice guidelines or recommendations, and this is currently being considered by the Brain Trauma Foundation, the main producer of guidelines in TBI.[442] While we strongly support a move towards living guidelines, an alternative approach could be to consider LSRs as the evidence base upon which more practical treatment recommendations can be tailored to national and local settings. A major criticism of current guidelines is that the emphasis on methodological rigour has decreased their practical value. Presenting the evidence base and practice recommendations separately might be a way to combine methodological rigour with practical applicability. There is also

a growing recognition of the value of practice recommendations based on expert consensus to facilitate care delivery for areas of clinical practice for which rigorous guidance is lacking or unclear.[443] While ongoing efforts continue to strengthen the evidence base, ensuring the practical relevance of guidelines is essential to stimulate their implementation into clinical practice.

[H3] Implementing evidence into practice: knowledge translation

Translating evidence into practice and policy has become a distinct science, which complements that of discovering, developing, and synthesising research results. The emerging field of knowledge translation is defined as "the science of developing strategies to integrate evidence-based knowledge into health policy and practice, based upon understanding of behavioural drivers of practice within specific settings".[432] The science of knowledge translation has developed in response to recognition of gaps between research evidence and clinical practice. The evidence-based practice movement of the early 1990s[444] reshaped clinical practice by promoting consideration of best evidence, clinical expertise, and patient preferences in making treatment decisions.[445] Nevertheless, a series of landmark studies published in the early 2000s revealed that only 55–67% of patients received recommended care, and 20–25% received care that was unnecessary or potentially harmful.[446–449] In the field of TBI, a recent systematic review[207] concluded that although guideline adherence was associated with improved outcome, general adherence to guidelines was highly variable, and in many instances, poor. For example, the mean figure for adherence to the Brain Trauma Foundation guidelines for ICP management was 31% (range 18–83%).[207]

There is much to be gained from harnessing knowledge translation to address the evidence–practice gap in TBI. Economic modelling has shown that more widespread adoption of Brain Trauma Foundation guidelines across the USA could save more than 3500 lives, and, by raising the proportion of favorable outcomes from 35% to 66%, could yield an estimated annual cost saving of US$4 billion.[155]

Use of a knowledge-translation approach involves three core tasks: defining the target behaviour, measuring current behaviour, and understanding current behaviour. Defining the target behaviour establishes the desired health-care standard by which the success of a knowledge-translation intervention can be measured. For example, the Brain Trauma Foundation guidelines on nutrition after TBI recommend "feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury" to decrease mortality.[255] Next, knowledge of current practice is required to determine the scope and nature of the evidence–practice gap.[447,450,451] Härtl and colleagues[452] examined adherence to the guideline on nutrition and found that patients not fed

within 5 and 7 days after TBI had a two-times and four-times increased risk of death, respectively, and that every 10-kcal/kg decrease in caloric intake was associated with a 30–40% increase in mortality rate.[452] These data underscore the importance of ensuring that practice reflects evidence.

Finally, understanding behaviour is necessary for successful implementation of new practices. Quantifying the evidence–practice gap defines the problem but does not give information on why practice is the way it is. The importance of gaining this understanding of behaviour before attempting a quality-improvement (knowledge-translation) strategy cannot be overestimated. Without this understanding, precious resources can be wasted. For example, a common assumption is that people do not follow guidelines because they are not aware of them. This frequently drives educationally focused strategies such as lecture presentations and passive guideline dissemination. However, there are numerous barriers to best practice other than lack of knowledge, including peer-group influence, attitudes and beliefs of health professionals, organisational barriers such as lack of equipment, and structural barriers such as financial disincentives (panel 14).[432] By addressing only the assumed barrier of lack of knowledge, an educational quality-improvement strategy risks being ineffective and wasting resources.

Advances in both the science and the uptake of knowledge translation are required to close the evidence–practice gap. A key challenge for knowledge-translation scientists is the existence of multiple terms (eg, "dissemination and implementation research", "quality improvement", "implementation science", and "research translation") and frameworks to understand, describe, and influence the behaviour of health-care practitioners. Knowledge-translation scientists are working to address this challenge through the development of conceptually simpler and shorter frameworks that can be used to standardise knowledge-translation interventions in a similar way to the standardisation achieved in the clinical trials arena with the CONSORT (Consolidated Standards of Reporting Trials) statement.[453] One such example is the AIMD framework, which seeks to characterise knowledge-translation interventions in terms of four domains identified as integral to all such interventions: Aims (purpose and target of behaviour change, Ingredients (what makes up the intervention), Mechanism (how the intervention is proposed to work on the basis of behavioural theory), and Delivery (mode of delivery—eg, online or printed material).[506] Uptake of knowledge-translation science needs to be increased in clinical and other communities that are less familiar with applying behavioural theory to close the evidence–practice gap. It is hoped that clinician engagement in universal and simple frameworks can contribute to this.

Health-care quality improvement is complex and there is never likely to be a one-size-fits-all approach. What is beyond dispute, however, are the words of the former Director General of the WHO, Lee Jong-wook: “Health work teaches us with great rigour that action without knowledge is wasted effort, and knowledge without action is a wasted resource”.[454]

[H3] Key messages and recommendations

(1) Substantial between-centre variability in treatment and outcome in TBI offers unique opportunities for CER to improve the strength of clinical evidence. CER should be funded to identify best practices and to improve the level of evidence for systems of care and diagnostic and therapeutic interventions.

(2) Coordinated research efforts on a global basis are needed to address the growing public health problem of TBI. Commitment of governmental and non-governmental funding bodies, as well as industrial partners, is needed to foster global collaborations and to establish national and international biorepositories and databases that could facilitate future TBI research.

(3) Standardisation of clinical data collection, based on the TBI common data elements, provides a common language for global research. The common data elements need to be made internationally applicable to ensure global standardisation of clinical data collection.

(4) CER studies and research on disease characterisation, outcome, and prognosis will require many patients, large datasets, and broad data sharing. Investment is needed in systems for efficient collection and sharing of data across borders, including funding of costs for rigorous data curation, annotation, and long-term database maintenance to maximise the returns on research investment from public funding.

(5) Collaborations formalised in data-use agreements offer the best guarantee for driving research and care forward, but existing frameworks for recognising the success of research projects, individual researchers, or institutions are a major obstacle to data sharing. The current way in which research is valued needs to be critically assessed and revised, and funders should provide incentives for data collection and sharing.

(6) TBI is often characterised by incapacity of patients to provide informed consent themselves. Regulatory frameworks for research should take account of acute loss of capacity to give consent in conditions such as TBI, and include appropriate provisions, such as recognition of waived, deferred, or proxy consent, to allow vital research to continue.

(7) Overly restrictive interpretation of privacy legislation can inhibit greatly needed research and productive data sharing, and might even make research and data sharing impossible in TBI and other conditions that result in loss of capacity to consent. Regulation should avoid

unnecessarily restrictive interpretation of privacy clauses and complex bureaucratic procedures.

(8) There are substantial delays in integrating research results into recommendations for best clinical practice. Funders and publishers should support rapid transfer of new research results into the evidence base, facilitated by new digital tools for their subsequent collation and integration into LSRs. LSRs should form the basis for practical treatment recommendations, with potential for a transition towards living clinical guidelines.

(9) In TBI, as in many areas of medicine, substantial gaps exist between best current evidence and clinical practice. Barriers to transfer of knowledge from research to the clinic include a lack of dissemination or awareness, attitudes and beliefs, and organisational and structural barriers. Such barriers can result in poorer patient outcomes. Information campaigns, resources, and strategies to change clinicians' behaviour are essential to overcome barriers to knowledge translation, and to ensure implementation of guidelines and best practice. Such approaches could optimise the benefits of future research advances in clinical practice, improve outcomes, and make cost savings in health care.

Panel 14: **A thought experiment about the importance of knowledge transfer in traumatic brain injury**

Suppose that strategies that maximise outcomes for patients with traumatic brain injury (TBI) have been identified through comprehensive studies and their efficacy determined beyond any doubt. Suppose that they apply to all severities of injury, all mechanisms of trauma, and all patient groups, regardless of age, gender, and ethnic origin. Moreover, suppose that the evidence has been compiled into guidelines that are considered to be influential within the field. Given these assumptions, what barriers, if any, would exist to a future with optimum patient outcomes?

Health care is delivered within a system that has multiple levels, each constraining or facilitating conscious or unconscious choices about whether and how to use evidence-based practices. Even in a future with perfect guidelines, obstacles to guideline implementation will remain at all levels, from individual health-care professionals and factors related to individual patients, to teams of clinicians working in hospital systems. Strategies to address the full range of barriers will be crucial to realise successful outcomes.

We invite the reader to engage in frank introspection, considering the range of barriers to evidence-based, guideline-driven care, and challenge decision makers and clinicians to develop a plan of attack for implementation that guides efforts to embed evidence into practice. Every hospital that seeks to

implement TBI guidelines will need to run its own thought experiment, because the barriers are likely to vary by location. Planning holds the promise of avoiding traditional pitfalls if sufficient resources can be brought to bear on the question of not just what to implement, but also how to implement evidence into practice. It is important that all stakeholders recognise the need for funding and resources to support knowledge transfer in TBI—a vital step in bridging the gap between evidence and practice. For more on this thought experiment, see appendix.

Conclusions

Traumatic brain injury (TBI) is predicted to remain the largest global contributor to neurological disability for the next two decades, with a disease burden that far exceeds that of conditions such as cerebrovascular disease and dementia.[4] Crucially, TBI-associated disability often affects young individuals at their productive peak, and results in huge burdens to individuals, families, and society (section 1). Extrapolation from available estimates suggests a global annual cost of TBI as high as US$400 billion[5]—a figure that represents approximately 0·5% of global gross domestic product (section 2). The precise magnitude of the problem, however, remains largely uncharted. Current estimates of 50–60 million new TBIs per year[3] are an approximation because wide variations in methodology exist between countries, including differences in data capture and reporting. We urgently need consensus on descriptors of TBI and its severity, as well as standardisation of methods for epidemiological monitoring across countries. Worldwide, patterns of TBI are changing, with increases in road traffic injuries in low-income and middle-income countries (LMICs) and a growing problem with falls among elderly individuals in high-income countries (HICs). Other key drivers that contribute to the burden of TBI include sports-related concussion and international conflict. Regardless of the cause, TBI results in an enduring burden of late morbidity and increased mortality, and might represent a risk factor for dementia in later life; the attributable risk from TBI to overall dementia incidence could be as high as 15%.[60] Improved knowledge of epidemiology will be key to more effective targeting of TBI prevention strategies in different populations (section 3).

When TBI does occur, we need better ways to organise systems of care that provide cost-effective approaches to minimise preventable mortality and morbidity, ensuring that patients receive appropriate health care as soon as possible (section 4). Substantial variations in outcome exist between centres, and tackling these differences has the potential to far outweigh any benefit that might be realistically expected from a new treatment. There is growing evidence of a relation between management in high-volume centres and improved centre outcomes,[210–212] which suggests that care for the most critically ill patients should be centralised. Substantial gains could be made from adequate prehospital care, appropriate referral, and continuity along the chain of care, with early access to effective rehabilitation. The solutions that relate to care systems for TBI must take account of local economic and social factors and, in particular, work is needed to develop cost-effective systems of care in LMICs.

Clinical management of TBI should be based on robust guidelines. However, evidence in support of guideline recommendations is often weak and not applicable to all patients, as most studies are population based and do not take into account the heterogeneity of TBI, its severity, and differences between individual patients. As a result, current management strategies are based on guidelines that favour a one-size-fits-all approach, and the care of patients with TBI is therefore poorly individualised (section 5). Moreover, despite investment of many billions of dollars by pharmaceutical companies, no effective drugs exist for treatment in the acute setting—a failing, in part, due to insufficient targeting of therapies to patients in whom the relevant mechanism is active. We need better methods to characterise TBI to allow identification of patient subgroups, with a common dominant disease mechanism, who are more likely to respond to specific treatments—a concept now being popularised as precision medicine (section 6). We also need to enable better characterisation of outcome after TBI: mortality is an inappropriate metric for a disease that can result in considerable disability in survivors, and current outcome assessment tools are limited by their unidimensional approaches. We need improved multidimensional outcome assessment schemes that take better account of the substantial physical, cognitive, behavioural, and mental health sequelae of TBI (section 7). Improved disease and outcome characterisation will also provide a robust foundation for better prognostication of outcome. This could support better counselling of relatives, improve comparative audit of care between centres and countries, facilitate research, and help in management planning for individual patients (section 8). Huge opportunities exist for improvements in characterisation of initial severity, outcome, and prognosis, and for more accurate tracking of disease processes, by building on the current scientific advances in modern neuroimaging, genomics, disease biomarker development, and pathophysiological monitoring. Developments in these technologies could facilitate the goals of precision medicine in TBI.

Comparative effectiveness research (CER) is a novel approach in which disease heterogeneity—in terms of clinical and pathophysiological type and outcome—and variations in clinical management and systems of care can be exploited to identify best practices (section 9).The data gathered from such research in real-world situations could enrich the limited evidence base on clinical care for TBI. Critical gaps in our knowledge of how best to treat TBI necessitate common methods and descriptors for collaborative research efforts. The development of common data elements for TBI research—allowing systematic collection and analysis of data across the research community —is an important step, but these tools need to be internationalised, particularly for use in LMICs. Clinical research in TBI is also hampered by vendor-specific differences in platforms used for neuroimaging and laboratory investigation. It is crucial that national and international regulators mandate common

standards for imaging and laboratory results, so that outputs from different studies can be usefully integrated. Industry has been a valuable partner in improving TBI care in the past, and we need to continue to facilitate such support through regulatory design and collaborative funding arrangements.

Large cohorts of patients are needed to deliver meaningful advances in precision medicine, for robust CER, and to improve prognostic schemes. Such studies can be realised only through global collaboration (section 9). Current international initiatives, such as the International Initiative for TBI Research (InTBIR), and a growing ethos of data sharing represent an unprecedented opportunity to achieve these aims. However, such collaborative approaches to research depend on regulatory frameworks that enable consent for research and data sharing —a growing concern in the context of ever more rigorous privacy legislation, particularly in the context of TBI, in which patients often lose the capacity to consent at the onset of injury. Given the high public health interest, regulatory frameworks need to find ways to legitimise research inTBI and other contexts, where explicit patient consent cannot be obtained, and to implement solutions that resolve the conflict between personal privacy and wide access to research data. Research funders also need to recognise the substantial costs of data sharing.

The knowledge that is gained from clinical research must be rapidly translated to improvements in care. There is typically a gap of up to 6·5 years before the results of a study are integrated into a systematic review[433,434] and a further delay before such integrated information is translated into clinical guidelines. Novel digital tools for literature searching and integration could speed up this process with the development of living systematic reviews (LSRs) and living guidelines, which are continually updated as new information becomes available.

The problems and potential solutions described in this Commission have been inspired by patients and brought together by a wide international group of active clinical researchers who seek to improve outcomes for people with TBI. Clinicians and researchers, in consultation with patients and their families, need to play their part in taking these recommendations forward. Collaboration between funding agencies is required to coordinate the strategy and conduct of research, and commitment from policy makers essential to facilitate research and ensure timely implementation of research outputs. Integration of all these efforts will result in an end-product that is more than the sum of its parts, with rich dividends in terms of better and more cost effective care, and improved patients outcomes.

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We are grateful to our patients who have taught us so much, but have also made us realize how little we know – and that something has to be done about it! The patient testimonies, written by James Piercy and Laura Gonzalez-Lara (panels 1 and 6), effectively summarize many stories we have heard from patients in the past. We are very grateful for their inputs, which speak for the most important stakeholders in this process.

This manuscript truly represents a team effort, in which we pioneered a "wiki-like" approach incorporating input from all InTBIR participants and investigators. We consider it important that investigators collecting data in large scale observational studies and clinical trials, such as the InTBIR studies, obtain scientific recognition for their efforts *(see section 9)*. Without their time and effort, there would be no data or evidence base for the scientific participants to work on. Perhaps more importantly, in the context of publication ethics, the output in this Commissioned Issue evolved as an organic whole through discussions in many fora which involved the Scientific Participants and Centre Investigators in InTBIR, either in person, or through web based wiki-editing interactions.

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