

OPEN

Andrew I.R. Maas, MD, PhD*

David K. Menon, MD, PhD‡

Ewout W. Steyerberg, PhD§

Giuseppe Citerio, MD¶

Fiona Lecky, MD, PhD||

Geoffrey T. Manley, MD, PhD#

Sean Hill, PhD**

Valerie Legrand, PharmD‡‡

Annina Sorgner, MEd§§

on behalf of the CENTER-TBI
Participants and Investigators
(see Appendix)

*Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium; †Division of Anaesthesia, University of Cambridge/Addenbrooke's Hospital, Cambridge, UK; ‡Department of Public Health, Center for Medical Decision Making, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands; ¶Department of Health Science, University of Milan-Bicocca; Neuro-Intensive Care, Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy; ||Emergency Medicine Research in Sheffield, Health Services Research Section, School of Health and Related Research (SciARR), University of Sheffield, Sheffield, UK; #Department of Neurological Surgery, University of California, San Francisco, California; **International Neuro-Informatics Coordinating Facility, Karolinska Institutet, Stockholm, Sweden; ‡‡ICON plc, VP Global project management, Dublin, Ireland; §§GABOxmi, International projects management, Munich, Germany

Correspondence:

Andrew I.R. Maas, MD, PhD,
Department of Neurosurgery,
Antwerp University Hospital/University
of Antwerp,
Wilrijkstraat 10,
2650 Edegem Belgium.
E-mail: andrew.maas@uza.be

Received, August 29, 2014.

Accepted, September 2, 2014.

Published Online, September 24, 2014.

Copyright © 2014 by the
Congress of Neurological Surgeons.



WHAT IS THIS BOX?

A QR Code is a matrix barcode readable by QR scanners, mobile phones with cameras, and smartphones. The QR Code above links to Supplemental Digital Content from this article.

Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study

BACKGROUND: Current classification of traumatic brain injury (TBI) is suboptimal, and management is based on weak evidence, with little attempt to personalize treatment. A need exists for new precision medicine and stratified management approaches that incorporate emerging technologies.

OBJECTIVE: To improve characterization and classification of TBI and to identify best clinical care, using comparative effectiveness research approaches.

METHODS: This multicenter, longitudinal, prospective, observational study in 22 countries across Europe and Israel will collect detailed data from 5400 consenting patients, presenting within 24 hours of injury, with a clinical diagnosis of TBI and an indication for computed tomography. Broader registry-level data collection in approximately 20 000 patients will assess generalizability. Cross sectional comprehensive outcome assessments, including quality of life and neuropsychological testing, will be performed at 6 months. Longitudinal assessments will continue up to 24 months post TBI in patient subsets. Advanced neuroimaging and genomic and biomarker data will be used to improve characterization, and analyses will include neuroinformatics approaches to address variations in process and clinical care. Results will be integrated with living systematic reviews in a process of knowledge transfer. The study initiation was from October to December 2014, and the recruitment period was for 18 to 24 months.

EXPECTED OUTCOMES: Collaborative European NeuroTrauma Effectiveness Research in TBI should provide novel multidimensional approaches to TBI characterization and classification, evidence to support treatment recommendations, and benchmarks for quality of care. Data and sample repositories will ensure opportunities for legacy research.

DISCUSSION: Comparative effectiveness research provides an alternative to reductionistic clinical trials in restricted patient populations by exploiting differences in biology, care, and outcome to support optimal personalized patient management.

KEY WORDS: Clinical study, Comparative effectiveness research, Protocol, Traumatic brain injury

Neurosurgery 76:67–80, 2015

DOI 10.1227/NEU.0000000000000575

www.neurosurgery-online.com

GENERAL INFORMATION

Short Study Title

CENTER-TBI Study

Protocol

Version 4.2

Version Date

28 August 2014

This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.neurosurgery-online.com).

Coordinators

Andrew I.R. Maas, Antwerp University Hospital; David K. Menon, University of Cambridge

Support

The European Union FP 7th Framework program (grant 602150)

Funding of additional elements has been provided by the Hannelore Kohl Foundation (Germany) and by the non-profit organization One Mind For Research (directly to INCF).

Contract Research Organization

ICON plc, South County Business Park, Dublin 18, Ireland

Central Laboratory

University of Pecs, 48-as tér 1, Pecs 7622, Hungary

Data Entry Tool Developed by

QuesGen, 800 Airport Blvd 410, Burlingame, CA94010, USA

Database and Data Analysis Platform

Coordinated by the International Neuroinformatics Coordinating Facility (INCF, Karolinska Institutet, Nobels väg 15A, 17177 Stockholm, Sweden) with additional support from One Mind for Research

Neuroimaging Repository

icoMetrix, Tervuursesteenweg 244, 3001 Leuven, Belgium

Study Registration

Clinicaltrials.gov: NCT02210221

The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) core data study and CENTER-TBI registry (NCT02210221) form part of the CENTER-TBI project: a large-scale project supported by the European Union Framework 7 program (grant 602150). It is embedded within the framework of the International Initiative on TBI Research (InTBIR).¹

Each year, approximately 2.5 million people will experience some form of traumatic brain injury (TBI) in Europe; of these, 1 million will be admitted to the hospital and 75 000 will die. TBI thus constitutes a major cause of death and disability, leading to great personal suffering for victims and relatives and huge direct and indirect costs to society. In the United States, the annual burden of TBI has been estimated at >\$75 billion in patients with TBI.² The lifetime costs-per-case is estimated at \$396 000, with disability and lost productivity costs outweighing medical and rehabilitation costs by a factor of 4.³

TBI is considered the most complex disease in our most complex organ. It is characterized by great heterogeneity in terms of etiology, mechanisms, pathology, severity, and treatment, with widely varying outcomes. Falls and high velocity road traffic incidents cause different types of injury. TBI may consist of diffuse damage, contusional brain

damage, or intracranial hematomas. Some structural abnormalities (particularly traumatic axonal injury) are poorly detected by conventional imaging. The clinical severity of TBI ranges from minor (minimal complaints, no visible structural damage) to virtually unsurvivable injuries. We have found large differences in outcome between centers with up to a 6-fold higher risk in poorer vs better centers after adjustment for chance effects and case mix.⁴ We now also recognize that TBI is not just an acute event, but can trigger a chronic process, with progressive injury over hours, days, weeks, months, and even years.⁵ The long-term sequelae related to behavior, emotion, and cognition, including early-onset dementia and psychiatric illness as well as later substance-use disorders particularly after repetitive mild TBIs, constitute an increasing societal and economic burden.⁶⁻⁸ While basic research has increased our knowledge of the mechanisms involved, improvements in clinical management have not kept pace. Guidelines for the treatment of TBI are available,^{9,10} but the evidence underpinning these recommendations is weak. Moreover, current approaches to the characterization of disease severity and outcome are unidimensional and have not undergone refinement for >3 decades. Treatment generally follows a one-size-fits-all approach and is not targeted to the needs of an individual. Clinical research in TBI is particularly challenging due to disease heterogeneity and has been further hampered by dispersion of efforts with little collaboration between researchers in acute and postacute settings, and by research that focuses on isolated disease mechanisms, testing highly specific neuroprotective agents in underpowered randomized clinical trials (RCTs). RCTs generally use strict enrollment criteria in order to study the investigational intervention in the cleanest setting. The downside of this approach is that results are only valid in such selected subpopulations and that generalizability to the real-world context is limited. Indeed, improvements in TBI care have come not from clinical trials, but rather from observational studies, guideline development, and meta-analysis of individual patient data.¹¹ However, the large-scale international observational studies on TBI in Europe and the United States that underpin these improvements date back at least 20 years¹² and do not reflect current clinical care.

Recent advances in genomics, advanced neuro-imaging, and biomarker development provide unparalleled opportunities for refinements in clinical characterization, offering more accurate disease phenotyping. Improved disease characterization will aid precision medicine, a concept recently enunciated by the US National Academy of Sciences.¹³ Such improved characterization and stratification will allow for more targeted therapies. Furthermore, comparative effectiveness research (CER) provides a promising framework to identify best practices and improve outcome after TBI. CER 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 CER is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve healthcare at both the individual and population levels.¹⁴

A basic concept of CER is to study differences in care and outcome in observational studies, thus turning natural variability

into an asset. In CENTER-TBI, we will exploit the existing heterogeneity in structure, process, and outcome to compare treatments and interventions that are standard practice in some centers and countries but not in others. The aim is to discover underlying pathophysiology, to refine characterization, and to identify effective clinical interventions. Natural links exist between CER and individualized approaches, because CER aims to identify the best treatment for the individual patient, with a specific type of injury, severity, comorbidities, and other aspects that determine optimal treatment. We see a great potential for CER in TBI because of various unique features. First, there are large between-center and between-country differences in both outcome and management. Second, robust risk adjustment models have been developed specifically for TBI, providing the possibility to adjust for patient characteristics that affect outcome. Third, advanced statistical models, including random effect models, are available to analyze differences between centers.¹⁵

The key driver of our research plan is to collect data from a large number of European centers and a sufficiently large cohort to enable CER analyses of differences in clinical care and management pathways in TBI. The CENTER-TBI population will be a unique and well-characterized resource, accessible for longer-term follow-up with continued funding. The integrated results of the project will be brought together in a process of translational outputs. We aim for real-world approaches to translating research outputs into practical information for patients, healthcare professionals, and policymakers. We will develop and sustain an international TBI knowledge community that integrates results of the project with high-quality living evidence reviews of the current state of knowledge, aiming to continuously provide evidence to underpin guidelines and treatment recommendations. The impact of CENTER-TBI will be enhanced by international collaborations within and beyond InTBIR. TBI is a global problem and requires a global approach. The CENTER-TBI database and repositories will be an invaluable resource for further research, which we wish to encourage. In this article, we present an abbreviated version of the CENTER-TBI protocol. The full version of the protocol is available as supplemental material (see **Supplemental Digital Content**, <http://links.lww.com/NEU/A688>).

STUDY GOALS AND OBJECTIVES

The study goals are

- To improve characterization and classification of TBI in Europe, with inclusion of emerging technologies.
- To identify the most effective clinical care and to provide high-quality evidence in support of treatment recommendations and guidelines.

The specific aims are

- To collect high-quality clinical and epidemiological data with repositories for neuro-imaging, DNA, and serum from patients with TBI.
- To refine and improve outcome assessment and develop health utility indices for TBI.



FIGURE 1. Distribution and number of sites per country that will participate in the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury.

- To develop multidimensional approaches to characterization and prediction of TBI.
- To define patient profiles that predict efficacy of specific interventions (precision medicine).
- To develop performance indicators for quality assurance and quality improvement in TBI care.
- To validate the common data elements (CDEs) for broader use in international settings.

TABLE 1. Inclusion and Exclusion Criteria of CENTER-TBI^a

Inclusion Criteria	Exclusion Criteria
CENTER-TBI core study	
Clinical diagnosis of TBI	Severe preexisting neurological disorder that would confound outcome assessments
Clinical indication for CT scan	
Presentation within 24 hours of injury	
Informed consent obtained according to local and national requirements	
CENTER-TBI registry	
Clinical diagnosis of TBI	None
Clinical indication for CT scan	

^aCENTER-TBI, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; CT, computed tomographic; TBI, traumatic brain injury.

- To develop an open database compatible with the Federal Interagency Traumatic Brain Injury Research (FITBIR).
- To intensify networking activities and international collaborations in TBI.
- To disseminate study results and management recommendations for TBI to healthcare professionals, policymakers, and consumers, aiming to improve healthcare for TBI at individual and population levels.
- To develop a knowledge commons for TBI, integrating CENTER-TBI outputs into systematic reviews.

STUDY DESIGN

Overall Design and Project Management

CENTER-TBI is a prospective longitudinal nonrandomized observational study across the severity spectrum of TBI in up to 80 sites from 22 countries for 18 months. A detailed overview of the distribution of sites is provided in Figure 1. With a large number of centers participating, it is to be expected that some changes may occur during the course of the project. Updated information will be provided on the CENTER-TBI website: www.center-tbi.eu. We will characterize centers with regard to their structural profile in order to explore effects of organizational aspects. The study will consist of 2 parts: CENTER-TBI core data study ($n = 5400$) and CENTER-TBI registry ($n = 15\,000$ - $25\,000$). Inclusion and exclusion criteria are summarized in Table 1. The CENTER-TBI registry will be based on pragmatic data collection of all patients with TBI seen in participating centers, aiming to establish the internal generalizability of our study, and to establish the external generalizability by comparison with national trauma registries. In the core data study, we will create and maintain well-curated biorepositories for analysis by the participants and to provide for legacy research with future new methodologies or longer follow-up of outcome (supported by future grant funding).

The CENTER-TBI study will be overseen by the Coordinators of the CENTER-TBI project, Prof Andrew I.R. Maas (University Hospital Antwerp) and Prof David Menon (University of Cambridge), supported by the project management committee.¹⁶ National coordinators have been designated to streamline study efforts in each country. The logistics and quality of the data collection will be overseen by ICON, Plc, a professional contract research organization. Source data verification will be performed in 10% of the subjects. The data entry and analysis platform are developed by Quesgen Inc¹⁷ in collaboration with Karolinska Institutet International Neuroinformatics Coordinating Facility (KI-INCF¹⁸), with additional support from One Mind for Research (<http://www.onemind.org/>).¹⁹

CENTER-TBI Core Data Study

In the CENTER-TBI Core data study, we will follow the disease course with detailed data collection up to 2 years postinjury for the most severely injured patients, thus bridging the acute and

postacute phases. Patients will be stratified upon enrollment into 3 clinical groups differentiated by clinical care path:

Emergency room (ER) stratum: patients evaluated in the ER and discharged ($n = 1800$).

Admission stratum: patients admitted to the hospital but not to the intensive care unit (ICU; $n = 1800$).

ICU stratum: patients admitted directly from ER or other hospital to the ICU ($n = 1800$).

We aim for an equal balance in numbers between the strata: approximately 1800 patients per stratum.

CENTER-TBI Registry

The CENTER-TBI registry will serve 2 important purposes: 1) assessing representativeness of the CENTER-TBI core study and 2) providing opportunities for comparative effectiveness analysis of organization of care. Elementary data from all patients excluded from the core data collection for whatever reason, but who do have a clinical diagnosis of TBI and undergo CT scanning, will be recorded in the registry.

Time Frames

The setup phase of the project (currently underway) will last approximately 1 year. Recruitment will be initiated across the participating study centers between November 2014 and January 2015. Recruitment is expected to last about 18 months, but may be extended in case of slower recruitment. The index follow-up for outcome assessment will be at 6 months. Allowing for data verification and cleanup, we expect definitive analyses on the complete database to start in 2017.

Sample Size Calculation and Statistical Analyses

The sample size estimate is based on:

- Practical logistic considerations.
- Power calculations for the different strata, targeting comparative effectiveness analyses, assuming a between-center and between-country heterogeneity as identified in previous research (expressed by variance parameter from a random effects model, τ^2 of 0.431).
- Postulated odds ratios for intervention effects of approximately 5% improvement in outcome.

Overall, these calculations provide a statistical power to detect odds ratios of ~ 1.2 associated with differences in process characteristics of specific interventions across the core dataset with a power of 80%. Somewhat larger odds ratios are required for interventions applicable in only 1 of the 3 individual strata in the core dataset. In the registry we expect to be able to detect differences (predominantly in organizational or system characteristics) with an odds ratio of 1.2 with a power of 82%.

Statistical analyses for the CER questions will primarily apply random effects modeling, in which the center is included at the higher level, and patients are considered clustered within centers. In some analyses, higher levels of clustering will also be considered (eg, country or European region) or lower levels (eg, physicians)

within hospitals. Confounding factors as measured at the individual patient or center level will be considered extensively and will be targeted to the specific research question.

The analyses for better characterization of TBI will be exploratory, aiming to better understand the complexity of the disease and to discover new associations. In addition to standard statistical descriptive and inferential techniques, we will also use novel machine learning techniques as appropriate.

Prognostic analyses will consider a range of variables, including genetic, demographic, and clinical data, physiological signals, imaging results, and biomarkers as predictors of early endpoints and physiologic derangement (eg, raised intracranial pressure), and late outcome, including mortality, functional outcome, quality of life, and neuropsychological performance. Previously and newly developed prediction models will be validated by comparison of observed to predicted outcome risks, with predictive performance summarized by measures for discrimination and calibration.

Data Management

Prior to upload to the study database, acquired data will be stored locally. All patients will be allocated a random Global Unique Personal Identification number (GUPI), which will be linked locally to hospital identifiers. Uploaded data will be de-identified and images will be defaced prior to upload. While blood samples and clinical data will be linked, both sets of data will be kept confidential and anonymized beyond the initial stage of correlation for analysis. Imaging and electronic data will be kept on individually password-protected servers. Clinical data will be entered into electronic Case Report Forms (eCRFs) and managed by the QuesGen data management platform,¹⁷ which will be developed in collaboration with KI-INCF.¹⁸ Data collection is based upon the CDEs,²⁰ thus providing evidence context for further refinement and updating of the CDEs in an international setting, which will inform global standardization of data collection in TBI. The database structure will be compatible with FITBIR.²¹ As data are entered into each form, the system will run data validation checks that include conditionally required data, validation across fields, and validation requirements based on subject type. If any validation check fails, the user is alerted immediately that the data do not meet quality assurance (QA) criteria and the issue can be addressed and corrected at that point. All de-identified electronic study data in the CENTER-TBI database will be stored securely in the European data space under supervision of KI-INCF for the duration of subject enrollment and follow-up and for a period afterwards for data analysis and preparation of publications. We estimate that the analysis and publication period will last for several years after the conclusion of subject enrollment.

Together with QuesGen Systems, KI-INCF will ensure that data standards are established for the data model (eg, conformity of field formats, field codes, and names to ensure consistency across all datasets). Any approved changes will be fully documented with dataset updates to maintain data quality and accuracy. KI-INCF will be responsible for importing cleaned datasets to other analytic

platforms as determined by the coordinators. ICON will undertake source data verification in 10% of datasets, using an approach for dataset selection, which depends (among other factors) on recruitment rates and assessment of data completion and accuracy on the online data entry forms.

Where applicable, derived information relevant to the patient's care will be made available to the physician responsible. Data, including blood samples collected as part of this study, will be shared in an anonymized form with collaborators from other European states (this is part of a European Union Framework7 funded program), and with selected collaborators in other countries who form part of the International Traumatic Brain Injury Research Initiative.

The KI-INCF will coordinate the establishment of an informatics platform for acquisition, storage, and analysis of CDE-based clinical data. The goal is to develop a next-generation open standards-based platform to support advanced large-scale analytics and model building. Such a platform also provides a model for future clinical studies on brain diseases and disorders. This development will receive additional support from One Mind for Research.¹⁹

Data sharing policies, providing open access, modelled on the Alzheimer's Disease Neuroimaging Initiative (ADNI²²) concept, will aim to broaden access to the data, encourage academic productivity, and accelerate outputs. CENTER-TBI participants and investigators will have equal access rights to the data.

Ethical Considerations

Informed consent procedures will follow local and national requirements in all cases. We anticipate that many potential patients will not be able to consent to their participation in this project. The nature of TBI means that some patients may lack the capacity to decide to participate in this study especially at the earliest time point. It is important to try and include these patients to ensure that representative samples of patients are included to avoid bias in the study findings. Every step will be taken to ensure that a test of capacity is undertaken before a decision on a person's capacity to consent or not to consent to participate in research is taken. If the subject is not capable of self-consent, all efforts will be made to locate a legally acceptable representative to act on behalf of the subject. When a legally acceptable representative (eg, consultee/proxy) is identified, an opinion will be sought about the potential participant's wishes and feelings in relation to the project, and whether he or she would have wanted to take part in the study.

Subjects are free to withdraw, or be withdrawn by their consultee/proxy if appropriate, at any point in the study, and they need not state a reason. All individual patient identifiers will be stripped from data before storage on the study database (see details under Data Management). The study will adhere to national and European regulatory requirements. We recognize that these may vary between European Union member states, and one of the aims of CENTER-TBI is to map this variance in the course of the study.

Subject Risks and Benefits

No structured adverse event reporting will be implemented, as this is an observational study without any therapeutic intervention. However, we will capture any serious complication that may occur during the clinical course in the CRF. Diagnostic interventions include blood sampling, outcome assessments, and, in selected sites, magnetic resonance (MR) imaging, high-resolution ICU monitoring, and extended blood sampling. The potential risks to the subject are minimal across all domains of data collection.

No direct benefit to study participants is expected, other than by enhanced contacts and more detailed study assessments. The results will be directly relevant to society in general and to future patients who have TBI.

METHODOLOGY

CENTER-TBI Registry

Data collection will be elementary and based on retrospective extraction from clinical records of data that are routinely collected clinically. No specific study interventions will be performed.

No target recruitment number has been set for the CENTER-TBI registry. We anticipate inclusion of approximately 15 000 to 25 000 subjects.

CENTER-TBI Core Study

A total of 5400 patients will be recruited and differentiated into 3 equal strata of approximately 1800: ER, admission, and ICU strata, as described above. Balance in numbers between the strata will be aimed for, but sites will be allowed to arrange recruitment strategies to best suit their local requirements. We would anticipate a far larger number of eventual subjects in the ER and admission strata than in the ICU stratum. Options for

achieving balance would be to limit the recruitment in the ER and admission strata to certain days per week or certain periods of time. It would be essential to maintain balance of recruitment across the days of the week.

A maximum cap of enrollment will be implemented per center in order to prevent overrepresentation. The cap is currently fixed at a maximum of 100 patients per stratum with a total number per center of no more than 250. The following broad categories of clinical data will be prospectively collected from all enrolled patients through medical records and personal interview:

- Baseline demographics: age, sex, race, ethnicity, and handedness.
- Baseline socioeconomic: education, employment, living situation, and types of support.
- Baseline medical history by system including substance abuse, prior TBI, and medications.
- Mechanism of injury, location, and surrounding circumstances.
- Prehospital clinical course variables: vital signs, transport times, and Glasgow Coma Scale score.
- Abbreviated injury scale (AIS) score and injury severity score (ISS).
- Brain computed tomographic (CT) report including presence of skull fracture and intracranial abnormalities.
- Emergency department clinical course: vital signs, GCS, fluids, labs, toxicology, and complications.
- Hospital admission clinical course: daily vital signs, GCS, fluids, labs, complications, and medications.
- Hospital surgeries and neuromonitoring.
- Reasons for clinical decisions.
- Physician-based satisfaction with care and prognostic estimates.
- Admission and discharge dates and times throughout full clinical course.
- Discharge destination and acute care outcome evaluation.

Source data can include patient medical records (paper and electronic), ambulance records, online test results, and information

TABLE 2. Timing of Follow-up Assessments*

Time Point	2-3 weeks	3 m	6 m	12 m	24 m
ER stratum (1800)					
Outcome					
Neuropsych	600 ^b	600 ^b	1150		
Questionnaires	1400	1300	1250		
Admission stratum (1800)					
Outcome					
Neuropsych			1200	300 ^b only	250 ^b
Questionnaires		1450	1300	1200 (non MR)	250
ICU stratum (1800)					
Outcome					
Neuropsych			1200	300 ^b only	250 ^b
Questionnaires		1450	1300	1200	250

ER, emergency room; ICU, intensive care unit; MR, magnetic resonance.

*Only in patients undergoing magnetic resonance studies.

Numbers at follow up are estimated to be lower than the size of the original cohort to allow for mortality and for anticipated loss of follow up.

held on clinical systems. The Web-based data entry system will use secure, encrypted connections for data upload. Coding of records by the GUPI will ensure that names and other identifying information will not be linked to study data, in compliance with existing regulations. No data with personal identifiers will leave the study site.

Blood Sampling

Blood samples will be drawn in all patients upon presentation for routine laboratory testing as dictated by standard clinical procedures. Details of assays will be captured in the CRF. For study purposes, adult patients from all strata will also have 19 mL of blood drawn <24 hours of injury for biomarker and genetic analysis. While local research protocols may require the banking of additional volumes of blood, this should not exceed 40 mL at admission. The blood sample will be drawn from an arterial or (central) venous catheter placed as a part of standard care where possible. In other cases, patients will need to undergo a separate venepuncture. No more than 2 venepunctures will take place. Whenever possible, blood draws will be combined with those of routine clinical care.

The additional blood draws performed for purposes of the study will not exceed 40 mL upon presentation, 75 mL during the acute clinical course (only ICU stratum), and no more than 30 mL annually during a 2-year follow-up period. In pediatric patients, blood draws will be limited to a maximum of 3% of the circulating volume.

In the ICU stratum, more extended sampling will be performed in a subset of patients. Cross sectional sampling at follow-up will be performed at 6 months in the admission and ICU strata and at other time points in those subjects undergoing MR investigations (Table 2). Sampling kits will be provided to the sites. These will be in separate biohazard bags for the biomarker, genetic, and advanced hemostasis samples. All sample tubes will be color-coded. The sample tube colors will be finalized once current tendering processes are completed, and details will be specified in site study manuals. Sampling kits will be provided to centers by the University of Pecs, which will lead the biomarker work package.

Processing of Samples for Protein Biomarker Sampling

Time points for protein biomarker sampling are specified in Table 3. For each sample, 9 mL of blood will be collected into a serum separator tube, centrifuged after 45 ± 15 minutes of coagulation at room temperature, at 4000 rpm for 10 minutes, and aliquoted as 8 × 0.5 mL serum into the barcoded 1.2 mL cryovials. Aliquots should be deep-frozen at -80°C within 3 hours. If deep freezing is not directly possible for logistic reasons, samples may be stored at -20°C non-frost-free freezer for a maximum of 48 hours before being transferred to -80°C. Samples will be transferred to the central laboratory at the University of Pecs at regular intervals.

Sampling for Genetic Analysis

For genetic studies, two 4.9 mL samples of whole blood will be collected in potassium EDTA tubes at enrollment and stored at -80°C within 6 hours. The 2 samples will be stored in 2 different racks. One sample will be retained at the site, while the other will be shipped, in batches, to the central facility in the University of Pecs along with biomarker and other blood samples. We have opted for such duplicate sampling in order to have a reserve sample available in case any sample gets lost during transport or that DNA extraction process may not be optimal. Collated blood samples from multiple centers will be batch transferred from Pecs to the Clinical Genetics Laboratory at Addenbrooke's Hospital in Cambridge, which will act as the repository for DNA samples, extract DNA, and provide aliquots for analysis.

Neuro-Imaging

All acute head CTs and at least 1 follow-up CT scan (if performed between day 2 and 7 for clinical care) will be collected and uploaded into the CENTER-TBI neuro-imaging repository. CT scans performed as part of clinical care will follow standard clinical practice of the hospital. This will generally include a follow-up scan in all patients treated surgically performed within 24 hours of surgery. We recommend 3-dimensional volumetric CTs with a multi-detector row scanner (32 rows or better).

TABLE 3. Planned Sampling Points for Biomarkers*

Time Point	Admission/Presentation	Day 1	Day 3	Day 4	Day 5	2-3 weeks	3 m	6 m	12 m	24 m
ER stratum (1800)										
Biomarkers	1800 (9)					600 (9)	200 (9)			
Genetics	1800 (10)									
Admission stratum (1800)										
Biomarkers	1800 (9)							1200 (9)	300 (9)	250 (9)
Genetics	1800 (10)									
ICU stratum (1800)										
Biomarkers	1800 (9)	1000 (9)	250 (9)	250 (9)	250 (9)	600 (9)		1200 (9)	300 (9)	250 (9)
Genetics	1800 (10)									

*ER, emergency room; ICU, intensive care unit.

Figures in columns represent the number of subjects expected to provide samples at each time point, allowing for mortality and loss to follow up. Figures in parentheses represent provisional amount of the drawn blood in milliliters.

TABLE 4. Outcome Assessment—Instruments and Approximate Time Requirements*

Questionnaire follow-up^b	
Telephone interview or postal questionnaire/ Web-based completion/personal interview	Time: 30 min
Participant questionnaire part A	10
GOSE	10
SF12v2	5
QOLIBRI-OS	5
Postal questionnaire/Web-based completion/ personal interview	Time: 50 min
QOLIBRI	12
Posttraumatic stress disorder (PCL-5)	5
Rivermead post concussion questionnaire	5
SF36v2	12
HADS	5
PHQ-9	5
Neuropsychology follow-up^b	
Neuropsychology face-to-face visit	Time: 102 min
GOAT	5
Testable patients	
RAVLT	15
TMT	7
CANTAB	60
10 m walk and timed up and go	5
Untestable patients (if GOAT ≤65)	
JFK Coma Recovery Scale—Revised	

*CANTAB, Cantab neuropsychological assessment tests; GOAT, Galveston Orientation and Amnesia Test; GOSE, Glasgow Outcome Scale Extended; HADS, Hospital Anxiety and Depression Scale; PCL-5, PTSD Check List; PHQ-9, Patient Health Questionnaire; QOLIBRI, Quality of Life after Brain Injury; QOLIBRI-OS, QOLIBRI-Overall Scale; RAVLT, Rey Auditory Verbal Learning Test; SF12v2, Short-Form 12 version 2; SF36v2, Short-Form 36 version 2; TMT, Trail Making Test.

^bFor times, see Table 3.

Final selection of instruments will depend on logistic considerations and obtaining applicable license agreements at reasonable conditions.

During upload, the images will be de-identified and defaced and will only be coded by the assigned GUPI code. All images will be read and coded by central reviewers at Icometrix in accordance with the neuro-imaging TBI CDE's. No additional CT scans will be performed for study purposes.

Outcomes

All outcome measures will be obtained from the patient if they are cognitively able, supplemented as appropriate by information from a caregiver or other proxy. Assessments will be administered by telephone/postal questionnaire/Web-based questionnaire and face-to-face visits. In order to maximize the number of subjects in whom outcome data are obtained, face-to-face visits may be conducted within the local study site, in the patient's home, or other residential/healthcare setting, as appropriate. Where subjects are resident within a long-term rehabilitation care facility, some assessments and neuropsychological evaluations (such as the JFK coma recovery scale—revised²³) may be available from the

clinical record. A detailed overview of times of outcome assessments is provided in Table 2.

A prespecified neuropsychological evaluation will be performed in all strata at 6 months after injury and longitudinally at various time points in the 3 strata up to 24 months after injury. These additional assessments will focus on earlier outcome assessments in ER stratum and later assessments in Admission and ICU strata.

Two main types of patient follow-up are planned depending on whether only questionnaires are being used or whether a more complete neuropsychological assessment is being conducted (Table 4). The neuropsychological assessment involves face-to-face contact. Travel expenses of patients will be reimbursed according to local site policy. Assessment that only involves questionnaires/interviews will be conducted by a mixture of telephone follow-up and postal/Web-based questionnaires. If more convenient, these questionnaire assessments may be completed as part of a visit.

Outcome assessment will include functional outcome (as assessed by the Glasgow Outcome Scale extended), health-related quality of life, and patient questionnaires. The preferred method of assessing the Glasgow Outcome Scale extended is by interview, but postal/Web-based questionnaires will also be options. The face-to-face visits will include formal neuropsychological testing, including paper and pencil tests, and the Cantab neuropsychological assessment tests neuropsychological test battery,²⁴ which is language independent and therefore admirably suited for a multinational study. Hardware and software for the Cantab neuropsychological assessment tests assessments will be provided by the project organization to sites free of charge. A detailed overview of the instruments used in the various assessments is summarized in Table 4. Where applicable, license fees will be covered by the coordinator.

Formal neuropsychological testing will only be performed in patients considered testable. Assessment of testability will be based upon the Galveston Orientation and Amnesia Test.²⁵ Patients with a score ≤65 will be considered untestable, and in these patients assessment will only consist of the JFK coma recovery scale.

Tests will be administered by trained study personnel. In case any clinically relevant problems are detected during outcome assessments, the research personnel will notify the medical staff according to local clinical policies and procedures. Any concerns related to a study participant will be discussed with the principal investigator or other senior clinical members of the research team to ensure appropriate arrangements for patient treatment or follow-up are in place. In nonurgent cases a letter may be sent to the patient's general practitioner outlining these concerns, which will also be copied to the relevant hospital department.

Extended Studies

Sites have been given the opportunity to contribute to more extended data collection in the following domains:

- MR imaging
- Extended coagulation and biomarker studies
- High-resolution ICU monitoring

- Electrocorticographic monitoring
- Continuous electroencephalography monitoring

The selection of sites for such advanced data collection is determined by expression of interest and logistic considerations. In addition to data collected specifically as part of CENTER-TBI, we will also record additional data that are available at individual centers.

None of these data will be mandated as part of CENTER-TBI, acquisition will depend on local clinical judgment, and will only be collected if part of routine clinical management or another ethically approved study with appropriate consent. Such data could include (but are not limited to) electrocorticography, continuous electroencephalography, cerebral microdialysis, brain oxygen monitoring, and other imaging studies. These data will be used in combined analyses to address the goals of precision medicine and comparative effectiveness research.

DISCUSSION

CENTER-TBI is a project embedded within the InTBIR,¹ which was founded in 2011 as a collaboration between the European Commission, the US National Institute of Neurological Disorders and Stroke, and the Canadian Institute of Health Research and its national funding partners.²⁶ This collaboration of international funding agencies is unique. However, perhaps even more unique is the fact that all the projects will undertake data collection to common standards based on the Common Data Elements scheme developed by the National Institute of Neurological Disorders and Stroke,²⁰ with the database structure that is compatible with FITBIR.²¹

InTBIR was founded in recognition of the importance of TBI as a global pandemic, culminating in significant costs to all societies in terms of mortality, residual disability, health, economic costs, and reduced activity. Although initiated by 3 funding agencies, InTBIR is an open community and welcomes participation of other agencies and funding bodies. With the aim of advancing the care for TBI, the primary intent of InTBIR is to focus on collecting, standardizing, and sharing clinical TBI data for comparative effectiveness research. Within the InTBIR framework, there are currently 10 studies supported by the participating agencies (Table 5).

CENTER-TBI has interactions with several other studies within the InTBIR community and has particularly close collaboration with TRACK-TBI (Transforming Research And Clinical Knowledge in Traumatic Brain Injury; PI, Dr Geoffrey Manley), with extensive harmonization of study procedures and data collection. Pediatric recruitment to CENTER-TBI involves a close collaboration with ADAPT (Approaches and Decisions for Acute Pediatric TBI; PI, Dr Michael Bell). The concept of CENTER-TBI and TRACK-TBI has already attracted substantial international interest, and satellite projects are currently being set up in Australia, China, and India. Thus, the philosophy that TBI is a global problem that requires a global approach is now being translated into research practice. The InTBIR studies and satellite projects linked to these initiatives have the potential to provide long-needed evidence to support practice recommendations and to improve treatment.

Details on the CENTER-TBI project and scientific work plan are available on the CENTER-TBI website: www.center-tbi.eu.

TABLE 5. International Initiative on Traumatic Brain Injury Research Studies^a

Project Title	Project Acronym and Sample Size	Funding Agency
Europe		
Collaborative European NeuroTrauma Effectiveness Research in TBI	CENTER-TBI (n = 5400)	European Commission
Collaborative REsearch on ACute Traumatic brain Injury in IntensIVe care Medicine in Europe	CREACTIVE (n = 7000)	European Commission
United States		
Transforming Research And Clinical Knowledge in Traumatic Brain Injury	TRACK-TBI (n = 2700)	NIH/NINDS
Approaches and Decisions for Acute Pediatric TBI	ADAPT (n = 1000)	NIH/NINDS
Managing severe TBI without ICP monitoring—guidelines development and testing	(n = 780)	NIH/NINDS
Canada		
Predicting and preventing postconcussive problems in paediatrics (5P) study: protocol for a prospective multicentre clinical prediction rule derivation study in children with concussion.	5P (n = 2000)	CIHR/ONF
Improving the diagnosis and treatment of mTBI in children and youth: the power of common data	Common data (n = 1000)	CIHR/FRQS
A longitudinal prospective study of mTBI in youth ice hockey players	Safe to play (n = 1000)	CIHR/HBI
Post-concussion Syndrome in youth: assessing the GABAergic effects of melatonin	PLAYGAME (n = 166)	CIHR
Neurocare: a clinical decision-making tool in youth mTBI	NEUROCARE (n = 1400)	CIHR/OBI

^aCIHR, Canadian Institute of Health Research; FRQS, Fonds de recherche du Quebec—Santé; GABA, gamma-aminobutyric acid; HBI, Hotchkiss Brain Institute; ICP, intracranial pressure; mTBI, mild TBI; NINDS, National Institute of Neurological Disorders and Stroke; NIH, National Institutes of Health; OBI, Ontario Brain Institute; ONF, Ontario Neurotrauma Foundation; TBI, traumatic brain injury.

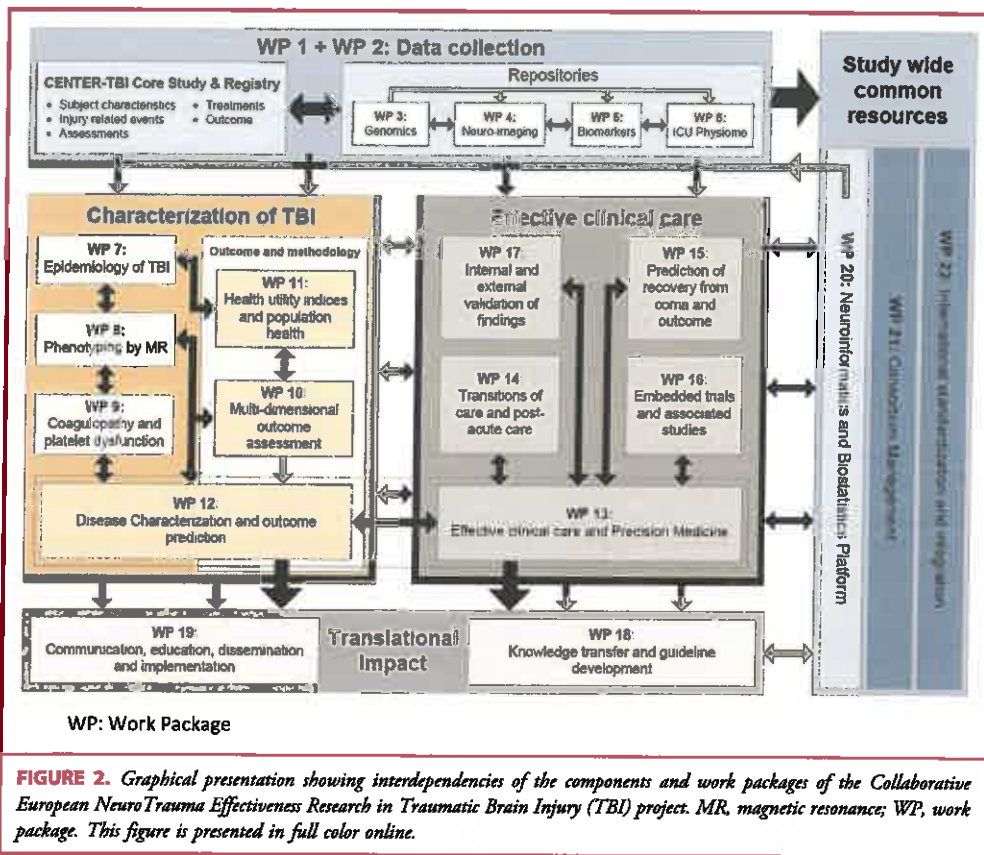


Figure 2 presents a graphical representation of the components and ambitions of the CENTER-TBI project, for which the CENTER-TBI core data study and registry form the basis.

We expect the CENTER-TBI project to bring benefits to patients, healthcare professionals, and policymakers.

Patients

TBI is not limited by any borders. The need for European action is dictated by national and regional differences in resource, treatment approaches, and healthcare delivery, which impact on outcome. These inequalities in treatment provision and outcome are not small: analysis of clinical trial data shows 3.8-fold differences in risk adjusted outcomes across Europe,⁴ and a recent EU report²⁷ recognized that 100 000 lives could be saved annually if injury mortality rates across Europe could be reduced to the lowest observed national rate. CENTER-TBI will provide robust guidelines on best clinical practice, ensuring that every EU citizen obtains the best possible care, regardless of country or region of residence. This will improve outcome and quality of life for individual patients. We will also develop accessible information for patients and families, empowering them as partners in their own care. This will include information on early and reliable outcome prediction (providing hope and decreasing unrealistic expectations).

Various approaches will be adapted to enhance visibility and interaction with patient groups; these include an open website, press releases, establishment of a public information platform, and use of social media. TBI is the commonest cause of deaths in hospital trauma attendances; hence, we would anticipate our CER findings to save ~20 000 EU lives per annum in a predominately economically active population, and reduce disability in survivors.

Healthcare Professionals

We anticipate that our study will transform characterization of TBI and improve detection and understanding of disease processes, mirroring the recommendations of the National Academy of Sciences on the importance of developing a new taxonomy in the context of precision medicine. The expected impact of CENTER-TBI is displayed in Figure 3, adapted from the NAS report. We expect that improved disease characterization and identification of best practices will lead to therapies that are better targeted and more individually oriented (precision medicine). Knowledge gained from the CER analyses will be integrated with systematic reviews of the existing literature to produce improved and harmonized clinical guidelines, facilitating constant improvement by the clinical neurotrauma community.

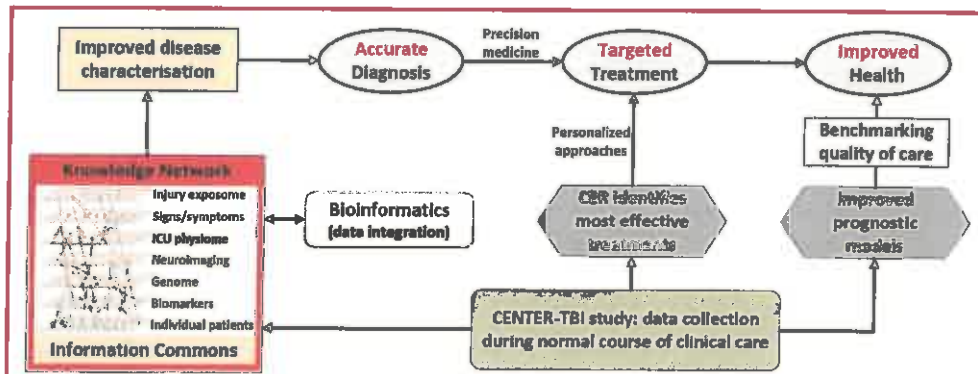


FIGURE 3. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) participants represent a knowledge network that will analyze the clinical database and associated biorepositories. This highly granular information commons, aided by novel bioinformatic approaches, will improve disease characterization, resulting in a new taxonomy of traumatic brain injury (precision medicine). Clinical data will be subjected to comparative effectiveness research (CER) analysis, both directly and after refinement with precision medicine to identify more effective and targeted therapies. The increased data inputs will improve prognostic accuracy, allowing better benchmarking of care (Adapted from the National Research Council¹³). This figure is presented in full color online.

Policymakers

Insight into current epidemiological patterns of TBI across member states will inform prevention campaigns, targeted to needs at national levels. Our focus on the impact of systems of care and organizational aspects of care delivery could yield substantial benefits: for example, introduction of the UK National Institute for Health and Care Excellence Guidelines for TBI management was associated with a 12% reduction in TBI mortality.²⁸ More efficient and targeted care and improved outcome will reduce costs. New performance indicators and improved prognostic models will facilitate benchmarking and assessments of quality of care.

In summary, the CENTER-TBI project will contribute towards the overall goals of InTBIR, by identifying more effective and efficient treatment provision, thus improving outcome and reducing costs. The science in the project will provide novel information on disease processes, treatment, outcome, and prognosis in TBI, identifying new therapeutic targets and therapies, while the CENTER-TBI repositories will ensure opportunities for legacy research. Thus, the project has the potential to improve current healthcare and its delivery at both population and individual levels, deliver early scientific advances that could improve the care of patients with TBI, and provide a rich investment for future biomedical research.

Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Funding of additional elements for this study has been provided by the Hannelore Kohl Foundation (Germany) and by the non-profit organization One Mind for Research (directly to International Neuroinformatics Coordinating Facility). The study registration is Clinicaltrials.gov: NCT02210221.

REFERENCES

1. International initiative for traumatic brain injury research. Available at: <http://intbir.nih.gov/>. Accessed August 22, 2014.
2. Coronado VG, McGuire LC, Sarmiento K, et al. Trends in Traumatic Brain Injury in the U.S. and the public health response: 1995-2009. *J Safety Res.* 2012; 43(4):299-307.
3. Faul M, Wald M, Rutland-Brown W, Sullivent E, Sartin R. Using a cost-benefit analysis to estimate outcomes of a clinical treatment guideline: testing the Brain Trauma foundation guidelines for the treatment of severe traumatic brain injury. *J Trauma.* 2007;63(6):1271-1278.
4. Lingsma HF, Roozenbeek B, Li B, et al. Large between-center differences in outcome after moderate and severe traumatic brain injury in the international mission on prognosis and clinical trial design in traumatic brain injury (IMPACT) study. *Neurosurgery.* 2011;68(3):601-607; discussion 607-608.
5. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *J Neurotrauma.* 2010;27(8):1529-1540.
6. Massagli TL, Fann JR, Burington BE, Jaffe KM, Katon WJ, Thompson RS. Psychiatric illness after mild traumatic brain injury in children. *Arch Phys Med Rehabil.* 2004;85(9):1428-1434.
7. Finkelstein EA, Corso PS, Miller TR. *The Incidence and Economic Burden Of Injuries in the United States.* New York: Oxford University Press; 2006:208.
8. Corrigan JD, Bogner J, Holloman C. Lifetime history of traumatic brain injury among persons with substance use disorders. *Brain Inj.* 2012;26(2):139-150.
9. Brain Trauma Foundation. *Online TBI Guidelines.* Available at: www.tbiguideines.org. Accessed August 22, 2014.
10. National Institute for Health and Care Excellence. Available at: www.nice.org.uk. Accessed August 22, 2014.
11. Maas AI, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. *J Neurotrauma.* 2012;29(1): 32-46.
12. Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet.* 2012;380 (9847):1088-1098.
13. National Research Council (US) Committee on A Framework for Developing a New Taxonomy of Disease. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease.* Washington, DC: National Academies Press (US); 2011.
14. Institute of Medicine. *Initial National Priorities for Comparative Effectiveness Research.* Washington, DC: National Academies Press; 2009.

15. Maas AI, Murray GD, Roozenbeek B, et al. Advancing care for traumatic brain injury: findings from the IMPACT studies and perspectives on future research. *Lancet Neurol*. 2013;12(12):1200-1210.
16. Collaborative European Effectiveness Research in TBI. Available at: www.center-tbi.eu/. Accessed August 26, 2014.
17. QuesGen Systems, Inc. Available at: <http://www.quesgen.com/>. Accessed August 22, 2014.
18. International Neuroinformatics Coordinating Facility. Available at: <http://www.incf.org/>. Accessed August 22, 2014.
19. One Mind for Research. Available at: <http://www.onemind.org/>. Accessed August 22, 2014.
20. NINDS Common Data Elements. Available at: <http://www.commondataelements.ninds.nih.gov/>. Accessed August 22, 2014.
21. Federal Interagency Traumatic Brain Injury Research. Available at: <https://fitbir.nih.gov/>. Accessed August 22, 2014.
22. Alzheimer's Disease Neuroimaging Initiative. Available at: <http://www.adni-info.org/>. Accessed August 22, 2014.
23. Giacino J, Kalmar K. *Coma Recovery Scale-Revised. The Center for Outcome Measurement in Brain Injury*. Available at: <http://tbims.org/combicrs/>. Accessed August 22, 2014.
24. Cambridge Cognition Ltd. Available at: <http://www.cambridgecognition.com/>. Accessed August 22, 2014.
25. Levin HS, O'Donnell VM, Grossman RG. The Galveston Orientation and Amnesia Test. The University of Texas Medical Branch at Galveston. Available at: <https://www.umb.edu/psychology/Adultrehab/GOAT.htm>. Accessed August 22, 2014.
26. Tosetti P, Hicks RR, Theriault E, et al. Towards an international initiative for traumatic brain injury research. *J Neurotrauma*. 2013;30(14):1211-1222.
27. Eurosafe. *Injuries in the European Union: Summary of Injury Statistics for the Years 2008-2010*. Amsterdam, The Netherlands: European Association for Injury Prevention and Safety Promotion (EuroSafe). Available at: http://ec.europa.eu/health/data_collection/docs/idb_report_2013_en.pdf. Accessed August 22, 2014.
28. Fuller G, Bouamra O, Woodford M, et al. Temporal trends in head injury outcomes from 2003 to 2009 in England and Wales. *Br J Neurosurg*. 2011;25(3):414-421.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.neurosurgery-online.com).

Appendix. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Participants and Investigators

Institutes that are scientific participants are in italics. Institutes that are investigating sites (sites for data collection) are in regular font. Institutes that are both scientific participants and investigating sites are in bold.

Nada Andelic,²⁸ Lasse Andreassen,¹⁰³ Peter Andrews,⁸² Gérard Audibert,¹⁰² Anke Audny,¹²⁶ Philippe Azouf,¹³ Pál Barzó,¹⁰⁸ Ronny Beer,⁶⁸ Bo-Michael Belander,⁷⁰ Antonio Belli,⁸⁴ Habib Benali,¹¹ Maurizio Bernardino,⁴⁵ Luigi Beretta,⁸⁹ Alexandra Bracková,⁷ Harald Binder,⁷⁹ Felix Brehar,⁴⁷ Andras Buki,⁸ Monika Bullinger,⁴³ Ela Cakmak,¹⁰⁰ Ina Callebaut,¹⁰⁵ Peter Cameron,³⁶ Guillermo Carbayo Lozano,⁶⁶ Kerri L.H. Carpenter,¹¹⁴ Arturo Chierogato,⁴⁴ Giuseppe Citerio,¹² Mark Coburn,²¹ Jonathan P. Coles,³ Jamie Cooper,¹²⁰ Maryse Cnossen,¹²¹ Nicola Curry,³⁰ Endre Czeiter,⁸ Marek Czosnyka,³ Claire Dahyot-Fitzelier,⁵⁸ François Damas,⁵⁵ Helen Dawes,²⁹ Véronique De Keyser,³ Alessandra De Luca,⁴⁴ Godard C.W. de Ruyter,⁷⁷ Olivier De Witte,⁹⁷ Francesco Della Corte,⁷⁵ Béla Demeter,⁴⁸ Bart Depreitere,¹⁰⁵ Diederik W.J. Dippel,¹²² Kernal Dizdarevic,⁷⁸ Jens P. Dreier,⁴¹ George Eapen,⁹² Ari Ercole,³ Patrick Esser,²⁹ Martin Fabricius,²⁷ Len Feremans,¹⁰ Valery L. Feigin,³⁷ Francesca Fossi,⁴⁴ Faye Forsyth,³ Stefan Florian,⁶¹ Shirin Kordasti Frisvold,¹²³ Caterina Frosini,⁴⁴ Alex Furmanov,⁶⁵ Janek Frantzen,⁹ Davide Gadda,¹²⁴ Pablo Gagliardo,⁶⁴ Damien Galanaud,¹¹ Guoyi Gao,³⁸ Alexandre Ghuyssen,¹²⁷ Alison Godbolt,¹¹⁹ Veronika Gonská,⁷ Zapulih Grigore,⁸⁰ Russel Gruen,³⁶ Juanita A. Haagsma,¹²¹ Giorgio Hallaert,¹¹⁰ Ermin Hadžić,⁸⁶ Ian Haitsma,⁹¹ Jed A. Hartings,³⁵ Raimund Helbok,⁶⁸ Eirik Helseth,¹¹⁸ Sean Hill,⁴ Stefan Hoefler,⁶ Markus Holling,¹⁰¹ Maaik

Hunfeld,¹¹⁴ Peter J. Hutchinson,¹¹³ Robert Ilie,⁵⁹ Koen Janssens,¹ Thamar J H. Bovend'Eerd,²⁹ Ji-yao Jiang,³⁸ Kelly M. Jones,³⁷ Jean-Pierre Kalala,¹¹⁰ Ferenc Kalovits,⁷⁶ Gregor Kaspran,⁷⁹ Ari Katila,⁹ Naomi Ketharanathan,⁵ Angelos G. Kolias,¹¹³ Felix Kolibay,¹⁰⁰ Daniel Kondziella,²⁷ Lars-Owe Koskinen,⁹⁸ Alfonso Lagares,⁶⁷ Linda Lanyon,⁴ Steven Laureys,²⁰ Fiona Lecky,¹⁹ Rolf Lefering,¹⁶ Leon Levi,⁸⁵ Roger Lightfoot,¹⁰⁶ Hester F. Lingsma,¹²¹ Dirk Loeckx,¹⁰ Laura-Nanna Lohkamp,⁴² Jyrki Löytönen,²⁵ Christiano Lumenta,⁷³ Mark Lytle,⁴⁹ Andrew Maas,¹ Marc Maeggele,¹⁵ Marek Majdan,⁷ Alex Manara,⁶³ Geoffrey T. Manley,³³ Hugues Maréchal,⁵⁵ Costanza Martino,⁵¹ Luciana Mascia,¹⁰⁹ Walter Mauritz,⁴⁰ Catherine McMahon,⁸⁵ David K. Menon,³ Tomas Menovsky,¹ Patrick Mitchell,⁸⁸ Nikolay Mladenov,⁸¹ Cristina Morganti-Kossmann,³⁶ David Nelson,⁷⁰ Eddy Neugebauer,¹⁶ Virginia F. Newcombe,³ Mauro Oddo,¹¹⁶ Matej Oresic,²⁵ Vanni Orzalesi,⁴⁴ Joanne G. Outtrim,³ Aarno Palotie,³² Paul Parizel,² Jean-François Payen,¹⁰⁴ Vincent Perlbarg,¹¹ Wilco Peul,¹⁸ Nicolas Pichon,⁵⁷ Anna Piippo,¹¹⁵ Sébastien Pili Flourey,⁵⁶ Horia Ples,⁶² Suzanne Polinder,¹²¹ Aidanas Preiksaitis,³⁴ Marek Psota,⁷ Pim Pullens,² Louis Puybasset,¹¹ Arminas Ragauskas,⁵⁴ Rahul Raj,¹¹⁵ Michael Reiner,¹⁰⁰ Jonathan K.J. Rhodes,¹²⁵ Sylvia Richardson,¹⁴ Samuli Ripatti,³² Saulius Rocka,⁵⁴ Jeffrey Roosenfeld,³⁶ Jonathan Rosand,⁵⁰ Christina Rosenlund,⁸³ Guy Rosenthal,⁶⁵ Rolf Rossaint,²¹ Sandra Rossi,⁴⁶ Daniel Rueckert,³⁰ Martin Rusznák,⁷ Michal A. Rynkowski,⁹⁷ Juan Sahuquillo,¹¹¹ Oliver Sakowitz,²³ Janos Sandor,⁵⁹ Silke Schmidt,³⁹ Herbert Schoechl,²⁶ Rico Schou,¹¹⁷ Toril Skandsen,⁹⁴ Morten Sonne,²⁷ Elisabeth Schwendenwein,⁷⁹ Dirk Smeets,¹⁰ Peter Smielewski,⁵² Jeannette Söderberg,⁴ Emmanuel Stamatakis,³ Simon Stanworth,³⁰ Roberto Stefani,⁹³ Robert Stevens,⁶⁹ William Stewart,²² Ewout W. Steyerberg,¹²¹ Nino Stocchetti,³¹ Walter Stummer,¹⁰¹ József Szabó,⁷⁶ Alexandru Tascu,⁴⁷ Olli Tenovuo,⁹ Alice Theadom,³⁷ Dick Tibboel,⁵ Christos M. Toliás,⁷² Andreas Unterberg,²³ Peter Vajkoczy,⁴² Alessia Vargiolu,¹² Joukje van der Naalt,¹¹⁰ Thomas van Essen,¹⁸ Wim Van Hecke,¹⁰ Dominique Van Praag,¹ Dirk Van Roost,²⁷ Tim Vandenbulcke,⁵³ Luc vande Hauwe,² Mathieu Van der Jagt,¹⁷ Emmanuel Vega,⁷⁴ Jan Verheyden,¹⁰ Vishwajit Verma,⁸⁷ Paul M. Vespa,¹¹² Anne Vik,⁹⁴ Rimantas Vilcins,⁷¹ Nicole von Steinbüchel,⁶ Peter Vulekovic,⁶⁰ Kevin K.W. Wang,³⁴ Eno Wildschut,⁵ Guy Williams,⁵² Mark Wilson,²⁴ Lindsay Wilson,²⁶ Stefan Wolf,⁴² Peter Ylén,²⁵ Menashe Zaaroor,⁸⁵ Parjam Zolfaghari,⁸⁷ Didier Martin,¹²⁸ Vincenzo D'Orto,¹²⁷ Pierre Damas,¹²⁹ Jean-Flory Luaba Tshibanda.¹³⁰

¹Department of Neurosurgery, Antwerp University Hospital and University of Antwerp, Edegem, Belgium.

²Department of Radiology, Antwerp University Hospital and University of Antwerp, Edegem, Belgium.

³Division of Anaesthesia, University of Cambridge, Cambridge, UK.

⁴INCF International Neuroinformatics Coordinating Facility, Karolinska Institutet, Stockholm, Sweden.

⁵Intensive Care and Department of Pediatric Surgery, Erasmus MC—University Medical Center Rotterdam, Sophia Children's Hospital, Rotterdam, The Netherlands.

⁶Department of Medical Psychology and Medical Sociology, Universitätsmedizin Göttingen, Göttingen, Germany.

⁷Department of Public Health, Trnava University, Faculty of Health Sciences and Social Work, Trnava, Slovak Republic.

⁸Department of Neurosurgery, University of Pécs and Clinical Neuroscience Image Center of Hungarian Academy of Sciences (HAS), Pécs, Hungary.

⁹Department of Rehabilitation and Brain Trauma, Turku University Central Hospital, Turku, Finland.

¹⁰iscoMetrix NV, Leuven, Belgium.

¹¹Anesthésie-Réanimation, Assistance Publique—Hôpitaux de Paris, Paris, France.

¹²Department of Health Science, University of Milan-Bicocca, Monza, Italy, NeuroIntensive Care, Department of Emergency and Intensive Care, San Gerardo Hospital, Monza, Italy.

¹³Assistance Publique—Hôpitaux de Paris, Raymond Poincaré hospital, Department of Physical Medicine and Rehabilitation, Garches, France.

¹⁴MRC Biostatistics Unit, Cambridge Institute of Public Health, Cambridge, UK.

- ¹⁵Cologne-Merheim Medical Center (CMMC), Department of Traumatology, Orthopedic Surgery and Sportmedicine, Witten/Herdecke University, Cologne, Germany.
- ¹⁶Institute of Research in Operative Medicine (IFOM), Witten/Herdecke University, Cologne, Germany.
- ¹⁷Departments of Intensive Care, Erasmus MC—University Medical Center Rotterdam, Rotterdam, the Netherlands.
- ¹⁸Department of Neurosurgery, Leiden University and Medical Center The Hague, The Hague & Leiden, The Netherlands.
- ¹⁹EMRIS Group, Heatl Services research, School of Health and Related Research, University of Sheffield, Sheffield, United Kingdom.
- ²⁰Coma Science Group, CRCyclotron and Neurology Department, University and University Hospital of Liège, Belgium.
- ²¹Department of Anaesthesiology, University Hospital RWTH Aachen, Aachen, Germany.
- ²²Department of Neuropathology, Southern General Hospital, Glasgow, UK.
- ²³Department of Neurosurgery, University Hospital Heidelberg, Heidelberg, Germany.
- ²⁴Department of Neurosurgery, Imperial College London, London, UK.
- ²⁵VTT Technical Research Centre, Tampere, Finland.
- ²⁶Division of Psychology, School of Natural Sciences, University of Stirling, Stirling, UK.
- ²⁷Departments of Neurology, Clinical Neurophysiology and Neuroanesthesiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.
- ²⁸Division of Surgery and Clinical Neuroscience, Oslo University Hospital and University of Oslo, Oslo, Norway.
- ²⁹Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK.
- ³⁰Department of Haematology, NHSBT/Oxford University Hospitals NHS Trust, Oxford, UK.
- ³¹Department of Physiopathology and Transplant, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy.
- ³²FIMM, Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland.
- ³³Department of Neurosurgery, University of California San Francisco, San Francisco, California.
- ³⁴Center of Neuroproteomics and Biomarkers Research, University of Florida, Gainesville, Florida.
- ³⁵Department of Neurosurgery, University of Cincinnati, Cincinnati, Ohio.
- ³⁶School of Public Health, Monash University, Melbourne, Australia.
- ³⁷National Institute for Stroke & Applied Neurosciences, Auckland University of Technology, Auckland, New Zealand.
- ³⁸Department of Neurosurgery, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.
- ³⁹Department Health and Prevention, University Greifswald, Greifswald, Germany.
- ⁴⁰International Neurotrauma Research Organisation, Vienna, Austria.
- ⁴¹Center for Stroke Research, Charité—Universitätsmedizin Berlin, Berlin, Germany.
- ⁴²Neurologie, Neurochirurgie und Psychiatrie, Charité—Universitätsmedizin Berlin, Berlin, Germany.
- ⁴³Department of Medical Psychology, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.
- ⁴⁴Anestesia e Rianimazione CTO, AOU Careggi Florence, Florence, Italy.
- ⁴⁵Department of Anesthesia & ICU, AOU Città della Salute e della Scienza di Torino—Orthopedic and Trauma Center, Torino, Italy.
- ⁴⁶Department of Anesthesia & Intensive Care, Azienda Ospedaliera Università di Padova, Padova, Italy.
- ⁴⁷Department of Neurosurgery, Bagdasar-Arseni Emergency Clinical Hospital, Bucharest, Romania.
- ⁴⁸Department of Neurosurgery, Borsod County University Teaching Hospital, Miskolc, Hungary.
- ⁴⁹Emergency Department, Bristol Royal Hospital for Children, Bristol, UK and Academic Department of Emergency Care, University of the West of England, Bristol, UK.
- ⁵⁰Division of Neurocritical Care and Emergency Neurology, Broad Institute, Cambridge; Harvard Medical School, Boston; Massachusetts General Hospital, Boston Massachusetts.
- ⁵¹Department of Anesthesiology, Bufalini Hospital, Cesena, Italy.
- ⁵²Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.
- ⁵³Biomina—Biomedical Informatics Research Group, Antwerp University Hospital and University of Antwerp, Edegem, Belgium.
- ⁵⁴Department of Neurosurgery, Kaunas University of Technology and Vilnius University, Vilnius, Lithuania.
- ⁵⁵Intensive Care Unit, CHR Citadelle, Liège, Belgium.
- ⁵⁶Intensive Care Unit, CHRU de Besançon, Besançon, France.
- ⁵⁷Intensive Care Unit, CHU Dupuytren, Limoges, France.
- ⁵⁸Department of Anesthesia & Reanimation, CHU Poitiers, Poitiers, France.
- ⁵⁹Faculty of Public Health Department of Preventive Medicine Division of Biostatistics and Epidemiology, University of Debrecen, Debrecen, Hungary.
- ⁶⁰Department of Neurosurgery, Clinical Centre of Vojvodina, Novi Sad, Serbia.
- ⁶¹Department of Neurosurgery, Cluj County Emergency Hospital, Cluj-Napoca, Romania.
- ⁶²Department of Neurosurgery, Emergency County Hospital of Timisoara, "Victor Babes" University of Medicine and Pharmacy Timisoara, Romania.
- ⁶³Department of Anaesthesia & Intensive Care, Frenchay Hospital Bristol, Bristol, UK.
- ⁶⁴Fundación Instituto Valenciano de Neurorehabilitación (FIVAN), Valencia, Spain.
- ⁶⁵Department of Neurosurgery, Hadassah-hebrew University Medical Center, Jerusalem, Israel.
- ⁶⁶Department of Neurosurgery, Cruces University Hospital, Bilbao, Spain.
- ⁶⁷Department of Neurosurgery, Hospital Universitario 12 de Octubre, Madrid, Spain.
- ⁶⁸Department of Neurology, Division of Neurocritical Care, Innsbruck Medical University, Innsbruck, Austria.
- ⁶⁹Departments of Anesthesiology/Critical Care Medicine, Neurology, Neurosurgery, and Radiology, John Hopkins University School of Medicine, Baltimore, Maryland.
- ⁷⁰Department of Clinical Neuroscience, section for Neurosurgery, Karolinska University Hospital Solna, Stockholm, Sweden.
- ⁷¹Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania.
- ⁷²Department of Neurosurgery, Kings college Hospital, London, UK.
- ⁷³Department of Neurosurgery, Klinikum Bogenhausen/Klinikum Schwabing, München, Germany.
- ⁷⁴Department of Anesthesiology-Intensive Care, Lille University Hospital, Lille, France.
- ⁷⁵Department of Anesthesia & Intensive Care, Maggiore Della Carità Hospital, Novara, Italy.
- ⁷⁶Department of Neurological & Spinal Surgery, Markosovszky University Teaching Hospital, Szombathely, Hungary.
- ⁷⁷Department of Neurosurgery, Medical Center Haaglanden, The Hague, Netherlands.
- ⁷⁸Department of Neurosurgery, Medical Faculty and Clinical Center University of Sarajevo, Sarajevo, Bosnia Herzegovina.
- ⁷⁹Trauma Surgery, Medical University Vienna, Vienna, Austria.
- ⁸⁰Department of Neurosurgery, Medical University, Chisinau, Moldova.

- ⁸¹Department of Anesthesiology & Intensive Care, Military Medical Academy, Sofia, Bulgaria.
- ⁸²Department of Anaesthesia, Critical Care & Pain Medicine, NHS Lothian & University of Edinburgh, Edinburgh, UK.
- ⁸³Department of Neurosurgery, Odense University Hospital, Odense, Denmark.
- ⁸⁴Department of Neurosurgery, Queen Elizabeth Hospital, Birmingham, UK.
- ⁸⁵Department of Neurosurgery, Rambam Medical Center, Haifa, Israel.
- ⁸⁶Department of Neurosurgery, Regional Medical Center "dr Safet Mujic"⁸⁷ Mostar, Bosnia Herzegovina.
- ⁸⁷Intensive Care Unit, Royal London Hospital, London, UK.
- ⁸⁸Department of Neurosurgery, Royal Victoria Infirmary, Newcastle, UK.
- ⁸⁹Department of Anesthesiology & Intensive Care, S Raffaele University Hospital, Milan, Italy.
- ⁹⁰Department of Computing, Imperial College London, London, UK.
- ⁹¹Department of Neurosurgery, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands.
- ⁹²Neurointensive Care, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK.
- ⁹³Department of Neurosurgery, Spedali Civili di Brescia, Brescia, Italy.
- ⁹⁴Department of Neurosurgery, St Olavs Hospital/Norwegian University of Science and Technology, Trondheim, Norway.
- ⁹⁵Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK.
- ⁹⁶*Ludwig Boltzmann Institute for Experimental and Clinical Traumatology and AUVA Research Centre, Vienna, Austria.*
- ⁹⁷Department of Neurosurgery, ULB Erasme, Brussels, Belgium.
- ⁹⁸Department of Neurosurgery, Umea University Hospital, Umea, Sweden.
- ⁹⁹Department of Neurosurgery, University Hospital Bratislava, Bratislava, Slovak republic.
- ¹⁰⁰Department of Neurosurgery, University Hospital Cologne, Köln, Germany.
- ¹⁰¹Department of Neurosurgery, University Hospital Münster, Münster, Germany.
- ¹⁰²Department of Anesthesiology & Intensive Care, University Hospital Nancy, Nancy, France.
- ¹⁰³Department of Neurosurgery, University Hospital Northern Norway, Tromso, Norway.
- ¹⁰⁴Department of Anesthesiology & Intensive Care, University Hospital of Grenoble, Grenoble, France.
- ¹⁰⁵Department of Neurosurgery, University Hospitals Leuven, Leuven, Belgium.
- ¹⁰⁶Department of Anesthesiology & Intensive Care, University Hospitals Southampton NHS Trust, Southampton, UK.
- ¹⁰⁷Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands.
- ¹⁰⁸Department of Neurology, University of Szeged, Szeged, Hungary.
- ¹⁰⁹Department of Anesthesiology & Intensive Care, University of Turin, Torino, Italy.
- ¹¹⁰Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium.
- ¹¹¹Department of Neurosurgery, Vall d'Hebron University Hospital, Barcelona, Spain.
- ¹¹²*Department of Neurocritical Care, David Geffen School of Medicine, University of California, Los Angeles.*
- ¹¹³**Academic Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital & University of Cambridge, UK.**
- ¹¹⁴Intensive Care and Pediatric Surgery, Department of Pediatric Neurology, Erasmus MC—University Medical Center Rotterdam, Sophia Children's Hospital, Rotterdam, The Netherlands.
- ¹¹⁵Department of Neurosurgery, Helsinki University Central Hospital, Helsinki, Finland.
- ¹¹⁶Department of Intensive Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), University Hospital, Lausanne, Switzerland.
- ¹¹⁷Department of Anesthesiology, Odense University Hospital, Odense, Denmark.
- ¹¹⁸Department of Neurosurgery, Oslo University Hospital, Oslo, Norway.
- ¹¹⁹University Dept of Rehabilitation Medicine, Karolinska University Hospital, Stockholm, Sweden.
- ¹²⁰*Department of Intensive Care Medicine, Monash University, Melbourne, Australia.*
- ¹²¹*Department of Public Health, Center for Medical Decision Making, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands.*
- ¹²²Department of Neurology, Erasmus MC—University Medical Center Rotterdam, Rotterdam, The Netherlands.
- ¹²³Department of Anaesthesiology and Intensive Care, University Hospital Northern Norway, Tromso, Norway.
- ¹²⁴Neuroradiologia, AOU Careggi Florence, Florence, Italy.
- ¹²⁵Department of Intensive Care, Western General Hospital, NHS Lothian & University of Edinburgh, Edinburgh, UK.
- ¹²⁶Department of Rehabilitation, University Hospital Northern Norway, Tromso, Norway.
- ¹²⁷Emergency Department, CHU Hospital Liège, Belgium.
- ¹²⁸Neurosurgery Department, CHU Hospital Liège, Belgium.
- ¹²⁹Intensive Care Unit, CHU Hospital Liège, Belgium.
- ¹³⁰Neuroradiology Department, CHU Hospital Liège, Belgium.