Advancing care for traumatic brain injury: findings from the IMPACT studies and perspectives on future research

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Research in traumatic brain injury (TBI) is challenging for several reasons; in particular, the heterogeneity between patients regarding causes, pathophysiology, treatment, and outcome. Advances in basic science have failed to translate into successful clinical treatments, and the evidence underpinning guideline recommendations is weak. Because clinical research has been hampered by non-standardised data collection, restricted multidisciplinary collaboration, and the lack of sensitivity of classification and efficacy analyses, multidisciplinary collaborations are now being fostered. Approaches to deal with heterogeneity have been developed by the IMPACT study group. These approaches can increase statistical power in clinical trials by up to 50% and are also relevant to other heterogeneous neurological diseases, such as stroke and subarachnoid haemorrhage. Rather than trying to limit heterogeneity, we might also be able to exploit it by analysing differences in treatment and outcome between countries and centres in comparative effectiveness research. This approach has great potential to advance care in patients with TBI.

Introduction

Traumatic brain injury (TBI) is a serious public health problem with an estimated annual incidence of up to 500 cases per 100 000 population in the USA and Europe.[1,2] A recent population-based study[3] from New Zealand reported an annual incidence of 790 per 100 000 person-years. In low-income and middle-income countries most injuries result from road traffic incidents; in high-income countries, falls are now a more frequent cause of TBI and commonly occur in older patients. TBI is a major cause of death and disability, leading to great personal suffering for patients and relatives and huge direct and indirect costs to society. In the USA these annual costs are estimated at more than US$76·5 billion.[4] Despite the magnitude of the socioeconomic and medical problem posed by TBI, the strength of evidence underpinning treatment recommendations is low. Since the first publication of guidelines for management of severe TBI in 1996,[5] strong evidence in support of treatment recommendations has not been forthcoming. Conventional approaches to clinical TBI research have been reductionist, attempting to isolate a single factor for treatment.[6] These approaches have ignored the heterogeneity of TBI in terms of causes, pathophysiology, treatment, and outcome. This heterogeneity makes research in TBI particularly challenging, and might partly explain why many randomised clinical trials have not had statistically significant positive results.[7] This aspect is being addressed in two ways. First, by applying novel methods to deal with the heterogeneity of TBI; for example, combining covariate adjustment with an ordinal approach to analysis as proposed by the International Mission on Prognosis and Analysis of randomized Controlled Trials in TBI (IMPACT) studies offers the potential to increase the statistical efficiency by up to 50%.[8] Second, rather than attempting to limit heterogeneity from care paths, treatments, and outcomes, we can exploit it by using comparative effectiveness research. Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care. The purpose of this research is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve health care at both the individual and population levels.[9] Comparative effectiveness research is broadly defined and can include pragmatic clinical trials. One approach is to make use of existing differences in treatment and outcome between countries and centres, with the aim of identifying best practices. Modern computational techniques and the availability of robust risk adjustment models allow such approaches, offering the potential to acquire high quality evidence in observational studies with greater generalisability.[7] In this Personal View we summarise the results of the IMPACT studies and discuss the potential of comparative effectiveness research to provide evidence in support of care paths and treatment recommendations in TBI. This discussion is pertinent because large observational studies in TBI will soon be initiated in the context of an international collaboration established by the European Commission, the US National Institute of Neurological Disorders and Stroke (NIH-NINDS), and the Canadian Institutes of Health Research (CIHR).

The IMPACT studies

Background

The IMPACT studies, funded by NIH-NINDS, were initiated in 2003. For 10 years this international, multidisciplinary study group has addressed methodological issues to improve the design and analysis of clinical trials in TBI. The IMPACT investigators were initially granted access to 11 large datasets of clinical trials (n=8) and observational studies (n=3) undertaken in North America and Europe.[10] Permission to access the datasets was obtained from principal investigators and, when appropriate, sponsoring companies. During the project, additional studies were added and collaborations were

developed with the MRC CRASH trial investigators and the TARN registry.[11,12] The available datasets were used to test and validate new approaches to trial design and analysis. As the project developed, three main directions of research evolved: first, standardisation of data collection; second, prognostic analysis and development of prognostic models; and third, improvements in the design and analysis of randomised clinical trials.

Standardisation of data collection

Merging of individual patient data for analysis across the constituent studies of the IMPACT database proved to be a major challenge. Not only did data field names and coding differ, but also the structures of the datasets were complex and the documentation poor. This emphasised the importance of consensus on a basic set of core variables to be collected in TBI studies, with agreement on appropriate definitions, field names, and coding. Obtaining such agreement would expedite study designs, allow individual patient data analysis across studies, and reduce costs to funding agencies and pharmaceutical companies. From this perspective the IMPACT investigators initiated a process of standardisation of data collection in TBI studies. This process was taken forward in the context of an international and interagency initiative towards "an integrated approach to research and psychological health and traumatic brain injury" in the USA.[13] This initiative proposed common data elements and included proposals for definitions and coding of demographic characteristics, basic clinical data, biomarkers, neuroimaging, and outcomes. The original intent was to focus on the most important variables for characterisation of TBI populations, including established prognostic indicators. The process was consensus-driven with multidisciplinary input from a broad range of experts, from emergency medicine to rehabilitation and late outpatient care.

The Working Group on Demographics and Clinical Assessments recognised that the required level of detail for coding a variable can vary with the aim of a specific study. Thus, up to three versions for coding data elements were developed: a basic, an advanced, and an extended format with the greatest level of detail. The coding of these variables was such that more detailed coding could always be collapsed into the basic version, thus enabling comparisons across studies.[14,15] In a version 2, the common data elements were refined.[16] This revised version also addressed variables for epidemiological, postacute care, and outcomes research. As a consequence, the number of variables has expanded substantially, resulting in a less user-friendly presentation and, regrettably, the initial focus on the most important elements has partly been lost. A broad discussion would seem appropriate as to whether the common data elements should be focused on the most important variables to be collected in all studies or that a more inclusive approach should be taken in the context of a

	Univariate analysis		Adjusted analysis	
	N	Odds ratio (95% CI)	N	Odds ratio (95% CI)
Predictors included in IMPACT model				
Age 46 years *vs* 22 years	11 022	2·09 (1·96–2·22)	11 022	2·3 (2·14–2·48)*
GCS motor score				
Localises or obeys	11 383	1	11 022	1†
None	..	4·34 (3·03–6·23)	..	3·31 (2·52–4·34)
Extension	..	6·75 (5·27–8·63)	..	5·13 (4·10–6·42)
Abnormal flexion	..	3·43 (2·73–4·30)	..	2·84 (2·34–3·44)
Normal flexion	..	1·71 (1·46–2·02)	..	1·59 (1·34–1·90)
Missing or untestable	..	2·29 (1·73–3·01)	..	2·02 (1·58–2·58)
Pupil response				
Both reacting	9830	1	9494	1‡
One reacting	..	2·69 (2·37–3·06)	..	2·2 (1·90–2·56)
Neither reacting	..	6·62 (4·85–9·06)	..	4·33 (3·45–5·44)
Hypoxia				
No	8195	1	7843	1
Suspected or definite	..	1·91 (1·56–2·35)	..	1·48 (1·27–1·72)
Hypotension				
No	9191	1	8838	1
Suspected or definite	..	2·44 (1·96–3·03)	..	1·86 (1·54–2·24)
CT class				
No visible pathology or diffuse	6407	1	6390	1
Swelling or shift	..	2·68 (2·08–3·46)	..	2·32 (1·84–2·92)
Mass lesion	..	2·36 (1·93–2·90)	..	1·63 (1·42–1·88)
Traumatic SAH				
No	9184	1	8996	1
Yes	..	2·69 (2·42–2·99)	..	2 (1·84–2·18)
Haemoglobin (142 *vs* 109 g/L)	4957	0·69 (0·62–0·77)	4953	0·76 (0·68–0·84)
Glucose (10·2 *vs* 6·6 mmol/L)	5889	1·64 (1·52–1·77)	5885	1·45 (1·36–1·54)
Other predictors				
Sex				
Male	11 379	1	11 021	1
Female	..	1·02 (0·94–1·10)		0·96 (0·88–1·05)
Race				
White	7075	1	7070	1
Black	..	1·37 (1·16–1·61)	..	1·54 (1·26–1·90)
Asian	..	1·21 (0·91–1·62)	..	1·43 (0·97–2·10)
Other	..	1·1 (0·90–1·34)	..	1·12 (0·91–1·39)
Education				
0–8 years	2559	1	2555	1
9–12 years	..	0·82 (0·64–1·06)	..	0·94 (0·73–1·20)
Longer than 12 years	..	0·74 (0·56–0·98)	..	0·79 (0·61–1·03)
Cause of injury				
Fall	11 363	1	11 005	1
Road traffic incident	..	0·71 (0·64–0·80)	..	1·11 (1·00–1·24)
Assault	..	0·68 (0·56–0·81)	..	1·07 (0·86–1·33)
Work-related	..	0·94 (0·75–1·18)	..	1·31 (1·02–1·69)
Sports or recreation	..	0·47 (0·32–0·68)	..	0·8 (0·59–1·08)
Other	..	0·85 (0·71–1·01)	..	1·06 (0·88–1·28)
GCS eye score				
Pain, sound, or spontaneous	11 383	1	11 022	1

(Continues on next page)

	Univariate analysis		Adjusted analysis	
	N	Odds ratio (95% CI)	N	Odds ratio (95% CI)
(Continued from previous page)				
None	..	2·69 (2·18–3·31)	..	1·63 (1·33–2·00)
Missing or untestable	..	2·3 (1·71–3·09)	..	1·39 (0·92–2·09)
GCS verbal score				
Sounds-orientated	11383	1	10637	1
None	..	2·43 (1·95–3·02)	..	1·49 (1·24–1·78)
Missing or untestable	..	2·6 (2·22–3·04)	..	1·47 (1·25–1·73)
Systolic blood pressure				
120–150 mm Hg	8172	1	8168	1
<120 mm Hg	..	1·48 (1·29–1·70)	..	1·23 (1·10–1·38)
>150 mm Hg	..	1·37 (1·19–1·57)	..	1·24 (1·07–1·44)
Mean arterial blood pressure				
85–110 mm Hg	8250	1	8245	1
<85 mm Hg	..	1·28 (1·13–1·45)	..	1·14 (1·02 –1·27)
>110 mm Hg	..	1·35 (1·16–1·58)	..	1·21 (1·02–1·42)
Hypothermia				
No	5034	1	5017	1
Suspected or definite	..	2·01 (1·47–2·75)	..	1·59 (1·18–2·14)
Cisterns				
Present	5233	1	5229	1
Compressed or absent	..	2·49 (2·05–3·04)	..	1·95 (1·68–2·25)
Shift				
No	5546	1	5542	1
1–5 mm	..	1·33 (1·11–1·59)	..	1·3 (1·12–1·52)
>5 mm	..	2·16 (1·68–2·77)	..	1·37 (1·06–1·77)
EDH				
No	9872	1	9531	1
Yes	..	0·65 (0·58–0·72)	..	0·67 (0·59–0·75)
SDH				
No	9881	1	9540	1
Yes	..	2·26 (1·85–2·75)	..	1·4 (1·24–1·57)
Contusion				
No	8953	1	8761	1
Yes	..	1·39 (1·16–1·67)	..	1·39 (1·19–1·61)
Sodium				
137–142 mmol/L	6335	1	6331	1
<137 mmol/L	..	1·38 (1·23–1·55)	..	1·16 (0·97–1·39)
>142 mmol/L	..	1·15 (0·99–1·34)	..	1·18 (1·03–1·35)
pH (7·45 *vs* 7·32)	4268	0·81 (0·75–0·88)	4264	0·84 (0·78–0·92)
Haematocrit (42·0% *vs* 32·6%)	1914	0·71 (0·60–0·83)	1914	0·83 (0·71–0·97)
Platelet count (253 *vs* 154 × 10^9/L)	2466	0·76 (0·64–0·92)	2466	0·85 (0·71–1·02)
Prothrombin time (14·4 *vs* 12·1 s)	1032	1·47 (1·13–1·92)	1032	1·57 (1·28–1·92)

Multivariable logistic regression analysis was done on the association between the prognostic factor of interest with and without adjustment for the core predictors: age, GCS motor score, and pupillary reactivity. The numbers in the adjusted analysis column show availability of each covariate in adults with non-missing outcome in the overall dataset. In the adjusted analyses missing values for pupillary response were replaced by imputed values.[22] For the continuous predictors with a linear relation to outcome, the odds ratios were scaled so that they correspond to change from the 25th percentile to the 75th percentile (IQR). The IQR is reported for each continuous variable. An odds ratio greater than 1 for a continuous prognostic factor indicates that the risk of a poor outcome increases as the variable increases over the IQR. GCS=Glasgow coma scale. SAH=subarachnoid haemorrhage. EDH=epidural haematoma. SDH=subdural haematoma. *Adjusted for GCS motor score and pupillary response. †Adjusted for age and pupillary response. ‡Adjusted for age and GCS motor score.

***Table 1*: Prognostic strength of outcome predictors in patients with traumatic brain injury, expressed as proportional odds ratios for Glasgow outcome scale at 6 months**

data dictionary. Version 2 of the common data elements represents a hybrid format of these approaches in which the most relevant variables for the different domains of TBI research are designated as core or basic. The TBI common data elements effort is an evolving process, and recent studies that have implemented the common data elements, such as TRACK-TBI,[17] will probably provide data to resolve some of these issues for the anticipated version 3. This revision should be informed by experience and evidence, rather than being based on consensus.

Prognostic analysis and development of models

Differences in patient population (casemix) can confound comparison of results between studies. In randomised controlled trials, the process of randomisation seeks to achieve balance between treatment groups. However, an imbalance in cumulative prognostic risk between treatment groups can occur, despite only minor differences in individual characteristics. Quantification of the initial prognostic risk is therefore highly relevant. Many studies have reported on associations between predictors and outcome after TBI, but most have focused on univariate analyses in small sample sizes. The few studies that integrated predictors into a prognostic model to predict outcome on an individual patient basis had many methodological shortcomings, in particular the absence of external validation.[18,19] The IMPACT database allowed extensive prognostic analyses on large numbers of patients (n>8000). Unique features included a systematic approach to the adjusted analyses of predictors,[20] non-linear analysis of continuous predictors, and proportional odds analysis of the Glasgow outcome scale, rather than use of a dichotomised analysis such as survival or unfavourable versus favourable outcome.[21] Table 1 updates Murray and colleagues' 2007 overview[20] of the prognostic strength of the most important predictors for outcome in TBI in more patients, based on the 2013 version of the IMPACT database. The importance of adjustment for other predictors in multivariable analysis is well illustrated by the prognostic strength of cause of injury. Cause of injury was strongly associated with outcome in univariate analysis, with falls having a significantly higher risk of poor outcome than road traffic incidents or other causes. However, after adjustment for age and other predictors in multivariable analysis, the association between cause of injury, specifically the occurrence of a fall, and outcome that was seen in univariate analysis is no longer found. Thus, the effect of cause of injury is confounded by the age of patients sustaining falls. Analysis of blood pressure emphasises the importance of continuous non-linear analysis of continuous predictors both low and high blood pressures were related to poor outcome, in a U-shaped relation (figure 1). This relation would not have been observed if one cutoff for blood pressure had been chosen.

The most important predictors of outcome were included in three prognostic logistic regression models

of increasing complexity:[23] a core model based on demographic characteristics and injury severity; an extended model additionally including CT information and second insults; and a laboratory model additionally including glucose and haemoglobin values. Predictions from the models for individual patients can be obtained from the IMPACT website . Specifically, we note that the simple core model (including age, motor score, and pupillary reactivity) contains most of the prognostic information. These models were initially validated both internally and externally in collaboration with the CRASH trial investigators,[23] and thereafter in various other datasets (table 2).[25,31–34] Although missing data should be avoided as far as possible in high-quality studies, this issue does occur and has to be dealt with. Multiple imputation was used to deal with missing covariates. Such imputation is deemed more efficient than complete case analysis, in which cases with incomplete data are dropped.[35,36] Discrimination was assessed by the area under the receiver operating characteristic curve (AUC) and was typically around 0·7–0·8 in ten external validation studies. The variability in discriminatory performance was mainly related to variation in the casemix in the validation sets, with better performance in more observational studies on more heterogeneous populations, such as TARN and POCON (table 2).[27,31,37]

This extensive validation illustrates the robustness of the IMPACT models and their generalisability across various settings. Nevertheless, several limitations in the use and interpretation of the IMPACT models should be acknowledged. First, as in any prognostic model, the output of the calculation remains a probability estimate with an inherent degree of uncertainty. Thus, particular care should be taken in the interpretation of prognostic estimates in individual patients. Second, the focus of the IMPACT prognostic analysis was the establishment of baseline prognostic risk and the studies did not include dynamic predictions, adding new information as it becomes available over the course of the disease process. Third, the IMPACT studies were limited by the selection and detail of predictors that had been collected in previous studies. Some, possibly relevant, predictors could not be analysed in adequate detail owing to the low number of patients in which these had been collected. Examples include details of coagulation status and the presence and severity of extracranial injuries.[33,38] Fourth, the IMPACT dataset did not include patients with mild TBI, and the IMPACT models are consequently not valid for this condition. Despite the fact that up to 95% of TBIs are mild, only one prognostic model has been developed specifically for mild TBI.[39] Finally, a further possible selection bias might have been introduced by the lack of population-based studies. This risk is however regarded as low because the focus of the IMPACT prognostic analysis was more on patients with severe and moderate TBI. Population-based studies are more relevant to mild TBI because most of these patients are not seen in the hospital setting.

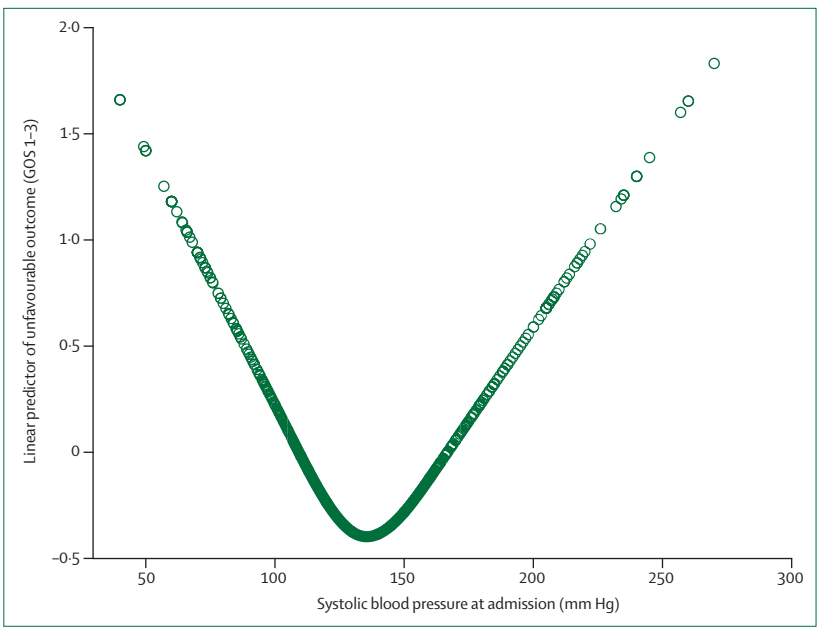

Figure 1: **Relation between systolic blood pressure and outcome (n=8172)**
A higher linear predictor corresponds to a higher probability of unfavourable outcome. GOS=Glasgow outcome score.

Improving the design and analysis of randomised controlled trials

For the **IMPACT website** see http://www.tbi-impact.org/

In TBI, nearly all randomised clinical trials have attempted to decrease heterogeneity by applying strict enrolment criteria or by targeting patients with an intermediate prognosis at randomisation. A contrasting approach was followed in the CRASH megatrial, in which large numbers of participants were predicted to overcome problems caused by prognostic heterogeneity and increase generalisability. The relative efficacy of these approaches was explored systematically in the IMPACT project. Simulation studies showed that exclusion of patients with an extreme prognosis—by the use of strict enrolment criteria or by prognostic targeting—indeed increases statistical power.[40] However, as a result of this strict selection many patients are excluded from study participation,[41] which limits the generalisability of the results. Moreover, strict selection will reduce the recruitment rate, thereby prolonging study duration. Beneficial effects in terms of increased statistical power of strict selection need to be balanced against negative effects on recruitment. On the assumption of a uniform treatment effect, this balance has been unfavourable for the execution of studies with such restrictive enrolment criteria.[40]

Despite the fact that conditional estimation of treatment effects, also by non-normal regression models such as logistic or Cox regression models, is more powerful than unadjusted estimation,[42–44] fairly few

	Sample size	Time period	Study design	Reference validation	Mortality			Unfavourable outcome		
					Core*	Extended*	Laboratory*	Core*	Extended*	Laboratory*
CRASH[24]	6272	1999–2004	RCT	Steyerberg et al[23]	0·78	0·80	NA	0·78	0·80	NA
TBI-TRAC	2513	2000–09	Observational	Roozenbeek et al[25]	0·79†	0·83†	NA	NA	NA	NA
APOE[26]	404	1996–99	Observational	Roozenbeek et al[27]	0·81	0·80	NA	0·76	0·78	NA
TARN TBI	6874	1989–2009	Observational	Roozenbeek et al[27]	0·83	0·86	NA	NA	NA	NA
NABIS Hypothermia[28]	385	1994–98	RCT	Roozenbeek et al[27]	0·70	0·74	0·75	0·73	0·75	0·75
Cerestat	517	1996–97	RCT	Roozenbeek et al[27]	0·75	0·76	NA	0·71	0·78	NA
Pharmos[29]	856	2001–04	RCT	Roozenbeek et al[27]	0·65	0·71	0·71	0·66	0·71	0·70
POCON[30]	415	2008–09	Observational	Lingsma et al[31]	0·85	0·88	0·90	0·82	0·85	0·87
Panczykowski et al[32]	587	1994–2009	Observational	Panczykowski et al[32]	0·78	0·83	0·83	0·76	0·79	0·76
Raj et al[33]	342	2009–10	Observational	Raj et al[33]	NA	NA	0·85	NA	NA	0·81

RCT=randomised controlled trial. NA=not available. CRASH=Corticosteroid Randomization After Significant Head Injury. TBI-TRAC=database of the Brain Trauma Foundation in New York for tracking the treatment of severe TBI patients. APOE=apolipoprotein E single-centre observational cohort study. TARN TBI=Trauma Audit and Registry Network TBI study. NABIS=National Acute Brain Injury Study. Cerestat=randomised controlled trial of a non-competitive NMDA antagonist. Pharmos=randomised controlled trial of dexanabinol. POCON=Prospective Observational COhort Neurotrauma registry. *Core model included age, GCS motor score, and pupillary reactivity; extended model included the core components plus CT information (CT classification and traumatic subarachnoid haemorrhage) and second insults (hypoxia and hypotension); laboratory model included the extended model plus glucose and haemoglobin. †14 day outcome.

***Table 2*: Discriminative ability of the IMPACT prognostic models in ten external validation studies, expressed as the area under the receiver operating characteristic curve (AUC) for 6-month mortality or unfavourable outcome**

randomised clinical trials have dealt with the problem of heterogeneity by adjusting the treatment effect for important predictors of outcome using covariate adjustment. Simulation studies with TBI trial data showed that covariate adjustment for seven strong predictors of outcome increased statistical efficiency up to 30% in more heterogeneous populations of observational surveys and up to 16% in trial populations that initially used stricter enrolment criteria.[40] In a reanalysis of the CRASH trial data,[45] covariate adjustment for age, Glasgow coma scale motor score, and pupillary reactivity reduced the required sample size by 21% to obtain the same statistical power compared with the unadjusted analysis. Covariate adjustment should be prespecified and include established strong predictors for outcome.[42] We note that risk adjustment models might need to be updated as newer prognostic information becomes available.

When testing the efficacy of a new therapy the aim is to prove that the new treatment yields better results than placebo treatment or conventional management, in other words that patients will have a better outcome than expected. The primary outcome measure in most randomised clinical trials for TBI is the Glasgow outcome scale or its extended version.[46,47] It is common practice to dichotomise this scale into favourable versus unfavourable outcomes. However, the practice of dichotomisation is clinically unattractive and statistically inefficient. The prognosis of patients at the extreme ends of the outcome distribution can be either so good that they will almost inevitably achieve a favourable outcome, even without the benefits of an effective therapeutic intervention, or so poor that it is unlikely that even an effective intervention would improve their outcome to such an extent that it would move from being unfavourable to favourable. Moreover, focusing only on one specific split of the outcome scale ignores the fact that other transitions of the outcome are clinically relevant. We considered two novel approaches to ordinal efficacy analysis: the sliding dichotomy approach and proportional odds regression (figure 2). With the sliding dichotomy approach, the point of the dichotomy is differentiated according to the baseline prognostic risk. For example, for patients with poor prognosis, survival might be most relevant, whereas in those with a good prognosis any outcome worse than good recovery might be deemed unfavourable. Proportional odds regression considers all possible ways in which the ordinal scale can be dichotomised, assuming that the odds ratio for a better versus worse outcome is identical wherever the scale is dichotomised (the proportional odds assumption). Conceptually, the model combines all potential splits to estimate an overall effect measure: the common odds ratio. This common odds ratio can be interpreted as the odds for a shift in outcome across the full ordinal scale.[48]

Simulation studies with the IMPACT database showed that ordinal approaches to the efficacy analysis reduced the sample sizes required by 23–30% compared with the traditional dichotomised analysis.[21] These gains were consistent across studies and, remarkably, also remained if the proportional odds assumption was violated. Applying covariate adjustment together with ordinal analysis reduced the sample size requirements by up to 50%. These findings were confirmed in the CRASH trial:[49] combining ordinal analysis with covariate adjustment increased statistical efficiency by about 50%

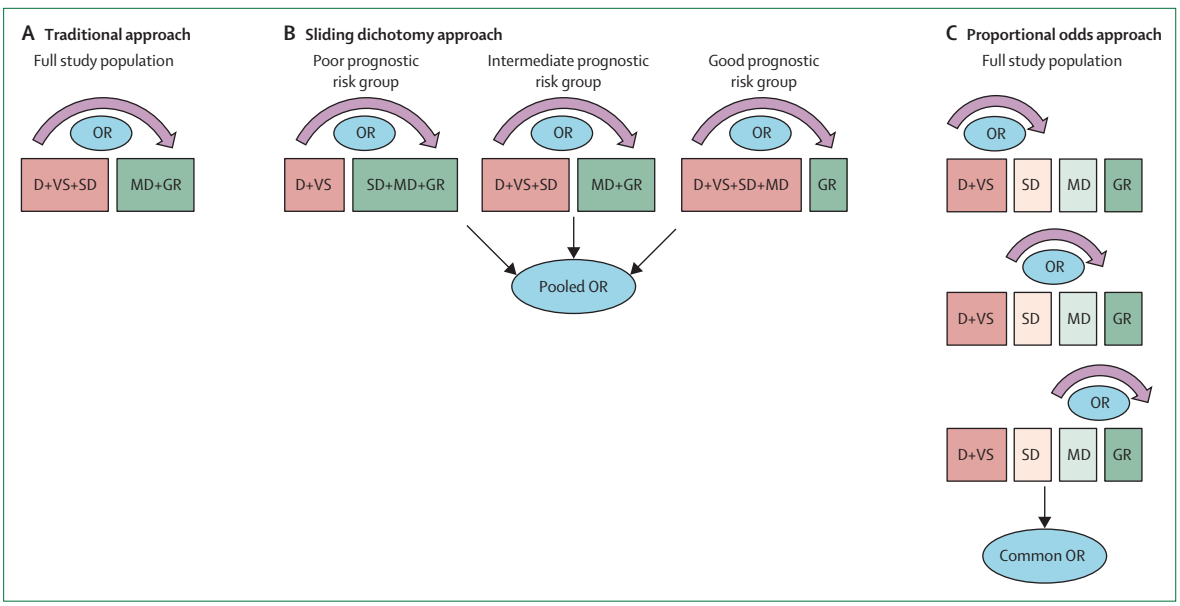

Figure 2: **Approaches to analyse the Glasgow outcome scale as the primary outcome measure in randomised controlled trials of traumatic brain injury**
The traditional approach (A) to efficacy analysis is to dichotomise the Glasgow outcome scale into unfavourable outcomes (dead [D], vegetative state [VS], or severe disability [SD]) versus favourable outcomes (moderate disability [MD] or good recovery [GR]). The proportions of patients with an unfavourable outcome in the treatment and placebo groups are compared by calculating an odds ratio (OR) with logistic regression analysis. With the sliding dichotomy approach (B), the study population is first subdivided in (for example, three) equally large prognostic risk groups. For each of the risk groups, the point of the dichotomy of the Glasgow outcome scale is based on the baseline prognostic risk (eg, for patients in the good prognostic risk group, only good recovery is judged a favourable outcome). A pooled odds ratio is calculated, which can be interpreted as the summary measure for having a better outcome than expected. With the proportional odds approach (C), the population is not subdivided. The proportional odds model considers every possible way the Glasgow outcome scale can be dichotomised, assuming that the odds ratio for a better versus a worse outcome is similar wherever the scale is dichotomised (the proportional odds assumption). The common odds ratio can be interpreted as a summary measure for the shift in outcome across the full scale.

and statistically significant effects were already present after enrolment of around 50% of the population.[49] The combined results of the simulation studies and empirical proof of effectiveness of the IMPACT recommendations in CRASH provide strong support to incorporate these approaches in the design of new clinical trials (panel).

Perspectives on future research

Standards for data collection and prognostic research

The IMPACT studies illustrate how international and multidisciplinary collaboration can accelerate research and how methodological research can lead directly to improved clinical research. The recent institution of the International Initiative for Traumatic Brain Injury Research (InTBIR) as a collaboration between funding agencies (the European Commission, NIH-NINDS, and CIHR) represents a milestone accomplishment and provides a platform for global collaboration in TBI research.[50,51]

The concepts developed by the IMPACT study group are being taken forward. Use of common data elements is currently required in all observational studies and trials in TBI that are funded by NIH-NINDS. A recent call by the European Commission also mandated use of core common data elements.[52] This adoption of common data elements by funding agencies might be expected to assist with comparisons between studies, meta-analyses of individual patient data across studies, and, importantly, will reduce costs in the design of case report forms for new studies. From a global perspective, the generalisability for use of the common data elements across different settings and empirical experience in their use should form the basis for

***Panel*: Recommendations for design and analysis of randomised controlled trials in traumatic brain injury[8]**

- Details of the major baseline prognostic characteristics should be provided in every report of a study; in trials they should be differentiated per treatment group. We also advocate the reporting of a summary of the baseline prognostic risk as determined by validated prognostic models.
- Inclusion criteria should be as broad as is compatible with the current understanding of the mechanisms of action of the intervention being evaluated. This approach will maximise recruitment rates and improve the generalisability of the results.
- The statistical analysis should incorporate (prespecified) covariate adjustment to mitigate the effects of heterogeneity.
- The statistical analysis should use an ordinal approach, based on either sliding dichotomy or proportional odds methods.

further refinements where compromises might need to be made between international generalisability and a national or local focus. The differentiation of coding into three levels of detail might provide opportunities for harmonisation of these two perspectives. Importantly, the common data elements should be presented in a user-friendly format.

The IMPACT prognosis studies have been instrumental in developing and setting standards for prognostic research in TBI. The predictive effects of many known prognostic variables have been confirmed in much larger numbers than before, and novel predictors have been identified. The development of the IMPACT prognostic models for severe and moderate TBI has provided opportunities to summarise the baseline prognostic risks in study populations and can be used as robust risk adjustment models. They have already been widely adopted in TBI research.[53] A major limitation is that these models were not developed for mild TBI. The CRASH prognostic models[54] included patients with milder injuries in their development and might consequently have broader generalisability across the range of severity. Prognostic models should never be thought of as final, but will need continuous evaluation and validation. In this context the added value of new predictors should be taken into consideration. New candidate predictors would include gene signatures, biomarkers, coagulation parameters, and the presence of systemic injuries. The application of prognostic models in TBI is broader than clinical trial design and might be used towards classification and benchmarking of the quality of healthcare delivery in TBI.[53]

Dealing with heterogeneity in clinical trials

The IMPACT recommendations for trial design have also been widely adopted. The Pharmos dexanabinol trial[29] was one of the first in TBI to use covariate adjustment and proportional odds approaches in the efficacy analysis. Since then, many completed and ongoing studies have adopted (parts of) the IMPACT recommendations. These studies include the DECRA trial on decompressive craniectomy in patients with diffuse traumatic brain injury[55] and the ongoing EuroTherm (therapeutic hypothermia for TBI; ISRCTN 34555414) and the SyNAPSe (NCT01143064) and PROTECT III (NCT00822900) trials of progesterone for severe TBI.

Prognostic heterogeneity of patient populations does not only apply to TBI, but also to other neurological diseases (eg, ischaemic stroke, subarachnoid haemorrhage, intracerebral haemorrhage, and Guillain-Barré syndrome) and to other specialties.[42,56–58] Methods to deal with heterogeneity in randomised controlled trials are essential for all these disciplines. In subarachnoid haemorrhage, the example of IMPACT is being followed by the Subarachnoid Hemorrhage International Trialists (SAHIT) data repository aiming to optimise the design and analysis of phase 3 trials in aneurysmal subarachnoid haemorrhage.[59] As in TBI, most large randomised controlled trials in acute ischaemic stroke have been neutral.[60] Stroke and TBI populations both have substantial prognostic heterogeneity, and an ordinal outcome measure is generally used (such as the modified Rankin scale), which is often dichotomised for analysis.[61,62] A recent report advises tailoring the analysis of the treatment effect to each individual trial, based on how the intervention under study is most likely to modify the distribution of outcomes; the ordinal analysis should be preferred over the traditional dichotomy, and covariate adjustment should be used.[63] The results of the SCAST,[64] IST-3,[65] and INTERACT2[66] stroke trials were only significant when ordinal analysis was used. Several acute stroke trials have been published that have used different aspects of the method described in the IMPACT recommendations.[67–71] Other ongoing stroke trials, such as STASH (statins for subarachnoid haemorrhage; NCT00731627), EuroHYP (hypothermia for acute ischaemic stroke; NCT01833312), MR CLEAN (endovascular treatment for acute ischaemic stroke; EudraCT 2009-017315-15), and others, plan to adopt parts of the recommendations.

Heterogeneity in comparative effectiveness research

We should recognise that many other issues (including deficiencies in preclinical studies and early clinical investigation, as well as uncertainty in time windows and dosing) than heterogeneity have contributed to the disappointments in clinical trials. These aspects have not been addressed by the IMPACT study group, but have been previously reviewed in detail.[72–74] Neither have the IMPACT studies addressed the problem of heterogeneity related to physiological mechanism. Early mechanistic endpoints, which can serve as intermediate outcomes in trials, are still lacking. We further recognise that it will be impossible to mount a sufficient number of adequately powered clinical trials to address all existing uncertainties in the management of TBI. Major advances in the care of patients with TBI have not come from clinical trials, but rather from observational studies and guideline developments.[7] Randomised controlled trials are not the only source of high-quality evidence to support practice recommendations. Alternative designs can be considered in a comparative effectiveness research framework.

Comparative effectiveness research is not new to TBI. Studies that compared treatment and outcome between centres in the 1980s would currently qualify as comparative effectiveness research.[75,76] Several features of TBI favour comparative effectiveness research approaches. First, there are large between-centre differences and between-country differences in management and outcome. In the IMPACT studies, analysing 9578 patients with moderate or severe TBI from 265 centres, we found a 3·3-fold difference in the odds of having an unfavourable outcome at 6 months between very good and very poor centres

	Institution and principal investigator	Project
European Commission		
CENTER-TBI	Antwerp University Hospital (A Maas) University of Cambridge (D Menon)	Collaborative European NeuroTrauma Effectiveness Research in TBI
CREACTIVE	IRCCS—Istituto di Ricerche Farmacologiche Mario Negri Milano (G Bertolini)	Collaborative Research on Acute Traumatic Brain Injury in Intensive Care Medicine in Europe
US National Institutes of Health		
ADAPT trial	Children's Hospital of Pittsburgh (M Bell)	Approaches and Decisions for Acute Pediatric TBI
TRACK-TBI	University of California (G Manley)	Transforming Research and Clinical Knowledge in Traumatic Brain Injury
Canadian Institutes of Health Research*		
Safe to Play	Hotchkiss Brain Institute, University of Calgary (C Emery)	A longitudinal research programme to establish best practice in the prevention, early diagnosis, and management of sport-related concussion in youth ice hockey players
Innovation through the use of common data	McGill University (I Gagnon)	Generating innovation through the use of common data: improving the diagnosis and treatment of paediatric and adolescent mild traumatic brain injury in Canada
Play Game	University of Calgary (K Barlow)	Post-concussion syndrome Affecting Youth: GABAergic effects of Melatonin
Postconcussion problems in paediatric TBI	Children's Hospital of Eastern Ontario, University of Ottawa (R Zemek)	Predicting Persistent Postconcussive Problems in Pediatrics (5P)
"NeuroCare" as Innovation in Intervention	University of Toronto (M Keightley)	A Neurophysiological Approach to Determine Readiness for Return to Activity

*Also 15 catalyst grants (1-year duration) and three new post-doctoral awards; cofunding partners for the team grants are Fonds de recherche du Québec Santé, Hotchkiss Brain Institute, Ontario Brain Institute, and Ontario Neurotrauma Foundation.

***Table 3*: Studies funded in the context of the International Initiative for Traumatic Brain Injury Research (InTBIR)**

(2·5 *vs* 97·5 percentile) after adjustment for chance effects and for differences in casemix.[77] In CRASH differences were even larger, with a 6·6-fold between-centre difference in 14-day mortality and a 15-fold difference between countries.[78] Second, robust risk adjustment models, specific for TBI, are available to adjust for differences in major prognostic factors (casemix). Third, advanced statistical methods, including random effect models, have been field-tested for TBI.[79]

Comparative effectiveness research offers opportunities to exploit the existing heterogeneity and differences between countries, centres, and patients in TBI to identify best practices.[7,80] This approach needs high-quality contemporaneous observational data to form the basis for comparative effectiveness research calls recently published in the European Commission Seventh Framework programme (FP7) and US National Institutes of Health (NIH) programmes. Recent data are important because, although methods for comparative effectiveness research are available, large-scale observational studies in TBI date back at least 20 years.[81] These calls will lead to improved characterisation of TBI and identification of the most effective clinical interventions. Improved characterisation will assist personalised medicine approaches, as recently advocated by the National Academy of Science.[82] Phenotypic heterogeneity might interact critically with genetics, and exploring this possibility will need studies with large patient numbers. Novel information will come forward about disease processes, treatment, outcome, and prognosis in TBI, while the establishment of biorepositories for neuroimaging, genetics, and biomarkers will ensure opportunities for future research, including legacy research. Data-sharing policies will need to be established to encourage academic productivity and to accelerate TBI research. Table 3 summarises initiatives currently being developed within the context of InTBIR. Every initiative has a different focus and, although individual analysis is expected to yield important contributions, the major benefit will most likely result from integration of analyses across studies.

The establishment of InTBIR marks a shift in TBI research towards international and multidisciplinary collaborations, which bridge the traditional disconnection between acute and postacute research. We further note a shift from current reductionistic approaches in clinical research towards broad approaches with increased generalisability. We note, however, that randomised clinical trials remain the preferred approach for evaluation of efficacy of novel treatment approaches and hope that the design of those trials will be affected by the results from the IMPACT studies, such as to optimise assessment of treatment effects.

Conclusions

The landscape of TBI research is changing.[45] Broad-based, sustainable, multidisciplinary, and international approaches are needed to address the complexity of

Search strategy and selection criteria

References for this Personal View were identified through searches of PubMed, by use of (combinations of) the terms "traumatic brain injury", "prognostic models", "heterogeneity", "clinical trial design", "clinical trial analysis", "comparative effectiveness research", and other appropriate terms up to May 31, 2013. Papers were also identified from the authors' own files and from references cited in relevant articles. We considered only publications written in English. The final reference list was generated on the basis of relevance to the topics covered in this Personal View.

TBI. Large international collaborations of not only researchers but also funding agencies are currently being implemented, as exemplified by InTBIR. Disconnects in research between acute and postacute care settings and between research in mild TBI and more severe injuries that need hospital admission are being addressed. The disappointing results of most clinical trials in TBI have led to a reappraisal of preclinical investigations and clinical trial methods. Weaknesses of previous preclinical studies include poor design, use of experimental models and paradigms that fail to incorporate key elements germane to severe TBI in human beings, insufficient preclinical testing before proceeding into clinical trials, insufficient attention to brain penetration and pharmacokinetics in clinical studies, as well as publication bias for positive results. Methodological challenges in clinical trials, in particular challenges posed by the inherent heterogeneity of the patient population, have been addressed in the IMPACT studies. These have resulted in recommendations that have the potential to increase statistical efficiency by up to 50%. This is a major advance, offering improved chances to show efficacy of new treatments in the context of randomised controlled trials. The IMPACT recommendations have broad applicability, and principles of the recommendations are also being applied to the study of stroke and subarachnoid haemorrhage. International consensus on standardisation of data collection is being sought in the development of common data elements that will increase comparability between studies and meta-analyses of individual patient data across studies. Reductionist approaches originating from traditional research paradigms in which single factors are isolated and targeted are slowly being replaced by more holistic approaches that are more representative of the clinical situation. The potential of these approaches is now being recognised by funding agencies as evidenced by recent calls in the European Commission FP7 and NIH programmes. Improved clinical trial methods and exploitation of the heterogeneity of TBI in the context of comparative effectiveness research holds great promise for advancing the care of patients with TBI.

Contributors
All authors contributed equally to the report.

Conflicts of interest
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